Nelson

Pediatric Symptom-Based Diagnosis

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PREFACE

This book is intended to help the reader begin with a specific chief complaint that may be seen in many different disease entities. It is arranged in chapters that cover specific symptoms mirroring clinical practice. Patients do not usually present with a chief complaint of cystic fibrosis; rather, they may present with a cough, respiratory distress, or chronic diarrhea.

With a user-friendly, well-tabulated, illustrated approach, this text will help the reader differentiate between the many disease states causing a common symptom. The inclusion of many original tables and figures should help the reader identify distinguishing features of diseases and work through a diagnostic approach to the symptom. Modified and borrowed artwork and tables from other outstanding current sources have been added as well. The combination of all of these illustrations and tables with diagnostic clues within the text will help provide a quick visual guide to the differential diagnosis of the various diseases under discussion. The diagnostic approach includes standard laboratory and radiologic testing, as well as advanced imaging studies and genetic-based analysis.

We appreciate the hard work of our contributing authors. Writing a chapter in this type of format is quite different from writing in the format of a disease-based book. In addition, we thank Kate Dimock and Jennifer Ehlers of Elsevier, whose patience and expertise contributed to the publication of this book. We are all also greatly appreciative of Carolyn Redman at the Medical College of Wisconsin Department of Pediatrics, whose editorial assistance and organization have made this new edition a reality. Finally, we are ever grateful for the understanding and patience of Diane Basel, Jessica Bordini, Ryan Festerling, Sharon Kliegman, and Dale Lye in supporting this work.

1

Sore Throat

Robert R. Tanz

Most causes of sore throat are nonbacterial and neither require nor are alleviated by antibiotic therapy (Tables 1.1, 1.2, and 1.3). Accurate diagnosis is essential: Acute streptococcal pharyngitis warrants diagnosis and therapy to ensure prevention of serious suppurative and nonsuppurative complications. Life-threatening infectious complications of oropharyngeal infections, whether streptococcal or nonstreptococcal, may manifest with mouth pain, pharyngitis, parapharyngeal space infectious extension, and/or airway obstruction (Tables 1.4 and 1.5). In many cases, the history and/or physical exam can help direct diagnosis and treatment, but the enormous number of potential causes is too large to address all of them.

VIRAL PHARYNGITIS

Most episodes of pharyngitis are caused by viruses (see Tables 1.2 and 1.3). It is difficult to clinically distinguish between viral and bacterial pharyngitis with a very high degree of precision, but certain clues may help the physician. Accompanying symptoms of conjunctivitis, rhinitis, cough, discrete ulcerations, croup, or laryngitis are common with viral infection but rare in bacterial pharyngitis.

Many viral agents can produce pharyngitis (see Tables 1.2 and 1.3). Some cause distinct clinical syndromes that are readily diagnosed without laboratory testing (Table 1.6; see also Tables 1.1 and 1.4). In pharyngitis caused by parainfluenza and influenza viruses, rhinoviruses, coronaviruses, and respiratory syncytial virus (RSV), the symptoms of coryza and cough often overshadow sore throat, which is generally mild. Influenza virus may cause high fever, cough, headache, malaise, myalgia, and cervical adenopathy in addition to pharyngitis. In young children, croup or bronchiolitis may develop. When influenza is suspected on clinical and epidemiologic grounds or confirmed by testing (polymerase chain reaction [PCR] is most accurate), specific antiviral therapy is available for treatment of patients and prophylaxis of family members. RSV is associated with bronchiolitis, pneumonia, and croup in young children. RSV infection in older children is usually indistinguishable from a simple upper respiratory tract infection. Pharyngitis is not a prominent finding of RSV infection in any age group. Parainfluenza viruses are associated with croup and bronchiolitis; minor sore throat and signs of pharyngitis are common at the outset but rapidly resolve. Infections caused by parainfluenza, influenza, and RSV are often seen in seasonal (winter) epidemics. *Many agents can be identified using multiplex or targeted PCR testing, but there is rarely reason to test outpatients and infrequent benefit to testing inpatients except to confirm and treat influenza.*

Adenoviruses can cause upper and lower respiratory tract disease, ranging from ordinary colds to severe pneumonia and multisystem disease, including hepatitis, myocarditis, and myositis. The incubation period of adenovirus infection is 2-4 days. Upper respiratory tract infection typically produces fever, erythema of the pharynx, and follicular hyperplasia of the tonsils, together with exudate. Enlargement of the cervical lymph nodes occurs frequently. When conjunctivitis occurs in association with adenoviral pharyngitis, the resulting syndrome is called **pharyngoconjunctival fever**. Pharyngitis may last as long as 7 days and does not respond to antibiotics. There are many adenovirus serotypes; adenovirus infections may therefore develop in children more than once. Laboratory studies may reveal a leukocytosis and an elevated erythrocyte sedimentation rate. Adenovirus outbreaks have been associated with swimming pools and contamination in health care workers.

The **enteroviruses** (coxsackievirus and echovirus) can cause sore throat, especially in the summer. High fever is common, and the throat is erythematous but usually not bright red; tonsillar exudate and cervical adenopathy are unusual. Symptoms resolve within a few days. Enteroviruses can also cause meningitis, myocarditis, rash, and two specific syndromes that involve the oropharynx.

Herpangina is characterized by distinctive discrete, painful, gray-white papulovesicular lesions distributed over the posterior oropharynx (see Table 1.6). The vesicles are 1-2 mm in diameter and are initially surrounded by a halo of erythema before they ulcerate. Fever may reach 39.5°C. The illness is due to enteroviruses and generally lasts less than 7 days, but severe pain may impair fluid intake and occasionally necessitates medical support.

Hand-foot-mouth disease is caused by coxsackievirus A16. Painful vesicles that ulcerate can occur throughout the oropharynx. Vesicles also develop on the palms, soles, and, less often, on the trunk or extremities. Fever is present in most cases, but many children do not appear seriously ill. This disease lasts less than 7 days.

Primary infection caused by **herpes simplex virus** (**HSV**) usually produces high fever with acute gingivostomatitis, involving vesicles (which become ulcers) throughout the anterior portion of the mouth, including the lips. There is sparing of the posterior pharynx in herpes gingivostomatitis; the infection usually occurs in young children. High fever is common, pain is intense, and intake of oral fluids is often impaired, which may lead to dehydration. In addition, HSV may

(See *Nelson Textbook of Pediatrics*, p. 2019)

TABLE 1.1 Etiology of Sore Throat

Infection
Bacterial (see Tables 1.2, 1.3)
Viral (see Tables 1.2, 1.3)
Fungal (see Table 1.3)
Neutropenic mucositis (invasive anaerobic mouth flora)
Tonsillitis
Epiglottitis
Uvulitis
Peritonsillar abscess (quinsy)
Retropharyngeal abscess (prevertebral space)
Ludwig angina (submandibular space)
Lateral pharyngeal space cellulitis-abscess
Buccal space cellulitis
Suppurative thyroiditis
Lemierre syndrome (septic jugular thrombophlebitis)
Vincent angina (mixed anaerobic bacteria–gingivitis–pharyngitis)

Irritation
Cigarette smoking
Inhaled irritants
Reflux esophagitis
Chemical toxins (caustic agents)
Paraquat ingestion
Smog
Dry hot air
Hot foods, liquids

Other
Tumor, including Kaposi sarcoma, leukemia
Granulomatosis with polyangiitis (formerly Wegener granulomatosis)
Sarcoidosis
Glossopharyngeal neuralgia
Foreign body
Stylohyoid syndrome
Behçet disease
Kawasaki syndrome
Posterior pharyngeal trauma—pseudodiverticulum
Pneumomediastinum with air dissection
Hematoma
Systemic lupus erythematosus
Bullous pemphigoid
Syndrome of periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA)

TABLE 1.2 Infectious Etiology of Pharyngitis

Definite Causes
Streptococcus pyogenes (Group A streptococci)
Corynebacterium diphtheriae
Arcanobacterium haemolyticum
Neisseria gonorrhoeae
Epstein-Barr virus
Parainfluenza viruses (types 1–4)
Influenza viruses
Rhinoviruses
Coronavirus
Adenovirus (types 3, 4, 7, 14, 21, others)
Respiratory syncytial virus
Herpes simplex virus (types 1, 2)

Probable or Occasional Causes
Group C streptococci
Group G streptococci
Chlamydia pneumoniae
Chlamydia trachomatis
Mycoplasma pneumoniae

TABLE 1.3 Additional Potential Pathogens Associated with Sore Throat

Bacteria
Fusobacterium necrophorum (Lemierre syndrome)
Neisseria meningitidis
Yersinia enterocolitica
Tularemia (oropharyngeal)
Yersinia pestis
Bacillus anthracis
Chlamydia psittaci
Secondary syphilis
Mycobacterium tuberculosis
Lyme disease
Corynebacterium ulcerans
Leptospira species
Mycoplasma hominis

Virus
Coxsackievirus A, B
Cytomegalovirus
Viral hemorrhagic fevers
Human immunodeficiency virus (HIV) (primary infection)
Human herpesvirus 6
Measles
Varicella
Rubella

Fungus
Candida species
Histoplasmosis
Cryptococcosis

manifest as pharyngitis in adolescents. Approximately 35% of new-onset HSV-positive adolescent patients have herpetic lesions; most teenage patients with HSV pharyngitis cannot be distinguished from patients with other causes of pharyngitis. The classic syndrome of herpetic gingivostomatitis in infants and toddlers lasts up to 2 weeks; data on the course of more benign HSV pharyngitis are lacking. The differential diagnosis of vesicular-ulcerating oral lesions is noted in Table 1.6.

A common cause of a local and large lesion of unknown etiology is **aphthous stomatitis** (Fig. 1.1). *PFAPA* (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis) is an idiopathic periodic fever syndrome that occurs predictably every 2-8 weeks. The onset of PFAPA is usually before the age of 5 years. In addition to aphthous stomatitis and pharyngitis, PFAPA is characterized by high fever lasting 4-6 days. Individual episodes resolve spontaneously but may respond

TABLE 1.4 Distinguishing Features of Parapharyngeal–Upper Respiratory Tract Infections

	Peritonsillar Abscess	Retropharyngeal Abscess (Cellulitis)	Submandibular Space (Ludwig Angina)*	Lateral Pharyngeal Space	Masticator Space*	Epiglottitis	Laryngotracheo-bronchitis (Croup)	Bacterial Tracheitis	Postanginal Sepsis (Lemierre Syndrome)
Etiology	Group A streptococci, oral anaerobes†	*Staphylococcis aureus,* oral anaerobes,† group A streptococci, "suppurative adenitis"	Oral anaerobes†	Oral anaerobes†	Oral anaerobes†	*Haemophilus influenzae* type b (rarely), group A streptococci, *Streptococcus pneumoniae*, *Staphyloccocus aureus*, and non-type b *H. influenzae*	Parainfluenza virus; influenza, adenovirus, and respiratory syncytial virus less common	*Moraxella catarrhalis, S. aureus, H. influenzae type b* or nontypable	*Fusobacterium necrophorum*
Age	Teens	Infancy, preteens, occasionally teens	Teens	Teens	Teens	2-5 yr	3 mo-3 yr	3-10 yr	Teens
Manifestations	Initial episode of pharyngitis, followed by sudden worsening of unilateral odynophagia, trismus, hot potato (muffled) voice, drooling, displacement of uvula	Fever, dyspnea, stridor, dysphagia, drooling, stiff neck, pain, cervical adenopathy, swelling of posterior pharyngeal space Descending mediastinitis (rare) Lateral neck radiograph reveals swollen retropharyngeal prevertebral space: infants, >1 × width of adjacent vertebral body (>2-7 mm); teens, > ⅓ × width of vertebral body (>1-7 mm) CT distinguishes cellulitis from abscess	Fever, dysphagia, odynophagia, stiff neck, dyspnea; airway obstruction, swollen tongue and floor of mouth (tender) Muffled voice	Severe pain, fever, trismus, dysphagia, edematous appearing, painful lateral facial (jaw) or neck swelling (induration) May lead to Lemierre syndrome	Pain, prominent trismus, fever Swelling not always evident	Sudden-onset high fever, "toxic" appearance, muffled voice, anxiety, pain, retractions, dysphagia, drooling, stridor, sitting up, leaning forward tripod position, cherry-red swollen epiglottis Usually not hoarse or coughing Lateral neck radiograph shows "thumb sign" of swollen epiglottis	Low-grade fever, barking cough, hoarseness, aphonia, stridor; mild retractions; radiograph shows "steeple sign" of subglottic narrowing on anteroposterior neck view	Prior history of croup with sudden onset of respiratory distress, high fever, "toxic" appearance, hoarseness, stridor, barking cough, tripod sitting position; radiograph as per croup plus ragged tracheal air column	Prior pharyngitis with sudden-onset fever, chills, odynophagia, neck pain, septic thrombophlebitits of internal jugular vein with septic emboli (e.g., lungs, joints), bacteremia

*Often odontogenic; check for tooth abscess, caries, tender teeth.
†*Peptostreptococcus, Fusobacterium, Bacteroides.*

TABLE 1.5 Red Flags Associated with Sore Throat

Toxic appearance
Shock
Fever >2 wk
Duration of sore throat >2 wk
Trismus
Drooling
Cyanosis
Hemorrhage
Asymmetric tonsillar swelling or asymmetric cervical adenopathy
Respiratory distress (airway obstruction or pneumonia)
Suspicion of parapharyngeal space infection
Suspicion of diphtheria (bull neck, uvula paralysis, thick membrane)
Apnea
Severe, unremitting pain
"Hot potato" voice
Chest or neck pain
Weight loss

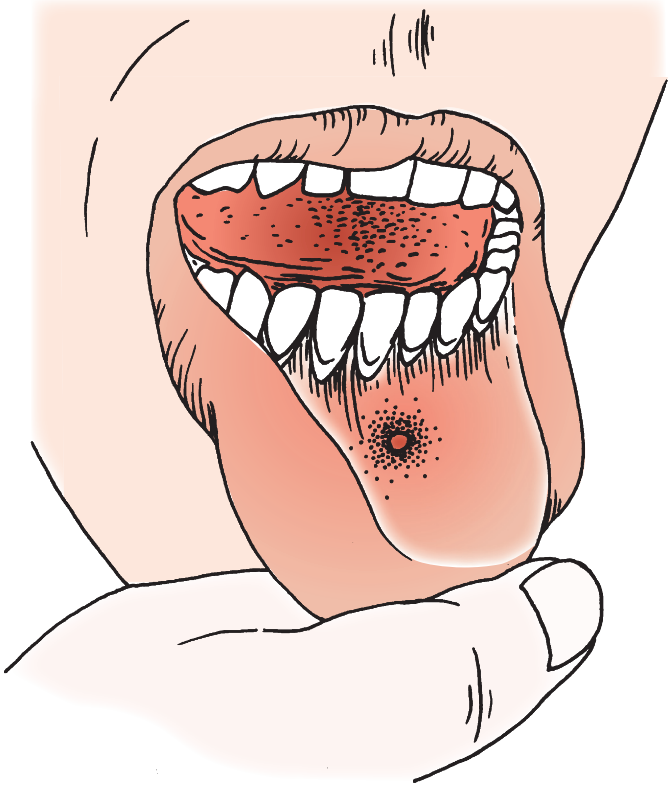


FIGURE 1.1 Aphthous stomatitis ("canker sore"). (From Reilly BM. Sore throat. In: *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991.)

to oral prednisone or cimetidine. There are reports of improvement after tonsillectomy. In most patients PFAPA completely resolves before puberty without sequelae. The diagnosis is based on clinical criteria after excluding cyclic neutropenia, other periodic fever syndromes, infections, and malignancy.

Infants and toddlers with **measles** often have prominent oral findings early in the course of the disease. In addition to high fever, cough, coryza, and conjunctivitis, the pharynx may be intensely and diffusely erythematous, without tonsillar enlargement or exudate. The presence of **Koplik spots**, the pathognomonic white or blue-white enanthem of measles, on the buccal mucosa near the mandibular molars provides the evidence of the correct diagnosis before the rash develops. Measles can be complicated by pneumonia and encephalitis. In the United States, widespread use of the measles vaccine has virtually eliminated transmission of natural measles infection except among unvaccinated subpopulations (children <12 months old, families who have refused immunization). Most cases are imported by unimmunized visitors from countries with endemic measles.

INFECTIOUS MONONUCLEOSIS

◆ Pathogenesis

Acute exudative pharyngitis commonly occurs with infectious mononucleosis caused by primary infection with the Epstein-Barr virus (EBV). Mononucleosis is a febrile, systemic, self-limited lymphoproliferative disorder that is usually associated with hepatosplenomegaly and generalized lymphadenopathy. Acute pharyngitis may be mild or severe, with significant tonsillar hypertrophy (possibly producing airway obstruction), erythema, and impressive tonsillar exudates. Regional lymph nodes may be particularly enlarged and slightly tender. Infectious mononucleosis usually occurs in adolescents and young adults; EBV infection is generally milder or subclinical in preadolescent children. In U.S. high school and college students, attack rates are 200-800 per 100,000 per year. EBV is transmitted primarily by saliva.

◆ Clinical Features

After a 2-4 week incubation period, patients with infectious mononucleosis usually experience an abrupt onset of malaise, fatigue, fever, and headache, followed closely by pharyngitis. The tonsils are enlarged with exudates and cervical adenopathy. More generalized adenopathy with hepatosplenomegaly often follows. Fever and pharyngitis typically last 1-3 weeks, and lymphadenopathy and hepatosplenomegaly resolve over 3-6 weeks. Malaise and lethargy can persist for several months and can affect school or work performance.

◆ Diagnosis

Laboratory studies of diagnostic value include atypical lymphocytosis; these lymphocytes are primarily EBVspecific, cytotoxic T lymphocytes that represent a reactive response to EBV-infected B lymphocytes. A modest elevation of serum transaminase levels, reflecting EBV hepatitis, is common. Tests useful for diagnosis include detection of heterophile antibodies that react with bovine erythrocytes (most often detected by the monospot test) and a specific antibody against EBV viral capsid antigen (VCA), early antigen (EA), and nuclear antigen (EBNA). Acute infectious mononucleosis is usually associated with a positive heterophile test result and antibody to VCA and EA (Fig. 1.2).

The findings of acute exudative pharyngitis together with hepatomegaly, splenomegaly, and generalized lymphadenopathy suggest infectious mononucleosis. Early in the disease and in cases without liver or spleen enlargement, differentiation from other causes of pharyngitis, including streptococcal pharyngitis, is difficult. Indeed, a small number of patients with infectious mononucleosis have a throat culture positive for group A streptococci. (They are likely streptococcal carriers; see subsequent text.) An indistinguishable syndrome can occur with cytomegalovirus, but differentiation is rarely of clinical importance. Serologic evidence of mononucleosis should be sought

(See *Nelson Textbook of Pediatrics*, p. 1586)

TABLE 1.6 Vesicular-Ulcerating Eruptions of the Mouth and Pharynx

	Gingivostomatitis	Herpangina	Hand-Foot-Mouth Disease	Chickenpox	Systemic Lupus Erythematosus (SLE)	Inflammatory Bowel Disease (IBD)	Aphthous Stomatitis	Behçet Disease	Vincent Stomatitis	Recurrent Scarifying Ulcerative Stomatitis (Sutton Disease)
Etiology	Herpes simples virus (HSV I)	Cocksackievirus A, B; echovirus or HSV (rarely)	Cocksackievirus A, cocksackievirus B (rarely)	Varicella-zoster virus	Autoimmune	Autoimmune	Unknown	Unknown; vasculitis	Unknown; or anaerobic bacteria	Unknown
Location	Ulcerative vesicles of pharynx, tongue, and palate plus lesions of mucocutaneous (perioral) margin	Anterior fauces (tonsils), soft palate (uvula), less often pharynx	Tongue, buccal mucosa, palate, palms, soles, anterior oral cavity	Tongue, gingiva, buccal mucosa, marked cutaneous lesions; trunk > face	Oral, nasal mucosa; palate, pharynx, buccal mucosa	Lips, tongue, buccal mucosa, oropharynx	As in IBD	Oral (similar to IBD); genital ulcers	Gingiva; ulceration at base of teeth	Tongue; buccal mucosa
Age	Less than 5 yr	3-10 yr	1 yr-teens	Any age	Any age	Any age	Teens and adulthood	Teens, adulthood, occasionally <10 yr	Teens; if younger, consider immunodeficiency and blood dyscrasia	Teens
Manifestations	Fever, mouth pain, toxic, fetid breath, drooling, anorexia, cervical lymphadenopathy; cracked, swollen hemorrhagic gums; secondary inoculation possible (fingers, eye, skin); reactivation with long latency (any age)	Fever, sore throat, odynophagia; summer outbreaks; 6-12 lesions (2-4 mm papule) → vesicle → ulceration; headache, myalgias	Painful bilateral vesicles, fever	Fever, pruritic cutaneous vesicles, painful oral lesions	Renal, central nervous system, arthritis, cutaneous, hematologic, other organ involvement; ulcers minimally to moderately painful; may be painless	Multiple recurrences; painful ulcerations 1-2 mm, but may be 5-15 mm	Similar to IBD	Painful ulcerations (heal without scarring); uveitis, arthralgia, arthritis, lower gastrointestinal ulceration (similar to IBD); recurrences; spontaneous remissions	Fever, bleeding gums; gray membrane	Deep, large, painful ulcerations; relapsing; scarring with distortion of mucosa

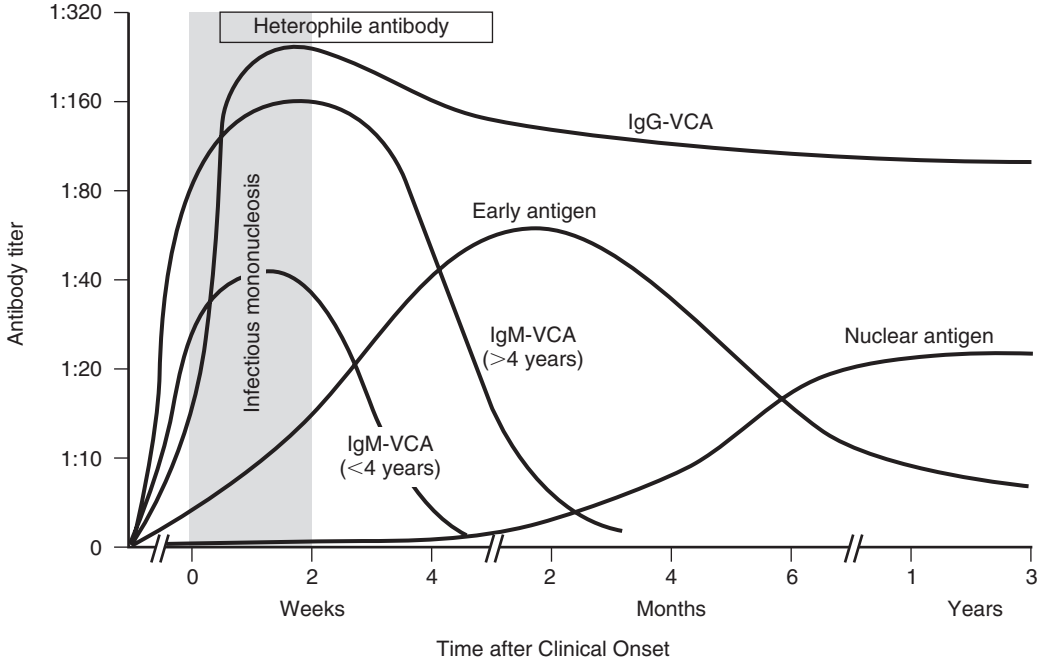


FIGURE 1.2 Schematic representation of the evolution of antibodies to various Epstein-Barr virus antigens in patients with infectious mononucleosis. The titers are geometric mean values expressed as reciprocals of the serum dilution. The minimal titer tested for viral capsid antigen (VCA) and early antigen antibodies was 1:10; for Epstein-Barr nuclear antigen, it was 1:2.5. The immunoglobulin (Ig)M response to capsid antigen was divided because of the significant differences noted according to age. (From Jenson HB, Ench Y, Sumaya CV. Epstein-Barr virus. In: Rose NR, de Macario EC, Folds JD, et al, editors. *Manual of Clinical Laboratory Immunology*. 5th ed. Washington, DC: American Society for Microbiology; 1997. p. 634-43.)

when splenomegaly or other features are present or if symptoms persist longer than expected.

Primary infection with **human immunodeficiency virus** (HIV) may produce a mononucleosis-like illness with sore throat, fever, lymphadenopathy, rash, myalgias, and hepatosplenomegaly. Early infection may be detected by viral RNA or DNA load because immunoglobulin (Ig)M or IgG titers may have not yet developed.

GROUP A STREPTOCOCCAL INFECTION

In the evaluation of a patient with sore throat, the primary concern in the United States is usually accurate diagnosis and treatment of pharyngitis caused by group A streptococci (GAS) or *Streptococcus pyogenes*, which accounts for about 15% of all episodes of pharyngitis. The sequelae of GAS pharyngitis, especially acute rheumatic fever (ARF) and acute glomerulonephritis (AGN), at one time resulted in considerable morbidity and mortality in the United States and continue to do so in other parts of the world. Prevention of ARF in particular depends on timely diagnosis of streptococcal pharyngitis and prompt antibiotic treatment. Group A streptococci are characterized by the presence of group A carbohydrate in the cell wall, and they are further distinguished by several cell wall protein antigens (M, R, T). These protein antigens, especially the M protein, a virulence factor, are useful for studies of epidemiology and pathogenesis but are not used in clinical care.

◆ Epidemiology

GAS pharyngitis is endemic in the United States; epidemics occur sporadically. Episodes peak in the late winter and early spring. Rates of GAS pharyngitis are highest among children aged 5-11 years old. Spread of GAS in classrooms and among family members is common, especially in the presence of crowded living conditions. Transmission occurs primarily by the inhalation of organisms in large droplets or by direct contact with respiratory secretions. Pets do not appear to be a frequent reservoir. Untreated streptococcal pharyngitis is particularly contagious early in the acute illness and for the first 2 weeks after the organism has been acquired, but antibiotic therapy effectively prevents disease transmission. Within 24 hours of institution of therapy with penicillin, it is difficult to isolate GAS from patients with acute streptococcal pharyngitis, and infected children can return to school.

Molecular epidemiology studies of streptococcal pharyngitis have shown that the prevalent M protein types vary among communities and over time. Numerous distinct strains of GAS can circulate simultaneously in a community during the peak season. GAS M proteins can be identified in research studies by using PCR to establish the specific M protein gene (*emm* gene); M protein identification is not available for use in clinical care. Children with streptococcal pharyngitis can serve as a local reservoir for strains that cause invasive disease (e.g., sepsis, streptococcal toxic shock syndrome, cellulitis, necrotizing fasciitis) in the same geographic area and season.

◆ Clinical Features

The classic patient presentation of acute streptococcal pharyngitis involves a sudden onset of fever and sore throat. Headache, malaise, abdominal pain, nausea, and vomiting occur frequently. *Cough, rhinorrhea, conjunctivitis, stridor, diarrhea, discrete ulcerated lesions, and hoarseness are distinctly unusual and suggest a viral etiology.*

Examination of the patient reveals marked pharyngeal erythema. Petechiae may be noted on the palate, but they can also occur in viral pharyngitis, especially mononucleosis. Tonsils are enlarged, symmetric, and red, with patchy exudates on their surfaces. The papillae of the

(See *Nelson Textbook of Pediatrics*, p. 2018)

tongue may be red and swollen, hence the designation "strawberry tongue." Anterior cervical lymph nodes are often tender and enlarged.

Combinations of these signs can be used to assist in diagnosis; in particular, tonsillar exudates in association with fever, palatal petechiae, and tender anterior cervical adenitis strongly suggest infection with GAS. However, other diseases can produce this constellation of findings, including infectious mononucleosis. Some or all of these classic characteristics may be absent in patients with streptococcal pharyngitis. Symptoms usually resolve within 5 days even in the absence of antibiotic therapy. Younger children can have a syndrome called **streptococcosis—**coryza with crusting below the nares, more generalized adenopathy, and a more chronic course. When rash accompanies the illness, accurate clinical diagnosis is easier. **Scarlet fever**, so-called because of the characteristic fine, diffuse red rash, is essentially pathognomonic for infection with group A streptococci. Scarlet fever is rarely seen in children younger than 3 years old or in adults.

Scarlet Fever

The rash of scarlet fever is caused by infection with a strain of GAS that contains a bacteriophage encoding for production of an erythrogenic (redness producing) toxin, usually erythrogenic (also called pyrogenic) exotoxin A (designated SPE A). Scarlet fever is simply GAS pharyngitis with a rash and should be explained as such to patients and their families. Although patients with the streptococcal toxic shock syndrome are also infected with GAS that produces SPE A, most GAS pharyngeal infections are not associated with development of severe invasive or systemic disease.

The rash of scarlet fever has a texture like sandpaper and blanches with pressure. It usually begins on the face, but after 24 hours, it becomes generalized. The face is red, especially over the cheeks, and the area around the mouth often appears pale in comparison, giving the appearance of circumoral pallor. Accentuation of erythema occurs in flexor skin creases, especially in the antecubital fossae (Pastia lines). The erythema begins to fade within a few days. Desquamation begins within a week of onset on the face and progresses downward, often resembling that seen after mild sunburn. On occasion, sheet-like desquamation occurs around the free margins of the fingernails; this is usually coarser than the desquamation seen with Kawasaki disease. The differential diagnosis of scarlet fever includes Kawasaki disease, measles, and staphylococcal toxic shock syndrome (Table 1.7).

◆ Diagnosis

Although signs and symptoms may strongly suggest acute streptococcal pharyngitis, laboratory diagnosis is strongly recommended, even for patients with scarlet fever (Fig. 1.3). Scoring systems for diagnosing acute GAS pharyngitis on clinical grounds have not proved very satisfactory. Using clinical criteria alone, physicians overestimate the likelihood that patients have streptococcal infection. The throat culture on blood agar plate has traditionally been used to diagnose streptococcal pharyngitis. Plating a swab of the posterior pharynx and tonsils on sheep blood agar, identifying β-hemolytic colonies, and testing them for the presence of sensitivity to a bacitracin-impregnated disk has long been the "gold standard" diagnostic test, but it takes 24-48 hours to obtain results. Rapid antigen detection tests (RADTs) that take less than 15 minutes can detect the presence of the cell wall group A carbohydrate antigen after acid extraction of organisms obtained by throat swab. RADTs are highly specific (generally >95%) when compared to throat culture. In comparison to hospital or reference laboratory throat culture results, the sensitivities of these tests are generally 75-85% and can be lower. The low sensitivity of these tests, coupled

TABLE 1.7 Differential Diagnosis of Scarlet Fever

	Scarlet Fever	Kawasaki Disease	Measles	Staphylococcal Toxic Shock Syndrome	Staphylococcal Scalded Skin Syndrome
Agent	Group A streptococci	Unknown	Measles virus	*Staphylococcus aureus*	*S. aureus*
Age range	All (peak, 5-15 yr)	Usually <5 yr	<2 yr, 10-20 yr	All (especially >10 yr)	Usually <5 yr
Prodrome	No	No	Fever, coryza, cough, conjunctivitis	Usually no	No
Enanthem	No	Occasionally	Koplik spots	No	Limited
Mouth	Strawberry tongue, exudative pharyngitis, palatal petechiae	Erythema; red, cracked lips, strawberry tongue	Diffusely red, no cracked lips	Usually normal	Erythema
Rash	Fine, red, "sandpaper," membranous desquamation, circumoral pallor, Pastia lines	Variable polymorphic; erythematous face, trunk, and diaper area; tips of fingers and toes desquamate 10–28 days after onset	Maculopapular; progressing from forehead to feet; may desquamate	Diffuse erythroderma; desquamates	Erythema, painful bullous lesions; positive Nikolsky sign; desquamates
Other	Cervical adenitis, gallbladder hydrops, fever	Coronary artery disease; fever >5 days; conjunctival (nonpurulent) injection; tender, swollen hands and feet; cervical adenopathy (size >1.5 cm); thrombocytosis; pyuria (sterile); gallbladder hydrops	"Toxic" appearance; dehydration; encephalitis, pneumonia; fever	Shock (hypotension, including orthostatic); encephalopathy; diarrhea; headache	Fever, cracked lips; conjunctivitis

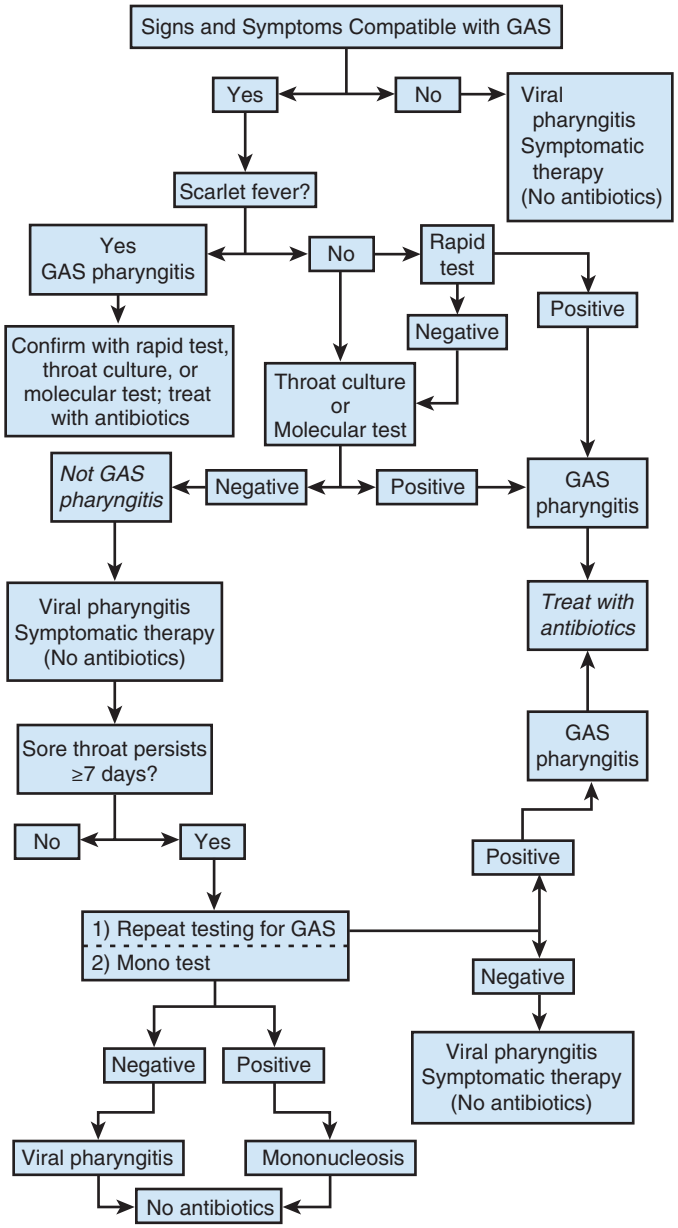


FIGURE 1.3 Management of patients with sore throat. GAS, group A streptococci.

with their excellent specificity, has led to the recommendation that two throat swabs be obtained simultaneously from patients with suspected GAS pharyngitis. One swab is used for a rapid test. When the RADT result is positive, it is highly likely that the patient has GAS pharyngitis, and the extra swab can be discarded. When the RADT is negative, GAS may nonetheless be present; thus, the extra swab should be processed for culture. The sensitivity of rapid tests can be improved by restricting testing to patients most likely to have acute GAS pharyngitis and avoiding testing patients more likely to have viral pharyngitis. This takes advantage of the spectrum effect (or spectrum bias) associated with many clinical tests including RADTs and throat cultures; the pretest probability of having the disease affects test results. One of the best validated scoring systems for children was developed by McIsaac, et al. Patients with greater likelihood of GAS infection tend to have more McIsaac criteria (fever, cervical adenopathy, tonsillar exudates, no cough, 3-15 years old), but the positive predictive value of the highest McIsaac score is only about 60% (Table 1.8). In contrast, a score ≤2 is

TABLE 1.8 Distribution of McIsaac Scores in a Study of Pediatric Patients With Pharyngitis*

McIsaac Score	Number of Patients (%)	GAS Culture-Positive† n (%)
0	42 (2%)	3 (7%)
1	200 (11%)	37 (19%)
2	576 (31%)	118 (20%)
3	552 (30%)	162 (29%)
4	365 (20%)	163 (45%)
5	113 (6%)	70 (62%)

*McIsaac criteria: Fever (temperature >38°C), tender anterior cervical adenopathy, tonsillar swelling or exudates, absence of cough, and age <15 years. One point is awarded for each criterion.
†Hospital laboratory throat culture result.
GAS, group A streptococci.
From Tanz RR, Gerber MA, Kabat W, et al. Performance of a rapid antigen detection test and throat culture in community pediatric offices: implications for management of pharyngitis. *Pediatrics.* 2009;123:437-444.

associated with a negative predictive value of about 80%. The presence of viral symptoms such as cough, rhinorrhea, conjunctivitis, laryngitis, stridor, croup, or diarrhea decreases the likelihood that the illness is due to GAS. Patients with a negative RADT result should not be treated before culture verification unless there is a particularly high suspicion of GAS infection (e.g., scarlet fever, peritonsillar abscess, or tonsillar exudates in addition to tender cervical adenopathy, palatal petechiae, fever, and recent exposure to a person with GAS pharyngitis).

Molecular "PCR-like" tests for GAS are available for use in hospital and reference laboratories. Some are cleared by the Food and Drug Administration (FDA) for use in physician office laboratories, particularly those offices that are certified to perform CLIA-moderate tests. These simplified molecular tests use methods that amplify the DNA of a specific GAS gene. They take less than 1 hour to perform and are reported to have both sensitivity and specificity ≥99% when compared to standard throat culture and PCR. They can be used as a "stand-alone" test for GAS or as a confirmatory test when the RADT is negative. There are three concerns with these molecular tests: (1) they are so sensitive it is likely they will identify more patients who are carriers than would ordinarily be identified by RADT and/or culture; (2) unless rigorous technique is followed they may be prone to contamination with exogenous GAS DNA from other swabs, a particular concern in physician offices when performed by staff who are not trained laboratory technologists; and (3) they are much more expensive than throat culture, and their costs may not be covered by all insurance plans.

Testing patients for serologic evidence of an antibody response to extracellular products of GAS is not useful for diagnosing acute pharyngitis. Because it generally takes several weeks for antibody levels to rise, streptococcal antibody tests are valid only for determining past infection. Specific antibodies that are often measured in the appropriate clinical setting include antistreptolysin O (ASO), anti-DNase B, and antihyaluronidase (AHT). When antibody testing is desired in order to evaluate a possible poststreptococcal illness, more than one of these tests should be performed to improve sensitivity.

◆ Treatment

Treatment begun within 9 days of the onset of GAS pharyngitis is effective in preventing acute rheumatic fever (ARF). Therapy does not

TABLE 1.9 Recommended Treatment Regimens for Acute Streptococcal Pharyngitis*

	Dose/Route	Duration	Frequency
Standard Treatment			
Amoxicillin	50 mg/kg up to 1000 mg/Oral	10 days	Once daily
Penicillin V	250 mg (500 mg for adolescents and adults)/Oral	10 days	bid
Benzathine penicillin G	600,000 U (weight <27 kg)/IM 1.2 million U (weight ≥27 kg)/IM	N/A N/A	Once
	Oral Dose	**Duration**	**Frequency**
Treatment for Penicillin-Allergic Patients			
Clarithromycin	15 mg/kg/day up to 500 mg/day	10 days	bid
Azithromycin†	12 mg/kg on day 1 then 6 mg/kg/d on days 2-5	5 days	Once daily
Clindamycin	21 mg/kg/day 20 mg/kg/day up to 900 mg/day	10 days	tid
Cephalosporins‡			
Cephalexin	40 mg/kg/day up to 1000 mg/day	10 days	bid
Cefadroxil	30 mg/kg/day up to 1000 mg/day	10 days	Once daily

*Based on Infectious Diseases Society of America 2012 and AAP Red Book recommendations.
†Maximum dose for children is 500 mg/day. Adult dosage: 500 mg the first day, 250 mg the subsequent 4 days.
‡First-generation cephalosporins (e.g., cephalexin and cefadroxil) are preferred but all cephalosporins are effective. Dosage and frequency vary among agents. Avoid use in patients with history of immediate (anaphylactic) hypersensitivity to penicillin or other β-lactam antibiotics.

appear to affect the risk of acute poststreptococcal glomerulonephritis (AGN). Antibiotic therapy also reduces the incidence of suppurative sequelae of GAS pharyngitis, such as peritonsillar abscess and cervical adenitis. In addition, treatment produces a more rapid resolution of signs and symptoms and terminates contagiousness within 24 hours. For these reasons, antibiotics should be instituted as soon as the diagnosis is supported by laboratory studies.

There are numerous antibiotics available for treating streptococcal pharyngitis (Table 1.9). The drugs of choice are penicillin and amoxicillin. Despite the widespread use of penicillin to treat streptococcal and other infections for many decades, resistance of GAS to penicillin or any other β-lactam antibiotic has not developed. Amoxicillin has been demonstrated to be effective in eradicating GAS when given by mouth once daily for 10 days. The convenience of once-daily dosing and palatability make amoxicillin an attractive approach despite its somewhat broader spectrum of antimicrobial activity. Penicillin can be given by mouth twice daily for 10 days or intramuscularly as a single injection of benzathine penicillin. Intramuscular benzathine penicillin alleviates concerns about patient compliance. A less painful parenteral alternative is benzathine penicillin in combination with procaine penicillin. Intramuscular procaine penicillin alone is not effective for prevention of ARF because adequate levels of penicillin are not present in blood and tissues for a sufficient time. Other β-lactams, including semisynthetic derivatives of penicillin and the cephalosporins, are at least as effective as penicillin for treating streptococcal pharyngitis. The broader spectrum of the cephalosporins and their higher cost relegate them to second-line status. The decreased dosing frequency of amoxicillin and some cephalosporins may improve patient adherence.

Patients who are allergic to penicillin can receive a cephalosporin if they have not had an immediate hypersensitivity reaction. Erythromycin or another non-β-lactam antibiotic, such as clarithromycin, azithromycin, or clindamycin, can be used. Resistance of GAS to macrolides has increased dramatically in many areas of the world where erythromycin has been widely used. Macrolide resistance also affects azithromycin and can affect clindamycin. Although this resistance has not yet emerged as a major problem in the United States, where the rate of macrolide resistance among GAS is generally 5-8%, there is much local variation. GAS resistance to clindamycin is in the range of 1-2%. Of note, both macrolide and clindamycin resistance are more common in Canada than in the United States. Sulfa drugs (including sulfamethoxazole combined with trimethoprim), tetracyclines, and chloramphenicol should not be used for treatment of acute streptococcal pharyngitis because they do not eradicate GAS.

Suppurative Complications

Antibiotic therapy has greatly reduced the likelihood of developing suppurative complications caused by spread of GAS from the pharynx or middle ear to adjacent structures. **Peritonsillar abscess** ("quinsy") manifests with fever, severe throat pain, dysphagia, "hot potato voice," pain referred to the ear, and bulging of the peritonsillar area with asymmetry of the tonsils and sometimes displacement of the uvula (Fig. 1.4; see also Table 1.4). There can be peritonsillar cellulitis without a well-defined abscess cavity. Trismus may be present. When an abscess is found clinically or by an imaging study such as a computed tomographic (CT) scan, surgical drainage is indicated. Peritonsillar abscess occurs most commonly in older children and adolescents.

Retropharyngeal abscess represents extension of an infection from the pharynx or peritonsillar region into the retropharyngeal (prevertebral) space, which is rich in lymphoid structures (Figs. 1.5 and 1.6; see also Table 1.4). Children younger than 4 years old are most often affected. Fever, dysphagia, drooling, stridor, extension of the neck, and a mass in the posterior pharyngeal wall may be noted. Surgical drainage is often required if frank suppuration has occurred. Spread of GAS via pharyngeal lymphatic vessels to regional nodes can cause **cervical lymphadenitis**. The markedly swollen and tender anterior cervical nodes that result can suppurate. Otitis media, mastoiditis, and sinusitis also may occur as complications of GAS pharyngitis. Additional parapharyngeal suppurative infections that may mimic streptococcal disease are noted in Table 1.4. Furthermore, any pharyngeal infectious process may produce **torticollis** if there is inflammation that extends

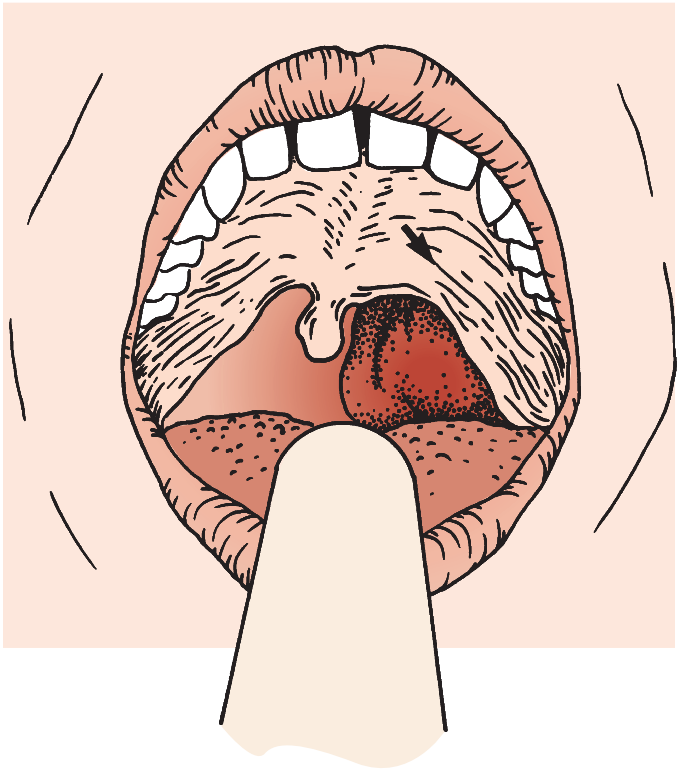


FIGURE 1.4 Peritonsillar abscess (quinsy, sore throat). The left tonsil is asymmetrically inflamed and swollen; there is displacement of the uvula to the opposite side. The supratonsillar space *(arrow)* is also swollen; this is the usual site of the surgical incision for drainage. Prominent unilateral cervical adenopathy typically coexists. (From Reilly BM. Sore throat. In: *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991.)

to the paraspinal muscles and ligaments, producing pain, spasm, and, on occasion, rotary subluxation of the cervical spine. Oropharyngeal torticollis lasts less than 2 weeks and is not associated with abnormal neurologic signs or pain over the spinous process. Invasive sterile site or bacteremic infection with GAS is unusual as sequelae to pharyngitis.

Nonsuppurative Sequelae

Nonsuppurative complications include acute rheumatic fever (ARF), acute glomerulonephritis (AGN), and possibly reactive arthritis/synovitis. In addition, an association between streptococcal infection and neuropsychiatric disorders such as tic disorder, obsessive-compulsive disorder, and Tourette syndrome has been postulated. This possible association has been called PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococci). The terminology has been modified to "pediatric acute-onset neuropsychiatric syndrome" (PANS) or "childhood acute neuropsychiatric syndrome" (CANS), in recognition that the etiologic role of GAS and benefit from antibiotic treatment have been difficult to establish, and it is likely that infections other than GAS infection are associated with the development, recurrence, or exacerbation of neuropsychiatric symptoms.

Therapy with an appropriate antibiotic within 9 days of onset of symptoms is highly effective in preventing ARF. Except in certain geographic areas (e.g., Salt Lake City) and populations (e.g., Hasidic Jewish communities) ARF is quite rare in North America. The impressive reduction in ARF prevalence in the United States since the mid-1960s may be related to reductions in the prevalence of so-called "rheumatogenic" GAS M types. The reason for the near disappearance of rheumatogenic types in the United States is unknown. Areas of the world with persistently high rates of ARF have different M types than the United States had in the past and has currently. AGN is not prevented by treatment of the antecedent streptococcal infection. Pharyngitis caused by one of the "nephritogenic" strains of GAS precedes

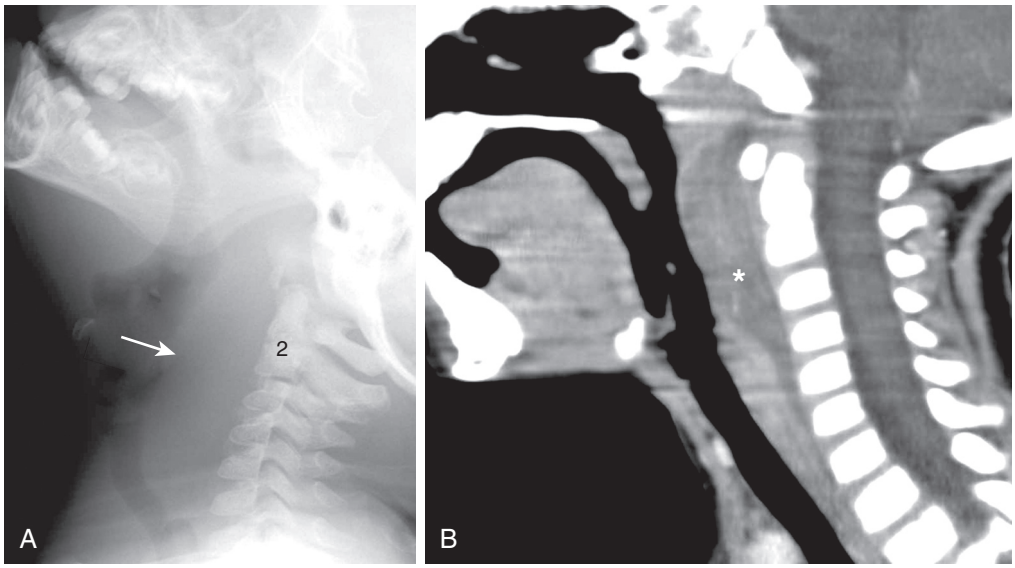


FIGURE 1.5 Retropharyngeal abscess in a 3-year-old female with sore throat and fever. *A,* Lateral soft tissue neck radiograph reveals extensive soft tissue swelling displacing the airway anteriorly from the skull base to C6 *(arrow). B,* Sagittal reconstructed contrast-enhanced computed tomography confirms thickened, enhancing retropharyngeal soft tissues indicating cellulitis. Region of hypoattenuating fluid is concerning for retropharyngeal abscess *(asterisk).* (From Lowe LH, Smith CJ. Infection and inflammation. In: *Caffey's Pediatric Diagnostic Imaging.* 12th ed. Vol 1. Philadelphia: Elsevier; 138; Figure 15.4.)

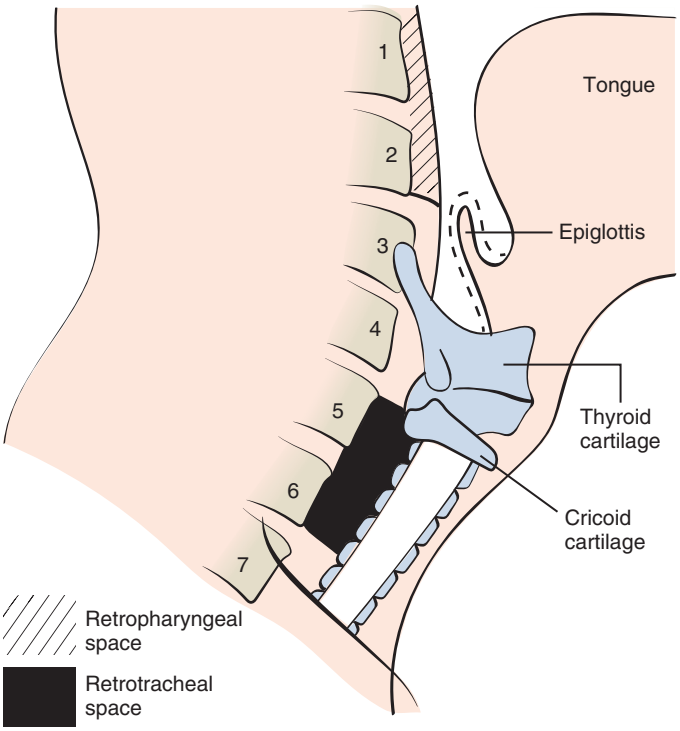


FIGURE 1.6 In an adolescent, the retropharyngeal space normally does not exceed 7 mm when measured from the anterior aspect of the C2 vertebral body to the posterior pharynx. In infants the retropharyngeal space is usually less than one width of the adjacent vertebral body. However, during crying, this distance may be three widths of the vertebral body. In addition, under normal circumstances, the retrotracheal space does not exceed 22 mm in adolescents when measured from the anterior aspect of C6 to the trachea. *Dotted lines* depict the "thumbprint" sign, noted on a lateral neck radiograph, made by a swollen epiglottis. (From Reilly BM. Sore throat. In: *Practical Strategies in Outpatient Medicine.* 2nd ed. Philadelphia: WB Saunders; 1991.)

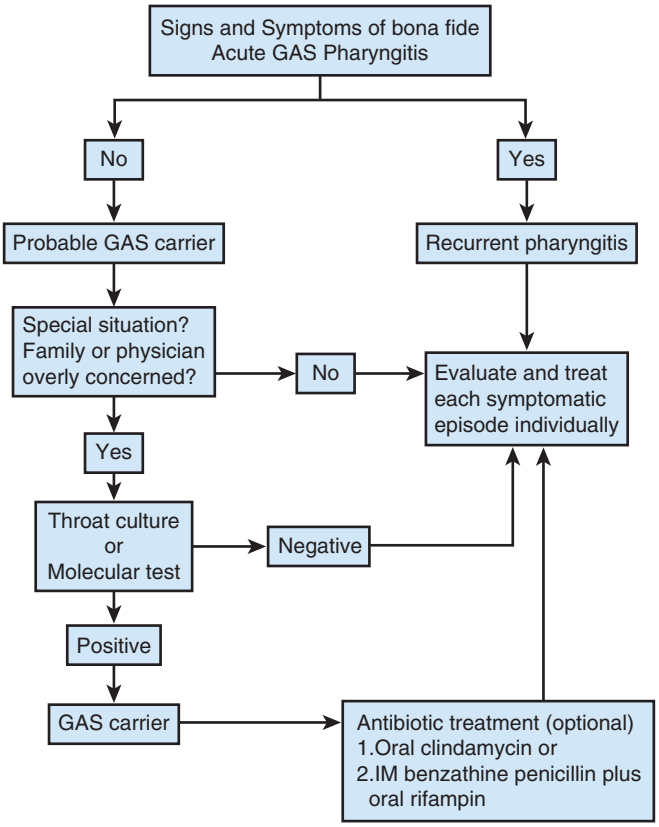


FIGURE 1.7 Management of patients with repeated or frequent positive rapid tests or throat cultures. GAS, group A streptococci; IM, intramuscular.

glomerulonephritis by about 10 days. Unlike ARF, which occurs only after GAS pharyngitis, AGN also can follow GAS skin infection.

Treatment Failure and Chronic Carriage

Treatment with penicillin cures GAS pharyngitis but does not eradicate GAS from the pharynx in as many as 25% of patients (Fig. 1.7). This causes considerable consternation among affected patients and their families. Resistance to penicillin is not the cause of treatment failure. A few such patients are symptomatic and are characterized as having clinical treatment failure. Re-infection with the same strain or a different strain is possible, as is intercurrent viral pharyngitis. Some of these patients may be chronic pharyngeal carriers of GAS who are suffering from a new superimposed viral infection; others may have been nonadherent to therapy. Many patients who continue to have positive tests for GAS despite antimicrobial treatment are asymptomatic and are identified only when follow-up throat swabs are obtained, a practice that is usually unnecessary in North America. Patients who adhered to therapy are at minimal risk for ARF. One explanation for asymptomatic persistence of GAS after treatment is that these patients are chronically colonized with GAS, were initially symptomatic because of a viral pharyngitis, and did not truly have acute streptococcal pharyngitis.

Patients who are chronically colonized with GAS are called chronic carriers. Carriers do not appear to be at risk for ARF or for development of suppurative complications, and they are rarely sources of spread of GAS in the community. There is no reason to exclude carriers from school. There is no easy way to identify chronic carriers prospectively among patients with symptoms of acute pharyngitis. The pathophysiology of chronic carriage is unknown. As resistance to penicillin is not a factor, many other causes have been hypothesized including non-adherence to antibiotic treatment, tolerance to antibiotics (suppression but lack of killing by antimicrobials), internalization of GAS by epithelial cells, and presence of β-lactamase-producing "co-pathogens," but none has been proven. The clinician should consider the possibility of chronic GAS carriage when a patient or a family member has multiple test-positive episodes of pharyngitis, especially when symptoms are mild or atypical. A culture or other test is usually positive for GAS when the suspected carrier is symptom-free or is receiving antibiotic treatment (intramuscular benzathine penicillin is recommended in order to eliminate concerns about compliance).

Carriers often receive multiple unsuccessful courses of antibiotic therapy in attempts to eliminate GAS. Physician and patient anxiety is common and can develop into "streptophobia." Unproven and ineffective therapies include tonsillectomy, prolonged administration of antibiotics, use of β-lactamase-resistant antibiotics, and culture or treatment of pets. Available treatment options for the physician faced with a chronic streptococcal carrier include the following:

1. Evaluate for GAS pharyngitis by throat swab each time the patient has pharyngitis with features that suggest streptococcal pharyngitis. Treat as acute GAS pharyngitis with amoxicillin or penicillin (or an alternative agent) each time a test is positive; this will prevent ARF if the GAS identified has been newly acquired. Avoid testing patients who do not have signs and symptoms suggestive of acute GAS pharyngitis.

2. Treating with one of the regimens effective for terminating chronic carriage.

The first option is simple, as safe as amoxicillin and penicillin, and appropriate for most patients. The second option should be reserved for particularly anxious patients; those with a history of ARF or living with someone who had it; or those living or working in nursing homes, chronic care facilities, and hospitals. Two antibiotic treatment regimens have been demonstrated in randomized trials to be effective for eradication of the carrier state:

- Intramuscular benzathine penicillin plus oral rifampin (10 mg/kg/dose up to 300 mg, given twice daily for 4 days beginning on the day of the penicillin injection)
- Oral clindamycin, given for 10 days (20 mg/kg/day up to 450 mg, divided into three equal doses)

Clindamycin is easier to use than intramuscular penicillin plus oral rifampin and may be somewhat more effective. Amoxicillin-clavulanate (40 mg amoxicillin/kg/day up to 2000 mg amoxicillin/day divided tid for 10 days) has also been used. Successful eradication of the carrier state makes evaluation of subsequent episodes of pharyngitis much easier, although chronic carriage can recur upon re-exposure to GAS.

Recurrent Acute Pharyngitis

Some patients seem remarkably susceptible to developing GAS pharyngitis. The reasons for frequent *bona fide* acute GAS pharyngitis are obscure. In contrast to chronic carriers, appropriate antibiotic treatment of each episode results in eradication of the organism.

The role of tonsillectomy in the management of patients with multiple episodes of streptococcal pharyngitis is controversial. The presence of tonsils is not necessary for GAS to infect the throat. Fewer episodes of sore throat were reported among patients treated with tonsillectomy (in contrast to patients treated without surgery) during the first 2 years after operation. Patients had experienced numerous episodes of pharyngitis over several years, and it appears that not all episodes were caused by GAS. By 2 years after tonsillectomy there was no difference between the groups in the frequency of pharyngitis. The postoperative complication rate among tonsillectomy patients was 14%. *Tonsillectomy cannot be recommended for treatment of* recurrent *pharyngitis except in unusual circumstances.* It is preferable to treat most patients with penicillin or amoxicillin whenever symptomatic GAS pharyngitis occurs. Obtaining follow-up throat specimens for culture can help distinguish recurrent pharyngitis from chronic carriage but is unnecessary in most instances.

INFECTION WITH STREPTOCOCCI THAT ARE NOT GROUP A (NON-A STREPTOCOCCI)

Certain β-hemolytic streptococci of serogroups other than group A cause acute pharyngitis. Well-documented *epidemics* of food-borne group C and group G streptococcal pharyngitis have been reported in young adults. In these situations, a high percentage of individuals who had ingested the contaminated food promptly developed acute pharyngitis, and throat cultures yielded virtually pure growth of the epidemiologically linked organism. There have been outbreaks of group G streptococcal pharyngitis among children. However, the role of non-A streptococcal organisms as etiologic agents of acute pharyngitis in *endemic* circumstances has been difficult to establish. Group C and group G streptococci may be responsible for acute pharyngitis, particularly in adolescents. However, the exact role of these agents, most of which are carried asymptomatically in the pharynx of some children and young adults, remains to be fully characterized. When they are implicated as agents of acute pharyngitis, groups C and G organisms do not appear to necessitate treatment, inasmuch as they cause self-limited infections. Acute rheumatic fever is not a sequela to these infections but acute glomerulonephritis has been documented in rare cases after epidemic group C and group G streptococcal pharyngitis.

FUSOBACTERIUM NECROPHORUM

Fusobacterium necrophorum, an anaerobic gram-negative organism, is increasingly recognized as a cause of pharyngitis in older adolescents and adults (ages 15-30 years). Prevalence in studies in Europe is reported to be about 10% in patients with pharyngitis not caused by GAS, but large surveillance studies have not been performed. In a U.S. study of students at a university health clinic, *F. necrophorum* was detected by PCR in 20.5% of patients with pharyngitis and 9.4% of an asymptomatic convenience sample; some had more than one bacterium detected by PCR of throat swabs. Many of the pharyngitis patients with *F. necrophorum* had signs and symptoms indistinguishable from patients with increased likelihood for GAS pharyngitis: About one-third had fever, one-third had tonsillar exudates, two-thirds had anterior cervical adenopathy, and most did not have cough. The symptomatic overlap of *F. necrophorum* and GAS and the presence of asymptomatic carriage could complicate the clinical assessment of sore throat in adolescents but *F. necrophorum* is difficult to culture from the throat and neither a rapid test nor PCR is available for use in clinical care.

F. necrophorum pharyngitis can be associated with development of septic thrombophlebitis of the internal jugular vein, known as Lemierre syndrome (Fig. 1.8). Approximately 80% of cases of Lemierre syndrome are due to this bacterium, but the proportion of patients infected or colonized with *F. necrophorum* who develop pharyngitis and Lemierre syndrome is unknown. Patients present initially with fever, sore throat, exudative pharyngitis, and/or peritonsillar abscess. The symptoms persist, severe neck pain and swelling develop, and the patient appears toxic. Septic shock may ensue along with metastatic complications, especially septic pulmonary emboli. Diagnosis is confirmed by computed tomography or magnetic resonance imaging of the neck and isolation of the organism on anaerobic blood culture. *F. necrophorum* is usually sensitive in vitro to penicillin, but some isolates produce β-lactamases, and treatment failure with penicillin has been reported. Many expert clinicians use metronidazole, clindamycin, a β-lactam in combination with a β-lactamase inhibitor (such as ampicillin-sulbactam), or a carbapenem. The septic thrombophlebitis of Lemierre syndrome can be polymicrobial; combination antibiotic therapy may be beneficial. Some patients require surgical debridement and/or incision and drainage. The case-fatality rate may be as high as 4-9%.

ARCANOBACTERIUM INFECTION

Arcanobacterium haemolyticum is a gram-positive rod that has been reported to cause acute pharyngitis and scarlet fever-like rash, particularly in teenagers and young adults. Detecting this agent requires special methods for culture, and it has not routinely been sought in patients with scarlet fever or pharyngitis. The clinical features of *A. haemolyticum* are indistinguishable from GAS pharyngitis; pharyngeal erythema is present in almost all patients, patchy white to gray exudates in about 70%, cervical adenitis in about 50%, and moderate fever in 40%. Palatal petechiae and strawberry tongue may also occur. The scarlatiniform rash usually spares the face, palms, and soles. The rash is erythematous and blanches; it may be pruritic and demonstrate minimal desquamation. Erythromycin appears to be the treatment of choice.

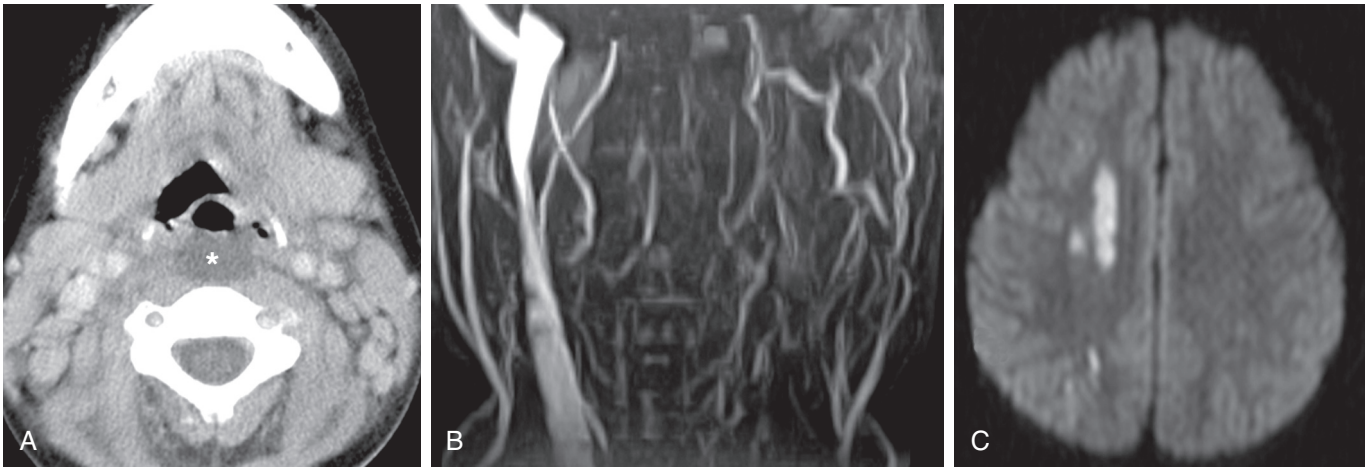


FIGURE 1.8 Lemierre syndrome (*Fusobacterium necrophorum* infection) complicated by stroke in a 6-year-old female presenting with fever, difficulty swallowing, and nuchal rigidity. *A,* Axial contrast enhanced computed tomography image shows low-attenuation retropharyngeal fluid *(asterisk). B,* Magnetic resonance imaging 2 days later, performed because of acute left arm weakness, confirms lack of left internal jugular vein patency on magnetic resonance venogram. *C,* Diffusion-weighted image of the brain reveals multiple small foci of bright signal infarction secondary to emboli from thrombophelebitis, vasospasm, or both. (From Lowe LH, Smith CJ. Infection and inflammation. In: *Caffey's Pediatric Diagnostic Imaging.* 12th ed. Vol 1. Philadelphia: Elsevier; 137; Figure 15.2.)

EPIGLOTTITIS AND BACTERIAL TRACHEITIS

Epiglottitis (or supraglottitis) is a life-threatening infection of the airway proximal to the vocal cords (Fig. 1.9; see also Fig. 1.6). Historically, it was an infection in 1-4 year-old children caused by *Haemophilus influenzae* type b. It presents with acute onset of fever and severe sore throat. This disease progresses rapidly to airway compromise. Patients are often drooling and leaning forward with the neck extended. Some patients may have stridor, but a muffled voice is more common. Management depends on establishing a secure airway by intubation and treating with antibiotics. When epiglottitis is suspected, the oropharynx should not be visualized or manipulated except in a controlled environment (intensive care unit or operating room) by someone with expertise in management of the airway who is prepared to immediately intubate the patient. Vaccination against *H. influenzae* type b has nearly eliminated this disease in childhood; however, epiglottitis caused by GAS, *Streptococcus pneumoniae*, *Staphyloccocus aureus*, and non-type b *H. influenzae* occurs occasionally.

Bacterial tracheitis (bacterial croup, bacterial laryngotracheitis) is a rare complication of viral croup. *S. aureus* is the most common superinfecting bacteria identified. Patients have a history of prolonged croup symptoms that become dramatically worse with fever and signs of airway obstruction. While sore throat may have been present at the onset of croup, it is not a prominent complaint once bacterial infection of the airway occurs. The clinical appearance of patients with bacterial tracheitis may mimic that of patients with epiglottitis.

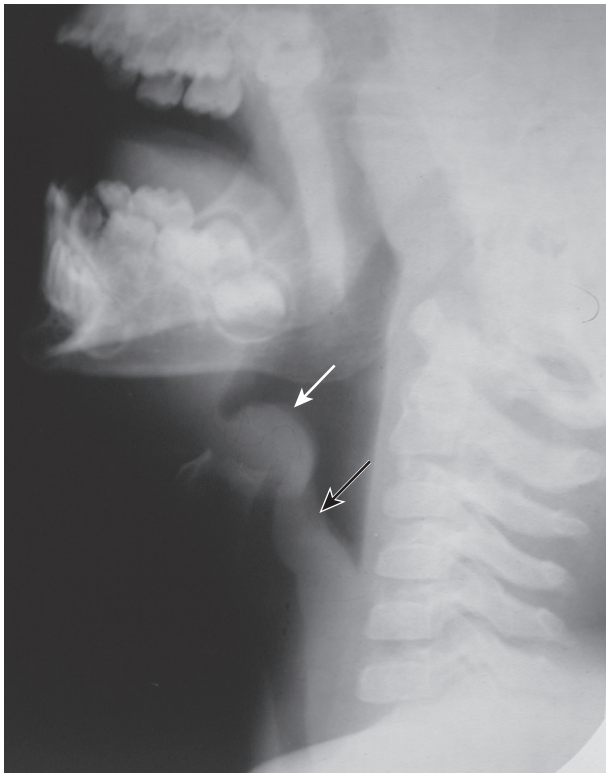


FIGURE 1.9 Epiglottis in a 5-year-old boy with respiratory distress and drooling. A lateral soft tissue neck radiograph shows a markedly thickened epiglottis *(white arrow)*, which is referred to as the "thumb" sign. The aryepiglottic folds *(black arrow)* also are thickened. (From Laya BF, Lee EY. Upper airway disease. In: *Caffey's Pediatric Diagnostic Imaging.* 12th ed. Vol 1. Philadelphia: Elsevier; 529; Figure 51.2.)

DIPHTHERIA

Diphtheria is a very serious disease that is caused by pharyngeal infection by toxigenic strains of *Corynebacterium diphtheriae.* It has become very rare in the United States and other developed countries as a result of immunization. The few diphtheria cases recognized annually in the United States usually occur in unimmunized individuals; the fatality rate is about 5%.

(See *Nelson Textbook of Pediatrics*, p. 2035)

◆ Pathogenesis

The pathogenesis of diphtheria involves nasopharyngeal mucosal colonization by *C. diphtheriae* and toxin elaboration after an incubation period of 1-5 days. Toxin leads to local tissue inflammation and necrosis (producing an adherent grayish membrane made up of fibrin, blood, inflammatory cells, and epithelial cells) and it is absorbed into the bloodstream. Fragment B of the polypeptide toxin binds particularly well to cardiac, neural, and renal cells, and the smaller fragment A enters cells and interferes with protein synthesis. Toxin fixation by tissues may lead to fatal myocarditis (with arrhythmias) within 10-14 days and to peripheral neuritis within 3-7 weeks.

◆ Clinical Features

Acute tonsillar and pharyngeal diphtheria is characterized by sore throat, anorexia, malaise, and low-grade fever. The grayish membrane forms within 1-2 days over the tonsils and pharyngeal walls and occasionally extends into the larynx and trachea. Cervical adenopathy varies but may be severe and associated with development of a "bull neck." In mild cases, the membrane sloughs after 7-10 days, and the patient recovers. In severe cases, an increasingly toxic appearance can lead to prostration, stupor, coma, and death within 6-10 days. Distinctive features include palatal paralysis, laryngeal paralysis, ocular palsies, diaphragmatic palsy, and myocarditis. Airway obstruction (from membrane formation) may complicate the toxigenic manifestations.

◆ Diagnosis

Accurate diagnosis requires isolation of *C. diphtheriae* on culture of material from beneath the membrane, with confirmation of toxin production by the organism isolated. Laboratories must be forewarned that diphtheria is suspected. Other tests are of little value.

GONOCOCCAL PHARYNGITIS

Acute symptomatic pharyngitis caused by *Neisseria gonorrhoeae* occurs occasionally in sexually active individuals as a consequence of oral-genital contact. In cases involving young children, sexual abuse must be suspected. The infection usually manifests as an ulcerative, exudative tonsillopharyngitis but may be asymptomatic and resolve spontaneously. Gonococcal pharyngitis occurs after fellatio in homosexual men and heterosexual women and is less readily acquired after cunnilingus. Gonorrhea rarely is transmitted from the pharynx to a sex partner, but pharyngitis can serve as a source for gonococcemia. Diagnosis requires culture on appropriate selective media (e.g., Thayer-Martin medium). Nucleic acid amplification tests (NAAT) may also detect the organism from pharyngeal and other sites. Examination and testing for other sexually transmitted infections and pregnancy are recommended.

CHLAMYDIAL AND MYCOPLASMAL INFECTIONS

Chlamydia species and *Mycoplasma pneumoniae* may cause pharyngitis, although the frequency of these infections is unclear. *Chlamydia trachomatis* has been implicated serologically as a cause of pharyngitis in as many as 20% of adults with pharyngitis, but isolation of the organism from the pharynx has proved more difficult. *Chlamydia pneumoniae* has also been identified as a cause of pharyngitis. Because antibodies to this organism show some cross reaction with *C. trachomatis*, it is possible that infections formerly attributed to *C. trachomatis* were really caused by *C. pneumoniae*. Diagnosis of chlamydial pharyngitis is difficult, whether by culture or serologically, and neither method is readily available to the clinician.

M. pneumoniae most likely causes pharyngitis. Serologic (positive mycoplasma IgM) or, less often, culture methods can be used to identify this infectious agent, which was found in 33% of college students with pharyngitis in one study. PCR is diagnostic but there is no need to seek evidence of these organisms routinely in pharyngitis patients in the absence of ongoing research studies of nonstreptococcal pharyngitis. The efficacy of antibiotic treatment for *M. pneumoniae* and chlamydial pharyngitis is not known, but these illnesses appear to be self-limited.

SUMMARY AND RED FLAGS

Sore throat is a common complaint. Most children with acute sore throat have a viral illness. Accurate diagnosis of acute streptococcal pharyngitis is essential because appropriate therapy ensures prevention of serious suppurative and nonsuppurative complications. Life-threatening infectious complications of oropharyngeal infections may manifest with mouth pain, pharyngitis, parapharyngeal space infectious extension, and/or airway obstruction. Other red flags are prolonged fever, prolonged sore throat, drooling, trismus, and severe, unremitting pain (see Table 1.5).

REFERENCES

A bibliography is available at ExpertConsult.com

(See *Nelson Textbook of Pediatrics*, p. 1493)

REFERENCES

Group A Streptococci

Anderson NW, Buchan BW, Mayne D, et al. Multicenter clinical evaluation of the illumigene group A streptococcus DNA amplification assay for detection of group A streptococcus from pharyngeal swabs. *J Clin Microbiol*. 2013;51:1474-1477.

Attia MW, Zaoutis T, Klein JD, et al. Performance of a predictive model for streptococcal pharyngitis in children. *Arch Pediatr Adolesc Med*. 2001;155:687-691.

Bisno AL. Group A streptococcal infections and acute rheumatic fever. *N Engl J Med*. 1991;325:783-793.

Bisno AL. Acute pharyngitis. *N Engl J Med*. 2001;344:205-211.

Carapetis JR, Steer AC, Mulholland EK, et al. The global burden of group A streptococcal diseases. *Lancet Infect Dis*. 2005;5:685-694.

Gerber MA, Shulman ST. Rapid diagnosis of pharyngitis caused by group A streptococci. *Clin Microbiol Rev*. 2004;17:571-580.

Gerber MA, Tanz RR, Kabat W, et al. Potential mechanisms for failure to eradicate group A streptococci from the pharynx. *Pediatrics*. 1999;104:911-917.

Henson AM, Carter D, Todd K, et al. Detection of *Streptococcus pyogenes* using the illumigene group A *Streptococcus* assay. *J Clin Microbiol*. 2013;51:4207-4209.

Hoge CW, Schwartz B, Talkington DF, et al. The changing epidemiology of invasive group A streptococcal infections and the emergence of streptococcal toxic shock-like syndrome: A retrospective population-based study. *JAMA*. 1993;269:384-389.

Leckman JF, King RA, Gilbert DL, et al. Streptococcal upper respiratory tract infections and exacerbations of tic and obsessive-compulsive symptoms: A prospective longitudinal study. *J Am Acad Child Adolesc Psychiatry*. 2011;50:108-118.

McIsaac WJ, Kellmer JD, Aufricht P, et al. Empirical validation of guidelines for the management of pharyngitis in children and adults. *JAMA*. 2004;291:1587-1595.

Podbielski A, Kreikemeyer B. Persistence of group A streptococci in eukaryotic cells—A safe place? *Lancet*. 2001;358:3.

Shulman ST, Bisno AL, Clegg HW, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2012;55:e86-e102.

Shulman ST, Stollerman G, Beall B, et al. Temporal changes in streptococcal M protein types and the near-disappearance of acute rheumatic fever in the U.S. *Clin Infect Dis*. 2006;42:441-447.

Singer HS, Gilbert DL, Wolf DS, et al. Moving from PANDAS to CANS. *J Pediatr*. 2012;160:725-731.

Tanz RR, Shulman ST. Streptococcal pharyngitis: The carrier state, definition and management. *Pediatr Ann*. 1998;27:281-285.

Tanz RR, Gerber MA, Kabat W, et al. Performance of a rapid antigen detection test and throat culture in community pediatric offices: Implications for management of pharyngitis. *Pediatrics*. 2009;123:437-444.

Torres-Martinez C, Mehta D, Butt A, et al. Streptococcus associated toxic shock. *Arch Dis Child*. 1992;67:126-130.

Veasy LG, Tani LY, Hill HR. Persistence of acute rheumatic fever in the intermountain area of the United States. *J Pediatr*. 1994;124:9-16.

Wheeler MC, Roe MH, Kaplan EL, et al. Outbreak of group A streptococcus septicemia in children: Clinical, epidemiologic, and microbiological correlates. *JAMA*. 1991;266:533-537.

Working Group on Severe Streptococcal Infections. Defining the group A streptococcal toxic shock syndrome: Rationale and consensus definition. *JAMA*. 1993;269:390-391.

Other Causes

Centor RM, Arkinson TP, Ratliff AE, et al. The clinical presentation of *Fusobacterium*-positive pharyngitis at a university health clinic: A cross-sectional study. *Ann Intern Med*. 2015;162:241-247.

Feder HM Jr. Periodic fever, aphthous stomatitis, pharyngitis, adenitis: clinical review of a new syndrome. *Curr Opin Pediatr*. 2000;12:253-256.

Gerber MA, Randolph MF, Martin NJ, et al. Community-wide outbreak of group G streptococcal pharyngitis. *Pediatrics*. 1991;87:598-603.

Karpathios T, Drakonaki S, Zervoudaki A, et al. *Arcanobacterium haemolyticum* in children with presumed streptococcal pharyngotonsillitis or scarlet fever. *J Pediatr*. 1992;121:735-737.

Komaroff AL, Branch WT, Aronson MD, et al. Chlamydial pharyngitis. *Ann Intern Med*. 1989;111:537-538.

Lajo A, Borque C, Del Castillo F, et al. Mononucleosis caused by Epstein-Barr virus and cytomegalovirus in children: A comparative study of 124 cases. *Pediatr Infect Dis J*. 1994;13:56-60.

McMillan JA, Weiner LB, Higgins AM, et al. Pharyngitis associated with herpes simplex virus in college students. *Pediatr Infect Dis J*. 1993;12:280-284.

Nakayama M, Miyazaki C, Ueda K, et al. Pharyngoconjunctival fever caused by adenovirus type 11. *Pediatr Infect Dis J*. 1992;11:6-9.

Straus SE, Cohen JI, Tosato G, et al. Epstein-Barr virus infections: Biology, pathogenesis, and management. *Ann Intern Med*. 1993;118:45-58.

Sumaya CV, Ench Y. Epstein-Barr virus infectious mononucleosis in children: I. Clinical and general laboratory findings. *Pediatrics*. 1985;75:1003-1010.

Sumaya CV, Ench Y. Epstein-Barr virus infectious mononucleosis in children: II. Heterophil antibody and viral-specific responses. *Pediatrics*. 1985;75:1011-1019.

Waagner DC. *Arcanobacterium haemolyticum*: Biology of the organism and diseases in man. *Pediatr Infect Dis J*. 1991;10:933-939.

Wurster VM, Carlucci JG, Feder HM Jr, et al. Long-term follow-up of children with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome. *J Pediatr*. 2011;159:958-964.

Complications

Chow AW. Life-threatening infections of the head and neck. *Clin Infect Dis*. 1992;14:991-1004.

de Marie S, Tham RT, van der Mey AGL, et al. Clinical infections and nonsurgical treatment of parapharyngeal space infections complicating throat infection. *Rev Infect Dis*. 1989;11:975-982.

Fiesseler FW, Riggs RL. Pharyngitis followed by hypoxia and sepsis: Lemierre syndrome. *Am J Emerg Med*. 2001;19:320-322.

Savolainen S, Jousimies-Somer HR, Makitie AA, et al. Peritonsillar abscess: Clinical and microbiologic aspects and treatment regimens. *Arch Otolaryngol Head Neck Surg*. 1993;119:521-524.

Wald ER, Guerra N, Byers C. Upper respiratory tract infections in young children: Duration of and frequency of complications. *Pediatrics*. 1991;87:129-133.

White B. Deep neck infections and respiratory distress in children. *Ear Nose Throat J*. 1985;64:30-38.

Treatment

Feder HM Jr, Gerber MA, Randolph MF, et al. Once-daily therapy for streptococcal pharyngitis with amoxicillin. *Pediatrics*. 1999;103:47-51.

Markowitz M, Gerber MA, Kaplan EL. Treatment of streptococcal pharyngotonsillitis: Reports of penicillin's demise are premature. *J Pediatr*. 1993;123:679-685.

Massel BF, Chute CG, Walker AM, et al. Penicillin and the marked decrease in morbidity and mortality from rheumatic fever in the United States. *N Engl J Med*. 1988;318:280-286.

Paradise JL, Bluestone CD, Bachman RZ, et al. Efficacy of tonsillectomy for recurrent throat infection in severely affected children: Results of parallel randomized and nonrandomized clinical trials. *N Engl J Med*. 1984;310:674-683.

Randolph MF, Gerber MA, DeMeo KK, et al. Effect of antibiotic therapy on the clinical course of streptococcal pharyngitis. *J Pediatr*. 1985;106:870-875.

Seppala H, Nissinen A, Jarvinen H, et al. Resistance to erythromycin in group A streptococci. *N Engl J Med*. 1992;326:292-297.

Shulman ST, Gerber MA, Tanz RR, et al. Streptococcal pharyngitis: The case for penicillin therapy. *Pediatr Infect Dis J*. 1994;13:1-7.

Snellman LW, Stang HJ, Stang JM, et al. Duration of positive throat cultures for group A streptococci after initiation of antibiotic therapy. *Pediatrics*. 1993;91:116-117.

Tanz RR, Poncher JR, Corydon KE, et al. Clindamycin treatment of chronic pharyngeal carriers of group A streptococci. *J Pediatr*. 1991;119:123-128.

Tanz RR, Shulman ST, Shortridge VD, et al. and the North American Streptococcal Pharyngitis Surveillance Group. U.S. community-based surveillance of macrolide-resistant pharyngeal group A streptococci during three respiratory disease seasons. *Clin Infect Dis*. 2004;39:1794-1801.

2

Cough

Louella B. Amos

INTRODUCTION

Cough is an important defense mechanism of the lungs and is a common symptom, particularly during winter months. In most patients, it is self-limited. However, cough can be ominous, indicating serious underlying disease, because of accompanying problems (hemoptysis) or because of serious consequences of the cough itself (e.g., syncope and hemorrhage).

◆ Pathophysiology

The cough reflex serves to prevent the entry of harmful substances into the tracheobronchial tree and to expel excess secretions and retained material from the tracheobronchial tree. Cough begins with stimulation of cough receptors, located in the upper and lower airways, and in many other sites such as the ear canal, tympanic membrane, sinuses, nose, pericardium, pleura, and diaphragm. Receptors send messages via vagal, phrenic, glossopharyngeal, or trigeminal nerves to the "cough center," which is in the medulla. Because cough is not only an involuntary reflex activity but also one that can be initiated or suppressed voluntarily, "higher centers" must also be involved in the afferent limb of the responsible pathway. The neural impulses go from the medulla to the appropriate efferent pathways to the larynx, tracheobronchial tree, and expiratory muscles.

The act of coughing (Fig. 2.1) begins with an inspiration, followed by expiration against a closed glottis (compressive phase), resulting in the buildup of impressive intrathoracic pressures (50-300 cm H_2O). These pressures may be transmitted to vascular, cerebrospinal, and intraocular spaces. Finally, the glottis opens, allowing for explosive expiratory airflow (300 m/sec) and expulsion of mucus, particularly from the larger, central airways. The inability to seal the upper airway (tracheostomy) impairs, but does not abolish, the effectiveness of cough. Weak ventilatory muscles (muscular dystrophy) impair both the inspiratory and the compressive phase.

◆ History

The patient history often provides the most important body of information about a child's cough. A diagnosis can often be discerned with relative certainty from the family history, the environmental and exposure history, and the acute nature and characterization of the cough.

Demographics

The patient's age (Table 2.1) helps to focus the diagnostic possibilities. Congenital anatomic abnormalities may be symptomatic from birth, whereas toddlers, who may have incomplete neurologic control over swallowing and often put small objects in their mouths, are at risk for foreign body aspiration; adolescents may experiment with smoking or inhaled drugs. Socioeconomic factors must be considered; a family that cannot afford central heating may use a smoky wood-burning stove; spending time at a daycare center may expose an infant to respiratory viruses; and several adult smokers in a small home expose children to a high concentration of respiratory irritants.

Characteristics of the Cough

The various cough characteristics can help determine the cause of cough. The causes of acute, recurrent, and chronic coughs may be quite different from each other (Fig. 2.2; see also Table 2.1). A cough can be paroxysmal, brassy, productive, weak, volitional, and "throat-clearing," and it may occur at different times of the day (Tables 2.2 and 2.3).

The previous response or lack of response to some therapies for recurrent and chronic cough can provide important information (see Table 2.3). Furthermore, some coughs may be caused or worsened by medications (Table 2.4).

Associated Symptoms

A history of accompanying signs or symptoms, whether localized to the respiratory tract (wheeze, stridor) or elsewhere (failure to thrive, frequent malodorous stools) can give important clues (Table 2.5; see also Tables 2.2 and 2.3). It is essential to remember that the daily language of the physician is full of jargon that may be adopted by parents but with a different meaning from that understood by physicians. If a parent says that a child "wheezes" or "croups" or is "short of breath," it is important to find out what the parent means by that term.

Family and Patient's Medical History

Because many disorders of childhood have genetic or nongenetic familial components, the family history can provide helpful information:

- Are there older siblings with cystic fibrosis (CF) or asthma?
- Is there a coughing sibling whose kindergarten class has been closed because of pertussis?
- Is there an adolescent or adult with chronic cough (bronchitis) who may have pertussis or tuberculosis?
- Was the child premature, and, if so, did he or she spend a month on the ventilator, and does he or she now have chronic lung disease (bronchopulmonary dysplasia)?
- Did the toddler choke on a carrot or other food 3 months ago?
- Did the child have RSV, bronchiolitis, or rhinovirus infection as an infant?
- Did the child receive a bone marrow transplant a year ago?
- Is the child immunized?
- Did the infant have a tracheoesophageal fistula repaired in the neonatal period?

(See *Nelson Textbook of Pediatrics*, p. 2027)

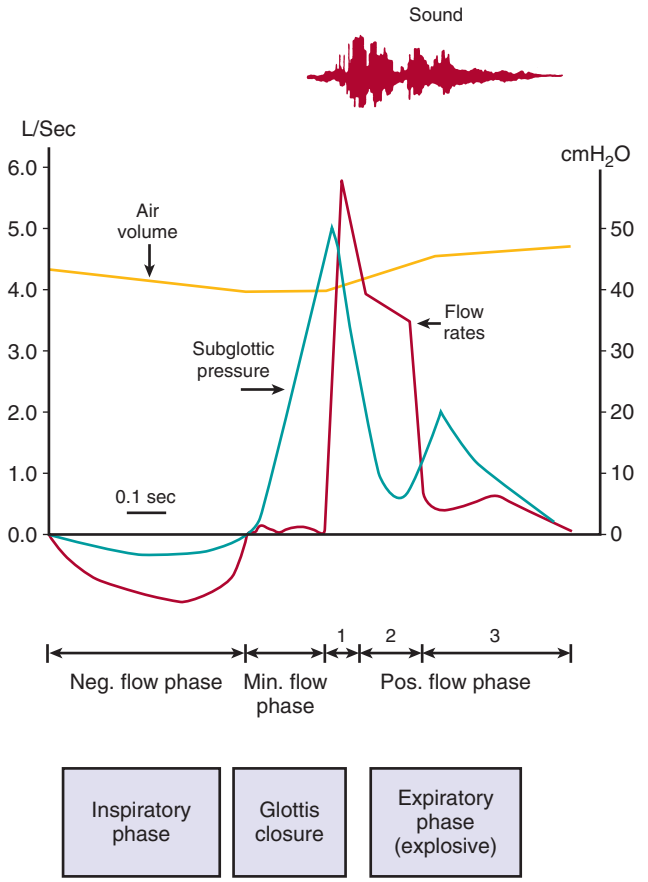


FIGURE 2.1 Cough mechanics, showing changes in expiratory flow rate, air volume, subglottic pressure, and sound recording during cough. (Modified from Yanagihara N, et al. The physical parameters of cough: the larynx in a normal single cough. *Acta Otolaryngol.* 1996;61: 495-510.)

TABLE 2.1 Causes of Cough

Age Group	Acute	Recurrent	Chronic (>4 wk)
Infants	Infection[1]* Aspiration[2] Foreign body[3]	Asthma[1] CF[1] GER[1] Aspiration[2] Anatomic abnormality[3†] Passive smoking[3]	Asthma[1] CF[1] GER[1] Aspiration[2] Pertussis[2] Anatomic abnormality[3†] Passive smoking[3]
Toddlers	Infection[1] Foreign body[2] Aspiration[3]	Asthma[1] CF[1] GER[1] Aspiration[2] Anatomic abnormality[3] Passive smoking[3]	Asthma[1] CF[1] GER[1] Aspiration[2] Pertussis[2] Anatomic abnormality[3] Passive smoking[3]
Children	Infection[1] Foreign body[3]	Asthma[1] CF[1] GER[1] Passive smoking[3]	Asthma[1] CF[1] GER[2] Pertussis[2] *Mycoplasma*[3] Psychogenic[3] Anatomic abnormality[3] Passive smoking[3]
Adolescents	Infection[1]	Asthma[1] CF[1] GER[1] Aspiration[2] Anatomic abnormality[3]	Asthma[1] CF[1] GER[2] Smoking[2] Tuberculosis[3] Psychogenic[2] Pertussis[3] Aspiration[3] Anatomic abnormality[3] Tumor[3]

*Infections include upper (pharyngitis, sinusitis, tracheitis, rhinitis, otitis) and lower (pneumonia, abscess, empyema) respiratory tract disease.
†Anatomic abnormality includes tracheobronchomalacia, tracheoesophageal fistula, vascular ring, abnormal position or take-off of large bronchi.
[1]Common; [2]less common; [3]much less common.
CF, cystic fibrosis; GER, gastroesophageal reflux.

◆ Physical Examination

Inspection

Initial inspection often reveals the seriousness of an illness:

- Is the child struggling to breathe (dyspnea)?
- Does the child have an anxious look?
- Can the child be calmed or engaged in play?
- Is the child's skin blue (representing cyanosis) or ashen?
- Does the child appear wasted, with poor growth that may indicate a chronic illness?

The respiratory rate is often elevated with parenchymal lung disease or extrathoracic obstruction. Respiratory rates vary with the age of the child (Fig. 2.3) and with pulmonary infection, airway obstruction, activity, wakefulness and sleep, fever, metabolic acidosis, and anxiety.

Odors may also give helpful clues. Does the examining room or the clothing smell of stale cigarette smoke? Is there a foul odor from a diaper with a fatty stool, which may suggest pancreatic insufficiency and CF? Is the child's breath malodorous, as can be noticed in sinusitis, nasal foreign body, lung abscess, or bronchiectasis?

Fingers. Cyanotic nail beds suggest hypoxemia, poor peripheral circulation, or both. The examiner looks for the presence of **digital clubbing** (Fig. 2.4), which makes asthma or acute pneumonia extremely unlikely. The absence of digital clubbing but a history of severe chronic cough in an older child makes CF unlikely.

Chest, abdomen, and spine. The shape of the chest gives information. Is the anteroposterior (AP) diameter increased, which indicates hyperinflation of the lungs from obstruction of small airways (asthma, bronchiolitis, CF)? Is this diameter small, as can be seen with some restrictive lung diseases with small lung volumes (muscular dystrophy, spinal muscular atrophy)? The normal infant has a "round" chest configuration, with the AP diameter of the chest about 84% of the transverse (lateral) diameter. With growth, the chest becomes more flattened in the AP dimension, and the AP-to-transverse ratio is between 70% and 75%. Although obstetric calipers can be used to give an objective assessment of the AP diameter of the chest, most clinicians rely on their

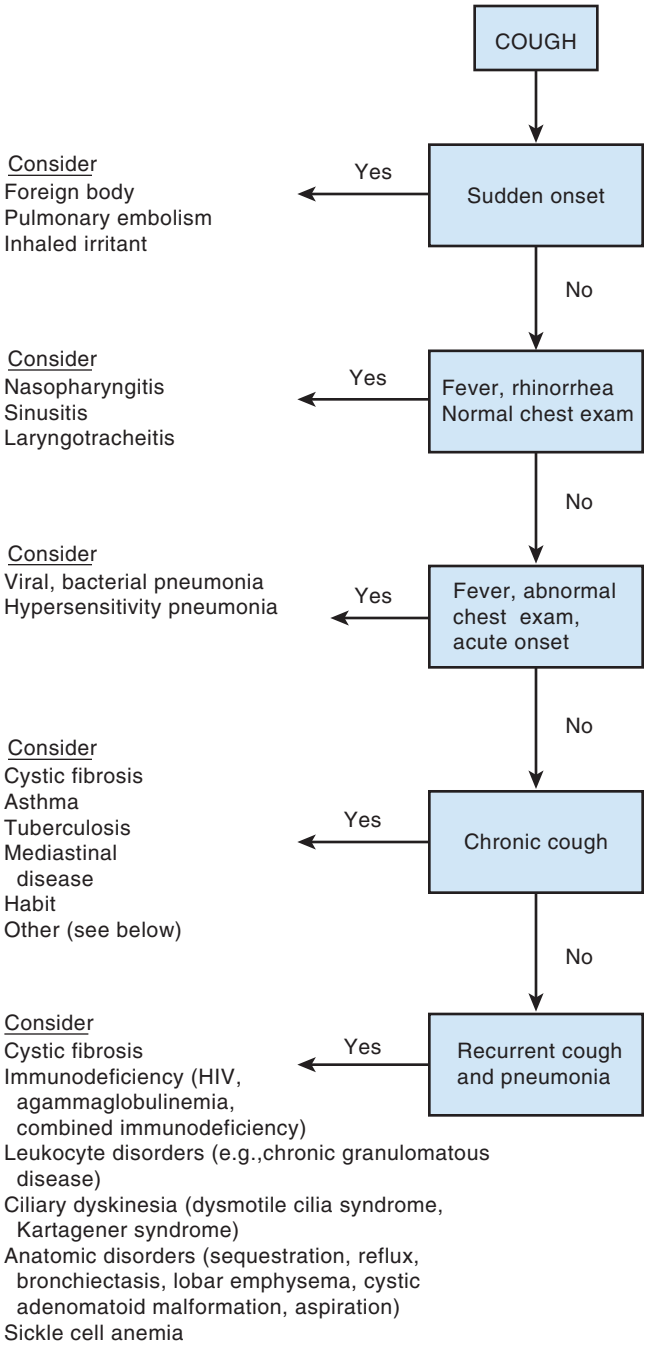


FIGURE 2.2 Algorithm for differential diagnosis of cough. HIV, human immunodeficiency virus.

TABLE 2.2 Clinical Clues About Cough

Characteristic	Think of
Staccato, paroxysmal	Pertussis, cystic fibrosis, foreign body, *Chlamydia* species, *Mycoplasma* species
Followed by "whoop"	Pertussis
All day, never during sleep	Psychogenic, habit
Barking, brassy	Croup, psychogenic, tracheomalacia, tracheitis, epiglottitis
Hoarseness	Laryngeal involvement (croup, recurrent laryngeal nerve involvement)
Abrupt onset	Foreign body, pulmonary embolism
Follows exercise	Asthma
Accompanies eating, drinking	Aspiration, gastroesophageal reflux, tracheoesophageal fistula
Throat clearing	Postnasal drip
Productive (sputum)	Infection
Night cough	Sinusitis, asthma
Seasonal	Allergic rhinitis, asthma
Immunosuppressed patient	Bacterial pneumonia, *Pneumocystis jiroveci*, *Mycobacterium tuberculosis*, *Mycobacterium avium–intracellulare*, cytomegalovirus
Dyspnea	Hypoxia, hypercarbia
Animal exposure	*Chlamydia psittaci* (birds), *Yersinia pestis* (rodents), *Francisella tularensis* (rabbits), Q fever (sheep, cattle), hantavirus (rodents), histoplasmosis (pigeons)
Geographic	Histoplasmosis (Mississippi, Missouri, Ohio River Valley), coccidioidomycosis (Southwest), blastomycosis (North and Midwest)
Workdays with clearing on days off	Occupational exposure

subjective assessment of whether the diameter is increased: Does the patient look "barrel-chested"?

Intercostal, subcostal, suprasternal, and supraclavicular retractions (inspiratory sinking in of the soft tissues) indicate increased effort of breathing and reflect both the contraction of the accessory muscles of respiration and the resulting difference between intrapleural and extrathoracic pressure. Retractions occur most commonly with obstructed airways (upper or lower), but they may occur with any condition leading to the use of the accessory muscles. Any retractions other than the mild normal depressions seen between an infant's lower ribs indicate a greater than normal work of breathing.

Less easy to notice than intercostal retractions is their bulging out with expiration in a child with expiratory obstruction (asthma). Contraction of the abdominal muscles with expiration is easier to notice and is another indication that a child is working harder than normal to push air out through obstructed airways.

Inspection of the spine may reveal kyphosis or scoliosis. There is a risk of restrictive lung disease if the curvature is severe.

Palpation

Palpating the trachea, particularly in infants, may reveal a shift to one side, which suggests loss of volume of the lung on that side or extrapulmonary gas (pneumothorax) on the other side. Placing one hand on each side of the chest while the patient breathes may enable the examiner to detect asymmetry of chest wall movement, either in timing or in degree of expansion. The former indicates a partial bronchial obstruction, and the latter suggests a smaller lung volume, voluntary guarding, or diminished muscle function on one side. Palpating the abdomen gently during expiration may allow the examiner to feel the contraction of the abdominal muscles in cases of expiratory obstruction. Hyperinflation may push the liver down making it palpable below the costal margin.

Palpation for tactile fremitus, the transmitted vibrations of the spoken word ("ninety-nine" is the word often used to accentuate these

TABLE 2.3 Cough: Some Aspects of Differential Diagnosis

Cause	Abrupt Onset	Only When Awake	Yellow Sputum	Responds to Inhaled Bronchodilator (by History)	Responds to Antibiotics (by History)	Responds to Steroids (by History)	Failure to Thrive	Wheeze	Digital Clubbing
Asthma	+	++	++	+++	+	+++	+	+++	–
Cystic fibrosis	+	++	++	+	+++	+	++	++	+++
Infection	+	+	++	–	++	–	+	+	–
Aspiration	+	+	+	+	+	+	++	++	+
Gastroesophageal reflux	+	++	–	–	–	+	++	++	–
Foreign body	+++	+	++	+	++	+	+	++	+
Habit	–	+++	–	–	–	–	–	–	–

+++, very common and suggests the diagnosis; ++, common; +, uncommon; –, almost never and makes examiner question the diagnosis.

TABLE 2.4 Drugs Causing Cough

Drug	Mechanism
Tobacco, marijuana	Direct irritants
β-Adrenergic blockers	Potentiate asthma
ACE inhibitors	(?) Possibly potentiate asthma
Bethanechol	Potentiates asthma
Nitrofurantoin	(?) Via oxygen radicals vs via autoimmunity
Antineoplastic agents	Various (including pneumonitis/fibrosis, hypersensitivity, noncardiogenic pulmonary edema)
Sulfasalazine	(?) Causes bronchiolitis obliterans
Penicillamine	(?) Causes bronchiolitis obliterans
Diphenylhydantoin	Hypersensitivity pneumonitis
Gold	(?) Causes interstitial fibrosis
Aspirin, NSAIDs	Potentiate asthma
Nebulized antibiotics	(?) Direct irritant
Inhaled/nebulized bronchodilators	Increases tracheal/bronchial wall instability in airway malacia; or via reaction to vehicle
Theophylline, caffeine	Indirect, via worsened gastroesophageal reflux (relaxation of lower esophageal sphincter)
Metabisulfite	Induces allergic asthma
Cholinesterase inhibitors	Induce mucus production (bronchorrhea)

ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs.

TABLE 2.5 Nonpulmonary History Suggesting Cystic Fibrosis

Maldigestion, malabsorption, steatorrhea (in 80–90%)
Poor weight gain
Family history of cystic fibrosis
Salty taste to skin
Rectal prolapse (up to 20% of patients)
Digital clubbing
Meconium ileus (in 10–15%)
Intestinal atresia
Neonatal cholestatic jaundice
Male sterility

vibrations), helps determine areas of increased parenchymal density and hence increased fremitus (as in pneumonic consolidation) or decreased fremitus (as in pneumothorax or pleural effusion).

Percussion

The percussion note determined by the examiner's tapping of one middle finger on the middle finger of the other hand, which is firmly placed over the patient's thorax, may be dull over an area of consolidation or effusion and hyperresonant with air trapping. Percussion can also be used to determine diaphragmatic excursion. The lowest level

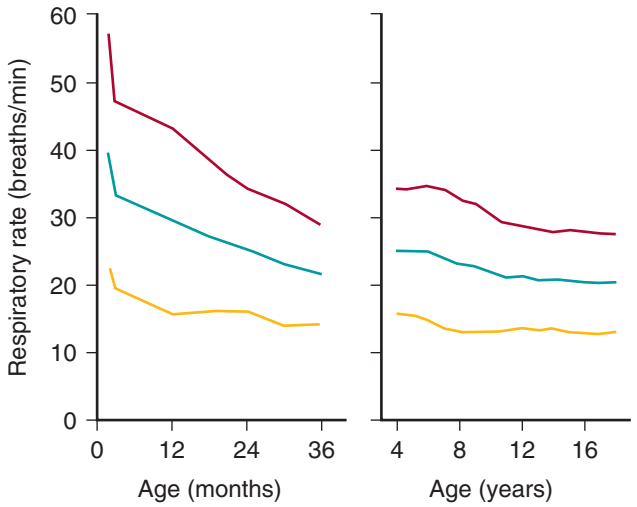


FIGURE 2.3 Mean values *(blue line)* ±2 standard deviations *(red and yellow lines)* of the normal respiratory rate at rest (during sleep in children younger than 3 years). There is no significant difference between the genders. (Data from Pasterkamp H. The history and physical examination. In: Chernick V, ed. *Kendig's Disorders of the Respiratory Tract in Children*. 6th ed. Philadelphia: WB Saunders; 1998:88.)

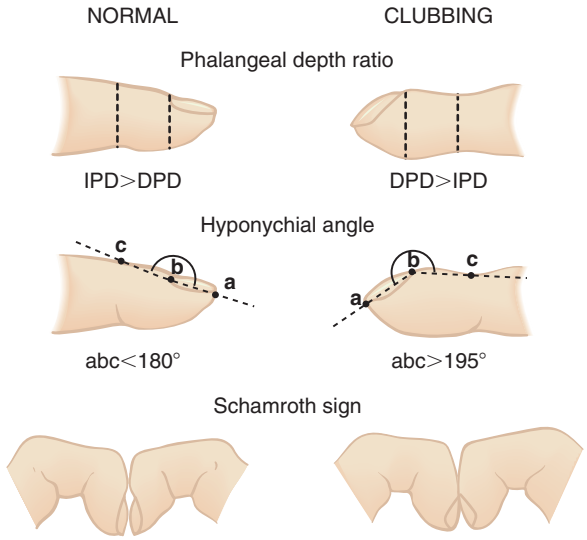


FIGURE 2.4 Measurement of digital clubbing. The ratio of the distal phalangeal depth (DPD) to the interphalangeal depth (IPD), or the phalangeal depth ratio, is normally less than 1 but increases to more than 1 with finger clubbing. The DPD/IPD ratio can be measured with calipers or, more accurately, with finger casts. The hyponychial angle is measured from lateral projections of the finger contour on a magnifying screen and is normally less than 180 degrees but greater than 195 degrees with finger clubbing. Schamroth sign is useful for bedside assessment. The dorsal surfaces of the terminal phalanges of similar fingers are placed together. With clubbing, the normal diamond-shaped aperture or "window" at the bases of the nail beds disappears, and a prominent distal angle forms between the end of the nails. In normal subjects, this angle is minimal or nonexistent. (From Pasterkamp H. The history and physical examination. In: Chernick V, ed. *Kendig's Disorders of the Respiratory Tract in Children.* 6th ed. Philadelphia: WB Saunders; 1998.)

of resonance at inspiration and expiration determines diaphragmatic motion.

Auscultation

Because lung sounds tend to be higher-pitched than heart sounds, the diaphragm of the stethoscope is better suited to pulmonary auscultation than is the bell, whose target is primarily the lower-pitched heart sounds (Table 2.6). The adult-sized stethoscope generally is superior to the smaller pediatric or neonatal diaphragms, even for listening to small chests, because its acoustics are better (Figs. 2.5 and 2.6).

Adventitious sounds come in a few varieties, namely, stridor, crackles, rhonchi, and wheezes. Other sounds should be described in clear, everyday language.

- **Stridor** is a continuous musical sound usually heard on inspiration and is caused by narrowing in the extrathoracic airway, as with croup or laryngomalacia.
- **Crackles** are discontinuous, representing the popping open of air-fluid menisci as the airways dilate with inspiration. Fluid in larger airways causes crackles early in inspiration (congestive heart failure). Crackles that tend to be a bit lower in pitch ("coarse" crackles) than the early, higher-pitched ("fine") crackles are associated with fluid in small airways (pneumonia). Although crackles usually signal the presence of excess airway fluid (pneumonia, pulmonary edema), they may also be produced by the popping open of noninfected fibrotic or atelectatic airways. Fine crackles are not audible at the mouth, whereas coarse crackles may be. Crackles is the preferred term, rather than the previously popular "rales."
- **Rhonchi**, or "large airway sounds," are continuous gurgling or bubbling sounds typically heard during both inhalation and exhalation. These sounds are caused by movement of fluid and secretions in larger airways (asthma, viral URI). Rhonchi, unlike other sounds, may clear with coughing.

TABLE 2.6 Physical Signs of Pulmonary Disease

Disease Process	Mediastinal Deviation	Chest Motion	Fremitus	Percussion	Breath Sounds	Adventitious Sounds	Voice Signs
Consolidation (pneumonia)	No	Reduced over area, splinting	Increased	Dull	Bronchial or reduced	Crackles	Egophony,* whispering pectoriloquy increased†
Bronchospasm	No	Hyperexpansion with limited motion	Normal or decreased	Hyperresonant	Normal to decreased	Wheezes, crackles	Normal to decreased
Atelectasis	Shift toward lesion	Reduced over area	Decreased	Dull	Reduced or absent	None or crackles	None
Pneumothorax	Tension deviates trachea and PMI to opposite side	Reduced over area	None	Resonant, tympanitic	None	None	None
Pleural effusion	Deviation to opposite side	Reduced over area	None	Dull	None	Friction rub; splash, if hemopneumothorax	None

*Egophony is present when *e* sounds like *a*.
†Whispering pectoriloquy produces clearer sounding whispered words (e.g., "ninety-nine").
PMI, point of maximal impulse.
Modified from Dantzker D, Tobin M, Whatley R. Respiratory diseases. In: Andreoli TE, Carpenter CJ, Plum F, Smith LH, eds. *Cecil Essentials of Medicine*. Philadelphia: WB Saunders; 1986:126-180.

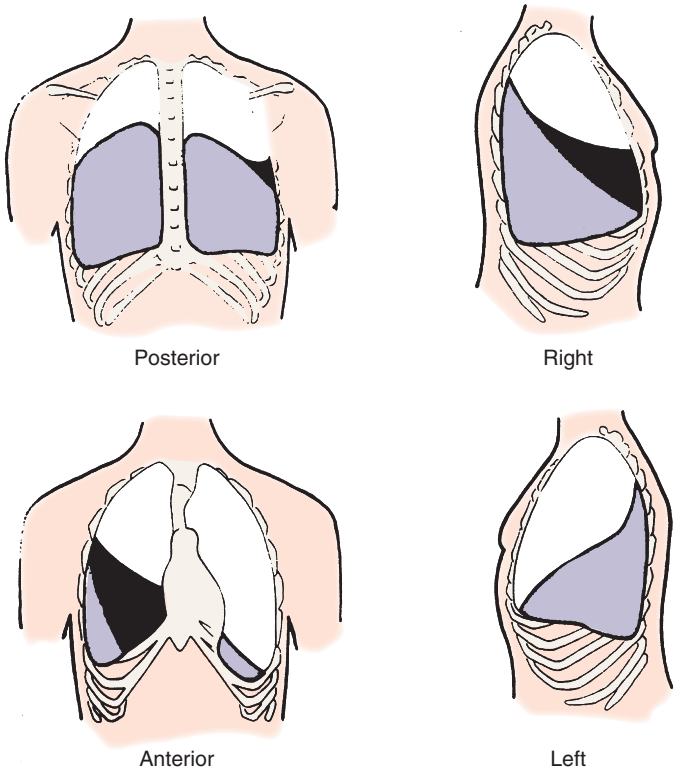


FIGURE 2.5 Projections of the pulmonary lobes on the chest surface. The upper lobes are *white*, the right-middle lobe is *black*, and the lower lobes are *purple*. (From Pasterkamp H. The history and physical examination. In: Chernick V, ed. *Kendig's Disorders of the Respiratory Tract in Children*. 6th ed. Philadelphia: WB Saunders; 1998.)

- **Wheezes** are continuous musical sounds (lasting longer than 200 msec), caused by vibration of narrowed airway walls, as with asthma, and perhaps vibration of material within airway lumens. These sounds are much more commonly heard during expiration than inspiration.

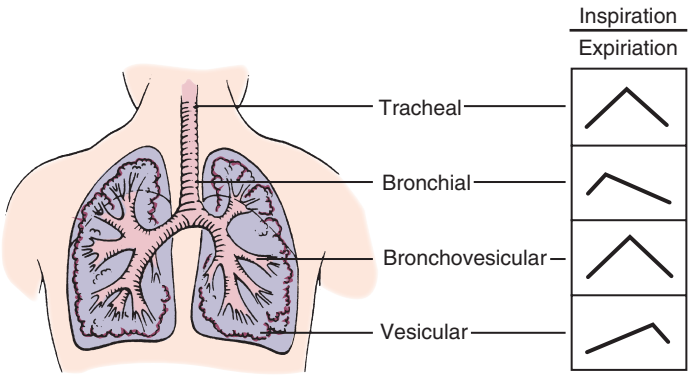
◆ Diagnostic Studies

Radiography

The chest radiograph is often the most useful diagnostic test in the evaluation of the child with cough. Table 2.7 highlights some of the radiographic features of the most common causes of cough in pediatric patients. Radiographic findings are often similar for a number of disorders, and thus these studies may not indicate a definitive diagnosis. Chest radiographs are normal in children with psychogenic (habit) cough and in children with sinusitis or gastroesophageal reflux (GER) as the primary cause of cough. A normal chest radiograph indicates the unlikelihood of pneumonia caused by respiratory syncytial virus (RSV), influenza, parainfluenza, adenovirus, *Chlamydia* species, or bacteria. Although children with cough resulting from cystic fibrosis (CF), *Mycoplasma* species, tuberculosis, aspiration, a bronchial foreign body, or an anatomic abnormality usually have abnormal chest radiographs, a normal radiograph does not exclude these diagnoses. Hyperinflation of the lungs is commonly seen on chest radiographs of infants with RSV bronchiolitis or *Chlamydia* pneumonia, and a lobar or round (coin lesion) infiltrate is the radiographic hallmark of bacterial pneumonia. The diagnosis of sinusitis cannot be sustained with normal sinuses on radiograph or computed tomography (CT) scan.

Hematology/Immunology

The white blood cell (WBC) count may help exclude or include certain entities for a differential diagnosis. For example, a WBC count of



Characteristic	Tracheal	Bronchial	Bronchovesicular	Vesicular
Intensity	Very loud	Loud	Moderate	Soft
Pitch	Very high	High	Moderate	Low
I:E ratio*	1:1	1:3	1:1	3:1
Description	Harsh	Tubular	Rustling, but tubular	Gentle rustling
Normal locations	Extrathoracic trachea	Manubrium	Over mainstem bronchi	Most of peripheral lung

*Ratio of duration of inspiration to expiration.

FIGURE 2.6 Characteristics of breath sounds. Tracheal breath sounds are very harsh, loud, and high-pitched; they are heard over the extrathoracic portion of the trachea. Bronchial breath sounds are loud and high-pitched; normally, they are heard over the lower sternum and sound like air rushing through a tube. The expiratory component is louder and longer than the inspiratory component; a definite pause is heard between the two phases. Bronchovesicular breath sounds are a mixture of bronchial and vesicular sounds. The inspiratory (I) and expiratory (E) components are equal in length. They are usually heard only in the first and second interspaces anteriorly and between the scapulae posteriorly, near the carina and mainstem bronchi. Vesicular breath sounds are soft and low-pitched; they are heard over most of the lung fields. The inspiratory component is much longer than the expiratory component; the latter is softer and often inaudible. (From Swartz MH, ed. The chest. In: *Textbook of Physical Diagnosis: History and Examination*. Philadelphia: WB Saunders; 1989.)

TABLE 2.7 Cough: Laboratory Evaluation

	CHEST RADIOGRAPH					Abnormal Sinus Radiograph	COMPLETE BLOOD COUNT								
	Normal	Hyper	Lobar Infil	Diff Infil	Other		↑WBC	↑LY	↑EOS	↑PMN	↑IgG	↑IgM	↑IgE	+ NP PCR	Other
Asthma	+	++	–	–	–	+	+	+	++	–	+	+	++		+bdilator[1]
Cystic fibrosis	+	++	+	+	++	+++	++	+	+	++	++	+	+		See Table 2.8
Other infection															
Croup	++	+	+	+	++[2]	–	–	+	+	–				Paraflu +++	
Epiglottitis	++	+	+	+	++[3]	–	+++	+	+	+++					Direct look
Sinusitis	+++	–	–	–	–	+++	++	–	+	+++	++		+		
Bronchiolitis	–	+++	+	++	+	–	+	+	+	+				RSV, metapneumovirus +++	
Pneumonia															
Influenza	–	++	+	++	+	–	++			+				+++	
Paraflu	–		+	++	+	–	++			+				+++	
Adenovirus	–		+	++	+	–	++	+	+	++				+++	
Pertussis	++	+	–	+	+	–	++	+++	+	+	++	+	–	++[4]	
Chlamydia	–	+++	+	+++	+	–	+	+	++	+	+++	+++	–	+++	
Mycoplasma	+	+	+	+	++[5]	+	+	+	+	+	–	++	–	++	+Cold agglutinin
TB	+	–	++	+	++	–	+	+	+	+					+PPD, Quantiferon
Bacterial	–	+	+++	+	++[5]	–	+++	+	+	+++	++	+	+	+	+Bld cult[6]
Foreign body	–	++[7]	++	–	++[7]	–	++	+	+	++					Bronch
GE reflux	+++	+	–	–	–	+	–	–	–	–	–	–	+	–	Esoph pH[8]
Aspiration	+	+	+	+	++[9]	+	+	–	+	+	–	–	+	–	[10]
Anatomic	+	+	+	–	++[11]	–	+	–	–	+	–	–	–	–	[12]
Habit	+++	–	–	–	–	–	–	–	–	–	–	–	–	–	

[1]Positive response to bronchodilators, either as a home therapeutic trial or in a pulmonary function test in the laboratory.
[2]"Steeple" sign: narrowing of upper tracheal air column.
[3]"Swollen thumb": sign of thickened epiglottis.
[4]Low yield in paroxysmal stage.
[5]Pleural effusion relatively common.
[6]Blood culture positive in 10%; needle aspiration of pleural fluid or lung fluid may yield organism; bacterial antigen in urine. In older infants and children, common pathogens include pneumococci and group A streptococci; *Staphylococcus aureus is* rare and may be associated with pneumatoceles or empyema.
[7]Localized hyperinflation is common; localized atelectasis is common; inspiratory-expiratory radiographs may show ball-valve obstruction.
[8]Esophageal biopsy specimen shows esophagitis.
[9]Multilobular or multisegmental, dependent lobes.
[10](?) Lipid-laden macrophages from bronchoscopy or gastric washings; barium swallow or radionuclide study showing aspiration.
[11]Right-sided arch, mass effect on airways, mass identified; magnetic resonance imaging (MRI).
[12]Bronchoscopy; computed tomography; MRI.
+++, almost always—if not present, must question diagnosis; ++, common; +, less common; –, seldom—if present, must question diagnosis.
+Bld cult, blood culture may be positive; Bronch, bronchoscopy can reveal the foreign body; Diff, diffuse or scattered; ↑EOS, increased eosinophil count; Esoph pH, prolonged esophageal pH probe monitoring; GE, gastroesophageal; Hyper, hyperinflated; Ig, immunoglobulin; Infil, infiltrates; ↑LY, increased lymphocyte count; +NP aspirate PCR, nasopharyngeal positive for specific organism; Paraflu, parainfluenza virus; PCR, polymerase chain reaction; ↑PMN, increased polymorphonuclear neutrophil count; PPD, purified protein derivative (TB); RAD, reactive airways disease; RSV, respiratory syncytial virus; TB, tuberculosis; ↑WBC, increased white blood cell count.

35,000 with 85% lymphocytes strongly suggests pertussis, but not every child with pertussis presents such a clear hematologic picture. The presence of a high number or large proportions of immature forms of WBCs suggests an acute process, such as a bacterial infection. Immunoglobulins provide supportive evidence for a few diagnoses, such as chlamydial infection, which rarely occurs without elevated serum concentrations of immunoglobulins G and M.

Bacteriology/Virology

Specific bacteriologic or virologic diagnoses can be made in a number of disorders causing cough, including RSV, influenza, parainfluenza, adenovirus, and *Chlamydia* pneumonia. In most cases, the viruses can be rapidly identified with amplification of the viral genome through polymerase chain reaction (PCR). In bacterial pneumonia, the offending organism can be cultured from the blood in a small proportion (10%) of patients. A positive culture provides definitive diagnosis, but a negative culture specimen is not helpful. Throat cultures are seldom helpful (except in CF) in identifying lower respiratory tract bacterial organisms. Sputum cultures and Gram stains may help guide initial empirical therapy in older children with pneumonia or purulent bronchitis, but their ability to identify specific causative organisms with certainty (with the exception of CF) has not been shown clearly.

Infants and young children usually do not expectorate but rather swallow their sputum. Specimens obtained via bronchoscopy may be contaminated by mouth flora, but heavy growth of a single organism in the presence of polymorphonuclear neutrophils certainly supports the organism's role in disease. If pleural fluid or fluid obtained directly from the lung via needle aspiration is cultured, the same rules apply: Positive cultures are definitive, but negative cultures are not.

Other Tests

A number of specific tests can help to establish diagnoses in a child with cough (see Table 2.7). These include a positive response to bronchodilators in a child with asthma; visualizing the red, swollen epiglottis in epiglottitis (to be done only under very controlled conditions); the bronchoscopic visualization of the peanut, plastic toy, or other offender in foreign body aspiration; a positive purified protein derivative (PPD) or Quantiferon assay in tuberculosis; and several studies of the esophagus in GER. Several imaging techniques, such as CT or magnetic resonance imaging (MRI), can help to delineate various intrathoracic anatomic abnormalities, pulmonary embolism, and bronchiectasis. Multiple tests can be employed to confirm the diagnosis of CF (Table 2.8).

◆ Differential Diagnosis and Treatment

Infection

Infections are the most common cause of acute cough in all age groups and are responsible for some chronic coughs. The age of the patient has a large impact on the frequency of the type of infection.

Infections in infants. Viral upper respiratory infections (common cold); croup (laryngotracheobronchitis); viral bronchiolitis, particularly with RSV or human metapneumovirus; and viral pneumonia are the most frequently encountered respiratory tract infections and hence the most common causes of cough in infancy. Viral illness may predispose to bacterial superinfection (croup and *Staphylococcus aureus* tracheitis or influenza and *H. influenzae* or *S. aureus* pneumonia).

Viral upper respiratory infections (URI). Viral URI symptoms and signs usually include stuffy nose with nasal discharge, sore throat, and sneezing. There may be fever, constitutional signs (irritability, myalgias, and headache), or both. Cough is common and may persist for 5-7 days. The mechanism by which URIs cause cough in children is undetermined. In adults, it is generally thought that "postnasal drip"—that is, nasal or sinus secretions draining into the posterior nasopharynx—causes cough and, in fact, may be one of the most frequent causes of cough. Indeed, sinus CT in older patients with URIs often reveals unexpected involvement of the sinus mucosa. Other authorities believe that cough in a child with a URI indicates involvement (inflammation or bronchospasm) of the lower respiratory tract. Over-the-counter cough and cold medications are commonly used. Evidence of efficacy of these medications for children with URI is lacking. Because of the known risk for unintentional overdose from these medications, their use is not recommended in children under age 4 years.

TABLE 2.8 Laboratory Tests for Cystic Fibrosis

Usefulness	Test	Sensitivity	Specificity	Cost
Definitive	Sweat chloride test	.99+	.95+	$96
	DNA analysis	.85–.90	.99	$962
Suggestive	Throat or sputum culture* positive for mucoid *Pseudomonas aeruginosa*	.70-.80	.85	$183
	Sinus radiographs			$179
	Pansinusitis	.95	.90	
	Positive IRT newborn screen	.98	.25	$1
Supportive	Fecal elastase			$587
	Pulmonary function tests:			$100–$800
	Obstructive pattern, especially small airways and especially if patient is poorly responsive to bronchodilator	.70+	?	
	Chest radiograph:			$160
	Hyperinflation, ± other findings; especially with right upper lobe infiltrate/atelectasis	.70+	?	
	Throat or sputum culture*:			$183
	Positive for *Staphylococcus aureus*	.20	.20	
	Positive for *Haemophilus influenzae*	.05-.20	.15	

*Throat is usually deep pharyngeal culture.
IRT, immunoreactive trypsinogen.

Common viral pathogens include rhinovirus, RSV, coronaviruses, and parainfluenza viruses. The differential diagnosis includes allergic rhinitis, which often demonstrates clear nasal secretions with eosinophils and pale nasal mucosa, and sinusitis, which presents with mucopurulent nasal secretions containing neutrophils and erythematous mucosa.

Croup (laryngotracheobronchitis). Infectious croup (see Chapter 3) is most common in the first 2 years of life. Its most dramatic components are the barking ("croupy") cough and inspiratory stridor, which appear a few days after the onset of a cold. In most cases, the patient has a low-grade fever, and the disease resolves within a day or two. In severe cases, the child can be extremely ill and is at risk for complete laryngeal obstruction. There may be marked intercostal and suprasternal retractions and cyanosis. *Stridor at rest signifies significant obstruction*. Diminishing stridor in a child who is becoming more comfortable is a good sign, but diminishing stridor in and of itself is not necessarily good: If the child becomes fatigued because of the tremendous work of breathing through an obstructed airway and can no longer breathe effectively, smaller-than-needed tidal volumes make less noise.

It is important to distinguish croup from epiglottitis in the child with harsh, barking cough and inspiratory stridor because the natural histories of the two diseases are quite different (see Table 2.7). Epiglottitis occurs more commonly in unimmunized toddlers than in infants (see Chapter 3).

Treatment of mild croup is usually not needed. For decades, pediatricians have recommended putting a child with croup in a steamy bathroom or driving to the office or emergency department with the car windows rolled down. It is likely that these remedies are effective because of the heat exchange properties of the upper airway; air that is cooler or more humid than the airway mucosa will serve to cool the mucosa, thus causing local vasoconstriction and probably decreasing local edema.

In a child who has stridor at rest, evaluation is indicated. Symptomatic, often dramatic relief through decreased laryngeal edema can usually be achieved with aerosolized racemic epinephrine (2.25% solution, 0.25 to 0.5 mL/dose). It is essential to remember that the effects of the epinephrine are transient, lasting only a few hours, although the course of the illness is often longer. The result is that when the racemic epinephrine's effect has worn off, the child's cough and stridor will probably be as bad or even worse than before the aerosol was administered. This is not a "rebound" effect: The symptoms are not worse because of the treatment but, rather, because of the natural progression of the viral illness. Repeating the aerosol will probably again have a beneficial effect. A child who responds favorably to such an aerosol needs to be observed for several hours because further treatment may be needed. A single dose of dexamethasone (0.6 mg/kg orally, intramuscularly, or intravenously) reduces the severity and hastens recovery. Aerosolized steroids (budesonide) may also be effective in patients with mild to moderately severe croup.

Bronchiolitis. Bronchiolitis is a common and potentially serious lower respiratory tract disorder in infants (see Chapter 3). It is caused usually by RSV but on occasion by parainfluenza, influenza, human metapneumovirus, adenovirus, enterovirus, and human rhinovirus. It mostly occurs in the winter months, often in epidemics. RSV bronchiolitis is seen uncommonly in children older than 4 years. Typically, "cold-like" symptoms of rhinorrhea precede the harsh cough, increased respiratory rate, and retractions. Respiratory distress and cyanosis can be severe. The child's temperature is seldom elevated above 38°C.

The chest is hyperinflated, widespread crackles are audible on inspiration, and wheezing marks expiration. The chest radiograph invariably reveals hyperinflation, as depicted by a depressed diaphragm, with an enlarged retrosternal air space in as many as 60% of patients, peribronchial thickening in approximately 50%, and consolidation and/or atelectasis in 10-25%.

The diagnosis is confirmed with demonstration of RSV by PCR of nasopharyngeal secretions. In most cases, no treatment is needed because the disease does not interfere with the infant's eating or breathing. Apnea is a common complication of RSV bronchiolitis in neonates and may necessitate close monitoring. In severe cases, often those in which there is underlying chronic heart, lung, or immunodeficiency disease, RSV can be life-threatening. In severe cases, hospital care with supplemental oxygen and intravenous fluids is indicated. Suctioning of secretions is an essential part of the treatment. Many other treatment modalities have been tried for hospitalized infants with bronchiolitis. Aerosolized bronchodilators and systemic glucocorticoids do not seem to alter clinical outcome and are not recommended in most patients. Nebulized saline may reduce the length of hospitalization. Use of high-flow nasal cannula may reduce the need for more invasive forms of respiratory support in infants with impending respiratory failure.

Viral pneumonia. Viral pneumonia can be similar to bronchiolitis in its manifestation, with cough and tachypnea, after a few days of apparent URI. There can be variable degrees of fever and of overall illness. Infants and children with viral pneumonia may appear relatively well or, particularly with adenovirus or influenza, may have a rapidly progressive course. Frequent symptoms include poor feeding, cough, cyanosis, fever (some patients may be afebrile), apnea, and rhinorrhea. Frequent signs include tachypnea, retractions, crackles, and cough. Cyanosis is less common.

The most common agents causing viral pneumonia in infancy and childhood are RSV, influenza, and parainfluenza. Adenovirus is less common, but it is important because it can be severe and leave residua, including bronchiectasis and bronchiolitis obliterans. Adenovirus pneumonia is often accompanied by conjunctivitis and pharyngitis, in addition to leukocytosis and an elevated erythrocyte sedimentation rate (ESR); the ESR and leukocyte count are usually not elevated in other types of viral pneumonia. Additional viral agents include enteroviruses, human metapneumovirus and rhinovirus. Radiographs most often reveal diffuse, bilateral peribronchial infiltrates, with a predilection for the perihilar regions, but occasionally lobar infiltrates are present. Pleural effusions are not common. On occasion, if an infant is extremely ill, bronchoscopy with bronchoalveolar lavage may be indicated to isolate the virus responsible for the pneumonia.

Treatment is largely supportive, with oxygen and intravenous fluids. Mechanical ventilation may be necessary in a small minority of infants.

In young infants, the **afebrile pneumonia syndrome** may be caused by *Chlamydia*, *Ureaplasma*, or *Mycoplasma* species; cytomegalovirus; or *Pneumocystis jiroveci*. In this syndrome, cough and tachypnea are common. Severe pneumonia may develop in neonates as a result of herpes simplex.

Pertussis (whooping cough). Pertussis is a relatively common cause of lower respiratory tract infection in infants, children, adolescents, and adults, especially in those who are underimmunized or not immunized. The causative organism, *Bordetella pertussis*, has a tropism for tracheal and bronchial ciliated epithelial cells; thus the disease is primarily bronchitis, but spread of the organism to alveoli, or secondary invasion by other bacteria, can cause pneumonia. The disease can occur at any age, from early infancy onward, although its manifestations in young infants and in those who have been partially immunized may be atypical.

Most commonly, pertussis has three stages:

- Catarrhal, in which symptoms are indistinguishable from a viral URI

(See *Nelson Textbook of Pediatrics*, p. 2032.)

(See *Nelson Textbook of Pediatrics*, p. 2091.)

- Paroxysmal, dominated by repeated forceful, paroxysmal coughing spells; spells may be punctuated by an inspiratory "whoop," post-tussive emesis, or both
- Convalescent, in which the intensity and frequency of coughing spells gradually diminish

Each stage typically lasts 1-2 weeks, except the paroxysmal stage, which lasts many weeks. (Pertussis is known as the "100 day cough" in China.) Most children are entirely well between coughing spells, when physical findings are remarkably benign. Infants younger than 6 months of age are at highest risk for complications. The majority of infants with pertussis need to be hospitalized.

Diagnosis can be difficult because the definitive result—namely, culturing the organism from nasopharyngeal secretions—requires special culture medium (Bordet-Gengou, which must be prepared fresh for each collection). Culture specimens are much less likely to be positive during the paroxysmal stage than during the catarrhal stage, when the diagnosis is not being considered. PCR assay of an adequate nasopharyngeal (NP) specimen is the most commonly used test because of improved sensitivity and faster turnaround time compared to culture. An elevated WBC count, as high as 20,000-50,000, with lymphocytes predominating is suggestive of pertussis in infants and children but often absent in adolescents. Chest radiographic findings are nonspecific. Infants with severe disease may require hospitalization.

Treatment is largely supportive, with oxygen, fluids, and small frequent feedings for patients who do not tolerate their normal feedings. Treatment with azithromycin decreases infectivity and may ameliorate the course of the disease if given during the catarrhal stage.

Complications include those related to severe coughing (Table 2.9) and those specific to pertussis, such as seizures and encephalopathy. The risk of acquiring pertussis is markedly reduced by immunizations (three primary immunizations and regular booster immunizations). Neither pertussis infection nor immunization produces lifelong immunity.

Chlamydial infection. *Chlamydia trachomatis* can cause pneumonia in young infants, particularly those aged 3-12 weeks. Cough, nasal congestion, low-grade or no fever, and tachypnea are common. Conjunctivitis is an important clue to chlamydial disease but is present in only 50% of infants with chlamydial pneumonia at the time of presentation. Affected infants may have a paroxysmal cough similar to that of pertussis, but post-tussive emesis is less common. Crackles are commonly heard on auscultation, but wheezing is much less common than the overinflated appearance of the lungs on radiographs would suggest. The organism may be recovered from the nasopharynx by culture or antigen testing. The complete blood cell count may reveal eosinophilia. Chlamydial infection responds to oral erythromycin therapy.

Ureaplasmal infection. *Ureaplasma urealyticum* pneumonia is difficult to diagnose but causes cough in some infants. There are no particularly outstanding features to distinguish this relatively uncommon infection from viral pneumonias.

Bacterial pneumonia. Bacterial pneumonia is relatively less common in infants than is viral pneumonia but can cause severe illness, with cough, respiratory distress, and fever. Chest radiographs are abnormal, and the WBC count is elevated.

Treatment is with antibiotics effective against pneumococci, group A streptococci, and, if illness is severe, *S. aureus*.

Infections in toddlers and children

Viral URIs. In early childhood, as children attend daycare and nursery schools, they are constantly exposed to respiratory viruses to which they have little or no immunity (e.g., RSV, rhinoviruses, adenoviruses, parainfluenza, and enteroviruses). Young children may have as many as 6-8 or even more URIs in a year. The remarks concerning colds and cough in infants (see previous discussion) apply to this older age group. The differential diagnosis of rhinorrhea is noted in Table 2.10.

Sinusitis. The sinuses may become the site for viral and subsequent secondary bacterial infection spreading from the nasopharynx (Fig. 2.7). The signs and symptoms are usually localized, including nasal congestion, a feeling of "fullness" or pain in the face (Fig. 2.8), headache, sinus tenderness, day or night cough, and fever. Maxillary toothache, purulent nasal discharge for more than 10 days, and a positive transillumination (opacification) are important clues. Sinus radiographs or (more accurate) CT scan may facilitate the diagnosis of sinusitis by demonstrating opacification of the sinus with mucosal thickening. Sinusitis is thought to be a cause of cough in adults and can probably be listed, with lower certainty, as a cause of cough in children.

Sinusitis is frequently seen in other conditions known to cause cough, especially CF, asthma, ciliary dyskinesia, and granulomatosis with polyangiitis with or without eosinophilia. It may be difficult to ascertain whether the cough is a direct result of the sinus infection or the underlying problem (purulent bronchitis in the child with CF or ciliary dyskinesia, exacerbation of asthma). In the first two situations, it may not matter because treatment is the same. In the case of the child with asthma, it is important to treat the asthma with bronchodilating and antiinflammatory agents, as well as to treat the infected sinuses with antibiotics.

TABLE 2.9 Potential Complications of Cough

Musculoskeletal	Rib fractures Vertebral fractures Rupture of rectus abdominis muscle Asymptomatic elevation of serum creatine phosphokinase
Pulmonary	Chest wall pain* Bronchoconstriction Pneumomediastinum Pneumothorax Mild hemoptysis Subcutaneous emphysema Irritation of larynx and trachea
Cardiovascular	Rupture of subconjunctival,* nasal,* and anal veins Bradycardia, heart block Transient hypertension
Central nervous system	Cough syncope Headache Subarachnoid hemorrhage
Gastrointestinal	Hernias (ventral, inguinal) Emesis Rectal prolapse Pneumoperitoneum
Miscellaneous	Anorexia* Malnutrition Sleep loss* Urinary incontinence Disruption of surgical wounds Vaginal prolapse Displacement of intravenous catheters

*Common.

(See *Nelson Textbook of Pediatrics*, p. 2014.)

TABLE 2.10 Differential Diagnosis of Rhinorrhea

Etiology	Frequency	Duration*	Discharge	Comment
Viral	Common	Acute	Purulent	Polymorphonuclear neutrophils in smear
Allergic	Common	Acute/Chronic	Clear	Eosinophils in smear, seasonal
Vasomotor	Common	Chronic	Variable	? Environmental triggers
Sinusitis	Common	Chronic	Purulent	Sinus tenderness
Rhinitis medicamentosusa	Common	Chronic	Variable	Medication use
Response to stimuli	Common	Acute	Clear	Odors, exercise, cold air, pollution
Nasal polyps	Uncommon	Chronic	Variable	Consider cystic fibrosis
Granulomatous disease	Uncommon	Chronic	Bloody	Sarcoid, Granulomatosis with polyangiitis, midline granuloma
Cerebrospinal fluid fistula	Uncommon	Chronic	Watery	Trauma, encephalocele
Foreign body	Uncommon	Chronic	Purulent	Often malodorous
Tumor	Uncommon	Chronic	Clear to bloody	Angiofibroma, hemangioma, rhabdomyosarcoma, lymphoma, nasopharyngeal carcinoma, neuroblastoma
Choanal atresia, stenosis	Uncommon	Chronic	Clear to purulent	Congenital
Nonallergic eosinophilic rhinitis syndrome	Uncommon	Chronic	Clear	Eosinophils in smear
Septal deviation	Unknown	Chronic	Clear	Congenital, trauma
Drugs	Uncommon	Chronic	Variable	Cocaine, glue and organic solvents, angiotensin-converting enzyme inhibitors, β blockers
Hypothyroidism	Uncommon	Chronic	Clear	
Cluster headache	Uncommon	Intermittent	Clear	Associated tearing, headache
Horner syndrome	Uncommon	Chronic	Clear	Ptosis, miosis, anhidrosis

*Less than 1 week is considered acute.

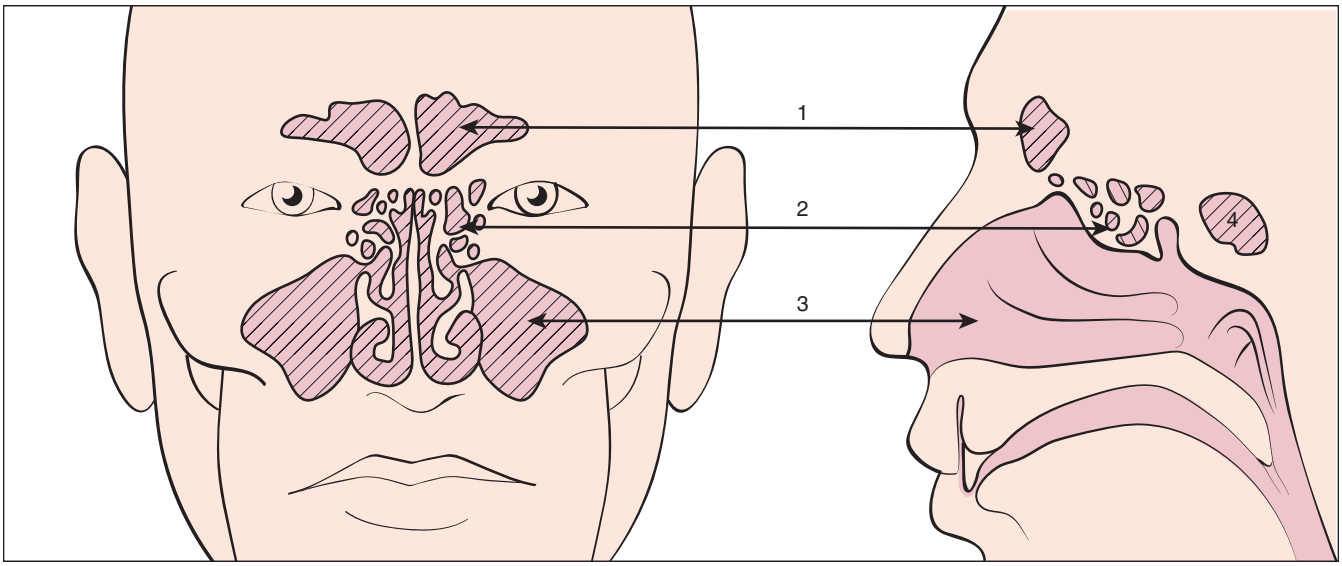


FIGURE 2.7 The paranasal sinuses. *1,* Frontal. *2,* Ethmoid. *3,* Maxillary. *4,* Sphenoid. (From Smith RP. Common upper respiratory tract infections. In: Reilly B, ed. *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991.)

The treatment of sinusitis involves the use of oral antibiotics active against the common pathogens (i.e., *Streptococcus pneumoniae*, nontypable *H. influenzae*, *Moraxella catarrhalis*, and, in rare cases, anaerobic bacteria or *Streptococcus pyogenes*). Treatment regimens include the use of amoxicillin, amoxicillin-clavulanate, cefuroxime, cefpodoxime, or cefdinir. *Amoxicillin is considered the initial agent of choice.* Oral (pseudoephedrine, phenylephrine) or topical (phenylephrine, oxymetazoline) decongestants may be of benefit by increasing the patency of the sinus ostia, which permits drainage of the infected and obstructed sinuses. Oral antihistamines may benefit patients with an allergic history. Treatment with antimicrobial agents should continue for at least 7 days after the patient has responded. This may require 14-21 days of therapy. Many patients with presumed sinusitis recover without antibiotic therapy.

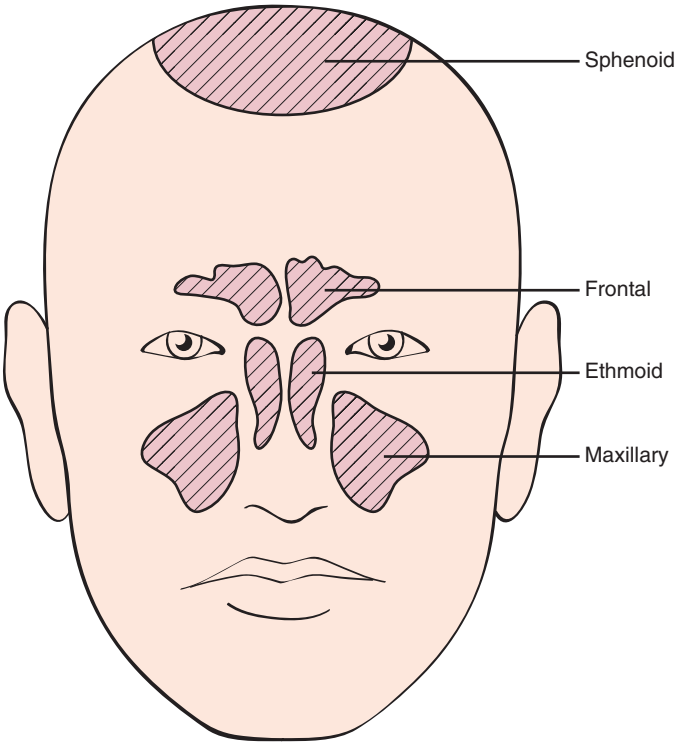


FIGURE 2.8 Typical pain locations in patients with various anatomic sites of acute sinusitis. (From Smith RP. Common upper respiratory tract infections. In: Reilly B, ed. *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991.)

Complications of acute sinusitis include orbital cellulitis, abscesses (orbital, cerebral), cranial (frontal) osteomyelitis (Pott puffy tumor), empyema (subdural, epidural), and thrombosis (sagittal or cavernous sinus).

Pneumonia. The features discussed for viral pneumonia in infants are relevant for viral pneumonia in older children. The differentiation of viral or atypical pneumonia from classical bacterial pneumonia is noted in Table 2.11. Adenovirus and influenza pneumonia may present similar to bacterial pneumonia in severity and acuteness.

Bacterial pneumonia is more common in toddlers and older children than in infants. The most common pathogen is *S. pneumoniae*. (Table 2.12). Cough may not be as prominent a presenting symptom or sign as tachypnea and grunting. Raised respiratory rates (>50 in infants 2-12 months old, >40 in children 1-5 years old) plus retractions and grunting with or without hypoxia (oxygen saturation <90%) have a high specificity and sensitivity for pneumonia. Chest pain, abdominal pain, headache, or any combination of these symptoms may occur. Upper lobe pneumonia may produce meningeal signs, and lower lobe involvement may cause abdominal pain and an ileus.

Examination of the chest shows tachypnea but may be otherwise surprisingly normal. In older children, there may be localized dullness to percussion, with crackles or amphoric (bronchial) breath sounds over a consolidated lobe. The chest radiograph may be normal in the first hours of the illness, inasmuch as the radiographic findings often lag behind the clinical manifestations. Nonetheless, both anterior-posterior and lateral views are the main diagnostic tools; lobar consolidation is usual, with or without pleural effusion. In infants, the pattern may be more diffuse and extensive.

TABLE 2.11 Differentiation of Classical Bacterial Pneumonia from Viral and Atypical Pneumonias*

	Bacterial	Viral/Atypical
History	Precedent URI	Headache, malaise, URI, myalgias
Course	Often biphasic illness	Often monophasic
Onset	Sudden	Gradual
Temperature	High fever	Low-grade fever
Rigors	Common	Uncommon
Vital signs	Tachypnea, tachycardia	Usually normal
Pain	Pleuritic	Unusual
Chest examination	Crackles, signs of consolidation	Consolidation unusual
Pleural effusion	Common	Uncommon
Sputum	Productive, purulent, many PMNs, one dominant organism on Gram stain	Scant, no organisms; PMNs or mononuclear cells
ESR	Elevated	Usually normal
WBC count	Elevated; left shift	Often normal; predominant lymphocytes
Chest radiography	Lobar consolidation, round infiltrate, parapneumonic effusion; may be "bronchopneumonia"	Diffuse, bilateral, patchy, interstitial or bronchopneumonia; lower lobe involvement common; chest radiograph may look worse than patient's condition
Progression	May be rapid	Rapid if *Legionella* species, hantavirus, SARS, herpesvirus, adenovirus
Diagnosis	Blood, sputum, and pleural fluid specimens for culture; antigen detection possible; BAL if progressive	Viral, chlamydial culture or PCR detection; acute and convalescent titers; BAL if progressive

*Atypical pneumonias include *Chlamydia pneumoniae, Mycoplasma pneumoniae*, Legionella species *(L. pneumophila, L. micdadei)*, Q fever, psittacosis.

BAL, bronchoalveolar lavage; ESR, erythrocyte sedimentation rate; PMNs, polymorphonuclear neutrophils; SARS, severe acute respiratory syndrome; URI, upper respiratory tract infection; WBC, white blood cell.

TABLE 2.12 Causes of Infectious Pneumonia

Bacterial	
Common	
Streptococcus pneumoniae	See Table 2.11
Group B streptococci	Neonates
Group A streptococci	See Table 2.11
*Mycoplasma pneumoniae**	Adolescents; summer-fall epidemics
*Chlamydia pneumoniae**	Adolescents (see Table 2.11)
Chlamydia trachomatis	Infants
Mixed anaerobes	Aspiration pneumonia
Gram-negative enteric	Nosocomial pneumonia
Uncommon	
Haemophilus influenzae type B	See Table 2.11
Staphylococcus aureus	Pneumatoceles; infants
Moraxella catarrhalis	
Neisseria meningitidis	
Francisella tularensis	Animal, tick, fly contact
Nocardia species	Immunosuppressed persons
*Chlamydia psittaci**	Bird contact
Yersinia pestis	Plague
Legionella species*	Exposure to contaminated water; nosocomial
Viral	
Common	
Respiratory syncytial virus	See Table 2.11
Parainfluenza types 1-4	Croup, Type 3 and 4 seen in the summer
Influenza A, B	High fever; winter months
Adenovirus	Can be severe; occurs all year round
Human metapneumovirus	Similar to RSV
Rhinovirus	Rhinorrhea
Uncommon	
Enterovirus	Neonates
Herpes simplex	Neonates
Cytomegalovirus	Infants, immunosuppressed persons
Measles	Rash, coryza, conjunctivitis
Varicella	Adolescents
Hantavirus	Southwestern United States
SARS agent	Asia
Fungal	
Histoplasma capsulatum	Geographic region; bird, bat contact
Cryptococcus neoformans	Bird contact
Aspergillus species	Immunosuppressed
Mucormycosis	Immunosuppressed
Coccidioides immitis	Geographic region
Blastomyces dermatitidis	Geographic region
Rickettsial	
*Coxiella burnetii**	Q fever, animal (goat, sheep, cattle) exposure
Rickettsia rickettsiae	Tick bite
Mycobacterial	
Mycobacterium tuberculosis	See Table 2.14
Mycobacterim avium–intracellulare	Immunosuppressed persons
Parasitic	
Pneumocystis jiroveci	Immunosuppressed, steroids
Eosinophilic	Various parasites (e.g., *Ascaris, Strongyloides* species)

*Atypical pneumonia syndrome (see Table 2.11); atypical in terms of extrapulmonary manifestations, low-grade fever, patchy diffuse infiltrates, poor response to penicillin-type antibiotics, and negative sputum Gram stain.
SARS, severe acute respiratory syndrome.

Some clinical and radiographic features may be suggestive of the bacterial cause of pneumonia. Children (especially infants) with staphylococcal pneumonia are more likely to have a rapid overwhelming course. Staphylococcal pneumonia may be accompanied by more extensive radiographic abnormalities, including multilobar consolidation, pneumatocele formation, and extensive pleural (empyema) fluid. The presence of a pleural effusion is not helpful in indicating the specific bacterial diagnosis because other bacterial pneumonias may be accompanied by pleural effusion. Pleural effusions may represent a reactive parapneumonic effusion or an empyema. Pleural fluid may be characterized as transudate, exudate, or empyema (Table 2.13). If the effusion is of sufficient size, as demonstrated by a lateral decubitus radiograph or ultrasonography, a thoracentesis may be indicated to differentiate the nature of the effusion and to identify possible pathogens. For young children who require sedation for thoracentesis and who have an effusion needing drainage, a primary chest tube placement is preferred over thoracentesis to decrease the risks from multiple procedures with sedation.

Differentiating among the causes of bacterial pneumonia can be done with certainty only with positive cultures from blood, pleural fluid, fluid obtained by direct lung tap, or, in rare cases, sputum. Current or previous antibiotic treatment diminishes the yield of such cultures. Bronchoscopy with or without lavage may yield helpful specimens from the progressively ill child or the child who has not responded promptly to empirical antibiotics.

Treatment of uncomplicated presumed bacterial pneumonia is with antibiotics. Ampicillin is the drug of choice for the previously healthy child who requires hospitalization with lobar pneumonia who is fully immunized. If the child is not fully immunized, either cefotaxime or ceftriaxone is indicated. For the critically ill child, vancomycin and cefotaxime/ceftriaxone may be considered for possible drug-resistant *S. pneumoniae* and methicillin-resistant *S aureus* (MRSA). Many children with pneumonia do well with oral antibiotics and respond within hours to the first dose. Repeated or follow-up chest radiographs may remain abnormal for 4-6 weeks after appropriate treatment and are not indicated for a single episode of uncomplicated pneumonia (i.e.,

TABLE 2.13 Differentiation of Pleural Fluid

	Transudate	Exudate	Complicated Empyema
Appearance	Clear	Cloudy	Purulent
Cell count	<1000	>1000	>5000
Cell type	Lymphocytes, monocytes	PMNs	PMNs
LDH	<200 U/L	>200 U/L	>1000 U/L
Pleural/serum LDH ratio	<0.6	>0.6	>0.6
Protein >3 g	Unusual	Common	Common
Pleural/serum protein ratio	<0.5	>0.5	>0.5
Glucose*	Normal	Low	Very low* (<40 mg/dL)
pH*	Normal (7.40–7.60)	7.20–7.40	<7.20
Gram stain	Negative	Usually positive	>85% positive unless patient received prior antibiotics

*Low glucose or pH may be seen in malignant effusion, tuberculosis, esophageal rupture, pancreatitis (positive pleural amylase), and rheumatologic diseases (e.g., systemic lupus erythematosus).
LDH, lactate dehydrogenase; PMNs, polymorphonuclear neutrophils.

no effusion, no abscess, and good response to treatment). *Mycoplasma pneumoniae* is a common cause of pneumonia among school-aged children. The disease often occurs in community outbreaks in the fall. The illness typically begins with extrapulmonary symptoms (i.e., sore throat, myalgias, headache, fever), which then progress to include cough, which can be paroxysmal at times. Patients do not often appear acutely ill, but cough may persist for weeks. There may be no specific abnormalities on the chest examination, although a few crackles may be heard, and about one third of younger patients wheeze.

The radiographic findings in mycoplasmal pneumonia can mimic almost any intrathoracic disease; scattered infiltrates with nonspecific "dirty" lung fields, predominantly perihilar or lower lobes, are common, and lobar infiltrates and pleural effusion are occasionally seen. Laboratory data (complete blood cell count, ESR, sputum culture) may not be helpful. A rise in antimycoplasma immunoglobulin G over 1-2 weeks may be demonstrated but is seldom helpful in guiding therapy. A positive immunoglobulin M response may be useful, although it can persist in serum for several months and, consequently, may not indicate current infection. *PCR is helpful*. The cold agglutinin test yields positive results in about 70% of patients with mycoplasmal pneumonia, but they are also positive in other conditions, including adenovirus infection. The more severe the illness is, the greater is the frequency of positive cold agglutinins. The diagnosis is often made from the history of an older child who has a lingering coughing illness in the setting of a community outbreak, unresponsive to most (nonerythromycin) antibiotic regimens.

Treatment with azithromycin, clarithromycin, or erythromycin in children <8 years old or tetracycline or doxycycline in children ≥8 years old usually shortens the course of illness. Extrapulmonary complications of mycoplasmal infection include aseptic meningitis, transverse myelitis, peripheral neuropathy, erythema multiforme, myocarditis, pericarditis, hemolytic anemia, and bullous otitis media (myringitis). In patients with sickle cell anemia, severe respiratory failure and acute chest syndrome may develop. Infection with *Chlamydia pneumoniae* mimics respiratory disease resulting from *M. pneumoniae*, inasmuch as it occurs in epidemics, is seen in older children, and produces an atypical pneumonia syndrome and pharyngitis.

Tuberculosis. Tuberculosis is uncommon in developed countries; 95% of the disease burden worldwide is in developing countries. Tuberculosis must be considered in the child with chest disease that is not easily explained by other diagnoses, especially if the child lives in or has migrated from an endemic area of the world or has been exposed to an adult with active tuberculosis. Nonetheless, tuberculosis is an infrequent cause of cough in children, even in those with active disease.

TABLE 2.14 Definitions of Positive Tuberculosis (TB) by Mantoux Skin Test (5 TU)*

Cutaneous Induration ≥5 mm
- Close exposure to known or suspected active TB
- Chest radiograph consistent with TB (old or active)
- Clinical evidence of TB
- Children receiving immunosuppresive therapy or with immunosuppressive conditions

Cutaneous Induration ≥10 mm

Children at increased risk
- Age < 4 yr of age
- Medical *high risks* (chronic renal failure, malnutrition, diabetes mellitus, lymphoma)

Children with likelihood of increased exposure
- Children born in high-prevalence regions of the world
- Children who travel to high-prevalence regions of the world
- Children frequently exposed to adults who are HIV infected, homeless, users of illicit drugs, residents of nursing homes, incarcerated, or institutionalized

Cutaneous Induration ≥15 mm
- All children ≥4 yr of age without any identifiable risk

*BCG vaccination status not relevant.
BCG, bacille Calmette-Guérin; HIV, human immunodeficiency virus; TU, tuberculin units.
Data from American Academy of Pediatrics. Tuberculosis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *2015 Red Book: Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:806.

The diagnosis is made primarily by skin testing (purified protein derivative [PPD]) or a positive Quantiferon test; a history of contact with a person who has tuberculosis; and recovery of the organism from sputum, bronchoalveolar lavage, pleural fluid or biopsy, or morning gastric aspirates (Table 2.14). The yield from these procedures is relatively low, even from children with active pulmonary tuberculosis.

The patterns of disease in normal hosts include primary pulmonary tuberculosis, with subsequent inactivation usually noted in young children and reactivation pulmonary disease among adolescents. **Primary pulmonary disease** is often noted as a lower or middle lobe infiltrate during the period of T lymphocyte reaction to the initial infection. Before resolution, the *Mycobacterium tuberculosis* infection may disseminate to the better oxygenated upper lobes and extrathoracic sites, such as bone, or the central nervous system. If the immune response contains the initial infection, the radiographic findings may be indistinguishable from those of any other pneumonic process. With altered immune function, however, there may be progressive local disease, dissemination to miliary pulmonary disease, or early reactivation (months to 5 years) at distal sites, which produces tuberculous meningitis or osteomyelitis. **Reactivation** of upper lobe pulmonary disease may produce cavities that are similar to the disease among adults. Cavitary and endobronchial lymph node involvement are highly infectious, in contrast to the much less contagious nature of the hypersensitivity reaction noted in primary pulmonary disease.

Aspiration

Inhaling food, mouth or gastric secretions, or foreign bodies into the tracheobronchial tree causes acute, recurrent, or chronic cough. Interference with normal swallowing disrupts the coordination of swallowing and breathing that prevents aspiration. Structural causes of disordered swallowing include esophageal atresia (in neonates), strictures, webs, or congenital stenoses. Mediastinal lesions (tumors, lymph nodes), including vascular rings, may compromise the esophageal lumen and esophageal peristalsis, increasing the likelihood of aspiration. Functional disorders include central nervous system dysfunction or immaturity, dysautonomia, achalasia, and diffuse esophageal spasm. Prior neck surgery, including tracheostomy, may alter normal swallowing. Tracheoesophageal fistula and laryngeal clefts are congenital malformations with direct physical connections between the tracheobronchial tree and the upper gastrointestinal tract; thus oral contents enter the lungs directly.

Making the diagnosis of aspiration as the cause of cough may be difficult. Barium contrast studies during swallowing may help characterize these disorders if barium enters the trachea. Because most patients aspirate sporadically, a normal barium swallow does not rule out aspiration. Radionuclide studies can be helpful if ingested radiolabeled milk or formula is demonstrated over the lung fields at several-hour intervals after the meal. Bronchoscopy and bronchoalveolar lavage that recover large numbers of lipid-laden macrophages suggest that aspiration has taken place; however, the finding is neither sensitive nor specific for aspiration.

Treatment depends largely on the cause of aspiration. Because many patients who aspirate do so because of lack of neurologic control of swallowing and breathing, it is often difficult to prevent. Even gastrostomy feedings cannot prevent aspiration of oral secretions. In extreme cases, tracheostomy with ligation of the proximal trachea has been employed. This not only prevents aspiration but also prevents phonation, and it must be considered only in unusual situations. Aspiration pneumonia is often treated with intravenous ampicillin-sulbactam or clindamycin to cover mouth flora of predominant anaerobes. Additional coverage against gram-negative organisms may be indicated if the aspiration is nosocomial.

Foreign Body

Any child with cough of abrupt onset should be suspected of having inhaled a foreign body into the airway. Toddlers, who by nature put all types of things into their mouths and who have incompletely matured swallowing and airway protective mechanisms, are at high risk. Infants with toddlers or young children in the household who may "feed" the baby are also at risk. In older children, it is usually possible to obtain an accurate history of the aspiration event. These events are described as choking, gagging, and coughing while something (e.g., peanuts, popcorn, small toys, sunflower seeds) is in the mouth. The child may come to the physician with cough and wheeze immediately after the event, with a clear history and a straightforward diagnosis. In many children with a tracheobronchial foreign body, however, the initial episode is not recognized; these children may not come to medical attention for days, weeks, or even months. The initial episode may be followed by a relatively symptom-free period lasting days or even weeks, until infection develops behind an obstructed segmental or lobar bronchus. At this point, cough, perhaps with hemoptysis, with or without wheeze, recurs.

On physical examination early after an aspiration episode, there is cough, wheeze, or both, often with asymmetry of auscultatory findings. There may be locally diminished breath sounds. Later, localized wheeze or crackles may be detected. The triad of wheezing, coughing, and decreased breath sounds is present in fewer than 50% of patients. The presence of laryngotracheal foreign bodies often manifests with stridor, retractions, aphonia, cough, and normal radiographs.

Chest radiographs may be normal in 15% of patients with intrathoracic foreign bodies but should be obtained in both inspiration and expiration because in some cases the only abnormality is unilateral or unilobar air trapping, which is occasionally more clearly identified with an expiratory radiograph. In this view, an overdistended lung that had appeared normal on the inspiratory view does not empty, but the normal, unobstructed lung empties normally. This phenomenon causes a shift of the mediastinum toward the emptying lung, away from the side with the obstructing foreign body (Fig. 2.9). In other patients, localized infiltrate or atelectasis may be present behind the obstructing object. In a few patients, it may be possible to identify the foreign body itself; nonetheless, most inhaled food particles are not radiopaque and cannot be seen on radiographs. Aspiration is usually unilateral (80%); 50-60% of the objects are in the right lung (the lobe depends on body position—supine versus standing—but is often the right middle lobe). The definitive diagnostic and therapeutic maneuver is bronchoscopy; either the flexible or rigid open-tube bronchoscope enables direct visualization of the object; the rigid instrument also enables its removal.

Gastroesophageal Reflux

GER is a common cause of cough in all age groups (see Chapter 12). The typical patient is an infant in the first 6 months of life who spits up small amounts of milk frequently after feedings. This "regurgitant reflux" most commonly resolves by 1 year of age. However, many toddlers and children continue to have reflux, although it may be "silent" or nonregurgitant (without spitting up).

In most people with GER, it is merely a nuisance or not noticed. In some there are sequelae, and this condition is designated gastroesophageal reflux disease (GERD). One manifestation is cough; the mechanisms for the cough are not fully understood. Aspiration of refluxed material is one mechanism for cough but is probably not very common in neurologically intact children. A major mechanism for GERD with cough is mediated by vagal esophagobronchial reflexes (bronchoconstriction), stimulated by acid in the esophagus. Whether acid in the esophagus is sufficient stimulus to cause bronchoconstriction by itself or whether it merely heightens bronchial reactivity to other stimuli is not yet clear. Many children with reactive airways disease have cough or wheeze that is difficult to control until their concurrent GER is also treated. Many episodes of cough caused by GERD occur in children with asthma that is difficult to control.

(See *Nelson Textbook of Pediatrics*, p. 1787.)

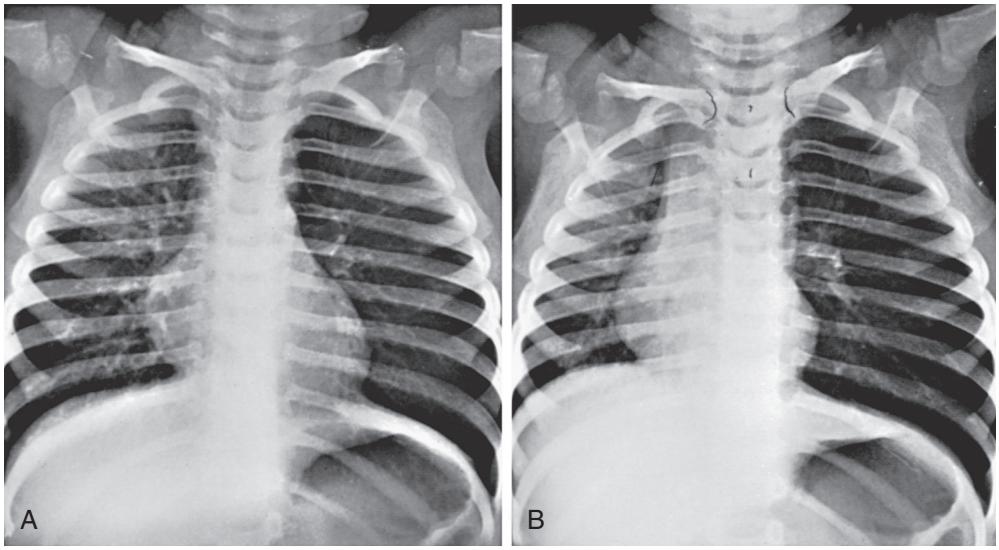


FIGURE 2.9 *A,* Normal inspiratory chest radiograph in a toddler with a peanut fragment in the left main bronchus. *B,* Expiratory radiograph of the same child showing the classic air trapping on the involved side. (From Schroeder JW Jr, Holinger LD. Foreign bodies in the airway. In: Kliegman RM, Stanton BF, St Geme JW III, Schor N, eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:2040, Fig. 387.2.)

The diagnosis of GERD must also be considered in the child with chronic or recurrent cough with no other obvious explanation. The child who coughs after meals or at night, when the supine position may provoke GER, should be evaluated for GER. If GER is confirmed, the next step is a therapeutic trial of antireflux therapy.

Treatment in a child whose cough is related to GER may be accomplished by treating the reflux (see Chapter 12) or by a combination of antireflux and antiasthma treatment (see Chapter 3). On occasion, the cough may be abolished by stopping all antiasthma medications. In such cases, the cough was a manifestation of reactive airways with esophageal acidification as the trigger for bronchospasm; the esophageal acidification was caused by the bronchodilator effects on the lower esophageal sphincter.

TABLE 2.15. Asthma as a Cause of Cough: History

Any age (even infants)
Coexistence of allergy increases likelihood, but absence of allergy does not decrease likelihood
Wheeze need not be present
↑Cough with upper respiratory infections
↑Cough with (and especially after) exercise
↑Cough with hard laughing or crying
↑Cough with exposure to cold
↑Cough with exposure to cigarette smoke
Usually a history of dramatic response to inhaled β-agonists

Asthma

Cough is frequently the sole or most prominent manifestation of asthma; wheezing may be entirely absent. In fact, asthma is almost certainly the most common cause of recurrent and chronic cough in childhood (see Chapter 3). Some of the features that characterize the cough of a child with asthma are listed in Table 2.15. Treatment for asthma manifesting as cough is the same as the treatment for asthma.

Cystic Fibrosis

Cystic fibrosis (CF) is a common cause of recurrent or chronic cough in infancy and childhood. CF occurs in 1 in 2000-3000 live births among white persons, is far less common among African Americans (1 in 15,000), and is rare among Native Americans and Asians. Early diagnosis improves the prognosis for untreated CF; if untreated, many patients die in infancy or early childhood. With current state-of-the-art care, median length of survival is upper 30s.

CF is a genetic disorder, inherited as an autosomal recessive trait. The CF gene is on the long arm of chromosome 7; more than 1900 mutations have been identified at the CF locus. Of these mutations, one (ΔF508, indicating a deletion, Δ, of a single phenylalanine, F, at position 508 of the protein product) is the most common, responsible for 70-75% of all CF chromosomes. The mutation affects the gene's protein product, termed cystic fibrosis transmembrane regulator (CFTR), which acts as a chloride channel and affects other aspects of membrane transport of ions and water. Not all the consequences of the defective gene and protein have been determined. In general, however, the defective gene product results in the long-observed clinical manifestations of the disease, including thick, viscid mucus in the tracheobronchial tree, leading to purulent bronchiolitis and bronchitis with subsequent bronchiectasis, pulmonary fibrosis, and respiratory failure; pancreatic duct obstruction, leading to pancreatic insufficiency with steatorrhea and failure to thrive; and abnormally high sweat chloride and sodium concentrations. The airway disease in CF is characterized by infection, inflammation, and endobronchial obstruction. The infection begins with *S. aureus*, *H. influenzae*, *Escherichia coli*, *Klebsiella* species, or combinations of these organisms but eventually is dominated by nonmucoid or mucoid *Pseudomonas aeruginosa*. Other organisms, such as *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, *Alcaligenes xylosoxidans*, *Aspergillus fumigatus*, or nontuberculous mycobacteria may also appear; their significance remains undetermined. In some patients, *B. cepacia* has been associated with rapid deterioration and death, and in others, *Aspergillus* species has caused allergic bronchopulmonary aspergillosis (ABPA). The airway inflammation in all patients with CF appears to be the result of toxic substances, including elastase, released by neutrophils as they respond

to the endobronchial infection and by similar enzymes released by the invading organisms.

CF may manifest at birth with meconium ileus (10-15% of patients), or later, with steatorrhea and failure to thrive despite a voracious appetite, in an apparent effort to make up for the calories that are lost in the stool (see Chapter 11). The most common presenting symptom is cough, which may appear within the first weeks of life or may be delayed for decades. The cough can be dry, productive, or paroxysmal. Cough may respond to antibiotics or perhaps steroids, but it is less likely to improve with bronchodilators (see Tables 2.3 and 2.5). Although CF is a genetic disease, there is often no family history. Furthermore, in atypical cases, patients may not have pancreatic insufficiency (~10% of patients) and thus may not demonstrate steatorrhea and failure to thrive. In addition, malabsorption may not be evident in the neonatal period.

There is no such thing as a child who looks "too good" to have CF; common abnormalities found on physical examination are noted in Table 2.16. One of the most important physical findings is digital clubbing. In most patients with CF, clubbing develops within the first few years of life. Although the list of conditions associated with digital clubbing (Table 2.17) is long, they are less common than CF, or the incidence of digital clubbing with these conditions is low. There is some relationship between the degree of pulmonary disease severity and the degree of digital clubbing. A child who has had years of severe respiratory symptoms without digital clubbing is not likely to have CF.

The diagnosis is confirmed by a positive sweat test or confirming the presence of two CF mutations on chromosome 7. The sweat test, if not performed correctly in a laboratory with extensive experience with the technique (as, for example, in an accredited CF center), yields many false-positive and false-negative results. The proper technique is to use quantitative analysis of the concentration of chloride in the sweat produced after pilocarpine iontophoretic stimulation. Chloride concentrations higher than 60 mmol/L are considered positive, and those lower than 40 mmol/L are negative (normal). Healthy adults have slightly higher sweat chloride concentrations than do children, but the same guidelines hold for positive tests in adults. The non-CF conditions yielding elevated sweat chloride concentrations are listed in Table 2.18. False-negative results of sweat tests can be seen in CF children presenting with edema or hypoproteinemia and in samples from children with an inadequate sweat rate. Sweat testing can be performed at any age. Newborns within the first few weeks of life may not produce a large enough volume of sweat to analyze (75 mg minimum), but in those who do (the majority), the results are accurate. Indications for sweat testing are noted in Table 2.19.

In patients for whom sweat testing is difficult (e.g., because of distance from an experienced laboratory, small infants who have not produced enough sweat, patients with extreme dermatitis, or patients with intermediate-range sweat chloride concentrations), DNA mutation testing can be useful. Demonstration of two known CF mutations confirms the diagnosis. Finding one or no known mutation makes the diagnosis less likely but is not exclusive, inasmuch as there are patients

TABLE 2.16 Physical Examination Features of Cystic Fibrosis

General
Low weight for height (>50% of patients)
Head, eyes, ears, nose, and throat
Nasal polyps (20%)
Chest
Cough
Barrel chest (↑anteroposterior diameter)
Intercostal, suprasternal retractions
Crackles, especially upper lobes
Wheeze
Abdomen
Hepatomegaly (10%)
Right lower quadrant fecal mass (5-10%)
Extremities
Digital clubbing (80%)
Reproductive tract
Bilateral atresia or absence of vas deferens (>95% of males)

TABLE 2.17 Causes of Digital Clubbing in Children

Pulmonary
- Cystic fibrosis ++
- Non–cystic fibrosis bronchiectasis +
- Ciliary dyskinesia
- Bronchiolitis obliterans
- Interstitial lung diseases
- Empyema
- Lung abscess
- Malignancy
- Tuberculosis
- Pulmonary arteriovenous fistula

Cardiac
- Cyanotic congenital heart disease ++
- Bacterial endocarditis +
- Chronic congestive heart failure

Gastrointestinal
- Crohn disease
- Ulcerative colitis
- Celiac disease +
- Severe gastrointestinal hemorrhage
- Small bowel lymphoma
- Multiple polyposis

Hepatic
- Biliary cirrhosis
- Chronic active hepatitis

Hematologic
- Thalassemia
- Congenital methemoglobinemia

Miscellaneous
- Familial
- Thyroid deficiency
- Thyrotoxicosis
- Chronic pyelonephritis
- Heavy metal poisoning
- Scleroderma
- Lymphoid granulomatosis
- Hodgkin disease
- Human immunodeficiency virus

++, very common cause of digital clubbing; +, common cause of digital clubbing.

TABLE 2.18 Conditions Other Than Cystic Fibrosis with Elevated Sweat Chloride

Adrenal insufficiency (untreated)
Ectodermal dysplasia
Autonomic dysfunction
Hypothyroidism
Malnutrition, including psychosocial dwarfism
Mucopolysaccharidosis
Glycogen storage disease (type I)
Fucosidosis
Hereditary nephrogenic diabetes insipidus
Mauriac syndrome
Pseudohypoaldosteronism
Familial cholestasis
Nephrosis with edema

TABLE 2.19 Indications for Sweat Testing

Pulmonary Indications

- Chronic or recurrent cough
- Chronic or recurrent pneumonia (especially RUL)
- Recurrent bronchiolitis
- Atelectasis
- Hemoptysis
- Staphylococcal pneumonia
- *Pseudomonas aeruginosa* in the respiratory tract (in the absence of such circumstances as tracheostomy or prolonged intubation)
- Mucoid *P. aeruginosa* in the respiratory tract

Gastrointestinal Indications

- Meconium ileus
- Neonatal intestinal obstruction (meconium plug, atresia)
- Steatorrhea, malabsorption
- Hepatic cirrhosis in childhood (including any manifestations such as esophageal varices or portal hypertension)
- Pancreatitis
- Rectal prolapse
- Vitamin K deficiency states (hypoprothrombinemia)

Miscellaneous Indications

- Digital clubbing
- Failure to thrive
- Family history of cystic fibrosis (sibling or cousin)
- Salty taste when kissed; salt crystals on skin after evaporation of sweat
- Heat prostration, especially under seemingly inappropriate circumstances
- Hyponatremic hypochloremic alkalosis in infants
- Nasal polyps
- Pansinusitis
- Aspermia

RUL, right upper lobe.
From Kercsmar CM. The respiratory system. In: Behrman RE, Kliegman RM, eds. *Nelson Essentials of Pediatrics*. 2nd ed. Philadelphia: WB Saunders; 1994:451.

with not-yet-characterized mutations. Furthermore, commercial laboratories do not identify all of the mutations.

Recovery of mucoid *Pseudomonas aeruginosa* from respiratory tract secretions is strongly suggestive of CF. Similarly pansinusitis is nearly universal among CF patients but is quite uncommon in other children. All 50 states are using a neonatal screen for CF. The CF screen assays include measuring serum immunoreactive trypsinogen (IRT) levels, which are elevated in most infants with CF for the first several weeks of life, and DNA analysis for CFTR mutations. The main drawback of the IRT assay is that it has relatively poor specificity; as many as 90% of the positive results on the initial screen are false-positive results. If an infant's IRT screen is positive, the test should be repeated, or DNA analysis for the 23 most common CFTR mutations should be performed. At 2-3 weeks of age, which is when the IRT is repeated, the false-positive rate has fallen dramatically but is still quite high (25%). Definitive testing with the sweat chloride test needs to be carried out on infants with positive screening results.

Laboratory data that may support the diagnosis of CF include low levels of fecal elastase. This suggests pancreatic insufficiency, which occurs most commonly in CF but can be seen in other diseases. The test is not perfect for confirming CF as some CF patients have sufficient pancreatic function. Pulmonary function test findings with an obstructive pattern, incompletely responsive to bronchodilators, are consistent with CF but, of course, can be seen in other conditions. Conversely, some patients with CF also have asthma and may show a marked response to a bronchodilator. Complications of CF that should suggest the diagnosis are noted in Table 2.20.

The treatment of patients with CF requires a comprehensive approach, best performed in, or in conjunction with, an approved CF center. Several studies have shown survival to be significantly better in center-based care than in non–center-based care.

Anatomic Abnormalities

Table 2.21 lists the main anatomic abnormalities that cause cough.

Vascular rings and slings. Vascular rings and slings are often associated with inspiratory stridor because the abnormal vessels compress central airways, most commonly the trachea (see Chapter 3). The patient may also have difficulty swallowing if the esophagus is compressed.

The diagnosis may be suspected from plain radiographs of the chest, especially those showing tracheal deviation and a right-sided aortic arch. Further support for the diagnosis can be found at bronchoscopy (which shows extrinsic compression of the trachea or a main stem bronchus), barium esophagram (which shows esophageal compression), or both. The definitive diagnosis is made with computed tomographic angiography or magnetic resonance angiography. Treatment is surgical.

Pulmonary sequestration. Pulmonary sequestration is relatively unusual, occurring in 1 in 60,000 children. It occurs most commonly in the left lower lobe and can manifest in several ways (Fig. 2.10; see also Table 2.21). The chest radiograph usually shows a density in the left lower lobe; this density often appears to contain cysts (Fig. 2.11). The feature distinguishing a sequestered lobe from a complicated pneumonia is that the blood supply arises from the aorta and not the pulmonary circulation. Doppler ultrasonography and CT angiography provide the definitive diagnosis. The treatment is surgical removal.

Congenital pulmonary airway malformation (CPAM). Congenital pulmonary airway malformations (formerly known as congenital cystadenomatoid malformations or CCAMs) are rare. They manifest in infancy with respiratory distress in nearly 50% of cases; the other half may manifest as cough with recurrent infection later in childhood or even adulthood. The chest radiograph reveals multiple cysts, separated by dense areas. Chest CT scans can help make the diagnosis with near certainty. Surgical removal is the treatment of choice if the lesion is symptomatic.

Congenital lobar emphysema. Congenital lobar emphysema occurs in one of 50,000 live births. It can manifest dramatically with

TABLE 2.20 Complications of Cystic Fibrosis

Pulmonary Complications
- Bronchiectasis, bronchitis, bronchiolitis, pneumonia
- Atelectasis
- Hemoptysis
- Pneumothorax
- Nasal polyps
- Sinusitis
- Reactive airways disease
- Cor pulmonale
- Respiratory failure
- Mucoid impaction of the bronchi
- Allergic bronchopulmonary aspergillosis

Gastrointestinal Complications
- Meconium ileus
- Meconium peritonitis
- Distal intestinal obstruction syndrome (meconium ileus equivalent) (nonneonatal obstruction)
- Rectal prolapse
- Intussusception
- Volvulus
- Appendicitis
- Intestinal atresia
- Pancreatitis
- Biliary cirrhosis (portal hypertension: esophageal varices, hypersplenism)
- Neonatal obstructive jaundice
- Hepatic steatosis
- Gastroesophageal reflux
- Cholelithiasis
- Inguinal hernia
- Growth failure
- Vitamin deficiency states (vitamins A, D, E, K)
- Insulin deficiency, symptomatic hyperglycemia, diabetes

Other Complications
- Infertility
- Edema/hypoproteinemia
- Dehydration/heat exhaustion
- Hypertrophic osteoarthropathy/arthritis
- Delayed puberty
- Amyloidosis

From Kercsmar CM. The respiratory system. In: Behrman RE, Kliegman RM, eds. *Nelson Essentials of Pediatrics*. 2nd ed. Philadelphia: WB Saunders; 1994:451.

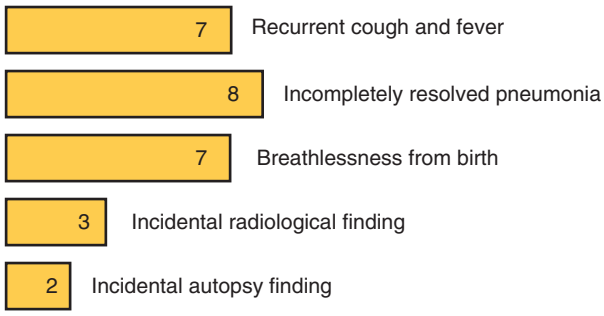


FIGURE 2.10 Different modes of presentation of sequestered lobe and number of children with each problem. (From Phelan PD, Olinsky A, eds. *Respiratory Illness in Children*. Oxford: Wiley-Blackwell; 1994.)

respiratory distress in the neonatal period or later (Fig. 2.12), with cough or wheeze, or as an incidental finding on a chest radiograph. Radiography shows localized overinflation, often dramatic, with compression of adjacent lung tissue and occasionally atelectasis of the contralateral lung because of mediastinal shift away from the involved side. The appearance on chest CT scan is typical, with widely spaced blood vessels (as opposed to congenital cysts, for example, which have no blood vessels within the overinflated area). Bronchoscopy can document patent bronchi and should probably be performed in older children in whom congenital lobar emphysema can be confused with acquired overinflation of a lobe as the result of bronchial obstruction, as with a foreign body. If the disease is symptomatic, treatment is surgical.

Tracheoesophageal fistula. Tracheoesophageal fistula is common, with an incidence of about one in 5000 live births. Of these fistulas, the large majority (85%) are associated with esophageal atresia; only 3% are the isolated, H-type fistula (a patent esophagus with fistulous tract connecting the esophagus and trachea). A neonate with esophageal atresia experiences respiratory distress, excessive drooling, and choking and gagging with feeding. The H-type fistula causes more subtle signs and may be undiagnosed for months or even years. The child may have only intermittent feeding trouble, especially with liquids. There may be recurrent lower respiratory tract infections.

The diagnosis is not challenging in the infant with esophageal atresia; a nasogastric tube cannot be passed, and swallowed barium outlines the trachea. In the older child with H-type fistula, a barium esophagogram may or may not reveal the fistula. Bronchoscopy and esophagoscopy should permit direct visualization of the fistula; however, the opening may be hidden in mucosal folds.

Treatment is surgical. Many children born with tracheoesophageal fistula have recurrent cough and lower respiratory tract infection for many years, even after successful surgical correction. The cough is characteristically the harsh cough of tracheomalacia, which is present at the site of the fistula. The infections result from several causes, including GER, with or without aspiration, and altered mucociliary transport. Treatment involves regular chest physiotherapy and early and aggressive use of antibiotics whenever there is evidence of increased pulmonary symptoms.

Hemangiomas. Hemangiomas may be present within the airway and can cause cough, rarely with hemoptysis. Stridor (if the hemangioma is high in the airway) and respiratory distress (if the hemangioma is large) may also occur. In rare cases, with very large airway hemangiomas, there may even be dysphagia from extrinsic compression. Children with cutaneous hemangiomas in the mandibular or neck region ("beard" distribution) are at risk for an airway hemangioma.

The diagnosis is made with bronchoscopy. These lesions may resolve spontaneously over the first year or so. However, if they cause symptoms, it may not be advisable or possible to wait for them to resolve.

Many airway hemangiomas regress with steroid treatment; however, due to the side effect profile, propranolol is considered the treatment of choice. Asthma is a contraindication for propranolol treatment due to its beta-blocking effect and potential to worsen asthma. Laser ablation may be indicated in some refractory cases that do not respond to first-line treatment. In the case of a large subglottic hemangioma, a tracheostomy is performed and maintained until the mass regresses.

Enlarged lymph nodes. Enlarged mediastinal lymph nodes, such as those resulting from tuberculosis, leukemia, other hematologic malignancies, or other infections, are occasionally a cause of cough in children (Table 2.22; see also Table 2.21). These nodes are usually seen on

TABLE 2.21 Anatomic Abnormalities Causing Cough

Condition	Other Symptoms	Diagnostic Evidence	Treatment
Vascular ring/sling	Stridor; dysphagia, emesis	Radiographic: deviated trachea, right-sided arch Barium swallow: esophageal indentation Bronchoscopy: extrinsic compression MRI/angiography: definitive	Surgical
Pulmonary sequestration	Fever, dyspnea; may be asymptomatic	Radiographic: left lower lobe density, usually with cysts Angiography: blood supply from aorta	Surgical
Congenital pulmonary airway malformation	Respiratory distress; recurrent infection	Radiographic: multiple cysts alternating with solid areas	Surgical
Congenital lobar emphysema	Respiratory distress; wheeze; may be asymptomatic	Radiographic: localized overinflation, other lobes (even other lung) collapsed Bronchoscopy to rule out foreign body	Surgical (if symptomatic)
Tracheoesophageal fistula, cleft	Gagging, choking with feeds; respiratory distress (especially with esophageal atresia)	Barium esophagram: barium in tracheobronchial tree Bronchoscopy: direct visualization	Surgical
Airway hemangioma	Stridor; wheeze; dysphagia; hemoptysis	Bronchoscopy	Propranolol, steroids; laser; occasionally tracheostomy required
Mediastinal lymph nodes	Stridor	Radiographic: hilar nodes; compressed tracheal air column	Treat cause
Bronchial stenosis	Wheeze; recurrent pneumonia	Bronchoscopy	Balloon dilatation; surgery
Bronchogenic cysts	Wheeze, stridor	Radiographic: hyperinflation of one lung; visible mass (carina, posterior mediastinum) Bronchoscopy: extrinsic compression CT: often definitive	Surgical

CT, computed tomography; MRI, magnetic resonance imaging.

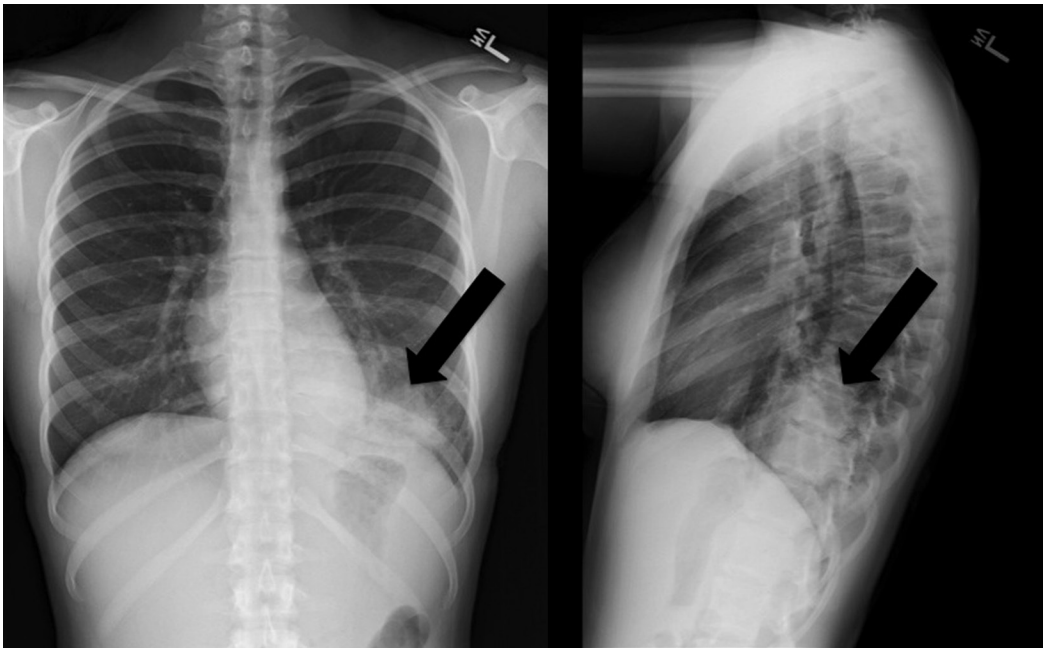


FIGURE 2.11 Anterior-posterior and lateral chest radiographs showing a left lower lobe pulmonary sequestration *(bold arrow)* in a 15-year-old girl.

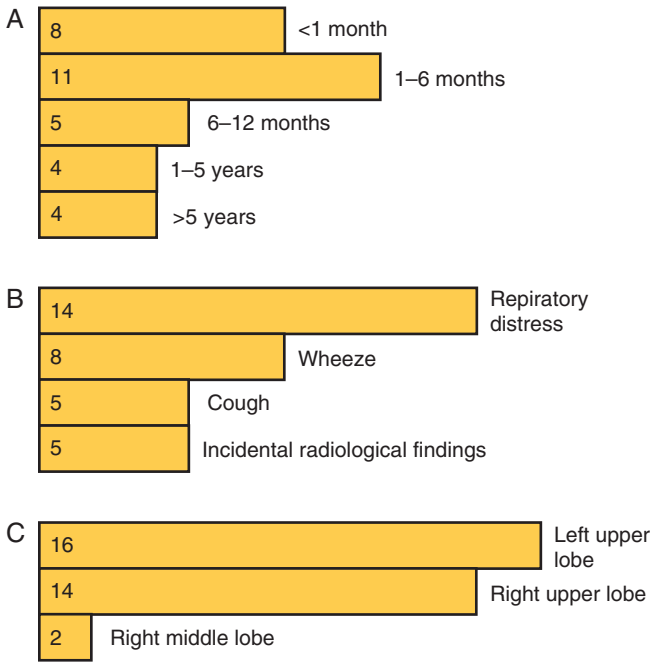


FIGURE 2.12 Different modes of presentation of congenital lobar emphysema. *A,* Age at presentation. *B,* Symptoms at presentation. *C,* Involved lobe. Numbers refer to the number of children in each category. (From Phelan PD, Olinsky A, eds. *Respiratory Illness in Children.* Oxford: Wiley-Blackwell; 1994.)

TABLE 2.22 Intrathoracic Mass Lesions

Anterior Mediastinum
- Thymus tumor
- T-cell lymphoma
- Teratoma
- Thyroid lesions
- Pericardial cyst
- Hemangioma
- Lymphangioma

Hilar–Middle Mediastinum
- Tuberculosis
- Histoplasmosis
- Coccidiomycosis
- Acute lymphocytic leukemia/lymphoma
- Hodgkin disease
- Sarcoidosis
- Hiatal hernia
- Pericardial cyst
- Bronchogenic or enteric cyst

Posterior Mediastinum
- Neuroblastoma/ganglioneuroma
- Other neural tumors
- Neuroenteric lesions
- Esophageal lesions (duplication)
- Vertebral osteomyelitis
- Diaphragmatic hernia
- Meningocele
- Aortic aneurysm

plain radiographs of the chest. The x-ray study or bronchoscopy may show extrinsic compression of the trachea. Treatment is directed at the underlying cause.

Bronchial stenosis. Occasionally bronchial stenosis, either congenital or acquired, may cause cough. The diagnosis is made with bronchoscopy, after suspicion has been raised by the child having recurrent infiltrates in the same lobe, especially with localized wheeze.

Treatment may be difficult. In some cases, endoscopic balloon dilatation or airway stent placement is successful; in others, surgical resection of stenotic areas may be necessary.

Bronchogenic cysts. Bronchogenic cysts are uncommon, but they can cause cough, wheeze, stridor, or any combination of these. They may also cause recurrent or persistent pneumonia if they block a bronchus sufficiently to interfere with normal drainage of the segment or lobe. Radiography may show localized overinflation if the cyst causes a ball-valve–type obstruction. The cyst itself may or may not be seen on plain radiographs. Bronchoscopy reveals extrinsic compression of the airway. CT studies often definitively show the lesion. Surgical removal is indicated.

Habit (Psychogenic) Cough

On occasion, a school-aged child may develop a cough that lasts for weeks, often after a fairly typical cold. This cough occurs only during wakefulness, never during sleep. In many cases, the cough is harsh and foghorn-like. It often disrupts the classroom, and the child is asked to leave. The child is otherwise well and may seem rather unbothered by the spectacle created. There is no response to medications. It seems that this type of cough, previously termed "psychogenic," or "psychogenic cough tic," but now called habit cough, has given the child valuable attention. This attention then serves as the sustaining force, and the cough persists beyond the original airway inflammation. In the small minority of cases, there may be deep-seated emotional problems of which the cough is the physical expression.

During the history or physical examination, the child appears completely well and may cough when attention is drawn to the child or when the word "cough" is uttered. The physical examination findings are otherwise completely normal, as are laboratory values. Because this may occur in any child, evidence of mild reactive airways disease (history or pulmonary function testing) does not rule out the diagnosis. Once a physician has seen a child with this problem, it is usually possible to make the diagnosis with certainty on entering the examining room or, indeed, from the hallway outside the room.

Treatment can prove more difficult. The child and family should be reassured that the child is well. Suggestion therapy empowers and encourages the patient to suppress the cough for short increments of time. The goal is for them to gradually lengthen the cough-free intervals. Speech therapy may be helpful (Table 2.23).

TABLE 2.23 Speech Therapy Techniques for Treating Habit Cough

Increase abdominal breathing
Reduce muscle tension in neck, chest, and shoulders
Interrupt early cough sensation by swallowing
Substitute gentle cough for racking cough
Interrupt cough sequence with diaphragm breathing and tightly pursed lips
Increase the patient's awareness of initial sensations that would trigger cough

Other Causes of Cough

Table 2.24 lists several miscellaneous causes of cough in children.

Bronchiectasis. Bronchiectasis is defined as an abnormal dilation of the subsegmental bronchi and is usually associated with chronic cough and purulent sputum production. It occasionally occurs after severe pneumonias (bacterial or viral); it eventually develops in nearly all patients with CF. Diagnosis may, on occasion, be made with plain-chest radiographs, but high-resolution CT scanning is the diagnostic procedure of choice. Treatment of bronchiectasis consists of airway clearance with chest physiotherapy with postural drainage or high-frequency chest wall oscillation, occasionally bronchodilators and mucolytic agents, and antibiotic therapy during exacerbations. Surgical resection may be indicated in cases that are progressive and localized when medical therapy has failed. The prognosis of bronchiectasis depends on the underlying cause. CF-associated bronchiectasis is a major cause of CF-related morbidity and mortality; whereas, non-CF bronchiectasis may remain stable or even regress with therapy.

Ciliary dyskinesia. Conditions in which the cilia do not function properly (immotile cilia or ciliary dyskinesia) lead to cough, usually because infection (and bronchiectasis) occurs in the absence of normal mucociliary transport. Treatment is similar to that for CF, with regular chest physiotherapy and frequent and aggressive use of antibiotics at the first sign of airways infection, most commonly increased cough.

Interstitial lung disease. Interstitial lung diseases are now classified based on those that occur during the neonatal period and those that are not as prevalent in infancy. Interstitial lung diseases that manifest with cough include aspiration (chronic and recurrent) pneumonitis, hypersensitivity pneumonitis, bronchiolitis obliterans, and cryptogenic organizing pneumonia (formerly known as bronchiolitis obliterans organizing pneumonia or BOOP). Lung biopsy may be required for a diagnosis.

Pulmonary hemosiderosis. Pulmonary hemosiderosis is a rare, and often fatal, condition of bleeding into the lung that can manifest with cough. If sputum is produced, it is often frothy and blood-tinged. There may be frank hemoptysis. However, the cough may be nonproductive, or the sputum may be swallowed. Some cases are associated with milk hypersensitivity (Heiner syndrome), and affected children may have upper airway obstruction. Some cases are associated with collagen vascular disorders. Radiographs usually show diffuse fluffy infiltrates, and there is invariably iron deficiency anemia. The diagnosis is based on lung biopsy findings.

Tumors. Tumors causing cough are rare in childhood. Cough occurs because of bronchial blockage, either extrinsic or endobronchial (see Table 2.22). The diagnosis is usually made from bronchoscopy, chest CT, or both. Treatment depends on the cell type, but it usually involves at least some surgical removal. Chemotherapy or radiation may be used in some cases.

Tracheomalacia and bronchomalacia. Isolated tracheomalacia or bronchomalacia is uncommon but can cause cough in some children. The cough of tracheomalacia is typically harsh and brassy. Treatment is difficult but, fortunately, is seldom needed.

Spasmodic croup. Some children, usually preschoolers, may episodically awaken at night with stridor and a harsh, barking cough indistinguishable from that of viral croup. This entity is termed spasmodic croup and is of unclear origin. Viral and allergic causes have been postulated. GER may be the cause in some patients.

Treatment with cool mist or racemic epinephrine is effective in most patients. If GER is the underlying cause, antireflux treatment is beneficial.

Obliterative bronchiolitis. Obliterative bronchiolitis is very rare except in lung transplant recipients. In other instances, it may arise after adenovirus, measles, or influenza pneumonia; after exposure to certain toxins; or in other rare circumstances. Children may exhibit cough, respiratory distress, and exercise intolerance.

The diagnosis is suggested by the pulmonary function test or radiographic evidence of small airways obstruction; however, these findings are not always present. Not all chest radiographs show overinflated lungs, and not all pulmonary function tests show decreased small airways function.

The definitive diagnosis is histologic via open or transbronchial biopsy. No specific treatment is available. Most children with obliterative bronchiolitis recover, but many progress to chronic disability or death.

TABLE 2.24 Miscellaneous Causes of Cough in Children

Postnasal drip (?)	Cerumen impaction
Bronchiectasis	Irritation of external auditory canal
Ciliary dyskinesia	Obliterative bronchiolitis
Interstitial lung disease	Follicular bronchiolitis
Heart failure/pulmonary edema	Mediastinal disease (nodes, pneumomediastinum)
Pulmonary hemosiderosis	Nasal polyps
Drug-induced (see Table 2.4)	Hypersensitivity pneumonitis (extrinsic allergic alveolitis)
α_1-Antitrypsin deficiency	Thyroid lesions
Graft-versus-host disease	Subphrenic abscess
Bronchopulmonary dysplasia	Sarcoidosis
Tumor (bronchial adenoma, carcinoid; mediastinal)	Anaphylaxis
Alveolar proteinosis	Pulmonary embolism
Tracheomalacia, bronchomalacia	Lung contusion
Spasmodic croup	

Hemoptysis

The child who coughs out blood or bloody mucus presents special diagnostic and therapeutic challenges. Although hemoptysis is relatively uncommon in children, particularly among those without CF, many conditions can cause it (Table 2.25). It is important (and not always easy) to distinguish cases in which blood has originated in the tracheobronchial tree (true hemoptysis), the nose (epistaxis), and the gastrointestinal tract (hematemesis). Table 2.26 gives some guidelines to help localize sites of origin of blood that has been reported or suspected as hemoptysis. None of these guidelines is foolproof, partly because blood that has originated in one of these sites might well end up in another before being expelled from the body; for instance, blood from the nose can be swallowed and vomited or aspirated and expectorated.

Infection is among the most common causes of hemoptysis. Lung abscess and tuberculosis need to be considered. Bronchiectasis can readily cause erosion into bronchial vessels, often made tortuous by years of local inflammation, and produce hemoptysis. Other infectious causes are less common and include necrotizing pneumonias and fungal and parasitic lung invasion.

Foreign bodies in the airway can cause hemoptysis by direct irritation, by erosion of airway mucosa, or by secondary infection.

Pulmonary embolus is uncommon in children and adolescents, but it needs to be considered in the differential diagnosis of an adolescent with hemoptysis of unclear origin. Clues to the diagnosis of pulmonary embolus include a positive family history, severe dyspnea, chest pain, hypoxia, a normal chest radiograph, an accentuated second

TABLE 2.25 Hemoptysis: Differential Diagnosis

Infection	Lung abscess
	Pneumonia*
	Tuberculosis
	Bronchiectasis* (cystic fibrosis, ciliary dyskinesia)
	Necrotizing pneumonia
	Fungus (especially allergic bronchopulmonary aspergillosis or mucormycosis)
	Parasite
	Herpes simplex
Foreign body	Retained
Congenital defect	Heart (various)
	Primary pulmonary hypertension
	Eisenmenger syndrome
	Arteriovenous malformation
	Telangiectasia (Osler-Weber-Rendu)
	Pulmonary sequestration
	Bronchogenic cyst
Autoimmune-inflammatory	Henoch-Schönlein purpura
	Goodpasture syndrome
	Systemic lupus erythematosus
	Sarcoidosis
	Granulomatosis with polyangiitis
Pulmonary hemosiderosis	Idiopathic or with milk allergy (Heiner syndrome)
Trauma	Contusion*
	Fractured trachea, bronchus
Iatrogenic	After surgery
	After transbronchial lung biopsy*
	After diagnostic lung puncture*
Tumors	Benign (neurogenic, hamartoma, hemangioma, carcinoid)
	Malignant (adenoma, bronchogenic carcinoma)
	Metastatic (Wilms tumor, osteosarcoma, sarcoma)
Pulmonary embolus	Cardiogenic
	Deep vein thrombosis
Other	Factitious
	Endometriosis
	Coagulopathy*
	Congestive heart failure
	After surfactant therapy in neonates
	Kernicterus
	Hyperammonemia
	Intracranial hemorrhage
	Epistaxis*
	Idiopathic

*A common cause of hemoptysis.

TABLE 2.26 Hemoptysis: Differentiating Sites of Origin of Blood

	Pulmonary	Gastrointestinal Tract	Nose
History	Cough, with or without gurgling in lung before episode	Nausea, vomiting, abdominal pain	With or without nosebleed dripping in back of throat
Physical	Cough; localized crackles or decreased breath sounds; digital clubbing	↑Liver, spleen, epigastric tenderness	Blood in nose

TABLE 2.27 Red Flags for Cough

If associated with severe, acute
Hemoptysis
Dyspnea
Hypoxemia
If associated with chronic
Failure to thrive
Steatorrhea
Decreased exercise tolerance
Digital clubbing
Persistence of
Cough for 6 weeks or more
Radiographic abnormality, especially if asymmetric
Failure to respond to empirical therapy
Antibiotics for presumed infection
Bronchodilators for presumed reactive airways

heart sound, an abnormal compression ultrasonographic study of the leg veins, a positive Homans sign, a positive helical CT scan, and a high-probability lung ventilation-perfusion scan.

The diagnosis of several causes of hemoptysis is straightforward. For example, hemoptysis that occurs immediately after a surgical or invasive diagnostic procedure in the chest should suggest an iatrogenic problem. The chest radiograph can help suggest lung abscess, pulmonary sequestration, bronchogenic cyst, or tumor. Chest CT can help with cases of arteriovenous malformations, and additional laboratory values can support the diagnosis of collagen vascular disease. Bronchoscopy can sometimes localize a bleeding site, identify a cause (e.g., a foreign body or endobronchial tumor), or recover an offending bacterial, fungal, or parasitic pathogen. In many instances, bronchoscopy does not help except by excluding some possibilities, because either no blood or blood throughout the tracheobronchial tree is found. Bronchial artery angiography may help to identify the involved vessel or vessels.

Treatment of hemoptysis depends on the underlying cause. It can be a terrifying symptom to children and their parents, and a calm, reassuring approach is essential. Because hemoptysis is seldom fatal in children, reassurance is usually warranted. Furthermore, hemoptysis most often resolves, and treatment of the bleeding itself is not often needed. What is required is treatment of the underlying cause of the hemoptysis, such as therapy for infection, removal of a foreign body, or control of collagen vascular disease. When death occurs from hemoptysis, it is more likely to be from suffocation than from exsanguination. In cases of massive bleeding, the rigid open-tube bronchoscope may help suction large amounts of blood while ventilating and keeping unaffected portions of lung clear of blood. Interventional radiologists treat as well as localize a bleeding site by injecting the offending vessel with occlusive substances (embolization). In extremely rare instances, emergency lobectomy may be indicated.

WHEN COUGH ITSELF IS A PROBLEM

Cough itself seldom necessitates specific treatment. Nonetheless, cough is not always completely benign (see Table 2.9). Most complications are uncommon, and most accompany only very severe cough, but some are serious enough to justify treatment of the cough itself.

Cough suppressants include codeine and hydrocodone (two narcotics) and dextromethorphan (a nonnarcotic D-isomer of the codeine analog of levorphanol). Such agents should be used only for severe cough that may produce significant complications (see Table 2.9). For most diseases, suppressing the cough offers no advantage. Disadvantages include narcotic addiction and loss of the protective cough reflex with subsequent mucous retention and possible superinfection. Demulcent preparations (sugar-containing, bland soothing agents or honey) temporarily suppress the cough response from pharyngeal sources, and decongestant-antihistamine combinations may reduce postnasal drip.

SUMMARY AND RED FLAGS

Cough is important because it is a symptom and sign of underlying disease that frequently merits treatment. In the acute setting, severe disease, including massive hemoptysis or profound dyspnea or hypoxemia, warrants immediate attention, rapid diagnosis, and rapid management. Certain chronic conditions, including those that suggest CF and those in which symptoms have persisted and interfere with a child's daily activities and quality of life, warrant further evaluation and treatment. Finally, a child whose cough fails to respond to what should have been reasonable treatment should be referred to a pulmonary specialist (Table 2.27).

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Cough

Black P. Evaluation of chronic or recurrent cough. In: Hilman BC, ed. *Pediatric Respiratory Disease: Diagnosis and Treatment*. Philadelphia: WB Saunders; 1993:143-154.

Chang A, Glomb WB. Guidelines for evaluating chronic cough in pediatrics. ACCP Evidence-based Clinical Practice Guidelines. *Chest*. 2006;129:260S-283S.

Shields MD, Bush A, Everard ML, et al. Recommendations for the assessment and management of cough in children. *Thorax*. 2008;63(suppl III):iii1-iii15.

Upper Respiratory Infection

Donnelly BW, McMillan JA, Weiner LB. Bacterial tracheitis: Report of eight new cases and review. *Rev Infect Dis*. 1990;12:729-735.

Heikkinen T, Jarvinen A. The common cold. *Lancet*. 2003;361:51-59.

Schaeffer MK, Shehab N, Cohen AL, et al. Adverse events from cough and cold medication in children. *Pediatrics [Internet]*. 2008;121:783-787.

Williams JW, Simel DL. Does this patient have sinusitis? Diagnosing acute sinusitis by history and physical examination. *JAMA*. 1993;270:1242-1246.

Pneumonia

American Academy of Pediatrics. Pertussis (whooping cough). In: Kimberlin DW, Brady MT, Jackson MA, et al., eds. *2015 Red Book: Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:608-621.

American Academy of Pediatrics. Tuberculosis. In: Kimberlin DW, Brady MT, Jackson MA, et al., eds. *2015 Red Book: Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:805-831.

Balfour-Lynn IM, Abrahamson E, Cohen G. BTS guidelines for the management of pleural infection in children. *Thorax*. 2005;60:i1-i21.

Bourke SJ. Chlamydial respiratory infections. *BMJ*. 1993;306:1219-1220.

Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: Clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;53:e25.

Brasfield DM, Stagno S, Whitley RJ, et al. Infant pneumonitis associated with cytomegalovirus, *Chlamydia*, *Pneumocystis*, and *Ureaplasma*: Follow-up. *Pediatrics*. 1987;79:76-83.

Gibson NA, Hollman AS, Paton JY. Value of radiological follow-up of childhood pneumonia. *BMJ*. 1993;307:117.

Harris M, Clark J, Coote N, et al. British Thoracic Society guidelines for the management of community acquired pneumonia in children: Update 2011. *Thorax*. 2011;66:ii1-ii23.

Hatzenbuehler LA, Starke JR. Tuberculosis *(Myconbacterium tuberculosis)*. In: Kliegman RM, ed. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:1445-1461.

McCracken GH Jr. Etiology and treatment of pneumonia. *Pediatr Infect Dis J*. 2000;19:373-377.

Meduri GU, Stein DS. Pulmonary manifestations of acquired immunodeficiency syndrome. *Clin Infect Dis*. 1992;14:98-113.

Mulholland EK, Simoes EAF, Costales MOD, et al. Standardized diagnosis of pneumonia in developing countries. *Pediatr Infect Dis*. 1992;11:77-81.

Onyango FE, Steinhoff MC, Wafula EM, et al. Hypoxaemia in young Kenyan children with acute lower respiratory infection. *BMJ*. 1993;306:612-614.

Perez-Velez CM, Marais BJ. Tuberculosis in children. *N Engl J Med*. 2012;367:348-361.

Ralston SL, Lieverthal AS, Meissner C, et al. Clinical practice guideline: The diagnosis, management, and prevention of bronchiolitis. *Pediatrics*. 2014;134:e1474-e1502.

Rubin BK. The evaluation of the child with recurrent chest infections. *Pediatr Infect Dis*. 1985;4:88-98.

Zhang L, Mendoza-Sassi RA, Wainwright C, et al. Nebulised hypertonic saline solution for acute bronchiolitis in infants. *Cochrane Database Syst Rev*. 2013;(31):CD006458.

Foreign Bodies

Black RE, Choi K-J, Syme WC. Bronchoscopic removal of aspirated foreign bodies in children. *Am J Surg*. 1984;148:778-781.

Friedman EM. Tracheobronchial foreign bodies. *Otolaryngol Clin North Am*. 2000;33:179-185.

Gay BB, Atkinson GO, Vanderzalm T, et al. Subglottic foreign bodies in pediatric patients. *Am J Dis Child*. 1986;140:165-168.

Puhakka H, Svedstrom E, Kero P, et al. Tracheobronchial foreign bodies. *Am J Dis Child*. 1989;143:543-545.

Cystic Fibrosis

Hamos A, Corey M. The cystic fibrosis genotype-phenotype consortium. Correlation between genotype and phenotype in patients with cystic fibrosis. *N Engl J Med*. 1993;329:1308-1316.

Hoffman LR, Ramsey BW. Cystic fibrosis therapeutics. The road ahead. *Chest*. 2013;143:207-213.

Kerem E, Reisman J, Corey M, et al. Wheezing in infants with cystic fibrosis: Clinical course, pulmonary function, and survival analysis. *Pediatrics*. 1992;90:703-706.

O'Sullivan BP, Freedman SD. Cystic fibrosis. *Lancet*. 2009;373:1891-1904.

Prasad SA, Tannenbaum EL, Mikelsons C. Physiotherapy in cystic fibrosis. *J R Soc Med*. 2000;93:27-36.

Ranasinha C, Assoufi B, Shak S, et al. Efficacy and safety of short-term administration of aerosolised recombinant human DNase I in adults with stable stage cystic fibrosis. *Lancet*. 1993;342:199-202.

Rosenstein BJ, Cutting GR. The diagnosis of cystic fibrosis: A consensus statement. Cystic Fibrosis Foundation Consensus Panel. *J Pediatr*. 1998;132:589-595.

Rubin BK. Emerging therapies for cystic fibrosis. *Chest*. 1999;115:1120-1126.

Taylor RFH, Gaya H, Hodson ME. *Pseudomonas cepacia*: Pulmonary infection in patients with cystic fibrosis. *Respir Med*. 1993;87:187-192.

Asthma

Agertoft L, Pederson S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med*. 2000;343:1064-1069.

Castro-Rodriguez JA, Holberg CJ, Wright AL, et al. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med*. 2000;162:1403-1406.

Palmer LJ, Rye PJ, Gibson NA, et al. Airway responsiveness in early infancy predicts asthma, lung function, and respiratory symptoms by school age. *Am J Respir Crit Care Med*. 2001;163:37-42.

Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: Asthma control and exacerbations. Standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med*. 2009;180:59-99.

Suissa S, Ernst T, Benayoun S, et al. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med*. 2000;343:332-336.

Hemoptysis

David M, Andrew M. Venous thromboembolic complications in children. *J Pediatr*. 1993;123:337-346.

Jean-Baptiste E. Clinical assessment and management of massive hemoptysis. *Crit Care Med*. 2000;28:1642-1647.

Jones DK, Davies RJ. Massive haemoptysis: Medical management will usually arrest the bleeding. *BMJ*. 1990;300:889-890.

Panitch HB, Schidlow DV. Pathogenesis and management of hemoptysis in children. *Int Pediatr*. 1989;4:241-244.

Respiratory Distress

Anjali Sharma

INTRODUCTION

The main function of the respiratory system is to supply oxygen to meet the body's demands and remove excess carbon dioxide. Many processes are involved in ensuring that this occurs, including ventilation (gas delivery to and from the lungs), perfusion (blood supply to the lungs) and diffusion (the exchange of gases along the alveoli). Respiratory distress arises when there is impaired air exchange that leads to decreased ventilation and oxygenation, and can be caused by problems in any of these pathways. It is essential to identify and treat the cause of respiratory distress to prevent respiratory failure, which ensues if the respiratory effort is inadequate to provide appropriate tissue oxygenation and maintenance of blood pH.

Respiratory distress occurs for a variety of reasons and with many levels of severity. It can be caused by a change in respiratory drive, impaired neuromuscular reserve, or increased ventilatory demand (Tables 3.1 and 3.2).

◆ Diagnostic Approach

Signs and symptoms of respiratory distress vary, depending on the severity and cause. The initial approach to a patient includes determining the severity of illness then determining if immediate treatment is needed by first ensuring that airway, breathing, and circulation are intact. After these steps are completed, further work-up into the cause of respiratory distress may be done. A careful history and physical examination is often sufficient to elucidate the cause of respiratory distress. Not all causes of respiratory distress arise within the respiratory tract. Heart failure, pulmonary edema, neuromuscular disorders, toxic ingestion, and central nervous system disorders may all manifest with respiratory signs and symptoms. In severe respiratory distress or suspicion of airway obstruction, a feeding trial should not be done as this may increase the risk of aspiration or further respiratory compromise.

◆ History

An appropriate medical history is important in the child with acute respiratory distress. The chief complaint provides insight into the nature of the distress (i.e., cough, wheezing, stridor, dyspnea, and/or chest pain). The onset, duration, and chronicity of symptoms should also be obtained. It is important to obtain data regarding any prodrome, exacerbating or ameliorating factors, history of trauma, previous occurrence of similar symptoms, and response to any therapy. Questions should also be directed toward any change in voice or cry, change with positioning, feeding problems, or any choking episode. The possibility of a foreign body should be raised, although this is often not observed. Past medical history of neonatal events (prematurity), previous endotracheal intubation, recurrent infections, hospitalizations, noisy breathing, and prior gagging or choking episodes may also provide valuable information. A family history of asthma and allergies, travel, and environmental exposure (i.e., smoking, pets, or irritants) may also uncover etiologic clues. A review of systems with regard to systemic signs and symptoms associated with respiratory disease, such as fever, weight loss, night sweats, or dysphagia, is useful (Table 3.3).

◆ Physical Examination

Pulmonary Physical Examination

The physical examination begins with measurement of vital signs, with attention paid to respiratory rate, pulse oximetry, heart rate, and blood pressure. Tachypnea is often the most prominent manifestation of respiratory distress. A respiratory rate of more than 50 breaths/min in infants 2-12 months of age, 40 breaths/min in children 1-5 years, and 30 breaths/min in children older than 5 years is abnormal. The physical examination should be performed in a warm, well-lit room, preferably with the child in the parent's lap and the child's chest exposed. It is essential to observe the child's general appearance, sense of well-being, degree of dyspnea or cyanosis, and respiratory pattern, including nasal flaring, retractions, and accessory muscle use. **Central cyanosis** (lips, tongue, sublingual tissue as well as hands and feet), which is an abnormal blue discoloration, is related both to the degree of oxygen desaturation and the hemoglobin level (Table 3.4). Cyanosis is detected when the average amount of deoxygenated hemoglobin is 5 g/dL. Any posture assumed in an effort to minimize the airway difficulties should be determined. The degree and location of retractions should be noted. Retractions may be intercostal, subcostal, or suprasternal, and often signify worsening respiratory distress, particularly in the older child. Infants have a particularly compliant chest wall, and are therefore more predisposed to intercostal and sternal retractions; in older children, these features may be less prominent. Nasal flaring and accessory muscle use signify significant respiratory distress; and, as fatigue sets in, head bobbing and/or grunting can be noted, which requires prompt management as this may be a sign of impending respiratory failure. Altered mental status (either agitation or somnolence) may be indicative of severe respiratory distress, hypoxemia, hypercapnia, and impending respiratory failure. Palpation of the chest wall and cervical region may enable the examiner to detect the presence of subcutaneous emphysema indicative of pulmonary air leak. On percussion of the chest and back, a hyperresonant note during percussion of the chest wall indicates hyperinflation; whereas, dullness to percussion suggests atelectasis, pulmonary consolidation, or pleural effusion.

Auscultation of the chest should focus on identifying the degree of air exchange and the presence, timing, and symmetry of adventitious breath sounds. Air entry should be evaluated over all discrete anatomic

(See *Nelson Textbook of Pediatrics,* p. 529.)

TABLE 3.1 Age-Related Causes of Respiratory Distress

Cause	Full-Term Neonate	Infant-Toddler	Child	Adolescent
Common	Meconium aspiration pneumonia Congenital heart disease Transient tachypnea Persistent fetal circulation Congenital pneumonia	Viral pneumonia[†] Bacterial pneumonia[‡] Aspiration[§] Croup (infectious, spasmodic) Bronchiolitis Cystic fibrosis Laryngomalacia Asthma	Pneumonia[‖] Asthma Cystic fibrosis Sickle cell acute chest crisis Aspiration[§] Tonsillitis	Pneumonia[#] Asthma Sickle cell acute chest crisis Tonsillitis Peritonsillar abscess Cystic fibrosis Panic attack
Uncommon	Pneumothorax Congenital anomalies* Pneumopericardium Polycythemia Vocal cord paralysis Pleural effusions Severe anemia Pulmonary hypoplasia Surfactant protein deficiency Pulmonary lymphangiectasia	Congenital anomalies Epiglottitis Near drowning Pulmonary hemosiderosis Pulmonary hemorrhage Retropharyngeal abscess Trauma Hydrocarbon aspiration Smoke inhalation (burn) Airway hemangioma Papilloma of vocal cords Bacterial tracheitis Heart failure HIV associated[‖‖]	ARDS Anaphylaxis Interstitial lung disease[¶] Hemoptysis Retropharyngeal abscess Near drowning Hydrocarbon aspiration Trauma Pulmonary fibrosis Desquamating interstitial pneumonia Pulmonary alveolar proteinosis Smoke inhalation (burn) HIV associated[‖‖]	ARDS Spontaneous pneumothorax Pulmonary embolism Drug-induced** Interstitial lung disease[¶] Collagen vascular disease[††] Hypersensitivity pneumonitis[‡‡] Allergic bronchopulmonary aspergillosis Alveolar proteinosis Trauma Anaphylaxis Smoke inhalation (burn) Scoliosis Bronchiectasis Mediastinal mass[§§] Hemoptysis HIV associated[‖‖]

*Congenital anomalies = tracheoesophageal fistula; choanal atresia; tracheal web-stenosis-atresia-cleft; diaphragmatic hernia; eventration of the diaphragm; congenital pulmonary airway malformation (previously called cystic adenomatoid malformation); lobar emphysema; cleft palate–macroglossia (Pierre Robin syndrome); thyroid goiter; pulmonary hypoplasia, including Potter syndrome (renal agenesis, oligohydramnios, pulmonary hypoplasia); lung cysts; chylothorax; pulmonary lymphangiectasia; asphyxiating thoracic dystrophy; vascular rings and slings; arteriovenous malformation; subglottic stenosis.

[†]Viral pneumonia: see Table 3.12 for common causes.

[‡]Pneumonia (infant–toddler): see Table 3.12 for common causes.

[§]Aspiration = gastric fluid or formula aspiration in gastroesophageal reflux, foreign body aspiration.

[‖]Pneumonia (child): see Table 3.12 for common causes.

[¶]Interstitial lung disease = idiopathic, rheumatoid, infection *(P. carinii)*, Langerhans cell histiocytosis, hypereosinophilia syndromes, Goodpasture syndrome, LIP, alveolar proteinosis, familial fibrosis, chronic active hepatitis, inflammatory bowel disease, vasculitis (granulomatosis with polyangiitis with or without eosiniphilia, hypersensitivity), graft-versus-host disease, pulmonary venoocclusive disease, sarcoidosis, leukemia, lymphoma, neurofibromatosis, tuberous sclerosis, Gaucher disease, Niemann-Pick disease, Weber-Christian disease, organic dusts (e.g., farmer's lung, humidifier/air-conditioner lung, bird feeder, pancreatic extract, rodent handler, cheese worker), inorganic dusts (pneumoconiosis), irradiation.

[#]Pneumonia (adolescent): see Table 3.12 for common causes.

**Drugs = azathioprine, bleomycin, cyclophosphamide, methotrexate, nitrosoureas, busulfan, nitrofurantoin, penicillin, sulfonamides, erythromycin, isoniazid, hydralazine, phenytoin, carbamazepine, imipramine, naproxen, penicillamine, cromolyn sodium, mineral oil, paraquat, inhaled drugs (cocaine, hydrocarbons), talc, shoe spray.

[††]Collagen vascular disease = rheumatoid arthritis, progressive systemic sclerosis, systemic lupus erythematosus, dermatomyositis, mixed connective tissue disease.

[‡‡]Hypersensitivity pneumonia (also called extrinsic allergic alveolitis): see[¶] above for some specific organic dusts (antigens).

[§§]Mediastinal masses = anterior (teratoma, T-cell lymphoma, thymus, thyroid), middle (lymph nodes–infection–tumor–sarcoidosis, cysts), posterior (neuroenteric cysts–duplication, meningocele, neural tumors–neuroblastoma, ganglioneuroblastoma, neurofibroma, pheochromocytoma), and parenchymal tumors (hamartoma, arteriovenous malformation, carcinoid, adenoma; metastatic–osteogenic sarcoma, Wilms tumor).

[‖‖]HIV associated = *P. jiroveci*, LIP, CMV, *Mycobacterium tuberculosis*, atypical mycobacteria, measles, common bacterial pathogens.

ARDS, acute respiratory distress syndrome; BPD, bronchopulmonary dysplasia; CMV, cytomegalovirus; HIV, human immunodeficiency virus; LIP, lymphocytic interstitial pneumonia; RDS, respiratory distress syndrome; RSV, respiratory syncytial virus.

TABLE 3.2 Causes of Respiratory Distress

Extrathoracic	Intrathoracic
Nervous System–Metabolic	**Pulmonary**
Intracranial hemorrhage	Airway obstruction
Acidosis	Parenchymal lesions: pneumonia, hemorrhage, malformation
Ingestion (aspirin)	
Ketoacidosis (diabetes)	
Meningitis	Air leaks: pneumomediastinum, pneumothorax
Shock/sepsis	
Neuromuscular disease	
Diaphragmatic paralysis, paresis	Pleural effusion, empyema
Psychologic (anxiety)	Acute respiratory distress syndrome
Vocal cord dysfunction	Chest wall trauma
Panic attack	Pulmonary embolus
	Foreign body (airway or esophagus)
	Tumor (cyst, adenoma)
	Cystic fibrosis
Lesions of Upper Airway	**Cardiac**
Malacia	Myocarditis
Web	Cardiomyopathy
Cyst	Shunt (left to right)
Hemangioma	Congestive heart failure
Stenosis (glottic or choanal)	Pulmonary edema
Papillamatosis	Pericardial effusion
Miscellaneous	
Abdominal masses, distention	
Ascites	
Anemia	

locations bilaterally. Homologous segments of each lung should be examined sequentially to compare similar areas. The presence of adventitious sounds should be determined next. The most commonly encountered sounds are wheezing, stridor, crackles, and rhonchi (Table 3.5).

Crackles (previously called "rales") are intermittent, nonmusical low or higher pitched, largely inspiratory noises that are produced by the opening of airways closed during the previous expiration.

Wheezing is a continuous, high-pitched musical noise, similar to a hiss or whistle.

Rhonchi are continuous sounds that are lower pitched and more rumbling or sonorous.

Stridor is a high-pitched musical noise generated by turbulent flow of air through the large upper airways.

Determination of the timing (inspiration, expiration, or biphasic) and distribution of the adventitious sounds offers clues as to the site of airway and lung involvement. Wheezing that is continuous and heard equally over both lung fields is associated with diffuse airway narrowing and limitation of airflow, whereas unilateral or very localized wheezing or decreased breath sounds suggest segmental airway obstruction, such as that found with retained foreign body aspiration, mucus plugging, or atelectasis. Additionally, inspiratory stridor is characteristic of partial airway obstruction at or above the vocal cords, whereas biphasic or expiratory stridor is characteristic of airway obstruction in the subglottic space or trachea (Fig. 3.1).

Other Parts of the Physical Examination

Other elements of the physical examination may have direct bearing on the respiratory system. Pulsus paradoxus, the difference between the systolic blood pressure obtained during inspiration and during exhalation, is exaggerated by airway obstruction and pulmonary hyperinflation. As pulmonary overinflation gets worse, pulsus paradoxus values increase and correlate well with the degree of airway obstruction. It is difficult to measure pulsus paradoxus in young children with rapid heart rates. A method that allows a reasonable approximation of the pulsus paradoxus can be obtained by using a sphygmomanometer and noting the difference between the pressure at which the first sporadic faint pulse sounds and the pressure at which all sounds are heard. Values greater than 10 mm Hg are abnormal, and values greater than 20 mm Hg are consistent with severe airway obstruction. Although digital clubbing is occasionally seen as a normal and familial variant, its presence in a child with respiratory distress suggests an acute illness superimposed on an underlying chronic condition. The most common pulmonary causes of digital clubbing in pediatric patients are cystic fibrosis, bronchiectasis, and other destructive pulmonary diseases. Digital clubbing is rarely seen in children with asthma. Other physical findings to observe include mouth breathing and morphologic features suggestive of craniofacial anomalies, such as maxillary hypoplasia, nasal septal deflection, micrognathia, retrognathia, absent nasal airflow (choanal obstructions), platybasia, or macroglossia.

◆ Laboratory Tests

The arterial blood gas analysis, obtained while the patient is breathing a known fraction of inspired oxygen (F_{IO_2}), is the "gold standard" for assessing oxygenation, ventilation, and acid-base status. In lieu of an arterial blood gas determination, capillary or venous blood gases may be utilized, but these are less helpful for evaluating oxygenation. Noninvasive measurement of oxygenation by pulse oximetry can provide valuable information. Oximetry measures the degree of hemoglobin saturation with oxygen and should not be confused with partial pressure of oxygen in the blood, as measured by blood gas analysis or estimated by transcutaneous measures. At or near sea level, hemoglobin oxygen saturation lower than 93% indicates that significant hypoxemia may be present, and saturations of 90% or lower are clearly abnormal. A blood gas analysis may be necessary to confirm the presence and degree of hypoxemia, as well as information on acid-base status (pH) and ventilation (P_{aCO_2}). Hemoglobin oxygen saturation, measured by pulse oximetry, cannot detect significant hypoxia, but it is relatively accurate at oxygen saturations of 70% or more. Various conditions, such as poor circulation, presence of carboxyhemoglobin or methemoglobin, nail polish, and improper sensor alignment and motion, can result in inaccurate oximetry measures.

◆ Imaging

Radiography

A plain radiograph of the chest, taken in the posterior-anterior and lateral projections, should be obtained in any patient with respiratory distress in which an etiology has not been determined from the history and physical examination. Important information regarding the presence of parenchymal infiltrates, effusion, airway obstruction, cardiac size, pulmonary vascular markings, extrapulmonary air leaks, and the presence of radiopaque foreign bodies may be obtained from this test. Radiopaque foreign bodies are generally seen easily on a radiograph. If there is a possibility of a radiolucent foreign body, inspiratory and expiratory chest radiographic studies must be performed. Demonstration of unilateral hyperinflation or a mediastinal shift during

TABLE 3.3 Focused History for a Patient with Respiratory Distress

Component	Comments and Examples
Onset, duration, and chronicity	Abrupt onset: suggests upper airway conditions such as foreign body, allergy, anaphylaxis, irritant exposure or pulmonary embolism Gradual onset: more consistent with process such as infection or heart failure
Alleviating and provoking factors	A child with respiratory distress caused by upper airway obstruction may have some degree of relief by assuming the "sniffing position" to maximize airway patency
Treatment attempted	A child with wheezing secondary to asthma may respond readily to inhaled bronchodilators, but a child with wheezing caused by foreign body aspiration may continue to show symptoms after treatment
Respiratory symptoms	Cold symptoms: may indicate viral upper respiratory infection Cough: "seal-like" or "barky" cough is commonly heard in patients with croup Eliciting descriptions of the difficulty breathing may provide clues to the underlying cause (e.g., supraclavicular or suprasternal retractions point to upper airway obstruction) Color change: Pallor may indicate anemia; cyanosis is indicative of decreased oxygen content in the blood, as seen in some forms of congenital heart disease and in methemoglobinemia Respiratory effort: Poor effort may be seen in patients with underlying muscular dystrophies Change in voice: Whereas muffled or hoarse voice points to upper airway pathology, lower airway disease does not typically change the character of the voice
Systemic or associated symptoms	Fever: Presence suggests an infectious cause Hydration status, including intake and output (urine, emesis, diarrhea, excessive perspiration, or high respiratory rate) Weight loss or failure to gain weight: may indicate systemic process (e.g., inborn error of metabolism) or the severity of respiratory distress is impairing growth (as seen in congestive heart failure) Abdominal pain: may suggest abdominal pathology such as obstruction or appendicitis or may represent referred pain from diaphragmatic irritation (as in basilar pneumonia)
Past medical history	Underlying disorders may predispose patients to certain conditions: For example, a patient with sickle cell disease and respiratory distress may be exhibiting signs of acute chest syndrome; a patient with known gastroesophageal reflux and coarse lung findings on examination could have an aspiration pneumonia
Exposures or environmental factors	For example, a patient involved in a fire may not only be affected by thermal injury to the airways but also systemic toxins such as carbon monoxide and cyanide A patient with allergy and a potential exposure to the allergen could be showing signs of anaphylaxis
Trauma	History of trauma suggests diagnoses such as pneumothorax, flail chest, cardiac tamponade, or abdominal injury
Immunization status	Children with incomplete or lack of immunization against *Haemophilus influenzae* type B are at increased risk for epiglottitis
Last oral intake	If advanced airway management becomes necessary (e.g., positive-pressure ventilation), the presence of stomach contents may increase the risk of pulmonary aspiration

From Viteri SD, Sampayo EM. Respiratory distress. In: Florin TA, Ludwig S, eds. *Netter's Pediatrics*. Philadelphia: Elsevier; 2011:17-23.

TABLE 3.4 Cyanosis and Hemoglobin Concentration

	CYANOSIS APPEARS AT*	
Hemoglobin Concentration (g/dL)	Oxygen Saturation (%) Below:	Arterial P_{O_2} (mm Hg) Below:
6	60	31
8	70	36
10	76	40
12	80	45
14	83	47
16	85	50
18	87	54
20	88	56

*These figures assume that central cyanosis begins to appear when 2.38 g/dL of deoxygenated hemoglobin accumulates in arterial blood. The corresponding P_{O_2} was obtained from standard hemoglobin dissociation curves for oxygen.

From McGee S: Cyanosis. In *Evidence-Based Physical Diagnosis*. 3rd ed. Philadelphia: Elsevier; 2012: 71.

expiration suggests localized bronchial obstruction, such as a retained foreign body. Lateral decubitus positioning of the patient during the radiographic procedure can reveal a pleural effusion in the lower dependent lung. Ultrasonography of the chest is also useful in detecting pleural fluid and loculations within pleural effusions.

In patients with stridor, anteroposterior and lateral soft tissue radiographic studies of the neck and chest are frequently needed. These should be obtained during inspiration, because the soft tissues of the pharynx may bulge with expiration, causing a false-positive finding of a soft tissue mass that may mimic a retropharyngeal infection.

Computed Tomography

Computed tomography (CT) of the upper airway and chest can help detect the relationship of the vasculature to the airways (trachea and large central airways); pulmonary parenchymal lesions (infiltrates, abscesses, cysts) or lesions (abscesses, inflammation) in the airway; and central airway caliber. Rapid, fine-cut CT is a technique of high resolution and short duration, which increases its acceptability for pediatric patients. It is the method of choice for noninvasive detection and evaluation of bronchiectasis and interstitial lung disease. Helical CT is a valuable method of detecting pulmonary embolism.

TABLE 3.5 Classification of Common Lung Sounds

	Acoustic Characteristics	American Thoracic Society Nomenclature	Common Synonyms
Normal	200-600 Hz Decreasing power with increasing Hz	Normal	Vesicular
	75-1600 Hz Flat until sharp decrease in power (900 Hz)	Bronchial	Bronchial Tracheal
Adventitious		Adventitious	Abnormal
	Discontinuous, interrupted explosive sounds (loud, low in pitch), early inspiratory or expiratory	Coarse crackles	Coarse crackles
	Discontinuous, interrupted explosive sounds (less loud than above and of shorter duration; higher in pitch than coarse crackles or crackles), mid- to late inspiratory	Fine crackles	Fine crackles, crepitation
	Continuous sounds (>250 msec, high-pitched; dominant frequency of 400 Hz or more, a hissing sound)	Wheezes	Sibilant rhonchus, high-pitched wheeze
	Continuous sounds (>250 msec, low-pitched; dominant frequency <200 Hz, a snoring sound)	Rhonchi	Sonorous rhonchus, low-pitched wheeze

From Davis JL, Murray JF. History and physical examination. In: Broaddus VC, Mason RJ, Ernst JD, et al. *Murray and Nadel's Textbook of Respiratory Medicine*. 6th ed. Philadelphia: Saunders-Elsevier; 2016: 263-277e2.

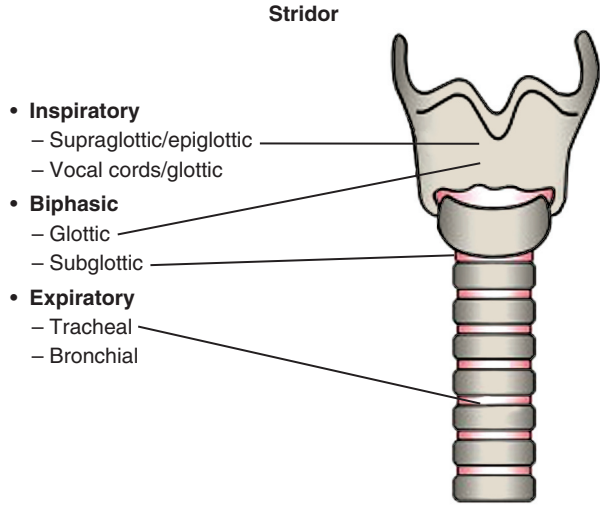


FIGURE 3.1 Stridor. Inspiratory stridor is characteristic of partial airway obstruction at or above the vocal cords (supraglottic/epiglottic and glottis areas). Biphasic stridor is characteristic at the glottis or subglottic areas, and is typically caused by a fixed obstruction. Expiratory stridor is characteristic of a high tracheal lesion as there is a decrease in airway diameter with expiration. (From Ida JB, Thompson DM. Pediatric stridor. *Otolaryngol Clin North Am.* 2014;47:795-819.)

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) of the pulmonary system may also be useful in elucidating the relationship of the great vessels to the airways and may be superior to CT for this purpose. MRI is less useful for imaging the lung parenchyma. The need for long imaging times often means sedation for young children, and this limits the utility of MRI imaging of the chest for some pediatric patients. Sedatives must be used very carefully, particularly in patients with respiratory distress, and only in monitored situations with the availability of experienced personnel and equipment to provide possible resuscitation.

Fluoroscopy

Fluoroscopic examination of the chest may be useful in determining the cause of respiratory distress. Real-time visualization of the diaphragm can determine whether paralysis or paresis of this major muscle of respiration is contributing to respiratory distress. Asymmetric chest wall motion or unilateral hyperinflation during the respiratory cycle suggests bronchial obstruction, such as that seen with a retained foreign body in the airways. An upper gastrointestinal (GI) series is useful to assess for abnormalities of swallowing causing aspiration, presence of tracheoesophageal fistula, or presence of a vascular ring.

Endoscopy

Endoscopy can provide direct visualization of the cause of the airway obstruction and lung lesions; its use involves manipulation of the airway, which should not be undertaken unless the personnel and equipment are present to manage possible worsening airway compromise. Flexible, direct laryngoscopy is widely used to visualize the upper airway without the need for sedation. Rigid bronchoscopy provides visualization of both the upper and lower airways; cardiopulmonary monitoring and intravenous access for sedative administration are required. In cases of significant upper airway obstruction necessitating intervention, or if there is any likelihood of a foreign body, direct laryngoscopy and rigid bronchoscopy in the operating room are the safest procedures that can secure the airway, provide a diagnosis, and accomplish treatment.

CAUSES OF RESPIRATORY DISTRESS

Wheezing

Wheezing is best characterized as a continuous, musical sound most often heard on expiration, but it may occur in both phases of respiration. The most common cause of acute wheezing in children is asthma. However, it is critical to rule out other causes of wheezing that necessitate different therapy (Table 3.6). Anatomic abnormalities of the airway, such as vascular ring, tracheobronchomalacia, ciliary dyskinesia, and foreign body aspiration, may cause airway obstruction and wheezing, especially in infants and young children. Viral infections, notably those of respiratory syncytial virus (RSV), human metapneumovirus, adenovirus, parainfluenza, and influenza, are also common causes of wheezing in infants and young children. Infection with *Mycoplasma* species may produce airway hyperactivity in older

TABLE 3.6 Causes of Wheezing in Childhood

Acute

Reactive Airways Disease
Asthma*
Exercise-induced asthma*
Hypersensitivity reactions
Anaphylaxis

Bronchial Edema
Infection* (bronchiolitis, ILD, pneumonia)
Inhalation of irritant gases or particulates
Increased pulmonary venous pressure

Bronchial Hypersecretion
Infection
Inhalation of irritant gases or particulates
Cholinergic drugs

Aspiration
Foreign body*
Aspiration of gastric contents (reflux, H-type TEF)

Chronic or Recurrent

Reactive Airways Disease (Same as in Acute)

Hypersensitivity Reactions, Allergic Bronchopulmonary

Aspergillosis

Dynamic Airways Collapse
Bronchomalacia
Tracheomalacia*
Vocal cord adduction*

Airway Compression by Mass or Blood Vessel
Vascular ring/sling
Anomalous innominate artery
Pulmonary artery dilation (absent pulmonary valve)
Bronchial or pulmonary cysts
Lymph nodes or tumors

Aspiration
Foreign body
Gastroesophageal reflux*
Tracheoesophageal fistula (repaired or unrepaired)

Bronchial Hypersecretion or Failure to Clear Secretions
Bronchitis, bronchiectasis
Cystic fibrosis*
Dyskinetic (immotile) cilia syndrome
Immunodeficiency disorder
Vasculitis
Lymphangiectasia
α_1-Antitrypsin deficiency

Intrinsic Airway Lesions
Endobronchial tumors
Endobronchial granulation tissue
Plastic bronchitis syndrome
Bronchial or tracheal stenosis
Bronchiolitis obliterans
Sequelae of bronchopulmonary dysplasia
Sarcoidosis

Congestive Heart Failure

*Common.
ILD, interstitial lung disease; TEF, tracheoesophageal fistula.
Modified from Kercsmar CM. The respiratory system. In: Behrman RE, Kliegman RM, eds. *Nelson Essentials of Pediatrics*. 2nd ed. Philadelphia: WB Saunders; 1994:445.

children. Other entities to consider are cystic fibrosis, interstitial lung disease, or vocal cord dysfunction. In comparison with asthma, one key distinguishing feature of these diagnoses is that the wheezing does not respond to treatment with bronchodilators.

Asthma

Asthma is defined as airway obstruction that is reversible either spontaneously or with the use of medication. Chronic airway inflammation and bronchial hyperresponsiveness are the likely causes of the airway obstruction. The airways of patients with even mild asthma demonstrate inflammation, manifested as mucosal edema, hypersecretion of mucus, smooth muscle constriction, and inflammatory cell infiltrate. Even when asthma symptoms are not present, airway inflammation may be demonstrated. Furthermore, bronchial hyperresponsiveness, the tendency of airway smooth muscle to constrict in response to a variety of environmental stimuli, is present in virtually all children with asthma and may be exacerbated by airway inflammation. Airway remodeling, the deposition of collagen in the subepithelial basement membrane area, occurs in some but not all asthmatic patients. Fixed airway obstruction is a long-term complication that may occur as a result of airway remodeling.

The diagnosis of asthma is made by a combination of history, physical examination and spirometry testing. For the child with acute wheezing and respiratory distress, a therapeutic trial of an inhaled ß-agonist is the best "diagnostic test" for reversible airway obstruction. Once the acute symptoms have improved, other diagnostic studies can be undertaken. Spirometry, particularly measurement of the forced expiratory volume in 1 second (FEV_1) and mid-maximal forced expiratory flow rates ($FEF_{25–75\%}$), provides a good indication of airflow obstruction in the larger and smaller airways, respectively. If airway obstruction is detected in the resting state, a bronchodilator (typically albuterol) is administered, and spirometry is repeated. An improvement of ≥12% and ≥200 mL in FEV_1 above baseline is considered significant and indicative of reversible airway obstruction (Fig. 3.2). If the baseline spirometry is normal, an inhalation challenge test, with either increasing doses of methacholine or hyperventilation of cold, dry air can provoke a statistically (but usually not clinically) significant decrease in FEV_1; a fall in FEV_1 of 10% or greater is considered diagnostic of airway hyperresponsiveness and asthma. In children too young to perform spirometry (typically under the age of 5 years), the repeated nature of wheezing episodes and the improvement in symptoms after treatment with antiinflammatory agents and

(See *Nelson Textbook of Pediatrics,* p. 1095.)

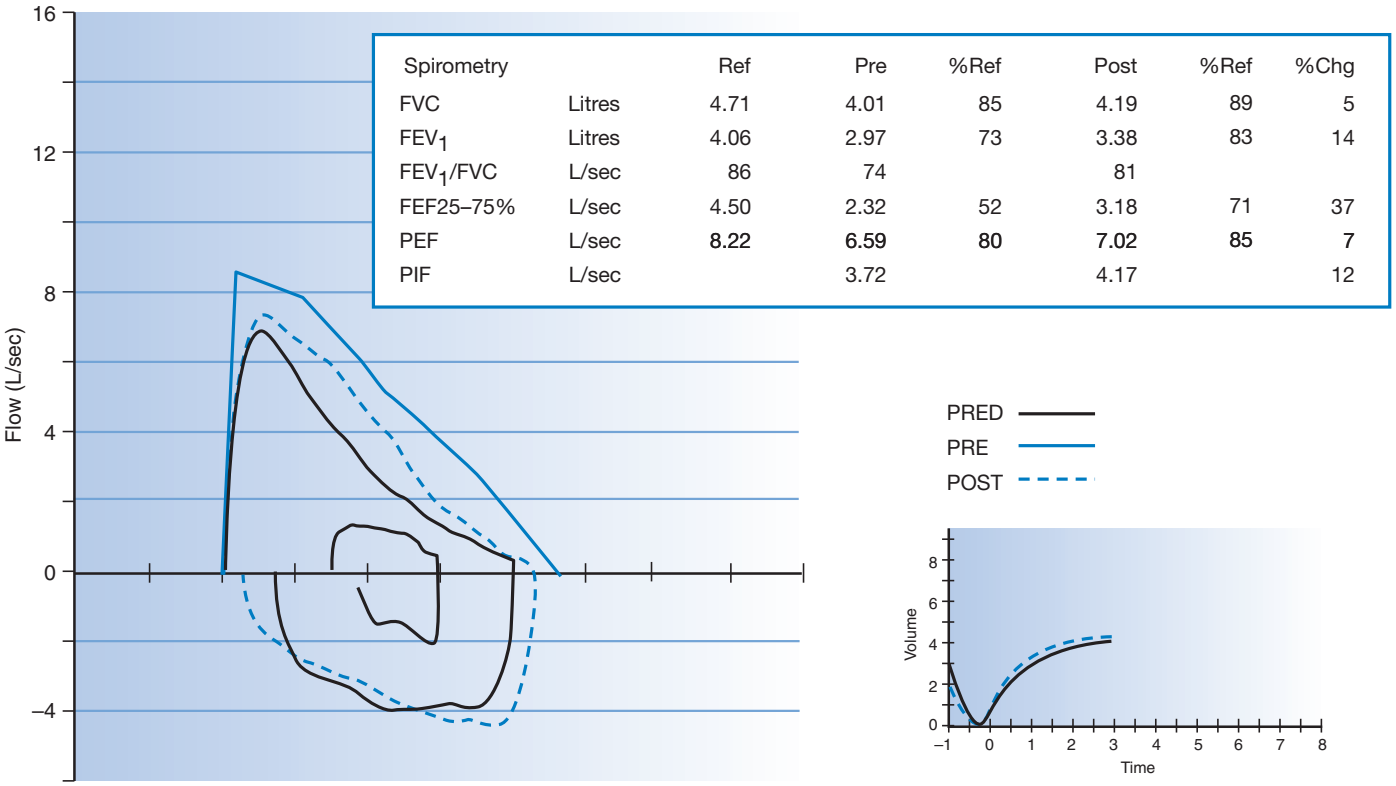


FIGURE 3.2 Spirometry demonstrating a scooped flow volume loop seen in obstructive disease in asthma. Following bronchodilator use (PRED, predicted) there is a positive bronchodilator response of >12% in forced expiratory volume in 1 second (FEV_1). FEF, forced expiratory flow rate; FVC, forced vital capacity; PEF, peak expiratory flow rate; PIF, peak inspiratory flow rate. (From South M, Isaacs D: *Practical Paediatrics*. 7th ed. Oxford: Churchill Livingstone; 2013.)

bronchodilators, peripheral blood eosinophilia (>4%), a family history of atopy, and/or a personal history of atopy (eczema, food allergy, or allergic rhinitis) are strongly suggestive of the diagnosis of asthma. Other studies include measurement of total serum immunoglobulin E (IgE) levels. This immunoglobulin is often elevated in individuals with asthma and/or allergy, as well as in those predisposed to asthma.

Patients with acute asthma typically present with shortness of breath, wheezing, cough, and increased work of breathing. Persistent cough may be the most prominent or even sole feature of acute asthma (see Chapter 2). Many asthma episodes are misdiagnosed as bronchitis (which is rare in children). Chest wall retractions and the use of accessory muscles indicate significant airway obstruction. Acute asthma exacerbations that are unresponsive to aggressive bronchodilator administration are termed **status asthmaticus**. The severity of asthma exacerbation may be assessed with the parameters presented in Table 3.7. Common triggers of acute episodes include upper respiratory tract infections, exposure to cold air, exercise, allergens, pollutants, strong odors, and tobacco smoke.

A brief history should be obtained for every child with acute asthma to determine the duration of symptoms, the character of previous episodes (severity, need for hospitalization, and need for intensive care, including mechanical ventilation), antecedent illness, symptoms, exposures, and both chronic and acute use of medications, including dose and time of last administration. History should also focus on identifying risk factors for severe asthma (Table 3.8) and classification of asthma type, which are based on age (Figs. 3.3, 3.4, and 3.5). It is also important to assess the degree of asthma control. The physical examination should focus on respiratory rate, air exchange, degree and localization of wheezing, other adventitious lung sounds, mental status, presence of cyanosis, and degree of fatigue. A chest radiograph should be obtained for all patients with a first episode of wheezing to evaluate for other causes of wheezing. Patients with recurrent asthma should have a chest radiograph if there is evidence for a foreign body or pneumonia, or concern for a pneumothorax. Chest radiograph findings in asthma are nonspecific, but they usually show symmetric hyperinflation and increased peribronchial thickening. Spirometry has limited efficacy in the emergency management of status asthmaticus. Although peak expiratory flow rates are often measured, this test is a measure of large airway function only, is effort dependent, and may be unreliable in an anxious, untrained patient. The major value of peak flow measurements in acute asthma is to provide an objective trend indicative of improvement (or lack thereof) in airway caliber if frequent and scheduled treatments are needed.

A complete blood cell count is not of use unless other complicating conditions (i.e., bacterial infection, anemia, hemoglobinopathy) are suspected. Serum electrolyte measurements are of little value unless dehydration is suspected. Hypokalemia is associated with the frequent administration of ß-agonists.

Treatment of acute asthma should be instituted in any child with wheezing, dyspnea, cough, and no other immediately discernible cause of the symptoms. Patients with moderate to severe airway obstruction have significant hypoxemia as a result of ventilation-perfusion mismatch. Consequently, supplemental humidified oxygen should be administered to any child who has significant wheezing, accessory muscle use, or an oxygen saturation of <93%. The mainstay of treatment for an asthma exacerbation is the administration of an inhaled

TABLE 3.7 Severity of Asthma Exacerbations

	Mild	Moderate	Severe	Respiratory Arrest Imminent
Symptoms				
Breathlessness	While walking	While at rest (infant—softer, shorter cry; difficulty feeding)	While at rest (infant—stops feeding)	
	Can lie down	Prefers sitting	Sits upright	
Talks in	Sentences	Phrases	Words	
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
Signs				
Respiratory rate	Increased	Increased	Often >30/min	
		Guide to rates of breathing in awake children:		
		Age	*Normal rate*	
		<2 mo	<60/min	
		2-12 mo	<50/min	
		1-5 yr	<40/min	
		6-8 yr	<30/min	
Use of accessory muscles; suprasternal retractions	Usually not	Commonly	Usually	Paradoxical thoracoabdominal movement
Wheeze	Moderate, often only end expiratory	Loud; throughout exhalation	Usually loud; throughout inhalation and exhalation	Absence of wheeze
Pulse/minute	<100	100-120	>120	Bradycardia
		Guide to normal pulse rates in children:		
		Age	*Normal rate*	
		2-12 mo	<160/min	
		1-2 yr	<120/min	
		2-8 yr	<110/min	
Pulsus paradoxus	Absent <10 mm Hg	May be present 10-25 mm Hg	Often present >25 mm Hg (adult) 20-40 mm Hg (child)	Absence suggests respiratory muscle fatigue
Functional Assessment				
PEF percent predicted or percent personal best	≥70%	~40-69% or response lasts <2 hr	<40%	<25% Note: PEF testing may not be needed in very severe attacks
Pa_{O_2} (on air)	Normal (test not necessary)	≥60 mm Hg (test not usually necessary)	<60 mm Hg: possible cyanosis	
and/or Pc_{O_2}	<42 mm Hg (test not usually necessary)	<42 mm Hg (test not usually necessary)	≥42 mm Hg: possible respiratory failure	
Sa_{O_2} (on air) at sea level	>95% (test not usually necessary)	90-95% (test not usually necessary)	<90%	
	Hypercapnia (hypoventilation) develops more readily in young children than in adults and adolescents.			

Pa_{O_2}, arterial oxygen pressure; Pc_{O_2}, partial pressure of carbon dioxide; PEF, peak expiratory flow; Sa_{O_2}, oxygen saturation.
From NHLBI/National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. NIH Publication; 2007.

ß-adrenergic agonist and systemic corticosteroids. Inhalation of ß-agonist by nebulizer or metered-dose inhaler is the route of choice because the onset of action is rapid, sustained, and relatively free of significant side effects even in the most severely affected patients. Anticholinergic agents (ipratropium bromide), when combined with a ß-agonist as inhaled treatment, can provide additional bronchodilation. The effect is most marked in children who present to the emergency department with significant airway obstruction. With few exceptions, any patient who presents with wheezing responsive to bronchodilator therapy or any patient requiring hospital admission should receive corticosteroids. In severe respiratory distress, intravenous (IV) magnesium or theophylline (or the intravenous formulation aminophylline) may be of benefit. A small percentage of children with acute asthma progresses to severe status asthmaticus and respiratory failure. A number of clinical signs and symptoms define respiratory failure in such severely affected patients: a Pa_{O_2} less than 60 mm in room air or cyanosis in 40% F_{IO_2}, a Pa_{CO_2} of 40 mm or higher or rising and accompanied by respiratory distress, deterioration in clinical status in spite of aggressive treatment, a change in mental status, and fatigue. Patients meeting any of these criteria should be admitted to an intensive care unit.

TABLE 3.8 Risk Factors for Death from Asthma

Asthma History

Previous severe exacerbation (e.g., intubation or ICU admission for asthma)
Two or more hospitalizations for asthma in the past year
Three or more ED visits for asthma in the past year
Hospitalization or ED visit for asthma in the past month
Using >2 canisters of SABA per month
Difficulty perceiving asthma symptoms or severity of exacerbations by patient, family, and physician
Other risk factors: lack of a written asthma action plan, sensitivity to *Alternaria*

Social History

Low socioeconomic status or inner-city residence
Illicit drug use
Major psychosocial problems

Comorbidities

Cardiovascular disease
Other chronic lung disease
Chronic psychiatric disease

ED, emergency department; ICU, intensive care unit; SABA, short-acting β_2-agonist.
From National Heart, Lung and Blood Institute. Expert Panel Report 3 [EPR 3]. Guidelines for the Diagnosis and Management of Asthma. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

Identification and treatment of chronic asthma requires careful assessment of the severity of the disease, according to frequency and intensity of symptoms, and subsequent grading into mild, moderate, and severe categories (see Figs. 3.3, 3.4, and 3.5). All patients except those with mild intermittent disease are best managed with chronic administration of an inhaled antiinflammatory agent (corticosteroids) and the intermittent use of an inhaled ß-agonist for treatment of acute wheezing episodes. Leukotriene receptor antagonists may be considered as an alternative preventive therapy for mild asthma. Oral corticosteroids are administered for short intervals to control more severe exacerbations. Avoidance of environmental triggers (allergens, tobacco smoke) is also paramount to successful management.

Bronchiolitis

Bronchiolitis is a common, acute viral infection of the distal lower respiratory tract, and is characterized as lower airway obstruction secondary to airway edema, mucous and cellular debris. Impaired gas exchange can occur as a result of airway obstruction and ventilation-perfusion inequalities. RSV is the most important respiratory pathogen in infants and young children. It has been identified as the etiologic agent in 5%-40% of pneumonias in young children. Other viruses, such as adenovirus, influenza, human metapneumovirus, and parainfluenza, can also cause bronchiolitis. The most severe disease occurs in infants younger than 6 months. By 5 years of age, 95% of all children have serologic evidence of RSV infection. Reinfections are common in older children and adults, because immunity to RSV is short lived and incomplete. In older children and adolescents, infections with RSV are often limited to the upper respiratory tract. In temperate climates, RSV epidemics occur yearly, beginning in midwinter and persisting through early spring.

In infected infants, upper respiratory tract symptoms usually precede the lower respiratory tract involvement by 3-7 days. Low-grade fever, rhinitis, and pharyngitis are common signs in the initial phase of the disease. This then progresses to cough, increased work of breathing, and wheezing (see Chapter 2). Apnea may also occur, particularly in infants less than 3 months of age. Chest wall retractions and dyspnea are frequently observed, and adventitious sounds (wheezing, crackles) are appreciated on auscultation of the chest. Most children with bronchiolitis demonstrate clinical improvement after 5-7 days, but the duration of illness can be as long as 21 days. *Bacterial superinfection of the lower respiratory tract is rare.* Approximately 30% of infants with bronchiolitis caused by RSV have recurrent episodes of wheezing caused by bronchial hyperactivity and are diagnosed with asthma. This is in part due to persistent inflammation of the distal respiratory tract produced by the viral infection.

The clinical determination of the severity of the lower respiratory tract involvement in infants infected with bronchiolitis can be difficult. Physical findings often associated with respiratory distress, such as tachypnea, intercostal retractions, and wheezing, are not necessarily correlated with the level of hypoxemia. Carbon dioxide retention secondary to alveolar hypoventilation is not a common finding in otherwise normal children, but hypercapnia and acute respiratory acidosis can be serious problems in infants with chronic pulmonary disease or congenital heart disease. Chest radiograph findings include a diffuse interstitial pneumonitis and bilateral lung overinflation; alveolar infiltrates or consolidation are present in approximately 20% of children. Infants with congenital heart disease, pulmonary hypertension, prematurity, and young age (<12 weeks) have an increased rate of severe disease and mortality; the course of illness is usually prolonged, and intensive care and mechanical ventilation are frequently needed.

The diagnosis of bronchiolitis is usually made on clinical grounds. Bronchiolitis is most common in children under 2 years of age and should be suspected in the wheezing child who has current or antecedent upper respiratory tract infection symptoms in the late fall or winter months. The definitive diagnosis of RSV or other viral infection is based on the presence of the viral genome in respiratory secretions. This testing is often not needed if the clinical findings are consistent with bronchiolitis. Polymerase chain reaction (PCR) testing is specific, accurate, and has a short turnaround time in identifying the virus from nasopharyngeal swabs.

Suctioning and supplemental oxygen remain the cornerstone of treatment for bronchiolitis. Unlike asthma, the wheezing accompanying bronchiolitis is often less responsive to bronchodilators. Nonetheless, patients with significant hypoxia and hypercapnia may receive a *trial treatment* with aerosol bronchodilators to determine if this may improve symptoms, which may be continued if infants do show improvement. Infants with bronchiolitis do not respond to treatment with antiinflammatory agents, such as corticosteroids, so these are not recommended. Severely ill patients may require mechanical ventilation; heated, humidified, high-flow nasal cannula oxygen has been shown to decrease intubation rates and can be used in children with severe respiratory distress. Other modalities, such as hypertonic or normal saline aerosols, PEP (positive expiratory pressure) therapy, and chest physiotherapy have shown mixed results, but may be of benefit for patients who are hospitalized. Treatment with exogenous surfactant or helium-oxygen mixtures for severely ill infants requiring intubation and mechanical ventilation has yielded mixed results and remains experimental.

Monthly administration (intramuscularly) of a humanized monoclonal antibody (palivizumab) against RSV can reduce morbidity from bronchiolitis but does not completely prevent infection. Infants at high risk (infants who are premature, those with bronchopulmonary dysplasia or other forms of chronic obstructive pulmonary disease, those

(See *Nelson Textbook of Pediatrics,* p. 2053.)

Components of Severity		Classification of Asthma Severity (0–4 years of age)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	≥2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	0	1–2x/month	3–4x/month	>1x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2 exacerbations in 6 months requiring oral systemic corticosteroids, or ≥4 wheezing episodes/1 year lasting >1 day AND risk factors for persistent asthma		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time. → Exacerbations of any severity may occur in patients in any severity category.			
Recommended Step for Initiating Therapy		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	
		In 2–6 weeks, depending on severity, evaluate level of asthma control that is achieved. If no clear benefit is observed in 4–6 weeks, consider adjusting therapy or alternative diagnoses.			

Key: EIB, exercise-induced bronchospasm

Notes

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past 6 months, or ≥4 wheezing episodes in the past year, and who have risk factors for persistent asthma may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

FIGURE 3.3 Classifying asthma severity ages 0-4. (From NHLBI/National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. NIH Publication; 2007.)

with complex congenital heart disease) who are younger than 2 years are most likely to benefit.

Mycoplasma pneumoniae Infections

One of the basic tenets regarding respiratory infections in children is that "bacteria do not make you wheeze." *Mycoplasma pneumoniae* is an exception to that rule and should be considered in an older child who presents with new-onset wheezing. In addition, infections with *M. pneumoniae* can precipitate exacerbations in patients with asthma. Other clinical manifestations of *M. pneumoniae* infections include cough, fever/chills, rhinorrhea, and otitis media (see Chapter 2). Extrapulmonary manifestations, such as hemolytic anemia, rash, cardiac disease, polyarthritis, transverse myelitis, and central nervous system (CNS) disease, may also be present. The incidence of *M. pneumoniae* infection peaks between the ages of 5 and 19 years; the organism usually does not produce disease in children younger than age 2. Infections with *M. pneumoniae* tend to be seasonal, occurring most frequently during autumn and early winter.

The findings of *M. pneumonia* on chest radiographs are variable. A diffuse, bilateral, reticular infiltrate is the classic appearance. However, lobar, alveolar, and interstitial infiltrates have also been described. Enlargement of hilar or peritracheal lymph nodes may also be evident. Pleural effusions (usually small) are found in 14% of patients with *M. pneumoniae*. Atypical pneumonia (diffuse infiltrates with nonlobar pattern; fever, malaise, myalgias) is often caused by *M. pneumoniae* but may also be caused by *Chlamydia pneumoniae*, *Legionella* species, and other related pathogens. PCR may help to confirm a diagnosis. Treatment is with azithromycin. Doxycycline or fluoroquinolones may also be used in older children.

Vocal Cord Dysfunction

A functional disorder that mimics asthma, vocal cord dysfunction is typically manifested as wheezing, dyspnea, and shortness of breath refractory to treatment with inhaled bronchodilators. Vocal cord dysfunction should be considered in patients with wheezing who present with atypical findings or those who are difficult to treat. The wheezing is produced by adduction of the vocal cords during inspiration and expiration. The resultant high-pitched inspiratory and expiratory noises are transmitted to the chest, although the sounds are best appreciated over the larynx. Despite the patient's apparent dyspnea, gas exchange is usually unaffected. Spirometry shows variable flattening of the inspiratory flow loop. The diagnosis is established by direct laryngoscopy, which demonstrates paradoxical motion of the vocal cords. Speech therapy is the treatment of choice.

Components of Severity		Classification of Asthma Severity (5–11 years of age)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1 /FVC >85%	• FEV_1 = >80% predicted • FEV_1 /FVC >80%	• FEV_1 = 60–80% predicted • FEV_1 /FVC = 75–80%	• FEV_1 <60% predicted • FEV_1 /FVC <75%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note)		
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category.			
		Relative annual risk of exacerbations may be related to FEV_1.			
Recommended Step for Initiating Therapy		Step 1	Step 2	Step 3, medium-dose ICS option and consider short course of oral systemic corticosteroids	Step 3, medium-dose ICS option, or step 4
		In 2–6 weeks, evaluate level of asthma control that is achieved, and adjust therapy accordingly.			

Key: EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids

Notes

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of the previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

FIGURE 3.4 Classifying asthma severity ages 5-11. (From NHLBI/National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. NIH Publication; 2007.)

Foreign Body Aspiration

Aspiration of a foreign body into the intrathoracic airways must be considered in the differential diagnosis of a child with the sudden onset of respiratory distress or wheezing. If both main stem bronchi or the trachea are obstructed (typically by larger foreign bodies), the patient may have asphyxia and sudden death; aspiration of foreign bodies in the distal airways often takes a more indolent course. Aspiration of foreign bodies is most common in children between 1 and 4 years of age, particularly in boys or in children with neurologic disorders or delayed development. It is rare in children younger than 6 months. The most common objects aspirated by children are small toy parts, coins, marbles, balloons, and food products (e.g., hot dogs, popcorn, seeds, nuts, grapes, carrots, and beans). Endobronchial aspiration of peanuts, raisins, popcorn kernels, or seeds tends to produce more difficulties than other kinds of foreign bodies (metallic or plastic objects) because, in addition to causing physical obstruction of the airway, vegetable matter produces an intense, local inflammatory response secondary to chemical and allergic bronchitis. Larger objects, such as coins, usually lodge in the esophagus. Esophageal foreign bodies can produce significant respiratory symptoms as a result of extrinsic compression of the posterior trachea. This compression can produce respiratory distress, stridor, and wheezing, especially in infants and young children. Dysphagia and vomiting can be late symptoms associated with an esophageal foreign body.

The typical clinical manifestation after the acute event is abrupt respiratory distress, characterized by choking, gagging, cyanosis, and a harsh, paroxysmal cough (see Chapter 2). However, because many aspiration events occur while children are unsupervised, the history of foreign body ingestion or aspiration is frequently not elicited. Chronic cough, dyspnea, hemoptysis, and wheezing may develop. Because the object is most frequently aspirated into the main stem or segmental bronchi (distal airway), the wheezing is typically unilateral. Physical examination may also reveal a decrease in breath sounds on the obstructed side, prolongation of the expiratory phase, and a tracheal shift. In some instances, retained foreign bodies in the airways can produce a persistent pneumonitis, and the chronic inflammatory response can result in bronchiectasis or lung abscess. Retained foreign body should be considered in a child with presumed asthma or pneumonia who is not improving with appropriate treatment.

The diagnosis of foreign body aspiration can be difficult to establish and necessitates a combination of clinical examination, radiographic

(See *Nelson Textbook of Pediatrics,* p. 2040.)

Components of Severity		Classification of Asthma Severity ≥12 years of age			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 8–19 yr 85% 20–39 yr 80% 40–59 yr 75% 60–80 yr 70%	Symptoms	≤2 days/week	≥2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily, and not more than 1x on any day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1 /FVC normal	• FEV_1 >80% predicted • FEV_1 /FVC normal	• FEV_1 >60% but <80% predicted • FEV_1 /FVC reduced 5%	• FEV_1 <60% predicted • FEV_1 /FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← Consider severity and interval since last exacerbation. → Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV_1.			
Recommended Step for Initiating Treatment		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	Step 4 or 5
		In 2–6 weeks, evaluate level of asthma control that is achieved, and adjust therapy accordingly.			

Key: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

FIGURE 3.5 Classifying asthma severity ages ≥12. (From NHLBI/National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. NIH Publication; 2007.)

studies, and ultimately endoscopic visualization. Radiopaque foreign bodies are generally easily visualized by radiographic studies. Radiolucent foreign bodies may become apparent on inspiratory or expiratory chest radiographs, lateral decubitus films, fluoroscopy, or barium swallow studies when an esophageal foreign body could be compressing the posterior tracheal wall. Because an occasional foreign body may not lodge in a bronchus, typical radiologic findings may not be seen. If a foreign body is likely to be present, rigid bronchoscopy for examination of the lower airway and foreign body removal is indicated. Flexible bronchoscopy provides an excellent visualization of the airway and should be reserved for when other diagnoses appear to be much more likely.

Stridor

Stridor, a harsh medium-pitched sound typically heard on inspiration, is caused by turbulent airflow in the upper airway. The phase of respiration in which stridor occurs is helpful in identifying the site of the airway obstruction (see Fig. 3.1). The relative anatomy of the upper airway in an adult versus in an infant is shown in Fig. 3.6. The most common cause of stridor of infants and young children is **laryngomalacia**, Congenital anomalies should be suspected in children with recurrent or persistent stridor. Acute inspiratory stridor is most commonly caused by acute inflammation/infection, typically **croup**; however, an acute foreign body aspiration in the upper airway may also cause acute-onset stridor. Epiglottitis is the most serious life-threatening infection in this area and must be identified quickly. A history of prior intubation in a patient with stridor and respiratory distress should raise concern for vocal cord paralysis or subglottic stenosis. An age-related differential diagnosis is noted in Table 3.9. Differentiating features of common disorders are noted in Table 3.10.

Croup

Laryngotracheal bronchitis (croup) is generally a slowly progressive, mild, self-limited viral inflammation of the subglottic larynx occurring in infants and young children. The most common causes are parainfluenza virus types 1 and 3, influenza A, respiratory syncytial virus, and adenovirus. The circumferential cricoid cartilage, which comprises the subglottic airway just below the vocal cords, is the narrowest part of the upper airway in a child (see Fig. 3.6). The inflammation associated with a viral infection in this location causes airway obstruction as edema develops within the confines of the cricoid cartilage. Most patients will develop mild rhinorrhea, cough, and low-grade fever prior to characteristic barky cough and inspiratory stridor (see Chapter 2). The cry or voice may become hoarse. Stridor typically worsens when the patient is upset or active, and improves with warm humidified air. Unless the airway obstruction is severe, the child generally has

(See *Nelson Textbook of Pediatrics,* Fig. 385-1.)

no trouble handling saliva. If a patient develops drooling or rapid progression of respiratory distress, epiglottitis or bacterial tracheitis should be considered. The diagnosis is usually apparent from the history and physical examination. If the diagnosis is not clear, obtaining a lateral neck radiograph is indicated and will show the classic "steeple" sign (Fig. 3.7).

Management varies from outpatient observation with parent education to endotracheal intubation. For mild cases, the patient must be well hydrated; the use of extra humidity is soothing to the airways and helps to keep secretions from being tenacious, so that they are less likely to become obstructive. In more severe cases (stridor at rest, retractions), nebulized epinephrine used as a mucosal vasoconstrictor may provide relief. Usually, patients being treated in this manner are observed in the hospital for a possible "rebound" effect that may occur 2-6 hours after treatment. Parenteral or oral dexamethasone is a safe and effective additional therapy for moderate to severe croup; steroid use has decreased the requirement for endotracheal intubation. Patients with severe croup are usually admitted to the hospital for observation. If intubation is needed, an endotracheal tube one-half to one size smaller than that used for a child with a normal airway of the same age and size is chosen. In atypical cases of recurrent croup or in patients in whom extubation is difficult, an endoscopic evaluation of the airway with laryngoscopy and bronchoscopy is necessary to exclude an underlying anatomic abnormality.

Bacterial Tracheitis

Bacterial tracheitis is a bacterial superinfection of a previous tracheal (croup, influenza virus) viral process and is usually caused by *Staphylococcus aureus*. A variety of other organisms, including *Moraxella*

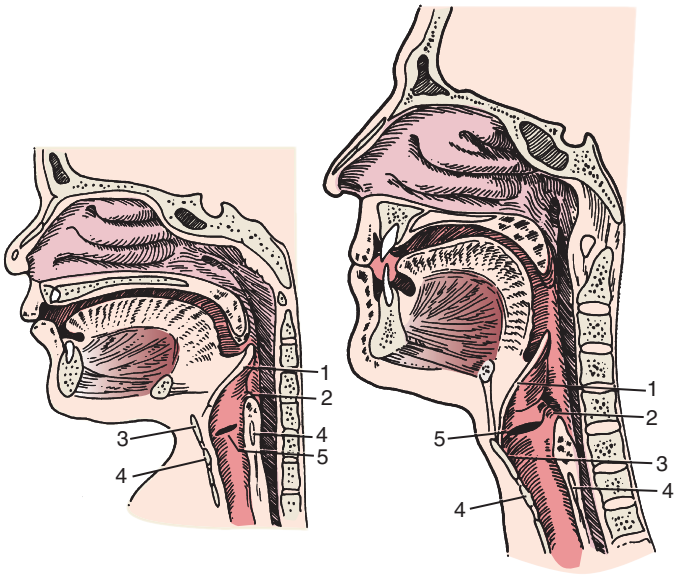


FIGURE 3.6 Anatomy of upper airway. Relative comparative anatomy of the larynx in an infant *(left)* and an adult *(right)*. Specific landmarks: *1,* epiglottis; *2,* arytenoid cartilages; *3,* thyroid cartilage; *4,* cricoid cartilage; *5,* laryngeal ventricle, the air space below the false vocal cords and above the true vocal cords. Its radiolucency is an excellent landmark on lateral radiograph. The infant larynx is situated relatively high in the cervical region. In addition, the base of the infant's tongue is close to the larynx, and the epiglottis is located near the palate. These anatomic differences partially explain the predominantly obligate nose breathing of the young infant, as well as the relative ease with which upper airway obstructions develop in infants.

TABLE 3.9 Age-Related Differential Diagnosis of Airway Obstruction

Newborn
Foreign material (meconium, amniotic fluid)
Congenital subglottic stenosis (uncommon)
Choanal atresia
Congenital cysts
Micrognathia (Pierre Robin syndrome, Treacher Collins syndrome, DiGeorge syndrome)
Macroglossia (Beckwith-Wiedemann syndrome, hypothyroidism, Pompe disease, trisomy 21, hemangioma)
Laryngeal web, clefts, atresia
Laryngospasm (intubation, aspiration, hypocalcemia, transient)
Lingual thyroid
Vocal cord paralysis (weak cry; unilateral or bilateral, with or without increased intracranial pressure from Arnold-Chiari malformation or other CNS pathology; birth trauma)
Tracheal web, stenosis, malacia, atresia
Pharyngeal collapse (cause of apnea in preterm infant)
Tumors*

Infant
Laryngomalacia (most common cause)
Subglottic stenosis (congenital; acquired after intubation)
Tumors*
Tongue tumor (dermoid, teratoma, ectopic thyroid)
Laryngeal papillomatosis
Vascular rings

Toddler
Viral croup (most common etiology in children 3 mo–4 yr of age)
Bacterial tracheitis (toxic, high fever)
Foreign body (sudden cough; airway or esophageal) (see Chapter 2)
Spasmodic (recurrent) croup (see Chapter 2)
Laryngeal papillomatosis
Retropharyngeal abscess
Diphtheria (uncommon)

Infant Older Than 2-3 Yr
Epiglottitis (epiglottis, aryepiglottic folds)
Inhalation injury (burns, toxic gas, hydrocarbons)
Foreign bodies
Angioedema (family history, cutaneous angioedema)
Anaphylaxis (allergic history, wheezing, hypotension)
Trauma (tracheal or larynx fracture)
Peritonsillar abscess (adolescents)
Ludwig angina
Diphtheria
Parapharyngeal abscess
Tumors*
Trauma

*Tumors include lymphangiomas, hemangiomas, papillomas, neuroblastoma, lymphoma, rhabdomyosarcoma, and chondrosarcomas.
CNS, central nervous system.
Modified from Kercsmar C. The respiratory system. In: Behrman RE, Kliegman RM, eds. *Nelson Essentials of Pediatrics*. 2nd ed. Philadelphia: WB Saunders; 1994:444.

TABLE 3.10 Differential Diagnosis of Upper Airway Obstruction

	Laryngotracheo-bronchitis (Croup)	Laryngitis	Spasmodic Croup	Epiglottitis	Membranous Croup (Bacterial Tracheitis)
Age	3 mo–3 yr	5 yr–teens	3 mo–3 yr	2–6 yr	Any age (3–10 yr)
Location	Subglottic	Subglottic	Subglottic	Supraglottic	Trachea
Etiology	Parainfluenza, influenza virus, RSV; rarely *Mycoplasma,* measles, adenovirus	As per croup	Unknown	*Haemophilus influenzae* type b	Prior croup or influenza virus with secondary bacterial infection by *Staphylococcus aureus, Moraxella catarrhalis, H. influenzae*
Prodrome onset	Insidious, URI	As per croup	Sudden onset at night; prior episodes	Rapid, short prodrome	Biphasic illness with sudden deterioration
Stridor	Yes—biphasic	No	Yes	Yes—soft inspiratory	Yes
Retractions	Yes	No	Rare	Yes	Yes
Voice	Hoarse	Hoarse; whispered	Hoarse	Muffled	Normal or hoarse
Position and appearance	Normal	Normal	Normal	Tripod sitting, leaning forward; agitation	Normal
Swallowing (dysphagia)	Normal	Normal	Normal	Drooling	Normal
Barking cough	Yes	Rare	Yes	No	Yes
Toxicity	Rare	No	No	Severe	Severe
Fever	<101°F	<101°F	None	>102°F	>102°F
Radiographic findings	Subglottic narrowing; steeple sign	Normal	Subglottic narrowing	Thumb sign of thickened epiglottis	Ragged irregular tracheal border; as per croup
WBC count	Normal	Normal	Normal	Leukocytosis with left shift	Leukocytosis with left shift
Therapy	Racemic epinephrine: aerosol, systemic steroids, aerosolized steroids, cool mist	None	Cool mist; occasionally as for croup	Endotracheal intubation, ceftriaxone	Vancomycin; ceftriaxone; intubation if needed
Prevention	None	None	None	*H. influenzae* type b conjugated vaccine	None

FFP, fresh-frozen plasma; HPV, human papillomavirus; IV, intravenous; RSV, respiratory syncytial virus; URI, upper respiratory tract infection; WBC, white blood cell.

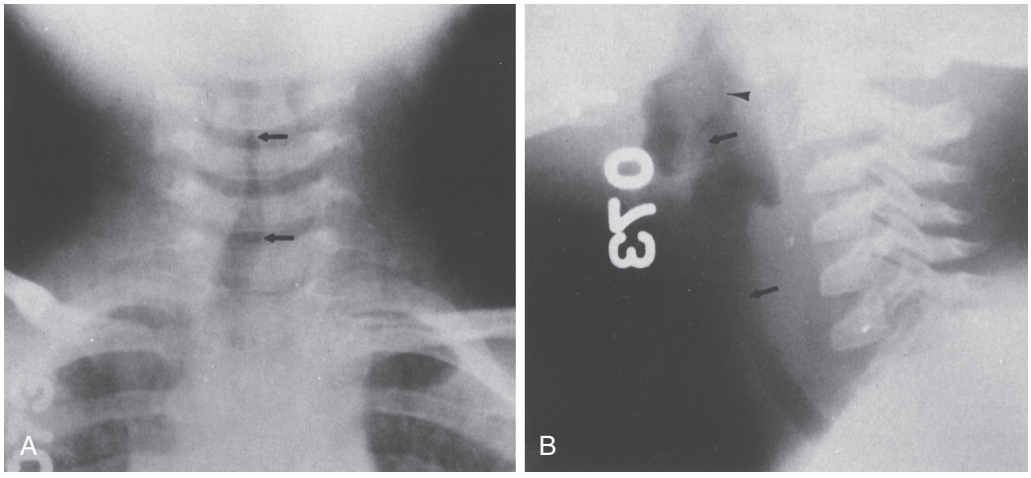


FIGURE 3.7 Croup in a 1-year-old child. *A,* Frontal radiograph of the neck shows a tapered reduction of the subglottic tracheal caliber from the level of the vocal cords *(upper arrow)* to the normal-caliber trachea below *(lower arrow)*. The right mild tracheal deviation is a normal sign resulting from the left aortic arch. *B,* Lateral view shows a normal epiglottis *(upper arrow)*, distention of the pharynx, normal palatine tonsils *(arrowhead)*, and increased density in the subglottic trachea *(lower arrow)*.

TABLE 3.10 Differential Diagnosis of Upper Airway Obstruction—cont'd

Retropharyngeal Abscess	Foreign Body	Angioedema	Peritonsillar Abscess	Laryngeal Papillomatosis
<6 yr	6 mo–5 yr	All ages	>10 yr	3 mo–3 yr
Posterior pharynx	Supraglottic, subglottic, variable	Variable	Oropharynx	Larynx, vocal cords, trachea
S. aureus, anaerobes	Small objects, vegetable, toys, coins	Congenital C-1 esterase deficiency; acquired anaphylaxis	Group A streptococci, anaerobes	HPV
Insidious to sudden	Sudden	Sudden	Biphasic with sudden worsening	Chronic
No	Yes	Yes	No	Possible
Yes	Yes (variable)	Yes	No	No
Muffled	Complete obstruction—aphonic; other variable	Hoarse, may be normal	"Hot potato," muffled	Hoarse
Arching of neck or normal	Normal	Normal; may have facial edema	Normal	Normal
Drooling	Variable; usually normal	Normal	Drooling, trismus	Normal
No	Variable; brassy if tracheal	Possible	No	Variable
Severe	No, but dyspnea	No, unless anaphylactic shock or severe anoxia	Dyspnea	None
>101°F	None	None	>101°F	None
Thickened retropharyngeal space	Radiopaque object may be seen	As per croup	None needed	May be normal
Leukocytosis with left shift	Normal	Normal	Leukocytosis with left shift	Normal
Clindamycin; ampicillin-sulbactam (or vancomycin); ceftriaxone; surgical drainage if abscess	Endoscopic removal	Anaphylaxis; epinephrine, IV fluids, steroids; C-1 esterase deficiency; replacement infusion therapy	Penicillin; aspiration	Laser therapy, repeated excision, interferon
None	Avoid small objects; supervision	Avoid allergens; FFP for hereditary angioedema	Treat group A streptococci early	Treat maternal genitourinary lesions; possible cesarean section? HPV vaccine to mother

catarrhalis, *Streptococcus pneumoniae*, and nontypable *H. influenzae* have also been identified as being occasionally involved. There is generally a virus-like mild phase, followed by a rapid deterioration, during which the patient clinically appears more ill with high fever and respiratory distress. Some patients have a two-phased illness with croup, initial recovery, followed by tracheitis. Neck and chest radiographs often show irregular scalloping of the trachea. Radiopaque densities from inspissated mucus may be seen. Close monitoring and intravenous antibiotic treatment directed toward the likely causative organisms are required. Endotracheal intubation for control of the airway is usually necessary, particularly in younger patients. Extubation is performed on the basis of clinical improvement and a resolution of excessive amounts of purulent secretions. Sometimes the exudate secondary to the tracheitis is thick and can cause airway obstruction similar to that from a foreign body.

Epiglottitis

Epiglottitis is an acute, rapidly progressive, potentially lethal infection of the epiglottis, aryepiglottic folds, and false vocal cord area. It is an emergency because of the potential for rapid airway obstruction; evaluation and treatment are directed toward establishing an airway while the physician is confirming the diagnosis and treating the infection. In the past, epiglottitis was caused by *Haemophilus influenzae* type b in nearly 100% of cases. Since the introduction of the polysaccharide conjugated *H. influenzae* type b vaccine, there has been a dramatic fall in the incidence of acute epiglottitis in the United States. However, in an internationally mobile world, patients who have not been vaccinated may acquire epiglottitis in any country. In addition, other, less common pathogens, such as *S. pneumoniae*, *S. aureus*, and ß-hemolytic streptococci, may produce epiglottitis. Unusual presentations will also become more common, with children presenting at a younger age and immunosuppressive diseases being caused by atypical organisms.

Typically, there is an abrupt onset, usually without an obvious prodrome, with rapid progression toward airway compromise. Initially, complaints of sore throat and odynophagia are common. Patients are usually febrile, and drooling is present. The typical presentation is an ill-appearing child sitting forward with her or his head hyperextended who does not want to lie down (Fig. 3.8). There is a "hot potato"

FIGURE 3.8 Child with epiglottitis. Characteristic posture in a patient with epiglottitis. The child is leaning forward and drooling, and the neck is hyperextended.

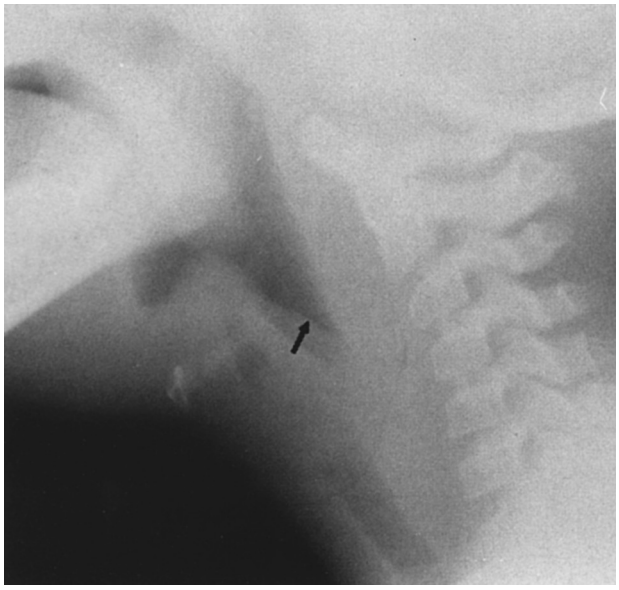


FIGURE 3.9 Epiglottitis. The patient is a 3 1/2 year old child with fever and sudden onset of stridor. Lateral radiograph shows an enlarged epiglottis ("thumb-print" sign) and aryepiglottic folds *(arrow)* and distention of the pharynx.

voice and drooling, the mouth is open, and the tongue is protruding. Mild inspiratory stridor and retractions may be present, but these are usually not obvious, because the patient generally takes short, shallow breaths. An intraoral examination is contraindicated because it may predispose to laryngospasm and airway obstruction.

If there is any question as to the diagnosis, a lateral soft tissue radiograph of the neck can be confirmatory (Fig. 3.9). Someone who has the expertise and equipment to handle sudden airway decompensation in a pediatric patient should accompany the patient to the radiology suite. When a clinical diagnosis of epiglottitis is at all likely, the patient should be taken immediately to the operating room and cared for by experienced pediatric anesthesiology and otolaryngology personnel capable of endotracheal intubation or less often tracheostomy.

Once the airway is secured and the diagnosis confirmed, blood specimens are obtained for culture and treatment is begun with ceftriaxone or cefotaxime. Patients usually require 36-48 hours of endotracheal intubation, with observation in the pediatric intensive care unit. If there is a question of safety of extubation, a second laryngoscopy is indicated.

Laryngomalacia

Laryngomalacia is the most common cause of inspiratory stridor and noisy respiration in neonates and infants. It is caused by the inspiratory collapse of the laryngeal cartilages, with prolapse of the epiglottis or arytenoid cartilages into the airway during inspiration. It typically presents with high-pitched inspiratory stridor. Stridor may occur at birth, but the onset is often delayed, occurring at 2-4 weeks of age. The condition is usually self-limited and resolves with time: often by 8-12 months of age but occasionally not until 18-24 months of age. Laryngomalacia should be suspected in infants with recurrent croup, as acute viral infections or agitation can worsen symptoms. Patients often will have associated gastroesophageal reflux disease, and some may have feeding difficulties or failure to thrive. Severe cases may cause apneic events or pulmonary hypertension.

The diagnosis is made on the basis of the clinical presentation (stridor is worse when the patient is supine or during activity, and exacerbations occur with upper respiratory tract infections) and findings on flexible laryngoscopy. Approximately 15-25% of patients with laryngomalacia may have other airway lesions. Therefore a complete airway evaluation with rigid bronchoscopy has been recommended in patients with severe respiratory distress, failure to thrive, any underlying concern for a concurrent airway lesion, and if the stridor of laryngomalacia does not follow the typical course. Unusually severe cases of laryngomalacia may necessitate operative intervention, such as a supraglottoplasty to trim redundant soft tissue or even a temporary tracheotomy. Laryngomalacia may be accompanied by tracheomalacia, a partial collapse of the tracheal cartilages with respiration. Tracheomalacia may be congenital or secondary to extrinsic compression by vascular rings or tumors. Patients with tracheomalacia manifest with wheezing, cough, stridor, dyspnea, tachypnea, or cyanosis.

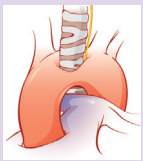
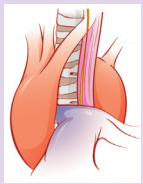
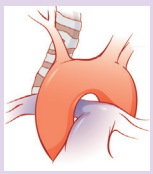
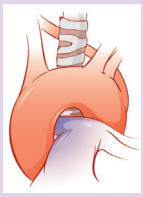
Vocal Cord Paralysis

Vocal cord paralysis is a common cause of congenital neonatal laryngeal obstruction, but can also occur in older children. Vocal cord paralysis may be bilateral or unilateral, and it often can cause difficulty feeding, respiratory distress, and a weak cry. In neonates with no surgical history, it is associated with neurologic syndromes, such as the Arnold-Chiari malformation. Traction on the brainstem or increased intracranial pressure and herniation puts pressure on the vagus nerve, which is thought to cause the paralysis. It can also be iatrogenic, particularly in neonates with a history of thoracic surgery or difficult delivery. Tracheotomy is often necessary to maintain the airway in bilateral vocal cord paralysis, and neurologic and MRI evaluation should be performed to identify any central causes. Vocal cord paralysis also occurs in older children and may be caused by a polyneuropathy (Guillain-Barré syndrome), brainstem encephalitis, neck or thoracic surgery, or compression by local masses.

Vascular Rings

Vascular rings are common and can produce symptoms related to compression of the trachea and/or the esophagus (Table 3.11). Feeding often exacerbates manifestations when the obstructed esophagus acts as an additional extrinsic force on the trachea. Patients present with

TABLE 3.11 Vascular Rings

Lesion	Symptoms	Plain Film	Barium Swallow	Bronchoscopy	MRI Echocardiography	Treatment
 Double arch	Stridor, respiratory distress Swallowing dysfunction Reflex apnea	AP—wider base of heart Lat.—narrowed trachea displaced forward at C3-C4	Bilateral indentation of esophagus	Bilateral tracheal compression—both pulsatile	Diagnostic	Ligate and divide smaller arch (usually left)
 Right arch and ligamentum/ductus	Respiratory distress Swallowing dysfunction	AP—tracheal deviation to left (right arch)	Bilateral indentation of esophagus R > L	Bilateral tracheal compression—R pulsatile	Diagnostic	Ligate ligamentum or ductus
 Anomalous innominate	Cough Stridor Reflex apnea	AP—normal Lat.—anterior tracheal compression	Normal	Pulsatile anterior tracheal compression	Unnecessary	Conservative
 Aberrant right subclavian	Occasional swallowing dysfunction	Normal	AP—oblique defect upward to right Lat.—small defect on right posterior wall	Usually normal	Diagnostic	Ligate artery
Pulmonary sling	Expiratory stridor Respiratory distress	AP—low L. hilum, R emphysema/atelectasis Lat.—anterior bowing of right bronchus and trachea	±Anterior indentation above carina between esophagus and trachea	Tracheal displacement to left Compression of right main bronchus	Diagnostic	Detach and reanastomose to main pulmonary artery in front of trachea

AP, anteroposterior; L, left; Lat., lateral; MRI, magnetic resonance imaging; R, right.
From Kliegman RM, Greenbaum LA, Lye PS. *Practical Strategies in Pediatric Diagnosis and Therapy*. 2nd ed. Philadelphia: Elsevier; 2004: 88.

cough, dysphagia, odynophagia, tachypnea, emesis, noisy breathing, stridor, and/or wheezing. Because they handle oral secretions poorly, they may develop aspiration pneumonia. They also do not tolerate neck flexion. The two most common symptomatic lesions are the right aortic arch with a left ligamentum arteriosus (or patent ductus arteriosus) and the double aortic arch. The diagnosis may be suspected on a chest radiograph by a demonstrated right-sided aortic arch or a narrow displaced trachea. An upper GI series demonstrates the indentation of the anterior and/or posterior esophagus, whereas endoscopy demonstrates the pulsatile extrinsic compressing vessels (Fig. 3.10). MRI or echocardiography is usually diagnostic; angiography is not needed to find most of these lesions.

Subglottic Stenosis

Congenital subglottic stenosis occurs when the subglottic space is narrowed, and typically presents in children younger than 3 months with respiratory distress, biphasic or inspiratory stridor, and recurrent croup. *Acquired* subglottic stenosis may develop secondary to endotracheal intubation, particularly if the intubation has been prolonged for several months, if an oversized tube was used, or if multiple intubations were required. Subglottic stenosis should be suspected in any child with these risk factors who does not tolerate extubation because of upper airway obstruction. Laryngoscopy and bronchoscopy are required for evaluation to diagnose subglottic stenosis and also evaluate for other lesions such as subglottic cysts or hemangiomas. Acquired subglottic stenosis is often more severe than the congenital type. In both types of subglottic stenosis, infection and gastroesophageal reflux may exacerbate symptoms and contribute to narrowing of the airway. A cricoid split operation, tracheotomy, or laryngotracheal reconstruction may be needed. Serial dilatations are no longer commonly used because they may continue to injure the cartilage and its overlying mucosa.

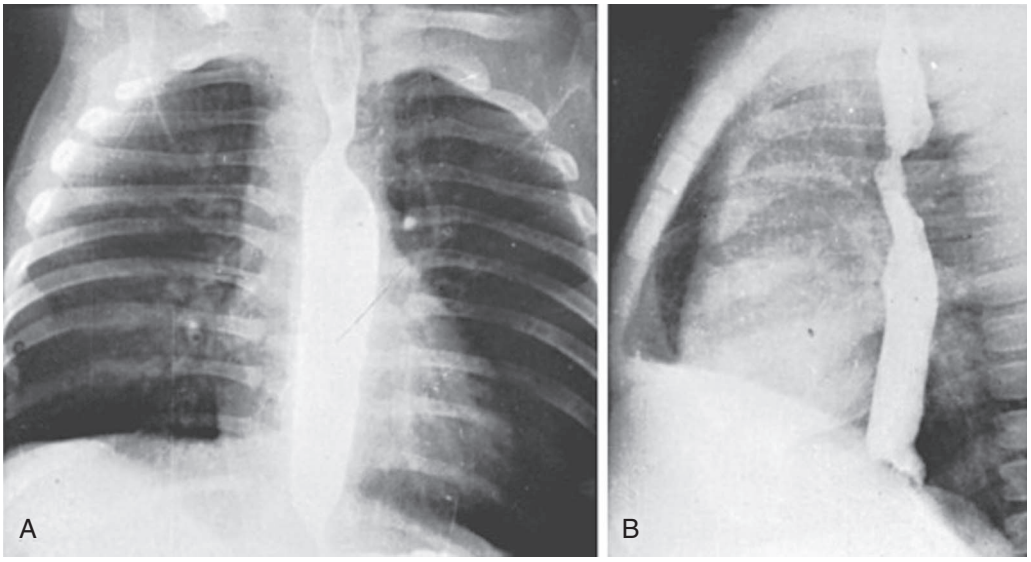


FIGURE 3.10 Double aortic arch in an infant aged 5 months. *A*, Anteroposterior view. The barium-filled esophagus is constricted on both sides. *B*, Lateral view. The esophagus is displaced forward. The anterior arch was the smaller and was divided at surgery. (From Bernstein D. Other congenital heart and vascular malformations. In: Kliegman RM, Stanton BF, St Geme JW, Schor NF, eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:2237.)

Cough

Cough is a common complaint in children (see Chapter 2). The nature of the cough is often helpful in establishing the etiology of respiratory distress. For example, a barky cough is typically associated with viral croup, whereas a more productive cough can be associated with pneumonia. Pneumonia is most commonly caused by bacteria or viruses; however, there are other common noninfectious causes of pneumonia and pneumonitis.

Viral and Bacterial Pneumonia

Pneumonia is a significant cause of mortality for children worldwide. Pneumonia is defined as acute inflammation of the lung parenchyma, and can be caused by viruses or bacteria. Clinically, it is often defined as a lower respiratory tract infection, associated with fever, respiratory symptoms, and evidence of lung parenchyma involvement, either by physical examination or chest radiograph findings. *S. pneumoniae* is the most common bacterial pathogen of community-acquired pneumonia; *H. influenzae* and *S. aureus* are less common causes. Viral pathogens are also a common cause of pneumonia in young children; it can be difficult to discern which pathogen is causing the clinical symptoms. Atypical pathogens, such as *M. pneumoniae*, are a common cause of pneumonia in school-aged children (Table 3.12). Children with immunodeficiency, sickle cell disease, cystic fibrosis, or HIV may present with more atypical pathogens.

Patients will often begin with an upper respiratory infection with rhinitis and cough (see Chapter 2). They then develop tachypnea and fever and then may develop respiratory distress with subcostal, intercostal, and suprasternal retractions, nasal flaring and use of accessory muscles, and hypoxia. Tachypnea and worsening cough are commonly noted. Patients with lower lobe pneumonias may also present with abdominal pain. Early in the course of illness, crackles, rhonchi, and wheezing are common findings. Later in the course of illness, as lungs consolidate and/or pleural effusions or empyema develop, decreased breath sounds and dullness to percussion may develop. Wheezing is more likely in viral or atypical pneumonia; however, unilateral wheezing may also correlate with a bacterial lobar pneumonia.

TABLE 3.12 Etiologic Agents of Pneumonia Grouped by Age of the Patient

Age Group	Frequent Pathogens (in Order of Frequency)
Neonates (<3 wk)	Group B streptococcus, *Escherichia coli,* other gram-negative bacilli, *Streptococcus pneumoniae, Haemophilus influenzae* (type b,* nontypable), herpes simplex
3 wk-3 mo	Respiratory syncytial virus, other respiratory viruses (rhinoviruses, parainfluenza viruses, influenza viruses, adenovirus), *S. pneumoniae, H. influenzae* (type b,* nontypable); if patient is afebrile, consider *Chlamydia trachomatis*
4 mo-4 yr	Respiratory syncytial virus, other respiratory viruses (rhinoviruses, parainfluenza viruses, influenza viruses, adenovirus), *S. pneumoniae, H. influenzae* (type b,* nontypable), *Mycoplasma pneumoniae,* group A streptococcus
≥5 yr	*M. pneumoniae, S. pneumoniae, Chlamydophila pneumoniae, H. influenzae* (type b,* nontypable), influenza viruses, adenovirus, other respiratory viruses, *Legionella pneumophila*

* ***H. influenzae*** type b is uncommon with routine *H. influenzae* immunization.

From Kelly MS, Sandora TJ. Community acquired pneumonia. In: Kliegman RM, Stanton BF, St. Geme JW, Schor NF, eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:2090

Diagnosis is made by chest radiograph, which will show a consolidation, and may show empyema or pleural effusion if present (Fig. 3.11). However, it is important to note that in children with mild lower respiratory tract disease with clinical symptoms consistent with pneumonia, a chest radiograph is not needed to make a diagnosis. Patchy infiltrates are most suggestive of atypical or viral

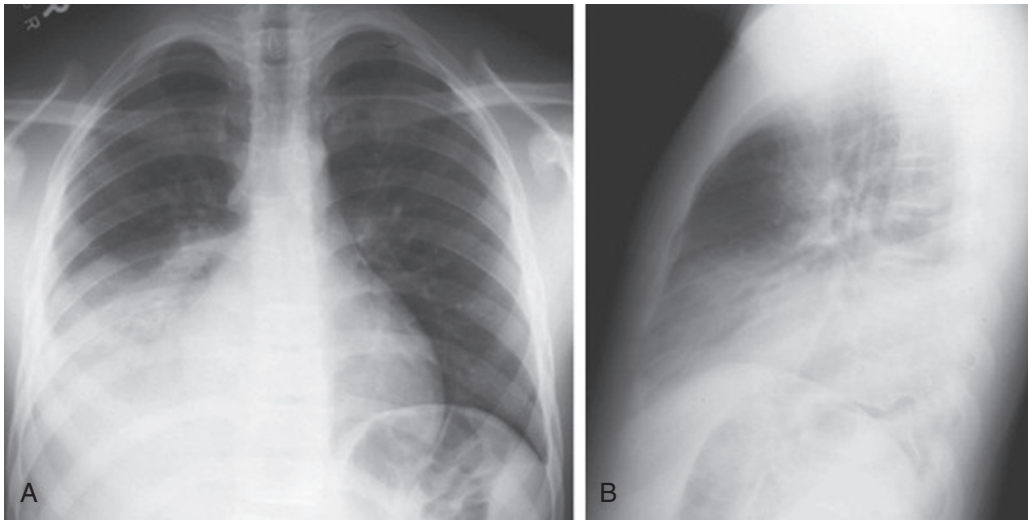


FIGURE 3.11 Radiographic findings characteristic of pneumococcal pneumonia in a 14-year-old boy with cough and fever. Posteroanterior *(A)* and lateral *(B)* chest radiographs reveal consolidation in the right lower lobe, strongly suggesting bacterial lobar pneumonia. (From Kelly MS, Sandora TJ: Community acquired pneumonia. In: Kliegman RM, Stanton BF, St. Geme JW, Schor NF, eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:2092, Figure 400-3.)

pneumonia. A lobar consolidation or large pleural effusion is likely from a bacterial etiology. Laboratory testing may be helpful in patients with more severe disease, but is not necessary in all patients. Peripheral white blood cell (WBC) count and acute phase reactants are likely elevated, and can be used to follow response to therapy along with clinical response. Blood cultures should be obtained for patients with moderate to severe disease, or who fail to demonstrate improvement after the initiation of antibiotics. Viral or atypical pathogen testing may be helpful as this may decrease need for additional testing or antibiotic use.

Treatment for bacterial pneumonia is antibiotics directed at suspected cause of pneumonia and supplemental care (oxygen, intravenous fluids) as indicated based on patient's clinical presentation. Hospitalization may be required for patients with hypoxia or toxic appearance, moderate to severe respiratory distress, age <6 months, or if there are concerns about observation or compliance with therapy at home. Those with complicated pneumonia (pleural effusion, empyema, abscess, or extrapulmonary infection) or suspected/documented pathogen with increased virulence are also likely to require hospitalization and further interventions.

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis, or extrinsic allergic alveolitis, results from the inhalation of organic dust particles. Although numerous causes have been identified, the clinical features of the various types of hypersensitivity pneumonitis are similar and depend on the intensity and frequency of exposure to the allergen; both acute and chronic forms have been described.

In the acute form of the disease, the patient typically has fever, rigors, cough, and dyspnea several hours after exposure. The symptoms usually resolve within 24 hours of the onset once the offending material is removed. In the chronic or subacute forms of hypersensitivity pneumonitis, the affected individual may have exercise intolerance, anorexia, weight loss, and a productive cough. Diffuse crackles are the prominent finding on physical examination; the patient may be cyanotic if gas exchange is significantly impaired. Digital clubbing is an unusual finding. In acute cases, inflammation of the alveoli and pulmonary interstitium are common reactions, whereas the chronic form can result in interstitial fibrosis and noncaseating granulomas. Chronic hypersensitivity pneumonitis can insidiously lead to respiratory failure and cor pulmonale.

A number of laboratory studies may be helpful in confirming the diagnosis of hypersensitivity pneumonitis. Chest radiograph demonstrates diffuse reticulonodular infiltrate. Pulmonary function studies (spirometry) characteristically show a restrictive defect, and the carbon monoxide diffusion capacity is reduced. During the acute phase of the disease, the patient may have a peripheral leukocytosis and eosinophilia. Serologic studies looking for precipitating immunoglobulin G antibodies to specific antigens are useful in identifying the offending agent. However, these antibodies may be found in asymptomatic individuals exposed to the allergen, and thus their presence is not necessarily correlated with severity of pulmonary disease. Percutaneous or intradermal tests may also be useful, particularly if an avian hypersensitivity pneumonitis is suspected.

Removal of the specific organic dust from the patient's environment is critical to treatment. Mild episodes of hypersensitivity pneumonitis may resolve spontaneously once the offending allergen is eliminated. Severe exacerbations often necessitate treatment with systemic corticosteroids; bronchodilators may be beneficial if the patient is experiencing symptoms of bronchospasm. Hypersensitivity pneumonitis must be differentiated from other causes of interstitial or diffuse lung disease (Table 3.13).

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is an immunologic disorder identified in patients with chronic lung disease, in which airway colonization (but not invasive infection) with *Aspergillus fumigatus* causes chronic antigen exposure and increased bronchial hyperactivity. This condition can lead to bronchiectasis, pulmonary fibrosis, and progressive respiratory insufficiency. Hypersensitivity to other fungal species that produces a clinical picture similar to that of ABPA has been reported.

It is important that the diagnosis of ABPA be made and that appropriate therapy with systemic corticosteroids be instituted, because this condition can result in irreversible lung damage. ABPA is characterized by fever, weight loss, wheezing, and productive cough yielding

TABLE 3.13 Classification of Interstitial Lung Disease (Pediatric Diffuse Lung Disease)*

I. Disorders More Prevalent in Infancy

A. Diffuse developmental disorders
   1. Acinar dysplasia
   2. Congenital alveolar dysplasia
   3. Alveolar–capillary dysplasia with pulmonary vein misalignment
B. Growth abnormalities
   1. Pulmonary hypoplasia
   2. Chronic neonatal lung disease
C. Prematurity-related chronic lung disease (bronchopulmonary dysplasia)
D. Acquired chronic lung disease in term infants
E. Structural pulmonary changes with chromosomal abnormalities
   1. Trisomy 21
F. Others
   1. Associated with congenital heart disease in chromosomally normal children
G. Specific conditions of undefined etiology
   1. Pulmonary interstitial glycogenosis
   2. Neuroendocrine cell hyperplasia of infancy
H. Surfactant dysfunction mutations and related disorders
   1. *SPFTB* genetic mutations—PAP and variant dominant histologic pattern
   2. *SPFTC* genetic mutations—CPI dominant histologic pattern; also DIP and NSIP
   3. *ABCA3* genetic mutations—PAP variant dominant pattern; also CPI, DIP, NSIP
   4. Others with histology consistent with surfactant dysfunction disorder without a yet recognized genetic disorder

II. Disorders Not Specific to Infancy

A. Disorders of the normal host
   1. Infectious and postinfectious processes
   2. Disorders related to environmental agents: hypersensitivity pneumonia, toxic inhalation.
   3. Aspiration syndromes
   4. Eosinophilic pneumonia
B. Disorders related to systemic disease processes
   1. Immune-related disorders
   2. Storage disease
   3. Sarcoidosis
   4. Langerhans cell histiocytosis
   5. Malignant infiltrates
C. Disorders of the immunocompromised host
   1. Opportunistic infection
   2. Disorders related to therapeutic intervention
   3. Disorders related to transplantation and rejection syndromes
   4. Diffuse alveolar damage of unknown etiology
D. Disorders masquerading as interstitial disease
   1. Arterial hypertensive vasculopathy
   2. Congestive vasculopathy, including venoocclusive disease
   3. Lymphatic disorders
   4. Congestive changes related to cardiac dysfunction

III. Unclassified

A. Includes end-stage disease, nondiagnostic biopsies, and those with inadequate material

*Many of these entities may present as child interstitial lung disease syndromes.
CPI, chronic pneumonitis of infancy; DIP, desquamative cell interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; PAP, pulmonary alveolar proteinosis.
From Kurland G, Deterding RR, Hagood JS, et al. An official American Thoracic Society clinical practice guideline: classification, evaluation, and management of childhood interstitial lung disease in infancy. *Am J Resp Crit Care Med.* 2013;188:376-394.

purulent or rust-colored sputum. This condition should be considered in patients with chronic or atypical and progressive or frequently relapsing lung diseases, such as asthma or cystic fibrosis, who have undergone clinical deterioration. In developing countries it is often misdiagnosed as pulmonary tuberculosis. ABPA is associated with peripheral eosinophilia and markedly elevated serum IgE levels. Although these laboratory findings are not pathognomonic for this condition, the presence of a normal serum IgE makes the diagnosis of active disease unlikely. Affected individuals have evidence of hypersensitivity to *Aspergillus fumigatus*, and sputum evaluation may demonstrate Aspergillus hyphal elements. Elevated levels of specific IgE and immunoglobulin G antibodies to *Aspergillus fumigatus* can be useful in establishing the diagnosis.

The typical chest radiographic findings include increased bronchopulmonary markings, opacification of the affected area, and localized pulmonary consolidation. Linear radiolucencies and parallel markings radiating from the hilum ("tram lines") caused by dilated, thickened bronchi may also be present. Chest CT may demonstrate bronchiectasis, mucoid impaction, and pleuropulmonary fibrosis. The treatment of choice is systemic corticosteroids, administered for weeks to months. Antifungal agents, such as itraconazole, may be effective in preventing exacerbations, but are not helpful in treating acute exacerbations; therefore these may be a helpful adjunctive therapy.

Other Causes of Respiratory Distress

Aspiration of Oropharyngeal Contents

Central nervous system or neuromuscular disease in infants and children can result in dysfunction of the swallowing mechanism, leading to repeated episodes of pulmonary aspiration. Aspiration is the most common cause of respiratory distress in such children and typically manifests with intractable wheezing, chronic airway inflammation, and recurrent pneumonias.

Video fluoroscopic swallow studies, in which barium-laced foods of a variety of textures and consistencies are fed to a child under direct visualization and fluoroscopy, can be useful in making the diagnosis and establishing that the child has an abnormal swallowing mechanism. These studies can be helpful with regard to therapy and may determine the appropriate feeding techniques, food consistencies, and feeding volumes that are less likely to cause aspiration in a vulnerable child.

Nasogastric tube or gastrostomy tube feedings may be necessary in children who do not respond to conservative management and who continue to have repeated episodes of aspiration. Nevertheless, the affected child can continue to have periodic aspiration of oropharyngeal secretions despite these interventions. A Nissan fundoplication or jejunostomy tube may be needed to reduce the incidence of gastric aspiration.

Gastroesophageal Reflux

Gastroesophageal reflux can be a primary cause of or an exacerbating factor in wheezing in infants and young children (see Chapter 12). Direct inhalation of stomach contents into the lungs can produce bronchospasm and a chemical pneumonitis. Gastroesophageal reflux with aspiration has also been implicated in cases of bacterial pneumonia, bronchiectasis, obliterative bronchiolitis, and lung abscesses. Tachypnea, wheezing, and cough are the usual clinical findings, typically occurring within 1 hour of the aspiration event. The signs and symptoms of the pneumonitis, however, can be delayed.

Although pulmonary aspiration of gastric contents was once assumed to be the basis of reflux-induced wheezing, reflex bronchoconstriction in response to esophageal acidification can also produce bronchospasm in some patients. Other respiratory symptoms associated with gastroesophageal reflux, such as stridor and obstructive apnea, can manifest as the result of reflex laryngospasm. Gastroesophageal reflux can also complicate and worsen underlying lung diseases, such as asthma or subglottic stenosis, by provoking bronchospasm and potentiating airway or laryngeal inflammation and possibly bronchial hyperactivity.

Pneumothorax

A pneumothorax occurs when air leaks from the alveoli or airways into the pleural space. The most common cause of pneumothorax in children is chest wall trauma. Children with asthma or other underlying chest disease may also develop a pneumothorax. However, spontaneous pneumothorax can occur in otherwise healthy children with no antecedent illness or injury, most commonly adolescent boys or young adult men who are tall, thin, and athletic. In patients with an acute pneumothorax with no history of trauma or asthma, the presence of Marfan syndrome should be considered. Clinical presentation usually includes acute onset of dyspnea and chest or shoulder pain. The physical examination reveals hyperresonance to percussion over the ipsilateral chest, with decreased breath sounds auscultated on the affected side. If the air dissects up through the mediastinum, it may escape into the subcutaneous tissues, producing subcutaneous emphysema. Diagnosis can be confirmed by chest radiograph. Progressive air leak without air escape can lead to a tension pneumothorax. With increasing pressure, there is mediastinal shift, airway compression, and a decrease in cardiac output. Tension pneumothorax can be life-threatening if it is not recognized and treated rapidly. Small, spontaneous pneumothoraces will often resolve with supportive care and supplemental oxygen. The treatment of choice for a pneumothorax of greater than 20% volume is drainage with needle aspiration or with an indwelling chest tube.

Cystic Fibrosis

Cystic fibrosis is a multisystem disorder that involves the eccrine and mucous secretory glands. Inherited as an autosomal recessive trait, cystic fibrosis is the most common life-shortening genetic disease in white children and is an important cause of chronic suppurative lung disease (see Chapter 2). Chronic infection and inflammation lead to the weakening and destruction of the airway wall, which results in bronchiectasis, the abnormal dilatation of the subsegmental airways, and in pulmonary abscesses. The pulmonary deterioration characteristic of cystic fibrosis is rather insidious and is characterized by increasing airway obstruction over a period of years. However, some infants and children with cystic fibrosis can present in acute respiratory distress because of pneumonia, empyema, or pneumothorax.

Dyskinetic Cilia Syndrome

Dyskinetic (immotile) cilia syndrome, another progressive lung disease, occurs in approximately 1 in 16,000 children and is the result of ultrastructural abnormalities of the cilia (see Chapter 2). The absence of dynein arms (inner and outer) is the most common form of the syndrome, but other structural abnormalities can result in decreased or absent ciliary movement. Acquired ciliary dyskinesia may be caused by a number of different environmental and infectious agents and is usually a temporary condition. The abnormal mucociliary clearance of endobronchial secretions causes a chronic bronchitis. Wheezing is a common clinical manifestation resulting from the obstruction of the airways by mucus. Repeated or persistent severe upper respiratory tract infections, usually in the form of chronic pansinusitis or recurrent suppurative otitis media, are typical. Male sterility resulting from the impaired movement of spermatozoa is also present. Although Kartagener initially described several patients with *situs inversus totalis*, chronic sinusitis, and bronchiectasis, dextrocardia is present in only 50% of patients with this syndrome.

Arriving at a diagnosis necessitates a high index of suspicion and warrants pursuit in the child with recurrent wheezing, bronchitis, sinusitis, and otitis media. Findings on chest radiographs are generally nonspecific, and frequently demonstrate areas of pulmonary consolidation. Extensive atelectasis with significant respiratory distress has been described in neonates with this condition. Bronchiectasis is a late sequela of dyskinetic cilia syndrome. Functional assays for mucociliary clearance or examination of respiratory epithelial cells for ultrastructural ciliary defects with electron microscopy is necessary to establish a diagnosis.

NONPULMONARY CAUSES OF RESPIRATORY DISTRESS

Cardiac

Cardiac disease is an important and common nonpulmonary cause of respiratory distress. Increased work of breathing and respiratory distress most commonly occur in cardiac diseases caused by large left-to-right shunts, dysfunction of the systemic ventricle, and vascular lesions that obstruct the airway (see Chapter 8). Cardiac failure from any cause is often manifested as respiratory distress. Infants with congenital heart defects that produce a large left-to-right shunt that results in pulmonary vascular engorgement, edema formation, and reduced lung compliance demonstrate tachypnea, dyspnea, and grunting. Wheezing or "cardiac asthma" can occur when there is compression of intrathoracic airways by vascular engorgement and interstial edema. With most congenital heart defects with left-to-right shunts, an abnormal heart murmur and cardiomegaly are prominent clues to the diagnosis. Acute myocarditis, usually of viral etiology, can manifest with tachypnea, dyspnea, grunting, and diaphoresis. The physical examination reveals tachycardia and decreased heart sounds, and chest radiography shows a massively enlarged heart. Cardiomyopathy may be congenital, may have a metabolic or toxic cause, may be familial, or may be idiopathic. Other causes of cardiac failure, such as severe hypertension, renal failure, and severe anemia, should also be sought. Systemic ventricular failure caused by obstructing lesions, such as aortic stenosis, coarctation of the aorta, or mitral stenosis, also causes increased pulmonary vascular engorgement and edema, which results in the same symptoms as those for a large left-to-right shunt. Depending on the severity of the left ventricular outflow obstruction, systemic blood flow may be decreased, resulting in poor perfusion and metabolic acidosis. If blood flow into the systemic ventricle from the

pulmonary veins or left atrium is decreased or obstructed, as in total anomalous pulmonary venous return or mitral stenosis, then severe pulmonary edema, hypoxemia, and respiratory distress ensues. Many of these lesions manifest early in infancy. Tachypnea, wheezing, cyanosis, and metabolic acidosis are typical presenting signs. Accurate diagnosis depends on echocardiography; cardiac catheterization may be needed in complex cases.

Neurologic

Children with certain primary neurologic disorders, such as increased intracranial pressure or neuromyopathic weakness, may present in respiratory distress. Common symptoms include irregular respirations, hypoventilation, or hyperventilation. These symptoms, accompanied by an altered mental status, should prompt an evaluation of the central nervous system for problems such as meningitis, cerebritis or encephalitis, intracranial hemorrhage, mass lesion, or toxic ingestion.

Other

Metabolic derangement that results in acidosis can produce tachypnea and possible dyspnea. Common causes of acidosis include diabetic ketoacidosis, sepsis, and ingestions (such as aspirin). The presence of multisystem involvement in addition to respiratory distress should lead to arterial blood gas determination, urinalysis, and possibly a toxicology screen.

SUMMARY AND RED FLAGS

Respiratory distress may be a result of disorders of the extrathoracic or intrathoracic airways (intrinsic or extrinsic compression-obstruction), alveoli, pulmonary vasculature, pleural spaces, or thorax. The distress may be secondary to respiratory, cardiovascular, hematologic, or central nervous system diseases. The most important aspect of the evaluation of a child with respiratory distress is observation of the child's breathing pattern and a brief, directed history and physical examination. Once the cause is identified, treatment should be started quickly to avoid progression to respiratory failure.

Red flags for impending respiratory failure include sudden onset of distress (epiglottitis, foreign body aspiration), hemoptysis, severe retractions, lethargy, a sitting up–leaning forward posture, dysphagia, drooling, or aphonia. It is imperative to identify the symptoms of impending respiratory failure and not delay treatment with unnecessary clinical or radiologic studies. Epiglottitis should be recognized quickly, and treatment initiated promptly. It is also important not to miss a foreign body, which with time may produce chronic respiratory disease that is often confused with pneumonia or asthma.

Signs of a more chronic process include lack of resolution with normal therapy, chronicity of symptoms, positive family history, digital clubbing, weight loss, and/or failure to thrive. These signs should prompt further work-up and consultation with a pulmonary specialist as needed. Asthma will rarely cause digital clubbing, so its presence should raise concern for another primary lung disease process.

REFERENCES

A bibliography is available at ExpertConsult.com

REFERENCES

General

Bohadana A, Izbicki G, Kraman SS. Fundamentals of lung auscultation. *N Engl J Med*. 2014;370:744-751.

Davis JL, Murray JF. History and physical examination. In: Broaddus VC, Mason RJ, Ernst JD, et al., eds. *Murray and Nadel's Textbook of Respiratory Medicine*. 6th ed. Philadelphia: Saunders-Elsevier; 2016:263-277, e2.

Haddad GG, Green TP. Diagnostic approach to respiratory disease. In: Kliegman RM, Stanton BF, St. Geme JW, et al., eds. *Nelson's Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:1993-1998.

Meeks M, Bush A. Primary ciliary dyskinesia (PCD). *Pediatr Pulmonol*. 2000;29:307-316.

Viteri SD, Sampayo EM. Respiratory distress. In: Florin TA, Ludwig S, eds. *Netter's Pediatrics*. Philadelphia: Elsevier-Saunders; 2011:17-23.

Zarogoulidis P, Kioumis I, Pitsiou G, et al. Pneumothorax: from definition to diagnosis and treatment. *J Thorac Dis*. 2014;6:S372-S376.

Wheezing

Bakker DA, Berger RM, Witsenburg M, et al. Vascular rings: A rare cause of common respiratory symptoms. *Acta Pediatr*. 1999;88:947-952.

Cave AJ, Atkinson LL. Asthma in preschool children: A review of diagnostic challenges. *J Am Board Fam Med*. 2014;27:538-548.

Ducharme FM, Tse SM, Chauhan B. Diagnosis, management, and prognosis of preschool wheeze. *Lancet*. 2014;383:1593-1604.

Esposito S, Blasi F, Arosio C, et al. Importance of acute *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* infections in children with wheezing. *Eur Respir J*. 2000;16:1142-1146.

Gardiner SJ, Gavranich JB, Chang AB. Antibiotics for community-acquired lower respiratory tract infections secondary to *Mycoplasma pneumoniae* in children. *Cochrane Database Syst Rev*. 2015;1:CD004875.

Johnson JD, Theurer WM. A stepwise approach to the interpretation of pulmonary function tests. *Am Fam Physician*. 2014;89:359-366.

NHLBI/National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. *NIH Publication*; 2007.

Principi N, Esposito S, Blasi F, et al. Role of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in children with community-acquired lower respiratory tract infections. *Clin Infect Dis*. 2001;32:1281-1289.

Ralston SL, Lierthal AS, Messiner HC, et al. The diagnosis, management, and prevention of bronchiolitis. *Pediatrics*. 2014;134:e1474-e1502.

Wagner T. Bronchiolitis. *Pediatr Rev*. 2009;30:386-395.

Stridor

Ahmad SM, Soliman AM. Congenital anomalies of the larynx. *Otolaryngol Clin North Am*. 2007;40:177-191.

Alcaide ML, Bisno AL. Pharyngitis and epiglottitis. *Infect Dis Clin North Am*. 2007;21:449-469.

Friedman ER, Robson CD, Hudgins PA. Pediatric airway disease. In: Som PM, Curtin HD, eds. *Head and Neck Imaging*. 5th ed. St. Louis: Mosby-Elsevier; 2011:1811-1903.

Halpin LJ, Anderson CA, Corriette N. Stridor in children. *BMJ*. 2010;340:c2193.

Ida JB, Thompson DM. Pediatric stridor. *Otolaryngol Clin North Am*. 2014;47:795-819.

Roosevelt GE. Acute Inflammatory Upper Airway obstruction (Croup, Epiglottitis, Laryngitis, and Bacterial Tracheitis). In: Kliegman RM, Stanton BF, St. Geme JW, et al., eds. *Nelson's Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:2031-2035.

Schroeder JW, Holinger LD. Congenital anomalies of the larynx, trachea, and bronchi. In: Kliegman RM, Stanton BF, St. Geme JW, et al., eds. *Nelson's Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:2036-2039.

Schroeder JW, Holinger LD. Laryngotracheal stenosis and subglottic stenosis. In: Kliegman RM, Stanton BF, St. Geme JW, et al., eds. *Nelson's Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:2041-2042.

Cough

Agrawal R, Chakabarti A, Shah A, et al. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. *Clin Exp Allergy*. 2013;43:850-873.

Bradley JS, Byington CL, Shah SS, et al. Executive summary: the management of community acquired pneumonia in infants and children older than 3 months: Clinical practice guidelines by the Pediatric Infectious Disease Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;53:617-630.

Gereige RS, Laufer PM. Pneumonia. *Pediatr Rev*. 2013;34:438-456.

Howenstine MS, Eigen H. Current concepts on interstitial lung disease in children. *Curr Opin Pediatr*. 1999;11:200-204.

Hu X, Lee JS, Pianosis PT, et al. Aspiration related pulmonary syndromes. *Chest*. 2015;147:815-823.

Kelly MS, Sandora TJ. Community acquired pneumonia. In: Kliegman RM, Stanton BF, St. Geme JW, et al., eds. *Nelson's Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:2088-2094.

Kurland G, Deterding RR, Hagood JS, et al. An official American Thoracic Society clinical practice guidelines: Classification, evaluation, and management of childhood interstitial lung disease in infancy. *Am J Resp Crit Care Med.* 2013;188:376-394.

Sullivan JS, Sundaram SS. Gastroesophageal reflux. *Pediatr Rev*. 2012;33:243-254.

Wark PA, Gibson PG. Allergic bronchopulmonary aspergillosis: New concepts of pathogenesis and treatment. *Respirology*. 2001;6:1-7.

Earache

Brittany Player

INTRODUCTION

Earache (otalgia) is pain that arises from a pathologic process in the external, middle, or inner ear or that is referred to the ear from another structure. Acute otitis media (AOM) is the most common cause of otalgia in children (Tables 4.1 and 4.2). At least 80% of children will experience one or more episodes of AOM in the first three years of life. The second most common cause of ear pain is otitis externa, followed by dermatitis and infections of the pinna (see Table 4.1). Other causes of otalgia are rare (Table 4.3). A careful examination of the pinna, external auditory canal, and tympanic membrane can help the clinician identify most causes of ear pain. When the findings are normal, the clinician should consider referred pain (Table 4.4).

◆ History

Older, verbal children with ear pain are often able to localize and accurately describe their symptoms. Younger children often cannot localize their pain and may present with a variety of nonspecific symptoms, including fever, irritability, rhinorrhea from an associated upper respiratory tract illness (URI), and ear pulling. *Even though ear pulling is associated with ear pain, it is neither specific nor sensitive in the diagnosis of ear disease.* In addition, infants with AOM may occasionally be afebrile and present with various degrees of irritability, such as sleep disturbances and/or eating or drinking inadequately. The clinician should be highly suspicious of ear disease in infants during the first year of life or in any preschool child with fever, irritability, or a URI.

In taking a history from a child who presents with ear pain, the clinician must distinguish between true ear pain and the sensation of fullness and discomfort that children experience when they have an effusion or retracted tympanic membrane secondary to a dysfunctional eustachian tube. The clinician should review the child's history for factors placing the child at risk for infection such as craniofacial (cleft palate) abnormalities, immunodeficiencies, autoimmune disease, diabetes, previous ear infections, placement of tympanostomy tubes, and recent dental procedures, trauma, and air travel. Immunization status should also be reviewed. A careful review of systems should elicit associated fevers, sore throat, reflux symptoms, otorrhea, neurologic symptoms, and symptoms of sinusitis. Children with a middle ear effusion may have decreased hearing acuity.

Acute otitis media presents with abrupt onset of otalgia associated with middle ear fluid, signs and symptoms of inflammation, and local or systemic infection. Risk factors for AOM include a family or personal history of recurrent AOM, trisomy 21, household cigarette smoke exposure, lack of breastfeeding, lower socioeconomic status, male gender, cleft palate, immunodeficiency, and group daycare attendance or siblings in the household.

Children with **otitis externa** ("swimmer's ear") present with either ear pain, purulent otorrhea, or both. Manipulating the tragus and pinna causes extreme pain. On otoscopic exam, the external canal is erythematous and there is typically drainage. Relapsing polychondritis also involves swelling and redness of the pinna; this condition is usually bilateral and recurrent, and other cartilaginous structures are affected. With referred ear pain, such as from tooth decay or teething, there are often additional symptoms associated with the respective head and neck structures (see Table 4.4). Patients with ear pain secondary to maxillary sinusitis may also complain of headaches and purulent rhinorrhea.

◆ Physical Examination

In a child presenting with a chief complaint of ear pain, the general examination includes the temperature, the respiratory rate, and a determination of whether the infant or child has a toxic appearance. Then the clinician proceeds with the complete head, eyes, ears, nose, oral cavity, and throat examination and with an appropriately focused physical examination of other pertinent systems.

The examination of the ear begins with the less symptomatic ear. The clinician should inspect the pinna and adjacent tissues for dermatitis, redness, and edema. The pinna, including the cartilaginous portions, and the mastoid process are palpated for any tenderness. Erythema, swelling, and tenderness over the mastoid process suggest **mastoiditis**; whereas localization of these findings to the external auditory canal and the pinna suggests otitis externa. In both conditions, the swelling may be so severe that the pinna is laterally displaced. The opening of the external ear canal is also examined for the presence of discharge or exudate. Most disorders of the external ear can be detected through this examination (see Tables 4.1 and 4.3).

Otoscopy provides an opportunity to indirectly view the middle ear through the tympanic membrane. The middle ear is normally an air-filled cavity that transmits sound from the eardrum to the ossicle and then into the internal ear (Fig. 4.1). Otoscopy begins by properly positioning and, if necessary, restraining the patient. Both shoulders and hips need to be stabilized so that the patient cannot roll during the examination. Infants are best examined on an examining table in the prone position, with a parent or an attendant firmly holding the patient's shoulders, thus preventing the patient from moving. Toddlers should sit on a parent's lap, with the examiner sitting in a chair opposite them. The child is held against the parent's chest, with one of the parent's hands and arms holding the child's arms and the other around the child's head so that one ear is exposed. To avoid trauma with movement, the otoscope should be held in the examiner's hand making direct contact with the patient's head, allowing the otoscope to move with the head.

Cerumen (ear wax) is a waxy substance consisting of glandular discharge from cells in the outer external canal mixing with exfoliated epithelial cells. Cerumen can both obscure visualization of the eardrum leading to diagnostic errors and be a cause of otalgia if

TABLE 4.1 Differential Diagnoses of Painful External Ear and Auditory Canal Disorders

Disorder	Clinical Features
Acute otitis externa	Diffuse redness, swelling, and pain of the canal with greenish to whitish exudate; often very tender pinna
Malignant otitis externa	Rapidly progressive, severe swelling and redness of pinna; pinna may be laterally displaced
Dermatitis	
Eczema	History of atopy, presence of lesions elsewhere; lesions are scaly, red, pruritic, and weeping
Contact	History of cosmetic use or irritant exposure; lesions are scaly, red, pruritic, and weeping
Seborrhea	Scaly, red, papular dermatitis; scalp may have thick, yellow scales
Psoriasis	History or presence of psoriasis elsewhere; erythematous papules that coalesce into thick, white plaques
Cellulitis	Diffuse redness, tenderness, and swelling of the pinna
Furuncles	Red, tender papules in areas with hair follicles (distal third of the ear canal)
Infected periauricular cyst	Discrete, palpable lesions; history of previous swelling at same site; cellulitis may develop, obscuring cystic structure
Insect bites	History of exposure; lesions are red, tender papules
Herpes zoster	Painful, vesicular lesions in the ear canal and tympanic membrane in the distribution of cranial nerves V and VII
Perichondritis	Inflammation of the cartilage, usually secondary to cellulitis
Tumors	Palpable mass, destruction of surrounding structures
Foreign body	Foreign body may cause secondary trauma to the ear canal or become a nidus for an infection of the ear canal
Trauma	Bruising and swelling of external ear; there may be signs of basilar skull fracture (cerebrospinal fluid otorrhea, hemotympanum)

TABLE 4.2 Differential Diagnosis of Painful Middle Ear Disorders

Disorder	Clinical Features
Acute otitis media	Immobile tympanic membrane that may appear bulging, red, and/or opaque
Bullous myringitis	Hemorrhagic or serous bullae on the tympanic membrane; more severe pain than AOM
Mastoiditis	Tenderness and erythema over mastoid with periostitis process; no destruction of bone trabeculae
Acute mastoid osteitis	Destruction of bone trabeculae; tenderness and erythema over mastoid process coupled with outward displacement of pinna
Granulomatosis	Severe necrotizing vasculitis; ulcerative and destructive granulomatous lesions of upper and lower respiratory tract with polyangiitis
Histiocytosis	Pituitary dysfunction, exophthalmos, seborrheic dermatitis, and bone lesions; if bone lesions involve the ear, patient presents with mastoid tenderness and otorrhea

impaction occurs. To view the eardrum properly, the examiner should remove the wax by irrigating the ear canal gently with lukewarm water, lift the wax out with a blunt curette, or dissolve the wax by placing 1-2 drops of docusate sodium liquid in the canal for 10-15 minutes. Contraindications for irrigation or use of a cerumenolytic solution are the presence of a tympanostomy tube, a perforated tympanic membrane, or an organic foreign body (e.g., legumes swell in contact with fluids).

During the insertion of the speculum, the clinician should note any redness, edema, tenderness, exudate, furuncles, or vesicles that may be present in the external auditory canal. In some illnesses (otitis externa), the ear canal may be so edematous that the speculum cannot be inserted and the eardrum cannot be seen. In addition, in neonates and in some children with craniofacial anomalies such as trisomy 21, the external canal may be so small that it precludes an accurate assessment of the tympanic membrane.

Pneumatic otoscopy allows evaluation of the tympanic membrane's mobility. Because it is more accurate than otoscopy alone in detecting middle ear effusion, pneumatic otoscopy should be part of every ear examination. In performing pneumatic otoscopy, the examiner should select a speculum that fits snugly in the external auditory canal. The examiner then partially depresses the rubber bulb of the pneumatic otoscope and inserts the otoscope into the ear canal (Fig. 4.2). Once the eardrum is seen, the examiner should observe the color, appearance, position, bony landmarks, and mobility of the tympanic membrane (Table 4.5, Fig. 4.3). If the eardrum is not perforated, the clinician observes its mobility by alternating positive and negative pressure by gently depressing and releasing the bulb of the pneumatic otoscope. Poor mobility of the eardrum may be secondary to middle ear effusion, a perforated tympanic membrane, or lack of an airtight seal (Fig. 4.4).

In neonates and young infants, the eardrum is less perpendicular to the observer, the bony landmarks are less distinct, and the eardrum is less mobile than in older infants and children. Failure to appreciate these normal otoscopic findings may lead to the overdiagnosis of middle ear effusion.

In the first few hours of AOM, the middle ear cavity may not yet be filled with fluid, and the mobility may be normal. By the time the patient is examined, the middle ear is usually filled with fluid, and the eardrum is opaque and bulging with decreased mobility (see Fig. 4.4). A reddened eardrum may indicate inflammation of the tympanic membrane (TM), but this physical finding is not specific because crying alone can induce diffuse redness of the eardrum. In addition, differentiation of color is highly variable among observers, which may in part result from the intensity and type of light source used in otoscopy.

In **otitis media with effusion (OME)**, also known as serous otitis media, the cardinal sign is decreased mobility of the eardrum. The eardrum may be opaque, but not bulging or grossly inflamed (Fig. 4.5; see Table 4.5). A challenge for the clinician is the child with symptoms consistent with AOM (ear pain) but with the physical findings of OME. In such cases, it is difficult to decide whether there is an acute infection

TABLE 4.3 Causes of Otalgia and Sources for Referred Pain

Intrinsic

I. External Ear
A. External otitis
B. Cerumen impaction
C. Foreign body
D. Perichondritis
E. Preauricular cyst or sinus
F. Insects
G. Myringitis
H. Trauma
I. Tumor

II. Middle Ear, Eustachian Tube, and Mastoid
A. Barotrauma
B. Middle ear effusion
C. Negative intratympanic pressure (eustachian tube dysfunction)
D. Acute otitis media
E. Mastoiditis
F. Aditus block
G. Complication of otitis media
H. Tumor
I. Eosinophilic granuloma
J. Granulomatosis with polyangiitis

Extrinsic

I. Trigeminal Nerve
A. Dental
B. Jaw
C. Temporomandibular joint
D. Oral cavity (tongue)
E. Infratemporal fossa tumors

II. Facial Nerve
A. Bell palsy
B. Tumors
C. Herpes zoster

III. Glossopharyngeal Nerve
A. Tonsil
B. Oropharynx
C. Nasopharynx

IV. Vagus Nerve
A. Laryngopharynx
B. Esophagus
C. Gastroesophageal reflux
D. Thyroid

V. Cervical Nerves
A. Lymph nodes
B. Cysts
C. Cervical spine
D. Neck infections

VI. Miscellaneous
A. Migraine
B. Neuralgias
C. Paranasal sinuses
D. Central nervous system
E. Drug induced (mesalazine, sulfasalazine)
F. Factitious disorder by proxy

From Bluestone CD, Stool SE, Alper CM, et al. *Pediatric Otolaryngology*. 4th ed. Vol 1. Philadelphia: Saunders; 2003:288.

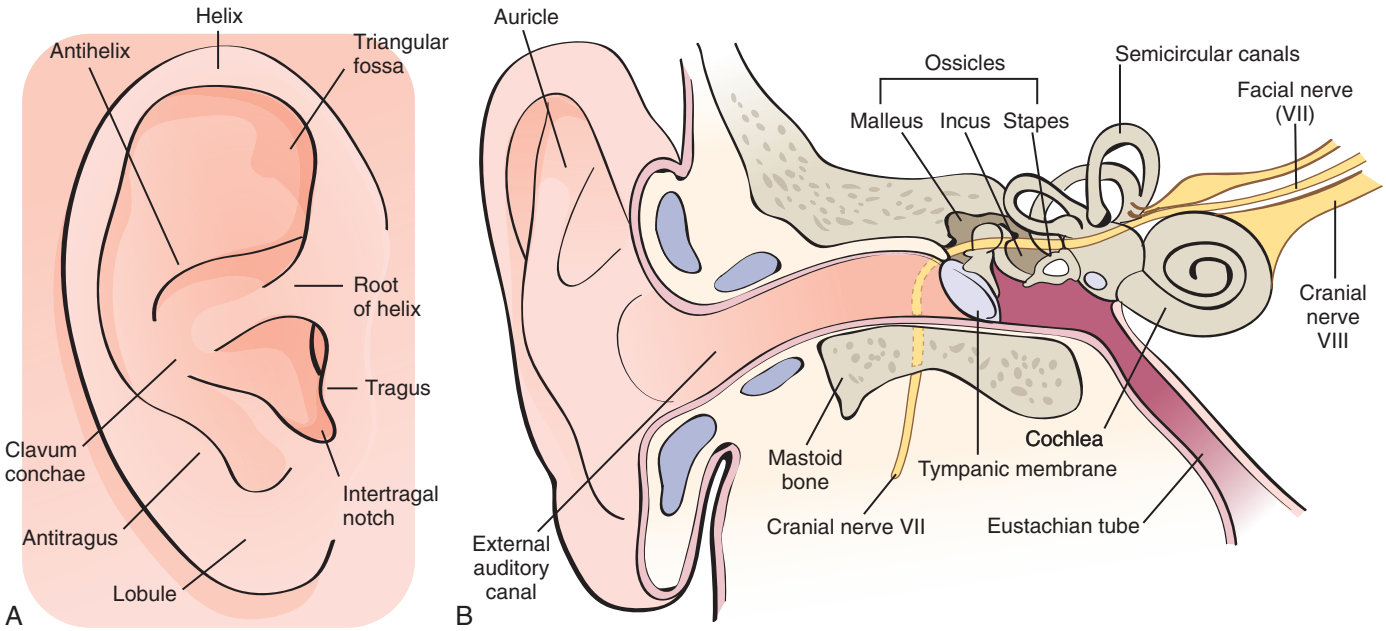


FIGURE 4.1 Anatomy of the ear. *A,* A normal external ear (auricle or pinna) is shown, with its various landmarks labeled. It is helpful to refer to such a diagram in assessing congenital anomalies. *B,* This coronal section shows the various structures of the hearing and vestibular apparatus. The three main regions are the external ear, middle ear, and inner ear. The eustachian tube connects the middle ear and the nasopharynx and serves to drain and ventilate the middle ear. (From Yellon R, Chi D. Otolaryngology. In: Zitelli, ed. *Atlas of Pediatric Physical Diagnosis*. 6th ed. Philadelphia: Elsevier; 2012:914).

TABLE 4.4 Causes of Referred Ear Pain

Neck
Cervical lymphadenitis
Infected cervical cysts
Subluxation of the atlantoaxial joint (torticollis and otalgia)

Salivary Glands
Parotitis

Thyroid
Thyroiditis

Teeth and Gums
Dental caries
Dental abscess
Impacted teeth
Gingivitis

Temporomandibular Joint
Temporomandibular disorder
Arthritis, juvenile idiopathic arthritis
Spasm from bruxism or dental malocclusion

Tonsils
Tonsillitis
Peritonsillar abscess
Post-tonsillectomy neuralgia

Pharynx
Pharyngitis

Paranasal Sinuses
Maxillary sinusitis

Other
Herpes zoster (Ramsey-Hunt syndrome: postherpetic neuralgia, migraine)
Bell palsy
Migraine
Tumors (e.g., of facial nerve)

of the middle ear or whether it is OME with an illness at another site causing the symptoms.

When the external ear and tympanic membrane are normal in a child with an earache, the clinician must consider the possibility of referred pain (see Table 4.4). Innervation of the external and middle ear includes pain fibers of the trigeminal, glossopharyngeal, and vagus nerves and, to a lesser extent, the facial nerve and upper cervical nerves. The clinician should examine the neck, parotid gland, thyroid, mouth, tongue, teeth, temporomandibular joint, tonsils, and throat. In children, the cause of referred pain is usually infectious rather than noninfectious (e.g., a tumor).

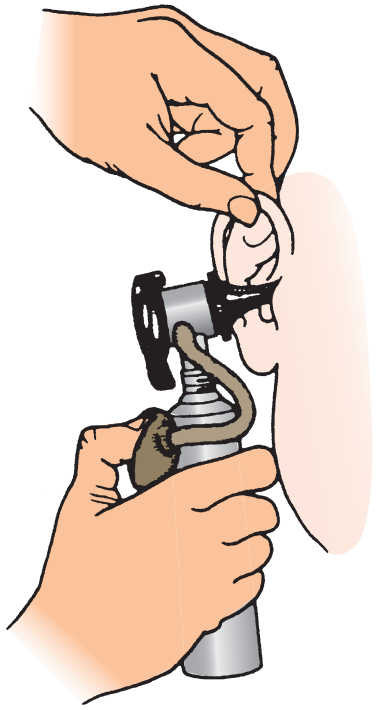


FIGURE 4.2 Technique for pneumatic otoscopy. (From Bluestone CD, Klein JO. *Otitis Media in Infants and Children*. 2nd ed. Philadelphia: WB Saunders; 1995:92.)

TABLE 4.5 The Tympanic Membrane in Acute Otitis Media and Otitis Media With Effusion

Characteristic	Normal Findings	Acute Otitis Media	Otitis Media With Effusion	Comments
Color	Gray to pink	Often red from inflammation; yellow to white from purulent fluid behind tympanic membrane	Usually gray to pink, but may still be yellow or white; not red	Interobserver variation of color is high; redness can occur from crying alone
Appearance	Translucent	Opaque	Translucent or opaque	Opacity is caused by opaque fluid or by scarring of tympanic membrane
Position	Neutral	Fluid under pressure produces bulging of tympanic membrane; bony landmarks may be distorted and the light reflex lost	Not bulging; may be retracted	
Mobility	Tympanic membrane moves freely	Mobility to positive and negative pressure reduced	Mobility to positive and negative pressure reduced	
Other findings		Perforation with otorrhea		

◆ Diagnostic Tests

Bacterial Cultures

Routine cultures of middle or external ear fluid are not required because most infections are self-limited and respond to empirical antimicrobial therapy. In selected instances (e.g., persistent treatment failure, severe pain, an immunocompromised host, a neonate), culture of otorrhea from the external auditory canal or cultures of middle ear fluid by tympanocentesis may guide therapy. In a child with AOM, the offending pathogen is usually present in the nasopharynx. Unfortunately, nasopharyngeal cultures are not helpful in directing therapy because multiple pathogens are present and it is unclear which organism is actually causing the middle ear infection. With the emergence of strains of *Streptococcus pneumoniae* that are resistant to commonly used antibacterials, the incidence of treatment failures may increase. This may necessitate a greater reliance on tympanocentesis for culture of middle ear fluid to determine the appropriate antimicrobial agent.

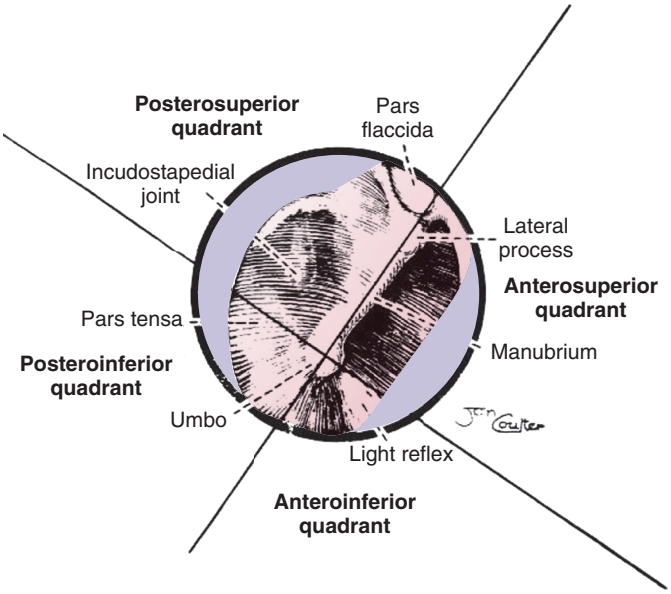


FIGURE 4.3 The four quadrants of a right tympanic membrane. (From Bluestone C, Klein J. Methods of examination: Clinical examination. In: Bluestone CD, Stool, SE, Kenna MA, eds. *Pediatric Otolaryngology*. 3rd ed. Vol 1. Philadelphia, WB Saunders; 1996:157.)

Tympanometry

Tympanometry is an objective, painless method for detecting the presence of middle ear effusion by providing information about tympanic membrane compliance. A soft plastic probe is inserted into the external auditory canal in order to obtain an airtight seal. The tympanometer measures the flow of sound energy into the middle ear under conditions of changing air pressure. When the air pressure is equal on both sides of an intact eardrum, with the drum in neutral position, the transmission of sound energy through the tympanic membrane is at its maximum. The peak on the tympanogram represents the pressure at which the flow of sound energy is maximal. For example, in a normal air-filled middle ear cavity, the peak occurs at ambient atmospheric pressure (Fig. 4.6*A*). With eustachian tube dysfunction (a retracted eardrum but no middle ear effusion), the peak occurs in the negative pressure range on the recording (Fig. 4.6*C*). With middle ear effusion, the sound energy flow into the middle ear is reduced, which produces a flat tympanogram (Fig. 4.6*B*). A flat tympanogram may also result from cerumen, foreign body, or from occlusion of the opening of the probe by the wall of the external auditory canal. In a perforated eardrum, the sound energy is readily transmitted through the hole in the drum throughout the entire pressure range, resulting in a flat tympanogram.

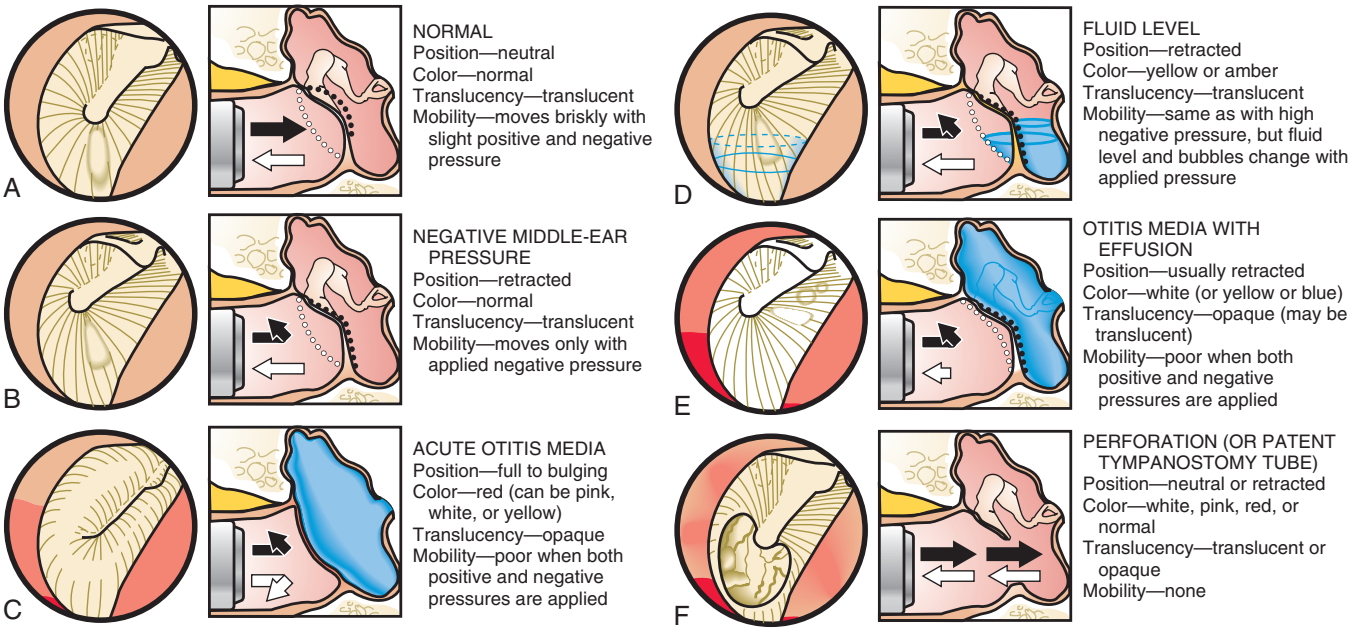


FIGURE 4.4A-F Common conditions of the middle ear, as assessed with the otoscope. (From Bluestone C, Klein J. *Otitis Media in Infants and Children*. 3rd ed. Philadelphia: Saunders; 2001:131.)

(See *Nelson Textbook of Pediatrics*, p. 3090.)

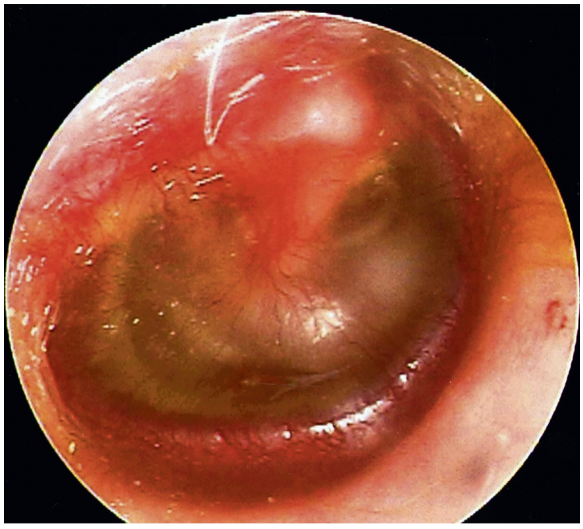


FIGURE 4.5 Tympanic membrane in otitis media with effusion. (From Kerschner J, Preciado D. Otitis media. In: Kliegman R, ed. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2015:3090.)

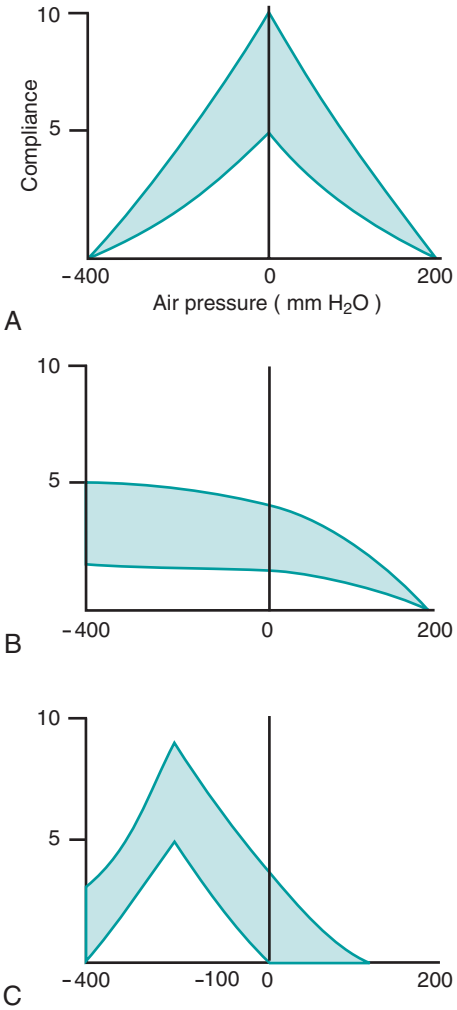


FIGURE 4.6 *A*, A normal tympanogram with a peak at atmospheric pressure, indicating an air-filled middle ear with normal (atmospheric) pressure. *B*, A "flat" tympanogram, indicating middle ear effusion. *C*, A tympanogram with a negative peak pressure, indicating eustachian tube obstruction.

The use of tympanometry can be limited by patient age and cooperation with testing, cerumen impaction, and the skill of the individual performing the testing. When performed by experts, tympanometry and pneumatic otoscopy have equivalent sensitivity (approximately 90%) and specificity (70%-80%). Tympanometry is neither more accurate nor more convenient than is properly performed pneumatic otoscopy. Some tympanometers do not perform well in infants younger than 6 months of age. Tympanometry is advantageous if the clinician is unsure of the otoscopic findings. *Tympanometry can only indicate middle ear effusion, but cannot distinguish between AOM and OME.*

Acoustic Reflectometry

Acoustic reflectometers are used to detect middle ear effusion. The device directs sonar-like sound waves of varying frequency toward the tympanic membrane and measures the intensity of reflected sound. This hand-held instrument is similar in size to an otoscope. The tip of the reflectometer is inserted into the ear canal. In contrast to tympanometry, an airtight seal is not required. The frequency of maximal reflected sound depends on the distance of the probe from the eardrum. Middle ear effusion is detected not by the frequency but by the magnitude of maximal reflected sound. When middle ear effusion is present, reflectance is increased in comparison with that in the air-filled middle ear.

Improvements in technology have been made such that reflectometry includes spectral gradient analysis. Reflectometry is easily learned, quick, convenient, and useful in a crying child. It has a lower sensitivity and specificity than properly performed pneumatic otoscopy in detecting middle ear effusion. Because the accuracy of current models decreases in infants younger than 1 year, this technique should not be used in infants younger than 6 months of age. Like tympanometry, reflectometry can reveal only whether middle ear effusion is present and cannot reveal whether the effusion is secondary to AOM or OME. Reflectometry is useful if otoscopic findings are indeterminate.

Diagnostic Imaging

Radiologic techniques are rarely required in the evaluation of external or middle ear disease, but they may be useful in the assessment of intratemporal and intracranial complications of otitis media. Opacification of the normally aerated mastoid air cells is usually seen in AOM because the mastoid air cells communicate with the middle ear space. By definition, this is acute mastoiditis; however, this opacification resolves concomitantly with the successful treatment of AOM. In contrast, in acute mastoid osteitis, also called acute coalescent mastoiditis, there is destruction of bone trabeculations in the mastoid air cells. Computerized tomography (CT) scan is the preferred imaging modality to aid in this diagnosis. Imaging studies can be useful in evaluating a patient for other intracranial complications of AOM. CT scans of the head can evaluate for suspected cholesteatomas. Magnetic resonance imaging should be used for diagnosing intracranial mass lesions (brain abscess) and soft tissue sequela of infection, while magnetic resonance venography would identify dural sinus thrombosis.

◆ Differential Diagnosis

Most disorders of the external and middle ear are readily apparent after the examination of the ear (see Tables 4.1 to 4.3). If examination findings are unremarkable, the clinician should consider referred pain (see Table 4.4). Most cases of otitis media are uncomplicated; however, the clinician should be alert to the complications and sequelae of AOM (Table 4.6).

TABLE 4.6 Manifestations of the Sequelae and Complications of Otitis Media

Complication	Clinical Features
Acute	
Perforation with otorrhea	Immobile tympanic membrane secondary to visible perforation, exudate in ear canal
Acute mastoiditis with periostitis	Tenderness and erythema over mastoid process, no destruction of bony trabeculae
Acute mastoid osteitis	Destruction of bony trabeculae; tenderness and erythema over mastoid process coupled with outward displacement of pinna
Petrositis	Infection of perilabyrinthine cells; may present with otitis, paralysis of lateral rectus, and ipsilateral orbital or facial pain (Gradenigo syndrome)
Facial nerve palsy	Peripheral cranial nerve VII paralysis
Labyrinthitis	Vertigo, fever, ear pain, nystagmus, hearing loss, tinnitus, nausea and vomiting
Lateral sinus thrombosis	Headache, fever, seizures, altered states of consciousness, septic emboli
Meningitis	Fever, headache, nuchal rigidity, seizures, altered states of consciousness
Extradural empyema	Fever, headache, seizures, altered states of consciousness
Subdural empyema	Fever, headache, seizures, altered states of consciousness
Brain abscess	Fever, headache, seizures, altered states of consciousness, focal neurologic examination
Nonacute	
Chronic perforation	Immobile tympanic membrane secondary to perforation
Otitis media with effusion (OME)	Immobile, opaque tympanic membrane
Adhesive otitis	Irreversible conductive hearing loss secondary to chronic OME
Tympanosclerosis	Thickened white plaques, may cause conductive hearing loss
Chronic suppurative otitis media	Following acute otitis media with perforation, secondary infection with *Staphylococcus aureus*, *Pseudomonas aeruginosa*, or anaerobes develops, causing chronic otorrhea
Cholesteatoma	White, pearl-like destructive tumor with otorrhea arising near or within tympanic membrane; may be secondary to chronic negative middle ear pressure
Otitic hydrocephalus	Increased intracranial pressure secondary to AOM; signs and symptoms include severe headaches, blurred vision, nausea, vomiting, papilledema, diplopia (abducens paralysis)

OTITIS EXTERNA

Otitis externa is an infection of the external ear canal. The external canal can become vulnerable to infection from excessive moisture from warm humid weather, moisture in the canal, or swimming. The moisture may cause small abrasions in the protective lipid layer of skin in the ear canal. These abrasions become infected on exposure to pathogenic bacteria. Dryness or presence of underlying skin conditions (such as eczema) and trauma (including cotton ear swabs) can also predispose the external canal to infection. Less commonly, otorrhea draining from a perforated tympanic membrane secondary to otitis media may cause otitis externa.

The presenting symptoms are often intense pain (especially with manipulation of the pinna, pressure on the tragus, or jaw movement), erythema, and otorrhea. On physical examination, the ear canal is red, edematous, and tender. Otorrhea may be present in the external canal. While otitis externa can occur at all ages, occurrence peaks between 7 and 12 years of age, with 10% of people having an episode in their lifetime. Otitis externa is rarely bilateral in nature.

Pseudomonas aeruginosa is the predominant organism causing otitis externa, but staphylococcal species (*Staphylococcus aureus* and coagulase-negative staphylococci) and streptococci have been isolated. Gram-negative organisms, such as *Enterobacter*, *Proteus*, and *Klebsiella* species, and fungal organisms, such as *Candida* and *Aspergillus* species, have also been isolated.

Treatment consists of a topical suspension, commonly ofloxacin or ciprofloxacin combined with hydrocortisone or dexamethasone. The addition of the topical steroid has shown improvement in pain relief. Most patients respond within a few days. If there is marked edema of the canal, antibacterials may not reach the site of infection. In this case, the canal should be cleaned with gentle suction, and a cotton wick should be inserted into the auditory canal. Antibacterial suspension is then dripped into the wick, which allows the medication to diffuse further into the ear canal. In some cases, daily cleaning and replacement of the wick are necessary. If the infection progresses, the patient may need parenteral antibacterials and consultation with an otolaryngologist.

Chondritis is a potential complication of severe otitis externa. It occurs when the infection progresses into the cartilaginous structures of the ear canal. This complication is rare without a history of previous trauma or surgery. The most common pathogens are *Pseudomonas* and *S. aureus*. Treatment requires systemic antibacterials and can require surgical debridement of tissue.

MALIGNANT OTITIS EXTERNA

Malignant otitis externa, also known as necrotizing otitis externa, is an extension of infection to the temporal bone and skull base causing extensive tissue destruction. The illness may result in chondritis and osteitis of both the middle and inner ears. This condition occurs

(See *Nelson Textbook of Pediatrics*, p. 3083.)

primarily in immunocompromised pediatric patients. In adults, diabetes mellitus is a common predisposing condition, though it is not a common comorbidity in children. Presenting symptoms include a markedly swollen and laterally displaced pinna associated with fever, malaise, and persistent, deep-seated otalgia out of proportion to findings on examination. Occasionally, facial nerve paralysis may be noted. Aggressive treatment with broad-spectrum parenteral antibiotics is indicated. *Pseudomonas aeruginosa* is the most commonly isolated pathogen, and coverage should include antibacterials directed against it. Surgical intervention may be necessary to obtain cultures for therapy guidance and provide local tissue debridement. This condition is rare in children.

ACUTE OTITIS MEDIA

Acute otitis media is most commonly a bacterial complication of a preceding or concurrent viral upper respiratory tract infection (URI), usually occurring several days after the onset of the URI. The viral infection enables pathogenic bacteria in the nasopharynx to ascend through the eustachian tube into the middle ear either by impairing local host defenses or by eustachian tube dysfunction. The bacterial pathogens then cause a secondary infection.

In 2013, the American Academy of Pediatrics (AAP) revised their guideline on the diagnosis of AOM. According to these guidelines, a diagnosis of AOM should be made in children presenting with:

- Moderate to severe bulging of the TM or new onset of otorrhea not due to acute otitis externa
- Mild bulging of the TM and recent (<48 hours) onset of significant TM erythema or ear pain (Fig. 4.7; see Table 4.5).

Bacteriology/Virology

The leading bacterial pathogens isolated from middle ear fluid in children with AOM are *Streptococcus pneumoniae,* nontypable *Haemophilus influenzae,* and *Moraxella catarrhalis*. *Staphylococcus aureus* and group A streptococci are uncommon pathogens, though *S. aureus* should be considered in patients with persistent otorrhea after tympanostomy tube placement. In the first month of life (especially the first 2 weeks), gram-negative enteric bacteria (e.g., *Escherichia coli, Klebsiella pneumoniae*) or group B streptococcus may also be isolated. Otitis media with ipsilateral conjunctivitis is often caused by nontypable *H. influenzae*.

The pneumococcal conjugate vaccine (PCV) 7 was introduced in 2000, covering serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F of *S. pneumoniae*. Widespread use of this vaccine resulted in a 29% reduction in AOM caused by all pneumococcal strains in children prior to 24 months of age. There was also a reduction in tympanostomy tube placement. In the first few years following introduction of PCV7, a shift from *S. pneumoniae* to nontypable *H. influenzae* as the leading pathogen causing AOM was noted. Shortly thereafter, a shift to non-PCV7 *S. pneumoniae* isolates as the primary pathogen of AOM, including multiresistant serotype 19A, was noted. Licensing and widespread use of the PCV13 vaccination began in 2010 in the United States, adding coverage for an additional 6 serotypes of *S. pneumoniae* (serotypes included in the PCV7 vaccination plus serotypes 1, 3, 5, 6A, 7F, and 19A). Preliminary studies have demonstrated a significant decline in the number of primary office visits related to AOM with the widespread use of this vaccine.

Viruses also have an important etiologic role. It is not clear whether the virus alone or a combination of virus and bacteria are involved in the pathogenesis. Several studies have documented the presence of viruses (10%-44% with or without bacteria) in the middle ear fluid of children with otitis media. URIs secondary to respiratory syncytial virus, influenza, and adenovirus have been associated with 30%-40% of AOM cases in children attending daycare. To a lesser degree, URIs secondary to parainfluenza, rhinovirus, and enteroviruses have also been associated with AOM. Viruses enhance bacterial adherence and colonization in the nasopharynx, impair local host immune defenses, and cause eustachian tube dysfunction.

Strains of *S. pneumoniae* have emerged with altered penicillin-binding proteins on the bacterial cell wall, which makes them less susceptible to β-lactam drugs (penicillins and cephalosporins). In addition, because resistance genes are frequently linked, organisms with resistance to β-lactam drugs are more likely to be resistant to sulfa antibacterials and to the macrolide class. Nonetheless, high-dose amoxicillin remains the best oral antibiotic available for drug-resistant *S. pneumoniae*. Currently, approximately 40% of *H. influenzae* strains and nearly all strains of *M. catarrhalis* produce β-lactamase enzymes, which hydrolyze penicillins and some cephalosporins, making them resistant to β-lactamase–producing antibacterials. Use of β-lactamase inhibitors such as clavulanate can overcome this resistance.

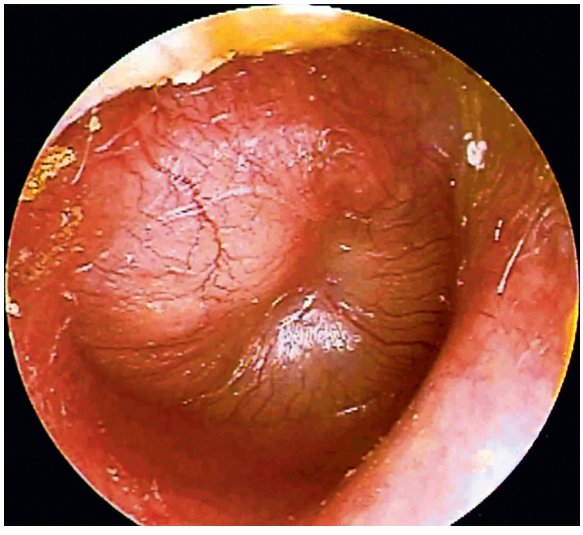


FIGURE 4.7 Tympanic membrane in acute otitis media. (From Kerschner J, Preciado D. Otitis media. In: Kliegman R, ed. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2015:3089.)

◆ Treatment

The goals of treatment in AOM are to relieve discomfort and to prevent infectious complications (Fig. 4.8). Evaluating the treatment of otitis media is complicated by the high rate of spontaneous resolution of the infection. Studies have shown that in children with AOM, up to 19% with *S. pneumoniae* and 48% with *H. influenzae* cultured on initial tympanocentesis would be culture negative within 1 week without antibacterial therapy. Despite *M. catarrhalis* resistance to amoxicillin, approximately 75% of children infected with that organism demonstrated cure when treated with amoxicillin. The emergence of drug-resistant *S. pneumoniae* strains and concerns about treating a disease with a high rate of spontaneous resolution has led to change in the recommended treatment for otitis media (see Fig. 4.8).

Some authorities suggest withholding antibacterials in children with low risk for complications. In the Netherlands, antibacterial therapy is commonly delayed until 48-72 hours after the diagnosis, to determine whether there is spontaneous resolution of the infection. Notably, in countries in which conservative use of antibacterials is the

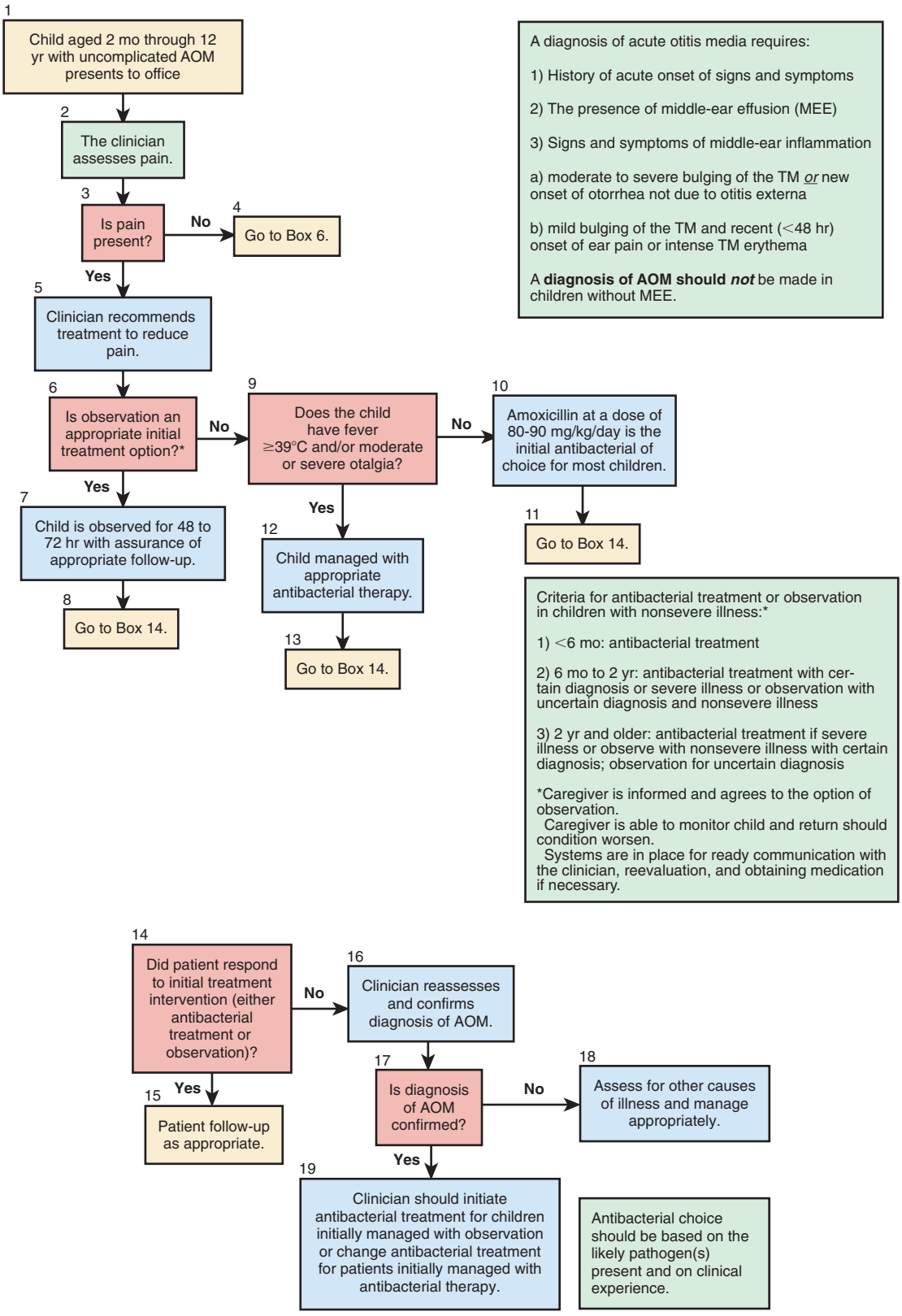


FIGURE 4.8 Management of acute otitis media (AOM). TM, tympanic membrane. (From Kerschner J, Preciado D. Otitis media. In: Kliegman R, ed. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier. 2015: 3093.)

standard, such as the Netherlands and Denmark, rates of acute mastoiditis are slightly higher (1-2 episodes per 100,000 person-years) than in countries with higher rates of antibacterial use. With the 2013 AAP guidelines, the watchful waiting method has been recommended in certain populations of patients (Table 4.7). However, the key to observation prior to antibacterial initiation is close follow-up for assessment of worsening symptoms or spontaneous resolution. Additionally, adequate analgesia, including acetaminophen and/or ibuprofen, should be provided during the observation period. *While watchful waiting is appropriate for certain populations, the benefits of antibacterial treatment are most clearly seen in children younger than 2 years.*

When an antibacterial is used, efficacy against *S. pneumoniae* is the most important consideration. In addition, the clinician must consider the drug's safety, convenience, palatability, and the cost of therapy. High-dose amoxicillin (80-90 mg/kg/day given in two divided doses) is the appropriate initial therapy for most cases (Table 4.8). Because otitis media is usually a self-limited illness, the use of broad-spectrum antibacterials for the initial treatment should be discouraged because

TABLE 4.7 Recommendations for Initial Management for Uncomplicated Acute Otitis Media (AOM)*

Age	Otorrhea With AOM	Unilateral or Bilateral AOM With Severe Symptoms†	Bilateral AOM Without Otorrhea	Unilateral AOM Without Otorrhea
6 mo to 2 yr	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy or additional observation
≥2 yr	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy or additional observation	Antibiotic therapy or additional observation‡

*Applies only to children with well-documented AOM with high certainty of diagnosis (see Fig.4.8).
†A toxic-appearing child, persistent otalgia more than 48 hr, temperature ≥39°C (102.2°F) in the past 48 hr, or if there is uncertain access to follow-up after the visit.
‡This plan of initial management provides an opportunity for shared decision-making with the child's family for those categories appropriate for additional observation. If observation is offered, a mechanism must be in place to ensure follow-up and begin antibiotics if the child worsens or fails to improve within 48-72 hr of AOM onset.
From Lieberthal A, Carroll A, Chonmaitree T, et al. The diagnosis and management of acute otitis media. *Pediatrics*. 2013;131:e976.

TABLE 4.8 Recommended Antibacterials for (Initial or Delayed) Treatment and for Patients Who Have Failed Initial Antibacterial Treatment

INITIAL IMMEDIATE OR DELAYED ANTIBIOTIC TREATMENT		ANTIBIOTIC TREATMENT AFTER 48-72 hr OF FAILURE OF INITIAL ANTIBIOTIC TREATMENT	
Recommended First-Line Treatment	**Alternative Treatment (if Penicillin Allergy)†**	**Recommended First-Line Treatment**	**Alternative Treatment**
Amoxicillin (80-90 mg/kg per day in 2 divided doses)	Cefdinir (14 mg/kg per day in 1 or 2 doses)	Amoxicillin-clavulanate* (90 mg/kg per day of amoxicillin, with 6.4 mg/kg per day of clavulanate in 2 divided doses)	Ceftriaxone, 3 d, or Clindamycin (30-40 mg/kg per day in 3 divided doses), with or without second- or third-generation cephalosporin
or	Cefuroxime (30 mg/kg per day in 2 divided doses	or	Failure of second antibiotic
Amoxicillin-clavulanate* (90 mg/kg per day of amoxicillin, with 6.4 mg/kg per day of clavulanate [amoxicillin to clavulanate ratio, 14:1] in 2 divided doses)	Cefpodoxime (10 mg/kg per day in 2 divided doses)	Ceftriaxone (50 mg/kg per day IM or IV for 3 d)	Clindamycin (30-40 mg/kg per day in 3 divided doses) plus third-generation cephalosporin
	Ceftriaxone (50 mg/kg per day IM or IV for 1 to 3 d)		Tympanocentesis‡ Consult specialist‡

Doses of antibiotics in this table are from the AAP Clinical Practice Guideline for the Diagnosis and Management of Acute Otitis Media.
*May be considered in patients who have received amoxicillin in the previous 30 days or who have the otitis-conjunctivitis syndrome.
†Cefdinir, cefuroxime, cefpodoxime, and ceftriaxone are highly unlikely to be associated with cross-reactivity with penicillin allergy on the basis of their distinct chemical structures.
‡Perform tympanocentesis/drainage if skilled in the procedure, or seek a consultation from an otolaryngologist for tympanocentesis/drainage. If the tympanocentesis reveals multidrug-resistant bacteria, seek an infectious disease specialist consultation.
IM, intramuscular; IV, intravenous.
From Lieberthal A, Carroll A, Chonmaitree T, et al. The diagnosis and management of acute otitis media. *Pediatrics*. 2014:133:347.

of their high cost, the increased risk of adverse reactions, and the increased likelihood of the development of resistant strains.

The dose of amoxicillin depends on the risk for the presence of drug-resistant pneumococci. Risk factors for drug resistance include age younger than 2 years, daycare attendance, recent antibacterial exposure, and cigarette smoke exposure. In addition, clinicians should consider resistance patterns within their own community. In penicillin-allergic patients, the cross-reactivity between penicillins and cephalosporins is likely lower than previously reported. Cephalosporins are therefore an alternative therapy option in patients without severe and/or recent allergic reaction to penicillins (see Table 4.8). Clindamycin is not effective against *H. influenzae*, but may be effective against some penicillin-resistant strains of *S. pneumoniae*. Macrolides (i.e., erythromycin, azithromycin) are minimally effective against *S. pneumoniae* or *H. influenzae* and therefore not appropriate alternatives.

Patients With Persistent Symptoms

After 48-72 hours of antibacterial therapy, most patients are either asymptomatic or experiencing improvement. Many patients may have an active viral infection; whereas others may have a persistent inflammatory reaction despite elimination of viable bacteria, both of which may be responsible for continued symptomatology. Studies are conflicting regarding continued presence of bacteria in the middle ear of persistently symptomatic patients. Some studies report continuous bacterial presence while others report sterile bacterial cultures of middle ear fluid in up to 50% of patients with persistent symptoms. Therefore, in children with mild persistent symptoms, a clinician should consider analgesic-antipyretic medications for relief of symptoms while addressing any issues of drug noncompliance, including palatability and dosing interval. In children with more severe, persistent signs of AOM without otologic improvement, a clinician should consider prescribing an alternative antibiotic effective against possible resistant *S. pneumoniae* and β-lactamase–producing *H. influenzae* and *M. catarrhalis*, such as amoxicillin-clavulanate (80-90 mg/kg/day of the amoxicillin component), cefuroxime axetil, or 3 days of intramuscular ceftriaxone (see Table 4.8). With the emergence of *S. pneumoniae* resistance, tympanocentesis with culture of middle ear effusion should be considered for bacteriologic diagnosis and susceptibility testing.

Recurrent Acute Otitis Media

Recurrent otitis media is defined as 3 episodes of AOM in a 6-month period or 4 episodes in a 12-month period with at least 1 episode in the preceding 6 months. Risk factors for recurrent AOM include:

- onset of AOM in the first year of life, especially if the first episode is before the patient is 6 months of age
- male gender
- a sibling's history of recurrent AOM
- cleft palate
- craniofacial anomalies
- trisomy 21
- daycare attendance
- household cigarette smoke exposure
- human immunodeficiency virus infection
- lack of breastfeeding
- history of atopy/allergies

Children with recurrent otitis media present a particular challenge with regard to treatment options. Long-term, low-dose antibacterial agents have been used as a method of prophylaxis in children with recurrent AOM in attempts to prevent additional episodes. While there is some evidence of decreased episodes of AOM, this only occurred while receiving the prophylactic antibacterial, without benefits after discontinuation of the antibacterial. Other studies have not demonstrated a difference in recurrence of AOM among children with or without prophylactic antibacterials. Given the risks of emergence of antibacterial resistance, side effects of antibacterials, and cost of therapy weighed against the questionable benefits of long-term antibacterial use, *prophylaxis is not recommended*.

The use of myringotomy and tympanostomy tube placement for the treatment of recurrent AOM or OME has remained controversial. While these procedures may decrease the number of episodes of acute otitis media and improve quality of life for children with recurrent AOM or OME, more stringent criteria are needed before determining the populations most likely to benefit. Additional considerations regarding cost of the procedure and the risks of surgery and anesthesia should be considered before recommendation for tympanostomy tube placement. Tympanostomy tubes are eventually extruded from the eardrum by the normal process of epithelial growth. Recurrent episodes of otitis media may then resume. Long-term consequences of tympanostomy tubes include focal atrophy, tympanosclerosis, and chronic perforation at the site of tube insertion.

OTITIS MEDIA WITH EFFUSION

Otitis media with effusion, also known as "glue ear," may occur after an acute episode of otitis media or because of eustachian tube obstruction resulting from another cause (most commonly, URI). OME differs from AOM in that there is middle ear effusion present without signs or symptoms of acute infection (Fig. 4.9). The most common presenting complaint with OME is decreased hearing. A middle ear fluid can persist for weeks after AOM. Two weeks after AOM, approximately 75% of children will have persistent effusion. The percentage drops to 50% at 1 month and 10%-25% at 3 months post-AOM. Because most cases of OME resolve without treatment, a period of observation is the most appropriate initial strategy. If effusion persists for 3 months or longer or any time language delay, learning difficulties, or significant hearing loss is suspected, hearing testing should be performed.

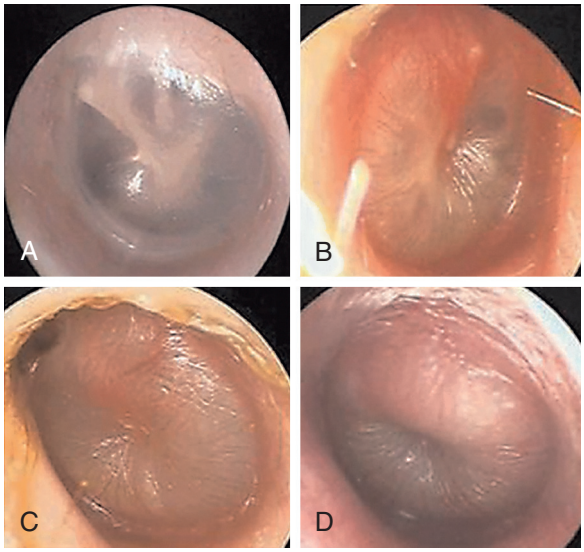


FIGURE 4.9 Examples of normal tympanic membrane *(A)* and of mild bulging *(B)*, moderate bulging *(C)*, and severe bulging *(D)* of the tympanic membrane from middle ear effusion. (From Kerschner J, Preciado D. Otitis media. In: Kliegman R, ed. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2015:3089.)

Medical therapy of OME has not been consistently successful. Antihistamines, decongestants, and nonsteroidal antiinflammatory agents do not promote the resolution of middle ear effusion and should not be used. With systemic corticosteroids (prednisone), the effusion may resolve initially, but it recurs within a few weeks of steroid discontinuation. Additionally, the side effect profile of systemic steroids precludes its use in children with OME. Although bacteria may be present in some cases, antibacterial therapy has only a minimal effect on the resolution of effusion and does not demonstrate long-term benefit. A period of observation for 4-6 months is recommended before surgical intervention is considered.

To assist the clinician in the diagnosis and management of OME, the American Academy of Pediatrics, American Academy of Family Physicians, and the American Academy of Otolaryngology-Head and Neck Surgery have developed a practice guideline for affected children between 2 months and 12 years. The guideline distinguishes between children with OME at risk for speech, language, or learning problems and children not at risk for such problems. The panel recommends documentation of laterality, duration, and severity of effusion with pneumatic otoscopy and confirmation of effusion by tympanometry when pneumatic otoscopy is inconclusive. The panel does not recommend decongestants, steroids, antihistamines, antibacterial agents, tonsillectomy alone, or adenoidectomy alone in the management of persistent OME. Based on the guidelines, the following children are candidates for surgical intervention:

- children with OME persisting for greater than 4 months with associated persistent hearing loss
- at-risk children with persistent OME regardless of hearing status
- children with structural damage to the middle ear or tympanic membrane secondary to OME

Tympanostomy tube placement is the recommended initial surgical intervention, with a mean 62% relative decrease in effusion and improvement in hearing loss by a mean of 6-12 dB. After tube extrusion, up to 50% of children will have a relapse of OME.

MASTOIDITIS

Mastoiditis is a potentially serious acute or chronic suppurative complication of otitis media. Life-threatening complications of mastoiditis are related to intracranial extension of the suppurative process.

Mastoiditis begins with the development of hyperemia and edema of the mastoid process. This progresses to a suppurative process that may produce demineralization and necrosis of bone, abscess formation, and contiguous spread to intracranial or other head and neck areas. Mastoiditis with periosteitis indicates that the infection has spread to the periosteum of the mastoid process and manifests most commonly in children younger than 2 years, although children of any age may be affected. Otalgia, posterior ear pain, fever, and otorrhea are frequent symptoms. Posterior auricular tenderness and erythema, anterior-inferior pinna protrusion, loss of the posterior auricular crease, middle ear effusion, a bulging or perforated tympanic membrane, and sagging of the posterior auditory canal wall are observable signs. Acute mastoid osteitis designates further spread of infection causing bony trabeculae destruction. Mastoiditis may result in transverse sinus thrombosis (Fig. 4.10).

Petrositis occurs when the infection spreads medially to the petrous portion of the temporal bone and often manifests as eye pain secondary to irritation of the ophthalmic branch of cranial nerve V (Fig. 4.11). **Gradenigo syndrome** is the triad of ipsilateral orbital or facial pain, paralysis of the lateral rectus muscle, and suppurative otitis media. Rarely, the infection can spread externally to musculature of the neck resulting in a neck abscess (**Bezold abscess**).

The pathogens responsible for mastoiditis are the same as those of AOM, including *S. pneumoniae* and *H. influenzae,* though *Pseudomonas* and group A streptococci are also causative agents. A CT scan is usually diagnostic and reveals various stages of mastoiditis:

- mastoiditis with periosteitis
- mastoiditis with osteitis with or without subperiosteal abscess

Treatment is based on the stage of the process. High-dose intravenous antibacterials plus tympanostomy and myringotomy with or without tympanostomy tube placement are important therapeutic (for drainage) and diagnostic (for culture) procedures. Mastoidectomy is usually indicated for severe osteitis, mastoid abscess formation, and all intracranial suppurative complications.

CHOLESTEATOMA

Cholesteatomas are cyst-like growths of the middle ear or mastoid formed by keratinizing squamous epithelial cells (Fig. 4.12). They can be either congenital or acquired. Congenital cholesteatomas likely result from epithelial cells implanted during otologic development in utero. Acquired cholesteatomas are potential complications from chronic otitis media or secondary to a deep retraction pocket (or invagination) in the tympanic membrane. The condition can also develop after tympanostomy tube placement with an incidence of 0.8%-1.4%. Cholesteatomas can cause bony resorption by expansion, often to the mastoid, but occasionally intracranially with potentially life-threatening consequences. This condition should be suspected in children with history of chronic OM, persistent otorrhea, and a tympanic membrane with a retraction pocket or perforation with white debris overlying the area. Cholesteatomas commonly present over the superior portion of the tympanic membrane. Urgent otolaryngology consultation should be obtained as delay in treatment can result in intracranial extension, permanent hearing loss, facial nerve injury, and middle and inner ear destruction.

INTRACRANIAL COMPLICATIONS

Meningitis, epidural empyema, brain abscess, and sigmoid sinus thrombosis can develop as complications of acute or chronic ear or mastoid infection. If suspected, imaging of the head should be done prior to lumbar puncture to evaluate for hydrocephalus or mass effect. Meningitis most commonly results from hematogenous spread of the infection and is diagnosed by cerebrospinal fluid (CSF) analysis and culture. Tympanocentesis should be performed for bacterial culture to aid in diagnosis and management choices. Brain abscess can occur from direct extension of an acute or chronic otitis media or can develop adjacent to petrositis (Fig. 4.13). Clinical signs and symptoms should lead one to suspect this complication, and diagnosis can be made with CT or MRI. CSF for culture should be obtained to aid in directing therapy; however, culture may be negative depending on the location and loculation of the abscess. Lateral sinus thrombosis, also known as sigmoid sinus thrombosis, forms when infection from the adjacent mastoid contacts and penetrates the venous wall and forms a thrombus. Embolization of the thrombus can cause distal disease. These intracranial complications require broad-spectrum antibacterials and consultation with otolaryngology and neurosurgery for possible surgical interventions.

(See *Nelson Textbook of Pediatrics*, p. 3082.)

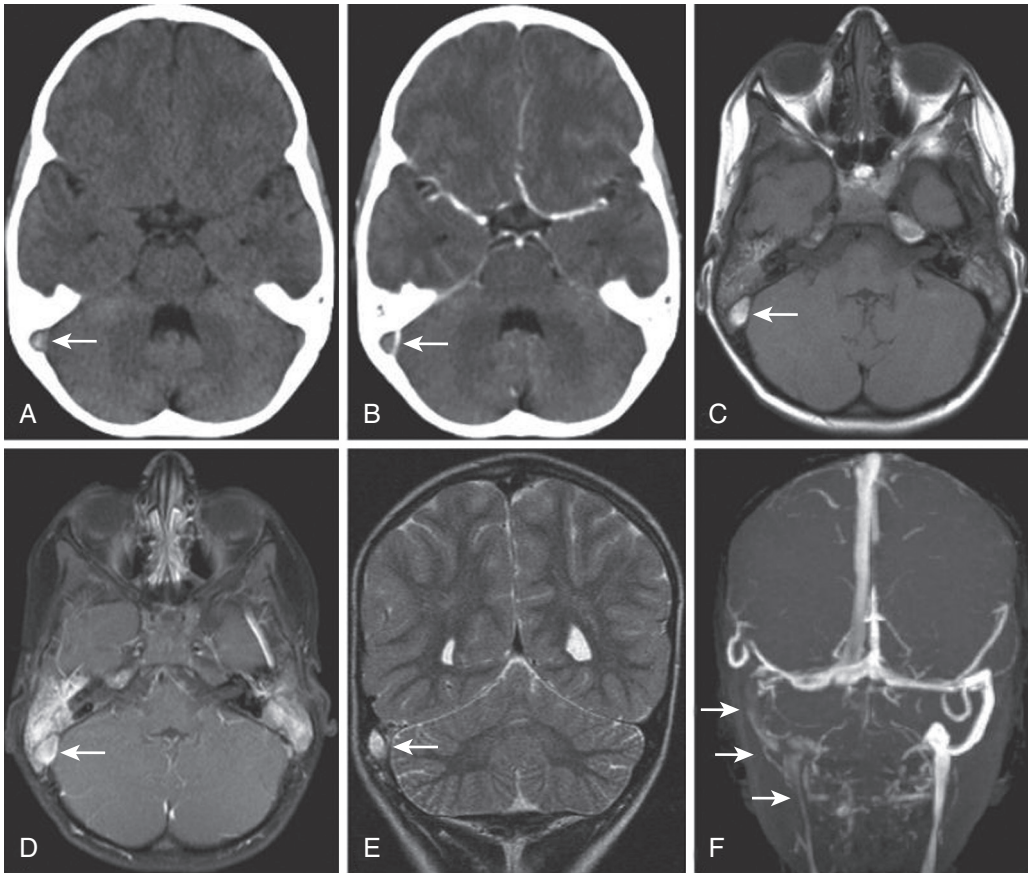


FIGURE 4.10 Transverse sinus thrombosis associated with otomastoiditis or middle ear disease. A patient with otitis media, headache, and papilledema. Axial noncontrast *(A)* and contrast-enhanced *(B)* computed tomography (CT) of the head through the level of the posterior fossa, axial magnetization transfer T1 precontrast *(C)* and postcontrast *(D)* magnetic resonance imaging scans, coronal T2 *(E)* and coronal multiple intensity projection image from a three-dimensional time-of-flight magnetic resonance venogram (MRV) *(F)* were obtained. Note the dense appearance within the right transverse sinus on the noncontrast CT study (*arrow* in *A*), with corresponding lack of contrast filling on the postcontrast CT study (*arrow* in *B*). Corresponding T1 shortening is seen in the precontrast magnetic resonance image (*arrow* in *C*), with corresponding abnormal signal on the postcontrast images in keeping with clot or slow flow within the region of the right transverse sinus or sigmoid sinus (*arrow* in *D*). Corresponding T2 prolongation is seen on the coronal T2 image (*arrow* in *E*). Note the striking asymmetry of flow within the right posterior fossa dural venous system or internal jugular vein on the right on the three-dimensional time-of-flight MRV (*arrows* in *F*). (From Coley BD, ed. *Caffey's Pediatric Diagnostic Imaging*. 12th ed, Vol 1. Philadelphia: Elsevier; 2013:360.)

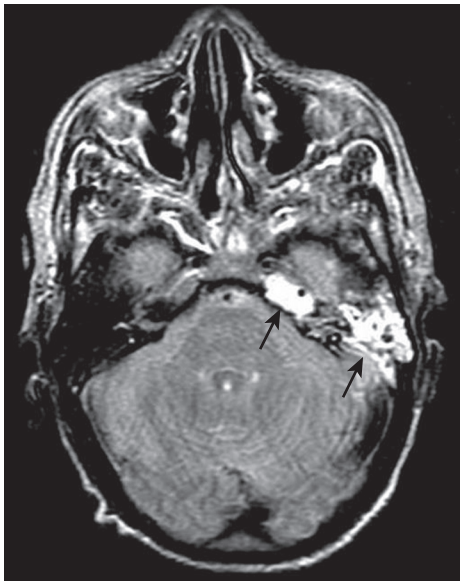


FIGURE 4.11 Axial T2-weighted MRI showing left mastoiditis and petrous apicitis *(arrows)* as high signal in mastoid and petrous apex. (From Flint PW, Haughey BH, Lund VJ, et al, eds. *Cummings Otolaryngology Head & Neck Surgery*. 5th ed. Vol 2. Philadelphia: Elsevier; 2010.)

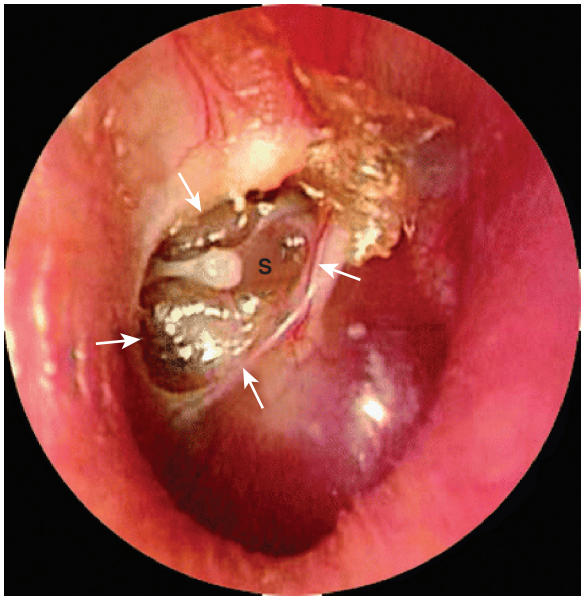


FIGURE 4.12 A retraction-pocket cholesteatoma of the posterosuperior quadrant. The incus long process is eroded, which leaves the drum adherent to the stapes head (S). An effusion is present in the middle ear, and squamous debris emanates from the attic. (From Isaacson G. Diagnosis of pediatric cholesteatoma. *Pediatrics*. 2007;120:603-608.)

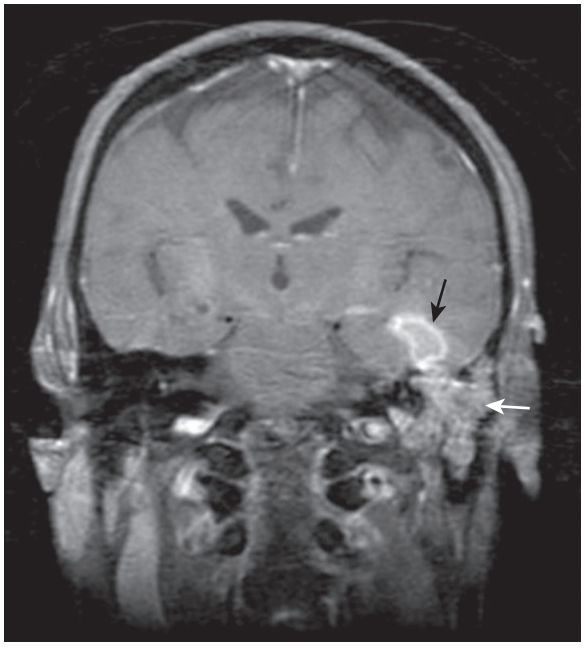


FIGURE 4.13 Coronal enhanced T1-weighted MRI of the patient showing enhancing tissue in left mastoid *(white arrow)* and temporal lobe abscess with enhancing capsule *(black arrow)*. (From Flint PW, Haughey BH, Lund VJ, et al, eds. *Cummings Otolaryngology Head & Neck Surgery*. 5th ed. Vol 2. Philadelphia: Elsevier; 2010:1995.)

SUMMARY AND RED FLAGS

A careful examination of the pinna, external auditory canal, and tympanic membrane can identify most causes of ear pain. If findings are normal, the clinician should consider pain referred from another source (see Table 4.3). Because young children may have trouble localizing their pain, clinicians should be highly suspicious of ear disease in any infant or preschool child with fever, irritability, or URI.

Even though most conditions causing ear pain respond readily to therapy, the clinician must be aware of the following red flags associated with these conditions:

- laterally displaced pinna (malignant otitis externa, mastoid osteitis)
- mastoid tenderness (mastoid osteitis)
- perforated tympanic membrane
- a pearl-like tumor in the tympanic membrane (cholesteatoma)
- subacute headache, meningismus, and altered mental status (brain abscess, subdural or epidural empyema)

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

American Academy of Pediatrics. Clinical practice guideline: Otitis media with effusion. *Pediatrics*. 2004;113:1412-1429.

Amundsen G. Tympanometry. In: Pfenninger J, Fowler G, eds. *Pfenninger and Fowler's Procedures for Primary Care*. 3rd ed. Philadelphia: Mosby; 2011:479-481.

Carfrae M, Kesser B. Malignant otitis externa. *Otolaryngol Clin North Am*. 2008;41:537-549.

Casey J, Adlowitz D, Pichicherio M. New patterns in the otopathogens causing acute otitis media six to eight years after introduction of pneumococcal conjugate vaccine. *Pediatr Infect Dis J*. 2010;29:304-309.

Casselbrandt M, Mandel E. Acute otitis media and otitis media with effusion. In: *Cummings Otolaryngology*. 6th ed. Philadelphia: Elsevier Saunders; 2015:3019-3037.

Centers for Disease Control and Prevention. Estimated burden of acute otitis externa. *MMWR Morb Mortal Wkly Rep*. 2011;60:605-609.

Coker T, Chan L, Newberry S, et al. Diagnosis, microbial epidemiology, and antibiotic treatment of acute otitis media in children. *JAMA*. 2010;304:2161-2169.

Conover K. Earache. *Emerg Med Clin North Am*. 2013;31:413-442.

Haddad J, Keesecker S. External otitis (Otitis externa). In: Kliegman R, ed. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2015:3083-3085.

Haddad J, Keesecker S. General considerations and evaluation. In: Kliegman R, ed. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia, PA: Elsevier; 2015:3069-3071.

Harris P, Hutchinson K, Moravec J. The use of tympanometry and pneumatic otoscopy for predicting middle ear disease. *Am J Audiol*. 2005;14:3-13.

Isaacson G. Diagnosis of pediatric cholesteatoma. *Pediatrics*. 2007;120:603-608.

Kerschner J, Preciado D. Otitis media. In: Kliegman R, ed. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2015:3085-3100.

Keyhani S, Kleinman L, Rothschild M, et al. Overuse of tympanostomy tubes in New York metropolitan area: Evidence from five hospital cohort. *BMJ*. 2008;337:a1607.

Klein J. Otitis externa, otitis media, and mastoiditis. In: *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. Philadelphia: Elsevier; 2015:767-773.

Lieberthal A, Carroll A, Chonmaitree T, et al. The diagnosis and management of acute otitis media. *Pediatrics*. 2013;131:e964-e999.

Majumdar S, Wu K, Bateman ND, et al. Diagnosis and management of otalgia in children. *Arch Dis Child Educ Pract Ed*. 2009;94:33-36.

Marom T, Tan A, Wilkinson G, et al. Trends in otitis media-related health care use in the United States, 2001-2011. *JAMA Pediatr*. 2014;168:68-75.

Neilan R, Roland P. Otalgia. *Med Clin North Am*. 2010;94:961-971.

Oliver A, Simpson E, Jerath R. A rare cause of ear pain in a young boy. *J Pediatr*. 2012;160:350.

Puhakka T, Pulkkinen J, Silvennoinen H, et al. Comparison of spectral gradient acoustic reflectometry and tympanometry for detection of middleear effusion in children. *Pediatr Infect Dis J*. 2014;33:e183-e186.

Rogers G, Arguedas A, Cohen R, et al. Global serotype distribution among *Steptococcus pneumoniae* isolates causing otitis media in children: Potential implications for pneumococcal conjugate vaccines. *Vaccine*. 2009;27:3802-3810.

Roland P, Smith T, Schwartz S, et al. Clinical practice guideline: cerumen impaction. *Otolaryngol Head Neck Surg*. 2008;139:S1-S21.

Roland P, Stroman D. Microbiology of acute otitis externa. *Laryngoscope*. 2002;112:1166-1177.

Rovers M. The burden of otitis media. *Vaccine*. 2008;26(S7):G2-G4.

Shea K, Weycker D, Stevenson A, et al. Modeling the decline in pneumococcal acute otitis media following the introduction of pneumococcal conjugate vaccines in the US. *Vaccine*. 2011;29:8042-8048.

Vergison A, Dagan R, Arguendas A, et al. Otitis media and its consequences: Beyond the earache. *Lancet Infect Dis*. 2010;10:195-203.

Zhang Y, Xu M, Zhang J, et al. Risk factors for chronic and recurrent otitis media—a meta-analysis. *PLoS One*. 2014;9:e86397.

Apparent Life Threatening Event–Brief Resolved Unexplained Event

Amanda Rogers and Sandra Gage

Apparent life-threatening event (ALTE) is a term used to describe an acute, unexpected episode that consists of a change in an infant's breathing, appearance, or behavior. It is a clinical description, rather than a specific diagnosis, and represents a wide variety of presentations with diverse underlying pathology.

DEFINITION

The current definition of ALTE was established at the 1986 National Institutes of Health Consensus Development Conference on Infantile Apnea and Home Monitoring (Table 5.1). ALTE was defined as "an episode that is frightening to the observer, that is characterized by some combination of apnea (central or occasionally obstructive), color change (usually cyanotic or pallid, but occasionally erythematous or plethoric), marked change in muscle tone (usually marked limpness), choking, or gagging."

The term ALTE was in part established to replace previously used labels, including "near-miss SIDS" or "aborted crib death," which inappropriately suggested a clear association between ALTEs and sudden infant death syndrome (SIDS). SIDS is defined as the sudden death of any infant or young child, which is unexplained by history and in which a thorough postmortem examination fails to demonstrate an adequate explanation of cause of death. Studies have failed to establish a clear association between ALTEs and SIDS. Although there are some overlapping risk factors between SIDS and ALTEs, they are separate entities. The vast majority of SIDS victims do not have a preceding ALTE. The American Academy of Pediatrics Task Force on SIDS is clear in its stance that there is no evidence that an ALTE is a precursor to SIDS.

The subjectivity and vagueness of the current definition has made it difficult to standardize the care of these patients. In 2016 the American Academy of Pediatrics (AAP) released a clinical practice guideline related to the care of these patients. This guideline includes a change in terminology to **BRUE (brief resolved unexplained event),** which is defined as an event lasting <1 min in an infant under one year of age that is associated with at least one of the following: cyanosis or pallor; absent, decreased, or irregular breathing; marked change in muscle tone (hypertonia or hypotonia); altered level of responsiveness in a patient who at the time of examination is otherwise well-appearing and back to baseline, and, on evaluation, has no condition that could explain the event. The guideline recommends limited interventions for patients designated as being at low risk for recurrence. Low-risk patients include those having their first event who are >60 days old, ≥32 weeks' gestational age, ≥45 weeks postconceptional age, had an event lasting <1 minute and did not require cardiopulmonary resuscitation, and who have no concerning historical or physical exam findings.

EPIDEMIOLOGY

The exact incidence of ALTEs is unknown because the definition of an ALTE is subjective, and not all children with ALTEs present for evaluation. Reported figures may underestimate the true incidence of patients presenting with ALTEs since studies may not include those cases where the underlying cause is ultimately identified. The incidence is estimated to be between 0.46 and 2.46 per 1000 live births, accounting for 0.6-1% of all emergency department visits by patients younger than 1 year and 2% of pediatric hospitalizations. Most occur in infants less than 1 year of age, with a peak incidence between 1 week and 3 months. Occurrence is equal between males and females. The mortality rates reported to be associated with ALTEs vary widely depending on the definition used and the population studied. Due to the diversity of the potential underlying etiology of an ALTE, clinicians should be cautious in the application of these rates to the ALTE population as a whole (Table 5.2).

ETIOLOGY

Because ALTE is a descriptive category based on broad symptomatology, the differential diagnosis is large. Comorbid conditions are frequently identified, but it can be challenging to identify true causation. Thus caution must be used in implicating a specific diagnosis as the true cause of an ALTE. A suspected diagnosis is found in approximately 50% of ALTEs. These diagnoses encompass a wide range of etiologies and systems.

The most commonly cited diagnoses include gastroesophageal reflux (GER), seizures, and lower respiratory tract infections. However, numerous less common but potentially dangerous and/or treatable conditions can also present as an ALTE (see Table 5.2). These need to be carefully considered in order to provide prompt life saving or outcome-altering treatment. A thorough and thoughtful history and physical examination is extremely important in the evaluation of a patient with an ALTE, as it provides essential clues to help narrow the differential. It is often helpful to consider the differential diagnosis by a systems-based approach, considering both common and rare but concerning diagnoses in each category. Key systems-based historical and physical examination findings may help discriminate among possible etiologies (Table 5.3).

CLINICAL EVALUATION

◆ History

The most important diagnostic tool in the evaluation of an ALTE is a thorough history elicited from the caretaker who observed the episode.

(See *Nelson Textbook of Pediatrics*, p. 2004.)

TABLE 5.1 Definitions from the 1986 National Institutes of Health Consensus Panel on Infantile Apnea and Home Monitoring

Apparent life-threatening event (ALTE)	An episode that is frightening to the observer and that is characterized by some combination of apnea (central or occasionally obstructive), color change (usually cyanotic or pallid but occasionally erythematous or plethoric), marked change in muscle tone (usually marked limpness), choking, or gagging
Apnea	Cessation of respiratory airflow which can be central (i.e., no respiratory effort), obstructive (usually due to upper airway obstruction), or mixed
Pathologic apnea	Apnea that is prolonged (20 sec) or associated with cyanosis; abrupt, marked pallor or hypotonia; or bradycardia
Periodic breathing	A breathing pattern in which there are three or more respiratory pauses of >3 sec in duration with <20 sec of respiration between pauses
Apnea of prematurity (AOP)	Periodic breathing with pathologic apnea in a premature infant that usually ceases by 37 wk of gestation but occasionally persists to several weeks past term
Apnea of infancy (AOI)	An unexplained episode of cessation of breathing for 20 sec or longer, or a shorter respiratory pause associated with bradycardia, cyanosis, pallor, and/or marked hypotonia in infants who are >37 wk of gestational age at onset of pathologic apnea
Sudden infant death syndrome (SIDS)	The sudden death of any infant or young child, which is unexplained by history and in which a thorough postmortem examination fails to demonstrate an adequate explanation of cause of death

History taking should start with open-ended questions to obtain the story from the caretaker, followed by specific questions geared at characterizing certain key aspects of the episode. The history should focus on the activities and behaviors preceding the event, characteristics of the episode itself, interventions performed and their effect, and post–episode events and behavior. A comprehensive past medical history, social history, and family history should also be obtained for identifying clues that may aid in narrowing the focus of the investigation. Information essential to a complete history is outlined in Table 5.4. Key historical findings by system can be useful in narrowing the differential (see Table 5.3).

The patient's activities and behaviors immediately preceding the episode are important to consider and may provide clues to the diagnosis. Key associations include those with sleep, feeding, crying, cough, and emesis. The location and position of the child prior to the event should also be noted, such as placement in a car seat, on a soft or firm surface, prone or supine, and with or without surrounding blankets or pillows.

Key characteristics of the actual event include respiratory effort, color change, change in tone or movements, level of alertness at onset and during the episode, duration of the event, and associated symptoms such as choking or emesis. ALTEs often include alteration of respiration or perceived apnea. In these cases, the duration of respiratory cessation aids in the determination of true pathologic apnea. Apnea is defined as cessation in breathing that is prolonged (>20 sec) or associated with cyanosis, marked pallor or hypotonia, or bradycardia. The degree of respiratory effort noted assists in differentiating central versus obstructive processes. Central apnea with no respiratory effort may suggest underlying neurologic, cardiac, metabolic, or infectious causes, while obstructive processes include GER, respiratory tract infections, foreign body, suffocation, or airway anatomic anomalies. If there is color change, providers should note not only the color itself (pale, red, cyanotic) but also the location, such as central cyanosis versus flushing or acrocyanosis. The latter two may be consistent with normal changes in perfusion. It is important to determine if tone was increased or decreased. If abnormal movements were identified, it should be noted if the movements were generalized or localized to a certain part of the body. The ability to suppress any abnormal movements should be documented, as this makes conditions such as seizure less likely.

Any interventions performed, by whom, and the effects of the interventions are also important to document. The need for resuscitation, especially when performed by health care providers, has been associated with more severe and significant underlying etiologies. It can be beneficial to obtain a direct history from any emergency personnel who may have been involved with the case.

Postepisode behavior should be carefully documented. Level of alertness following the event and time until return to normal behavior are of particular importance.

Regarding past history, it is essential to note the birth history including gestational age, any prior similar episodes, preceding illnesses, and known medical conditions. Family history should also be obtained with a focus on the presence of ALTEs, SIDS, early deaths, metabolic, or neurologic disorders in first or second degree family members. Social factors to consider include a full list of caregivers, illness exposures, medications in the home, and exposure to smoke.

Three major factors suggestive of risk for future adverse events and/or a serious underlying diagnosis include prematurity, multiple ALTEs, and suspected child maltreatment. Prematurity is a frequently noted risk factor for an ALTE, perhaps due in part to the preterm infants' immature respiratory centers, arousal mechanisms, and airway reflexes. A history of multiple ALTEs raises the concern for serious underlying pathology and progression of future events. With a history of multiple events over days to months, the concern for child maltreatment, seizures, intracranial pathology, and inborn errors of metabolism increases. Multiple events occurring over the course of the day of presentation escalate concern for serious infections and child maltreatment. Clinical suspicion of child maltreatment also increases the likelihood of future adverse events. A history of resuscitation attempt, cyanosis, and more than one ALTE in 24 hours are independent risk factors for the need for subsequent intensive care.

◆ Physical Examination

One of the diagnostic challenges of the evaluation of a child with an ALTE is that in a majority of cases the infant is well-appearing after the event. Infants should undergo a complete head-to-toe examination fully unclothed, including vital signs with pulse oximetry, growth parameters with head circumference, and complete ear, nose, throat, cardiac, respiratory, abdominal, neurologic, musculoskeletal, and skin examinations.

TABLE 5.2 Conditions That Can Cause Apparent Life-Threatening Events or Sudden Unexpected Infant Death

Central Nervous System
Arteriovenous malformation
Subdural hematoma
Seizures
Congenital central hypoventilation*
Neuromuscular disorders (Spinomuscular atrophy)
Chiari crisis
Leigh syndrome*

Cardiac
Subendocardial fibroelastosis*
Aortic stenosis
Anomalous coronary artery
Myocarditis
Cardiomyopathy*
Arrhythmias (prolonged Q-T syndrome, Wolff-Parkinson-White syndrome, and congenital heart block)*

Pulmonary
Nasal obstruction
Pulmonary hypertension
Vocal cord paralysis
Aspiration
Laryngotracheal obstructive diseases

Gastrointestinal
Diarrhea and/or dehydration
Gastroesophageal reflux
Volvulus

Endocrine–Metabolic
Congenital adrenal hyperplasia*
Malignant hyperpyrexia*
Long- or medium-chain acyl coenzyme A deficiency*
Hyperammonemias (urea cycle enzyme deficiencies)*
Glutaric aciduria*
Carnitine deficiency (systemic or secondary)*
Glycogen storage disease type I*
Maple syrup urine disease*
Congenital lactic acidosis*
Biotinidase deficiency*

Infection
Sepsis
Meningitis
Encephalitis
Brain abscess
Pyelonephritis
Bronchiolitis (respiratory syncytial virus)
Infant botulism
Pertussis

Trauma
Child abuse*
Accidental or intentional suffocation
Physical trauma
Factitious syndrome (formerly Munchausen syndrome) by proxy*

Poisoning (Intentional or Unintentional)
Boric acid
Carbon monoxide
Salicylates
Barbiturates
Ipecac
Cocaine
Insulin
Others

*May be seen with recurrences in siblings.
Modified from Hunt CE, Hauck FR. Sudden infant death syndrome. In: *Nelson Textbook of Pediatrics*, 20th ed. Philadelphia: Elsevier; 2016:1999.

Any abnormalities on the presenting examination may indicate various possible diagnoses and should prompt additional evaluation for the suggested etiology (see Table 5.3). Particular attention should be paid to the child's general appearance for any dysmorphic features which might suggest an underlying genetic or metabolic syndrome. Abnormal growth parameters may identify failure to thrive, which can be suggestive of pathologic reflux, cardiac disease, or metabolic disorders. Signs of trauma, including retinal hemorrhages, unexplained bruising, or evidence of oral pharyngeal trauma (torn frenulum) suggestive of child maltreatment should also be noted. Abnormality of the neurologic examination should be fully assessed, with concern for intracranial bleed or mass requiring prompt attention.

◆ Diagnostic Evaluation

In approximately 20% of patients with an ALTE, the history and physical examination alone yields the cause; in about 50% of patients, a likely diagnosis is suspected from the history and physical examination and is subsequently confirmed by diagnostic testing. Diagnostic testing alone yields an etiology in only about 15% of patients. When testing is performed, it is most successful when done in a focused and targeted manner geared toward diagnoses suggested by the history and physical examination.

In the patient presenting with an ALTE, it is often difficult to determine the degree to which diagnostic work-up is indicated, especially in well-appearing infants with a nonspecific history and physical examination. The most common laboratory tests performed include a complete blood count (CBC) and serum electrolytes, while the most common radiographic tests/procedures are chest radiograph and electrocardiogram (ECG). Although there are numerous evidence-based algorithms for the diagnostic evaluation of patients with an ALTE, there is no uniformly accepted approach that has been found to be beneficial in the evaluation of all patients.

Well-appearing patients after ALTE, who have reassuring histories and normal examination findings at the time of presentation, require careful follow-up and may not require admission or additional

TABLE 5.3 System-Based Approach to ALTEs/BRUEs

Diagnostic Categories	Common and/or Concerning Causes to Consider	Suggestive Historical Findings	Suggestive Physical Examination Findings	Testing to Consider
Gastrointestinal	GER Intussusception Volvulus Swallowing abnormalities	Coughing, vomiting, choking, gasping Feeding difficulties Recent preceding feed Irritability following feeds Milk in mouth/nose Bilious emesis Pulling legs to chest Bloody/mucousy stool Lethargy following event	Gastric contents in the nose and mouth Abdominal distention Abdominal tenderness	Upper GI to assess for anatomic anomalies Swallow evaluation Abdominal ultrasound pH probe
Infectious	Upper and lower respiratory tract infection (RSV, pertussis, pneumonia) Bacteremia Meningitis Urinary tract infection	Preceding URI symptoms Multiple events on the day of presentation Sick exposures Foul-smelling urine	Fever/hypothermia Lethargy Ill appearance Coryza Cough Wheeze Tachypnea	NP swab for RSV, pertussis Chest radiograph CBC and Blood culture Cerebrospinal fluid analysis and culture Urinalysis and culture
Neurologic	Seizures Breath holding spells Congenital central hypoventilation syndrome Neuromuscular disorders Congenital malformations of the brain and brainstem Malignancy Intracranial hemorrhage	Multiple events Loss of consciousness Change in tone Abnormal muscular movements Eye deviation Preceding triggers	Papilledema Abnormal muscular movements Hypertonicity or flaccidity Abnormal reflexes Micro- or macrocephaly Dysmorphic features	EEG Neuroimaging
Respiratory/ ENT	Apnea of prematurity Apnea of infancy Periodic breathing Airway anomaly Aspiration Foreign body Obstructive sleep apnea	Prematurity Foreign body Aspiration Noisy breathing	Wheezing Stridor Crackles Rhonchi Tachypnea	Chest radiograph Neck radiograph Laryngoscopy Bronchoscopy Esophagoscopy Polysomnography
Child maltreatment	Non-accidental head trauma Smothering Poisoning Factitious syndrome (formerly Munchausen syndrome) by proxy	Multiple events Unexplained vomiting or irritability Recurrent ALTEs Historical discrepancies Family history of unexplained death, SIDS, or ALTEs Single witness of event Delay in seeking care	Bruising (especially in a non-mobile child) Ear trauma, hemotympanum Acute abdomen Painful extremities Oral bleeding/trauma Frenulum tears Unexplained irritability Retinal hemorrhages Depressed mental status	Skeletal survey Computed tomography of the head Dilated funduscopic examination Toxicology screen
Cardiac	Dysrhythmia (prolonged QT syndrome, Wolff-Parkinson-White syndrome) Cardiomyopathy Congenital heart disease Myocarditis	Abrupt onset Feeding difficulties Failure to thrive Diaphoresis Prematurity	Abnormal heart rate/rhythm Murmur Decreased femoral pulses	4 extremity blood pressure Pre- and post-ductal oxygen saturation measurements ECG Echocardiogram Serum electrolytes, calcium, magnesium

TABLE 5.3 System-Based Approach to ALTEs/BRUEs—cont'd

Diagnostic Categories	Common and/or Concerning Causes to Consider	Suggestive Historical Findings	Suggestive Physical Examination Findings	Testing to Consider
Metabolic/ genetic	Inborn errors of metabolism Electrolyte abnormalities Genetic syndromes including those with craniofacial malformations	Severe initial event Multiple events Event associated with period of stress or fasting Developmental delay Associated anomalies Failure to thrive Severe/frequent illnesses Family history of ALTE, consanguinity, seizure disorder, or SIDS	Dysmorphic features Microcephaly Hepatomegaly	Serum electrolytes; glucose, calcium, and magnesium levels Lactate Ammonia Pyruvate Urine organic and serum amino acids Newborn screen

ALTE, apparent life-threatening event; BRUE, brief resolved unexplained event; GER, gastroesophageal reflux; GI, gastrointestinal; RSV, respiratory syncytial virus; URI, upper respiratory infection; NP, nasopharyngeal; CBC, complete blood count; EEG, electroencephalogram; ENT, ear, nose, and throat; SIDS, sudden infant death syndrome; ECG, electrocardiogram.

evaluation. *However, any concerning historical or physical features require the need for further in-patient evaluation performed in a focused manner based on the clinical presentation and suspected diagnosis* (see Table 5.3).

DIFFERENTIAL DIAGNOSIS BY SYSTEM

Gastrointestinal

A variety of gastrointestinal (GI) etiologies can present as an ALTE, including GER, intussusception, and volvulus.

GER is one of the most commonly cited comorbid conditions in patients presenting with an ALTE. Some infants will present with overt symptoms such as coughing, choking, and laryngospasm following regurgitation. Others can present without visible regurgitation but rather with posturing including arching of the back, torsion of the neck, and lifting up of the chin. This phenomenon, known as **Sandifer syndrome**, can be frightening to the observer and is often confused with seizure activity. Historical findings that should raise the index of suspicion for GER include a history of frequent reflux, the ALTE being immediately preceded by a feeding, poor weight gain, irritability following a feed, or gastric contents noted in the infant's nose or mouth during the episode. However, one must be careful when attributing an ALTE to GER. Approximately 50% of all normal infants less than 3 months of age experience daily regurgitation, and temporal association does not necessarily equate with causation. Although GER may occasionally cause apneic episodes, it also occurs very commonly in most healthy infants without any sequelae. It is therefore important not to let a history of GER in an infant presenting with an ALTE preclude the consideration of other underlying causes.

Although less common, additional GI pathology that can present with an ALTE include conditions such as intussusception or volvulus. Patients who present with these conditions will typically have additional historical and examination findings to suggest their underlying etiology. Patients with intussusception can have sudden and severe abdominal pain, inconsolable crying, and drawing up of the legs to the abdomen. The classic presentation of intussusception is the triad of abdominal pain, a sausage-shaped abdominal mass, and currant-jelly stool. However, this classic triad is frequently not seen at presentation. Some infants present solely with lethargy or altered consciousness, and thus intussusception should be high on the differential for patients with an ALTE presenting in this manner. Similarly, infants with volvulus can present with sudden onset abdominal pain accompanied by emesis. Volvulus is a medical emergency, which can lead to bowel necrosis and death. As such, it should always be considered in patients with an ALTE and a suggestive clinical presentation.

Most studies do not support routine testing for GER in patients presenting with an ALTE. Because there is a high prevalence of GER in infants, it is expected that a high number of these patients will have positive GER testing. When testing is considered, it is important to understand the utility of various modalities. Upper gastrointestinal fluoroscopy is frequently performed in patients presenting with an ALTE. Although this can be useful in identifying underlying anatomic anomalies that can lead to an ALTE, it should not be used to delineate GER as the cause for the event. This study frequently demonstrates regurgitation in normal infants, and a positive finding on the study does not necessarily indicate that GER was the cause of the inciting event. Although typically not indicated, if further GER testing is desired, esophageal pH analysis via a pH probe could be considered to help demonstrate a causal link by correlating low pH findings with documented apnea on concurrent cardiorespiratory monitoring (see Chapter 12).

Infectious Disease

Various infectious etiologies can present as an ALTE, ranging from common illnesses caused by respiratory viruses to less common, but serious infections such as bacteremia and meningitis. A history of multiple events on the day of presentation is associated with an infectious etiology. Additional historical clues include recent fever, irritability, altered level of arousal, cough, or coryza. Physical examination findings may confirm the suspicion of an infectious etiology, while hypothermia and ill appearance at presentation should lead to concern for more serious infectious etiologies.

Viral respiratory infections are a leading cause of ALTEs. Apnea may be the presenting symptom of viral lower respiratory tract infections, with the telling symptoms of coryza and cough delayed by hours to days. In particular, pertussis and bronchiolitis caused by respiratory syncytial virus (RSV) are commonly reported conditions associated with apnea in young infants. Suspicion of respiratory infection must remain high, especially during peak respiratory illness periods, or if there is a history of recent exposure. Neonates with pertussis may present with or develop few other symptoms, so a careful history of potential exposure is essential for early diagnosis. Although

TABLE 5.4 Important Historical Features of an ALTE–BRUE

Preevent	
Condition of child	Awake vs asleep
Location of child	Prone vs supine, in crib/car seat, with pillows, blankets
Activity	Feeding, crying
Event	
Respiratory effort	None, shallow, gasping, increased Duration of respiratory pauses
Color	Pallor, red, cyanotic Peripheral, whole body, circumoral
Tone/movement	Rigid, tonic-clonic, decreased, floppy Focal vs diffuse Ability to suppress movements
Level of consciousness	Alert, interactive, sleepy, nonresponsive
Duration	Time until normal breathing, normal tone, normal behavior Detailed history of caregiver actions during event to aid in defining time course
Associated symptoms	Vomiting, sputum production , blood in mouth/nose, eye rolling
Post-Event	
Condition	Back to baseline, sleepy, postictal, crying If altered after event, duration of time until back to baseline
Interventions	
What was performed	Gentle stimulation, blowing in face, mouth-to-mouth, cardiopulmonary resuscitation
Who performed intervention	Medical professional vs caregiver
Response to intervention	Resolution of event vs self-resolving
Duration of intervention	How long was intervention performed
Medical History	
History of present illness	Preceding illnesses, fever, rash, irritability, sick contacts
Past medical history	Prenatal exposures, gestational age, birth trauma Any medical problems, prior medical conditions, prior hospitalizations Developmental delay Medications
Feeding history	Gagging, coughing with feeds, poor weight gain
Family history	Neurologic problems Cardiac arrhythmias Sudden death, childhood deaths, ALTEs Neonatal problems Consanguinity
Social history	Home situation Caregivers Smoke exposure Medications in the home

ALTE, apparent life-threatening event; BRUE, brief resolved unexplained event.

uncommon in infants, strong suspicion or the development of a staccato cough with posttussive emesis, or a classic "whoop," should prompt treatment while waiting appropriate testing.

Although the incidence of bacteremia or meningitis is low in patients presenting with an ALTE, the morbidity and mortality of these diagnoses are such that they should always be considered. A history of irritability and/or altered level of arousal may suggest a serious infection. Paradoxical irritability (crying when held) suggests soft tissue or bone infection or a fracture. Examination findings of concern include ill appearance, fever, hypothermia, lethargy, nuchal rigidity, and poor peripheral perfusion. Prompt action is required for the evaluation and treatment of these infants.

Urinary tract infections (UTIs) have also been shown to be a potential cause of ALTEs, with studies reporting a rate of 0-8%. The infection can lead to cardiorespiratory compromise, which can manifest as apnea, color change, altered levels of consciousness, or change in muscle tone. The majority of patients with UTIs significant enough to cause an ALTE will be ill-appearing at presentation. Therefore, most studies indicate that urinalysis and urine culture could be reserved for infants who are febrile, ill-appearing, or who have other clinical symptoms consistent with a UTI.

Neurologic

Neurologic disorders that can lead to an ALTE include seizure, breath holding spells, congenital central hypoventilation syndrome (CCHS), metabolic encephalopathies, and brain or brainstem abnormalities.

The most common neurologic disorder associated with ALTEs is **seizure**, with a rate of up to 25%. Factors that support the diagnosis of seizure include a history of loss of consciousness, poor tone, unresponsiveness, eye deviation, or rhythmic movements that are not able to be suppressed. A history of choking, while commonly reported among patients presenting with an ALTE in general, is typically absent in those presenting with seizure. Thus the lack of this historical fact should raise the suspicion for seizure in the differential.

Breath holding spells have been reported to present to medical attention as an ALTE. These are typically divided into two types: cyanotic and pallid. In cyanotic breath holding spells, there is usually an emotional trigger such as anger or frustration. The infants cry, then become silent and hold their breath in expiration with subsequent cyanosis. This can then be followed by limpness and possible loss of consciousness. Pallid breath holding spells are less common and are typically triggered by pain or fright. The child may gasp, then lose consciousness and become pale, diaphoretic, and limp. This can be followed by a period of increased tone and clonic movements. To determine if an ALTE is consistent with a breath holding spell, it is important to obtain a stepwise history of the event, including any emotional or painful precipitant.

CCHS is a rare but known cause of ALTEs. This is classically characterized by adequate ventilation while awake but hypoventilation while asleep, associated with normal respiratory rates and shallow breathing. In severe cases, patients with CCHS can present similarly to patients with cyanotic heart disease, with cyanosis, edema, and signs of right heart failure. However, in less severe cases, CCHS may present with tachycardia, diaphoresis, or cyanosis during sleep.

Additional rare, but potentially life-threatening, neurologic disorders to consider include brain tumors, neuromuscular disorders, metabolic encephalopathies, and malformations of the brain and brainstem. Examiners should therefore pay particular attention to any focal weakness, cranial nerve abnormalities, or signs of increased intracranial pressure including papilledema and Cushing triad (bradycardia, respiratory irregularities, and hypertension).

Given the relatively high incidence of seizures in infants presenting with an ALTE, some diagnostic algorithms recommend electroencephalograms (EEGs) in the initial investigation. However, at only 15%, the sensitivity of EEGs in diagnosing future epilepsy is poor. Since infants presenting with an ALTE who go on to develop chronic epilepsy will likely have recurrent events, most experts recommend that EEGs be reserved for those patients with recurrent events or historical or physical examination findings specifically concerning for seizures. In patients with suspected seizures, evaluation of serum electrolytes may also be beneficial to identify possible derangements including hypo- or hypernatremia, hypocalcemia, or hypoglycemia. If specific electrolyte abnormalities are identified, further work-up should be undertaken to determine underlying pathology.

Neuroimaging is frequently obtained in patients presenting with an ALTE. Current evidence does not support routine neuroimaging for asymptomatic infants presenting with an ALTE given the low diagnostic yield, high cost, and radiation concerns. However, neuroimaging should always be considered in the infant with an abnormal neurologic examination or a clinical concern for seizure, child maltreatment, metabolic encephalopathies, or tumor to assess for intracranial malformation, bleeding, or mass.

Airway/Pulmonary

Infections of the upper and lower respiratory tract are common causes of ALTEs, but other respiratory etiologies have been cited as well. These include apnea of prematurity and infancy, periodic breathing, and airway abnormalities.

The most common cause of apnea in preterm infants is **apnea of prematurity**. It occurs in virtually all infants born at less than 28 weeks' gestation, and the frequency is indirectly proportional to the gestational age. Apnea of prematurity is thought to be due to immature respiratory control in premature infants and typically presents with either central or mixed (central and obstructive) apnea. It is a diagnosis of exclusion and should be considered only after other etiologies have been ruled out. The apneic events typically begin within the first week of life, and as such, symptom onset after that time should stimulate consideration of other causes. Apnea of prematurity typically resolves by 37 to 40 weeks' postconceptual age in infants delivered at ≥28 weeks but can persist later in infants delivered prior to 28 weeks.

Apnea of infancy (AOI) refers to apnea that develops in neonates older than 37 weeks' postconception. The etiology is unknown. It is reserved for cases when a cause for an ALTE is not identified and is typically seen as a diagnosis of exclusion.

Periodic breathing is a common entity that is often confused by parents for an ALTE. Periodic breathing is defined as three or more respiratory pauses of greater than 3 seconds' duration within a 20 second portion of the breathing cycle. Sometimes several pauses occur, one after the other, followed by a set of short rapid respirations before the respiratory rhythm is restored. Importantly, no associated change in color, tone, or heart rate and no prolonged respiratory pauses (>20 seconds) are reported in association with periodic breathing. A clear history of the ALTE event is essential in differentiating true apnea from periodic breathing. Video of concerning events can prove very helpful. If determined to be periodic breathing, it is a benign entity and does not require any additional work-up or intervention.

Less common respiratory etiologies to consider include **anatomic airway abnormalities** such as anomalies of the pharynx (adenotonsillar hypertrophy), the larynx (laryngomalacia, edema, subglottic ductal cyst, subglottic stenosis), or the trachea (tracheomalcia, aberrant innominate artery). A history of associated respiratory distress, obstructive apnea, positional symptoms, or noisy breathing, or physical examination findings such as stridor should raise the index of suspicion for these otolaryngologic etiologies. Aspiration can also present as an ALTE and can be the result of a foreign body, neurologic abnormalities leading to swallowing dysfunction, or anatomic disorders such as cleft palate or tracheoesophageal fistula.

Chest and neck radiographs can be beneficial in assessing for signs of airway abnormalities or radiopaque foreign bodies. If there is high concern for anatomic abnormalities, evaluation by direct laryngoscopy, bronchoscopy, and/or esophagoscopy could be considered. However, in patients who are well-appearing without clinical concern for airway anomalies, the yield for these tests is low. Polysomnography can be useful in differentiating between central versus obstructive processes.

Child Maltreatment

Child maltreatment should always be considered in infants presenting with an ALTE, especially given the detrimental consequences of missing the diagnosis. Possible etiologies include head trauma (direct injury or repetitive shaking), smothering, ingestions, and factitious syndrome (formerly Munchausen syndrome) by proxy.

Concerning historical facts include unexplained vomiting or irritability, recurrent ALTEs, historical discrepancies (history is confusing, varies among caregivers, changes over the course of the evaluation), or a family history of ALTEs, SIDS, or unexplained death. There is a higher rate of child maltreatment in infants presenting with more severe initial episodes and in those requiring resuscitation.

Any bruising should be noted, especially in a nonambulatory infant. A careful ear, nose, and throat examination should be performed, noting any ear bruising, bleeding from the nose or mouth, or frenulum tears. A thorough neurologic examination is also essential, assessing for altered sensorium, fontanelle fullness, pupillary abnormalities, or other focal neurologic findings. These findings should all raise suspicion for child maltreatment. However, it is also important to note that infants with child maltreatment may appear well on presentation with no external signs of trauma; the absence of these findings does not rule out maltreatment as the cause for the ALTE.

If there is clinical suspicion for child maltreatment, a skeletal survey, cranial/brain imaging, select laboratory studies, and a dilated funduscopic examination should be considered to assess for supportive findings. Video surveillance while the infant is hospitalized can also be considered in these cases. In addition, if there is concern for possible intentional or unintentional poisoning, a toxicology screen could be considered to identify the presence of medications that could cause the presenting symptoms. However, in patients without historical or physical examination findings concerning for child maltreatment, the evidence does not support the routine use of any of these assessments.

Cardiac

Though relatively rare, with a reported rate of 0-2%, cardiac pathology can lead to an ALTE in a myriad of ways. Children with structurally normal hearts may experience an ALTE due to arrhythmias, cardiomyopathy, and myocarditis. Those with structurally abnormal hearts, such as vascular anomalies, cyanotic heart disease, and left-sided obstruction may also present with an ALTE. A history of multiple and/or escalating events over days to weeks, feeding difficulties, diaphoresis, failure to thrive, or a positive family history of cardiac disease should raise the index of suspicion for cardiac pathology. A complete cardiac examination should be performed, noting abnormalities that might suggest underlying cardiac pathology, such as irregular rhythms, decreased femoral pulses, or murmurs.

Given the low rate of cardiac disease in patients presenting with an ALTE, routine echocardiograms are generally not useful in the initial work-up of these patients. ECGs may be a more useful screening tool,

as they are relatively easy to perform and are highly sensitive in identifying cardiac abnormalities. Therefore ECG could be considered to help exclude cardiac etiologies in patients where this is a clinical concern. However, the examiner should note that there is a high false-positive rate for ECGs in these patients, which could lead to additional unnecessary testing. If arrhythmia is strongly suspected or identified, assessment for electrolyte disturbances, such as hypo- or hyperkalemia should be undertaken.

Metabolic/Genetic

ALTEs can be the initial presentation of various metabolic disorders including organic acidemias, urea cycle disorders, fatty acid oxidation disorders, and mitochondrial disorders. Similarly, an ALTE can be the presenting symptom of hypoglycemia and hypocalcemia. Although metabolic entities are rare, they can be progressive and life threatening and therefore should be considered in the differential for these patients.

Clinical findings that may suggest an inborn error of metabolism include: recurrent or severe events, associated developmental delay, failure to thrive, or positive family history of seizure disorders, SIDS, or early infant deaths. Physical findings such as dysmorphic features should also be noted as these could suggest an underlying syndromic etiology. Disorders of the face and upper airway, such as cri du chat and Pierre Robin syndromes, can lead to obstructed respiratory patterns.

Serum chemistries, while not necessarily diagnostic of an inborn error of metabolism, can be helpful in screening patients with potential metabolic abnormalities and should be considered in patients when this is a clinical concern. Serum glucose, bicarbonate, ammonia, lactate, and pyruvic acid levels are useful screening tests in these patients because abnormalities signal the possibility of metabolic disorders requiring additional evaluation. The **newborn screen** should also be reviewed to ensure no abnormalities were identified. If there is a high index of suspicion, it is prudent to repeat the newborn screen to ensure that the findings remain normal following the introduction of enteral feeds.

TABLE 5.5 Red Flags in Infants Presenting with an ALTE–BRUE

Prematurity
Congenital anomalies or known syndromes
Severe initial event
Recurrent events
Concern for child maltreatment
Cyanosis
Need for resuscitation, especially if performed by medical professional
Family history of ALTE, SIDS, or unexplained death
Abnormal physical examination findings at the time of presentation
Dysmorphic features
Hypothermia
Lethargy
Signs of trauma

ALTE, apparent life-threatening event; BRUE, brief resolved unexplained event; SIDS, sudden infant death syndrome.

SUMMARY AND RED FLAGS

A thorough history and physical examination is paramount in the evaluation of patients with an ALTE–BRUE. Concerning historical factors and physical examination findings, such as multiple ALTEs, suspicion for child maltreatment, and requirement for resuscitation should prompt further evaluation (Table 5.5).

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Apparent Life-Threatening Event

Brand D, Altman R, Purtill K, et al. Yield of diagnostic testing in infants who have had an apparent life-threatening event. *Pediatrics*. 2005;115:885-893.

Davies F, Gupta R. Apparent life threatening events in infants presenting to an emergency department. *Emerg Med J*. 2002;19:11-16.

Fu LY, Moon RY. Apparent life-threatening events: an update. *Pediatr Rev*. 2012;33:361-368.

Kahn A. European Society for the Study and Prevention of Infant Death. Recommended clinical evaluation of infants with an apparent life-threatening event. Consensus document of the European Society for the Study and Prevention of Infant Death, 2003. *Eur J Pediatr*. 2004;163:108.

Kaji AH, Claudius I, Santillanes G, et al. Apparent life-threatening event: multicenter prospective cohort study to develop a clinical decision rule for admission to the hospital. *Ann Emerg Med*. 2013;61:379-387.

Mittal MK, Sun G, Baren JM. A clinical decision rule to identify infants with apparent life threatening event who can be safely discharged from the emergency department. *Pediatr Emerg Care*. 2012;28:599-605.

National Institutes of Health. Consensus Development Conference on Infantile Apnea and Home Monitoring. *Pediatrics*. 1987;79:292-299.

Okada K, Miyako M, Honma S, et al. Discharge diagnoses in infants with apparent life-threatening event. *Pediatr Int*. 2003;45:560-563.

Shah S, Sharieff G. An update on the approach to apparent life-threatening events. *Curr Opin Pediatr*. 2007;19:288-294.

Tieder JS, Altman RL, Bonkowsky JL, et al. Management of apparent life-threatening events in infants: a systematic review. *J Pediatr*. 2013;163:94-99.

Brief Resolved Unexplained Event

Tieder JS, et al. Brief resolved unexplained events (formerly apparent life-threatening events) and evaluation of lower-risk infants. *Pediatrics*. 2016;137:e20160590.

Srinivasan M, Chiles J, Gremse D, et al. Evidence-based diagnostic evaluation of infants presenting with an apparent life-threatening event. Presentation at: Pediatric Hospital Medicine Conference; 2015 July 23-26; San Antonio, TX.

Gastrointestinal

Mousa H, Woodley FW, Metheney M, et al. Testing the association between gastroesophageal reflux and apnea in infants. *J Pediatr Gastroenterol Nutr*. 2005;41:169-177.

Infectious

Claudius I, Mittal MK, Murray R, et al. Should infants presenting with an apparent life-threatening event undergo evaluation for serious bacterial infections and respiratory pathogens? *J Pediatr*. 2014;164:1231-1233.

Neurologic

Bonkowsky JL, Guenther E, Srivastava R, et al. Seizures in children following an apparent life-threatening event. *J Child Neurol*. 2009;24:709-713.

Genizi J, Pillar G, Ravid S, et al. Apparent life-threatening events: neurological correlates and the mandatory work-up. *J Child Neurol*. 2008;23:1305-1307.

Tirosh E, Jaffe M. Apparent life-threatening event: a neurologic perspective. *J Child Neurol*. 1995;10:216-218.

Airway/Pulmonary

McMurray JS, Holinger LD. Otolaryngic manifestations in children presenting with apparent life-threatening events. *Otolaryngol Head Neck Surg*. 1997;116(6 Pt 1):575-579.

Child Maltreatment

Altman RL, Brand DA, Forman S, et al. Abusive head injury as a cause of apparent life-threatening events in infancy. *Arch Pediatr Adolesc Med*. 2003;157:1011-1015.

Altman RL, Forman S, Brand DA. Ophthalmologic findings in infants after an apparent life-threatening event. *Eur J Ophthalmol*. 2007;17:648-653.

Bonkowsky JL, Guenther E, Filloux FM, et al. Death, child abuse, and adverse neurological outcome of infants after an apparent life-threatening event. *Pediatrics*. 2008;122:125-131.

Guenther E, Powers A, Srivastava R, et al. Abusive head trauma in children presenting with an apparent life-threatening event. *J Pediatr*. 2010;157:821-825.

Pitetti RD, Maffei F, Chang K, et al. Prevalence of retinal hemorrhages and child abuse in children who present with an apparent life-threatening event. *Pediatrics*. 2002;110:557-562.

Truman TL, Ayoub CC. Considering suffocatory abuse and Munchausen by proxy in the evaluation of children experiencing apparent life-threatening events and sudden infant death syndrome. *Child Maltreat*. 2002;7:138-148.

Cardiac

Hoki R, Bonkowsky JL, Minich LL, et al. Cardiac testing and outcomes in infants after an apparent life-threatening event. *Arch Dis Child*. 2012;97(12):1034-1038.

Woolf PK, Gewitz MH, Preminger T, et al. Infants with apparent life threatening events. Cardiac rhythm and conduction. *Clin Pediatr*. 1989;28:517-520.

6

Syncope and Dizziness

Gary Cohen

Dizziness is a common but very nonspecific chief complaint about which some elaboration by the patient is generally required for the physician to understand exactly what the patient is experiencing. The description of the sensation is critical in distinguishing whether it is caused by vertigo, disequilibrium, lightheadedness, presyncope, or even ataxia (Table 6.1). Although the differential diagnoses of these entities may overlap, there are conditions that are most specific to the individual symptom. All of the entities are conditions that may affect children at any age, but older children are more capable of articulating the abnormal sensation they feel. Children younger than 6 years of age may present with nausea, vomiting, ataxia, or frank syncope.

Syncope is the transient loss of consciousness and postural tone that results from inadequate cerebral perfusion. Syncope is a common phenomenon in children and adolescents that is usually benign. Between 20% and 35% of all young adults have had one episode of syncope.

Presyncope is the feeling that the person is "about to pass out." The patient feels as if he or she is going to lose consciousness but does not. Presyncope may or may not reflect the same pathophysiologic process as true syncope. The diagnostic approach to presyncope is the same as for syncope.

Dizziness must be considered a change in mental status. It may potentially herald serious underlying central nervous system dysfunction. Dizziness must be better defined to distinguish vertigo from lightheadedness. The principal distinction with *vertigo* is the description of perceived motion: swaying, whirling, or spinning. **Lightheadedness** is frequently associated with psychological stress, including anxiety, hyperventilation, depression, and panic attacks. The history surrounding episodes of lightheadedness is vital for formulating the differential diagnosis.

Disequilibrium refers to "balance problems" without vertigo. The characteristic historical feature is difficulty ambulating. A rare complaint among children, disequilibrium in the young is most often caused by vestibular or cerebellar dysfunction and manifests as ataxia. **Ataxia** is an impairment of coordination, movement, and balance; this impairment is generally associated with dysfunction of the cerebellum or of the sensory and/or motor pathways connecting to the cerebellum. There are transient forms and progressive degenerative conditions that produce ataxia.

SYNCOPE

Syncope is a common phenomenon among children and adolescents. As many as 25% of children experience a syncopal event between the ages of 8 and 18 years. Before age 6 years, syncope is very unusual except in the setting of seizure disorders, breath-holding spells, and primary cardiac dysrhythmias. Syncopal episodes cause a large number of health care visits and a surprising number of admissions to hospitals. The differential diagnosis of syncope is noted in Tables 6.2 and 6.3; distinguishing features are noted in Tables 6.4 and 6.5.

The pathophysiologic mechanism of syncope follows a common pathway with many inciting stimuli. Cerebral perfusion is compromised by a transient decrease in cardiac output as a result of vasomotor changes, decreasing venous return, primary dysrhythmia, or impairment of cerebral vascular tone. Adolescents with syncope subjected to a head-up tilt-table test report blurred vision and constriction of visual fields before losing consciousness, as well as nausea, pallor, sweating, and dizziness, which are accompanied by hypotension (systolic blood pressure <60 mm Hg) and by bradycardia (heart rate <40 beats/min) with an occasional junctional rhythm and even asystole. Symptoms are relieved by returning to the supine position. Several situational factors can exacerbate this response, including warm temperature, a confined space such as being in a crowded room, anxiety or fear, sudden surprise, the sight of blood, pain, such as needle sticks or shots. Other situational factors include urination, swallowing, coughing, defecation, and hair combing.

This response is caused by an imbalance of parasympathetic and sympathetic tone, which results in peripheral vasodilatation, including venodilation, but in no augmentation of venous return, because there is no accompanying increase in large skeletal muscle activity to augment systemic venous return and maintain cardiac filling. Subsequent vagal output results in inappropriate bradycardia and further compromises cardiac output. The child faints and becomes supine, which restores systemic venous return. Awakening is accompanied by increased sympathetic output, which restores the heart rate. The episode tends to be brief but may recur if the patient is "helped up" too quickly.

In obtaining the history of a syncopal episode, attention should be paid to the time of day, time of last meal, activities leading up to the

(See *Nelson Textbook of Pediatrics*, p. 514.)

TABLE 6.1 Syncope and Dizziness

	Vertigo	Presyncope	Disequilibrium	Lightheadedness
Patient complaint	"My head is spinning" "The room is whirling"	"I feel I might pass out" "I feel faint" "I feel like blacking out"	"I feel unsteady" "My balance is off"	"I feel dizzy" "I feel disconnected, drugged"
Associated features	Motion, swaying, spinning, nystagmus	Syncope: loss of postural tone, brief loss of consciousness Situational	Poor balance No vertigo or ataxia	Anxiety, hyperventilation, paresthesias, respiratory alkalosis, panic attacks
Usual cause	Vestibular disorders	Impaired cerebral perfusion	Sensory and/or central neurologic dysfunction	Anxiety and/or depressive disorders
Key differential diagnoses	Peripheral (labyrinthine-cochlear) vs Central neurologic disorder	Neurocardiogenic (vagal) vs Cardiac syncope vs Neuropsychiatric syncope	Sensory deficit vs Central neurologic disease	Anxiety/depression vs Hyperventilation vs Medication effects

event, and associated symptoms (e.g., palpitations, racing heartbeat, chest pain, headache, shortness of breath, nausea, diaphoresis, visual changes, and hearing changes). **Cataplexy** may be confused with syncope and is characterized by partial or complete paralysis of skeletal muscles resulting in a rapid progression of weakness of the face and neck followed by the muscles of the trunk and extremities. The patient loses tone and may fall to the floor but remains awake and immobile for 1-2 minutes. Triggers include intense positive or negative emotions, such as laughing, frustration, fright, or anger. Details of the syncopal event, such as the patient's position (syncope while supine suggests a cardiac arrhythmia) when symptoms appeared, duration of the episode, and characterization of the patient's appearance during and immediately after the episode are also important. Almost without exception, by the time the patient presents to the office or emergency room, the physical examination findings are normal. Therefore, the history becomes the most important piece of information for developing the differential diagnosis, diagnostic evaluation, and management plan.

NEUROCARDIOGENIC SYNCOPE

There are several causes of **neurocardiogenic syncope**. Excessive vagal tone may be primary or secondary to breath-holding, cough, (deglutition syncope), micturition or defecation, carotid sinus pressure sensitivity, and orthostasis. Neurocardiogenic syncope has been described in association with hair brushing, swallowing, stretching, orthodontic maneuvers, anomalies of the cervical spine, and dental trauma. Many of these episodes may actually be forms of carotid sinus sensitivity. Cough syncope probably is related to prolongation of high intrathoracic pressure that results in decreased venous return and subsequent decreased cardiac output.

The prodromal history is very important in evaluating neurocardiogenic syncope. *In contrast, syncope without warning, while the patient is supine or during exercise implies a primary cardiac and usually more serious etiology; it is associated with greater morbidity and potential mortality* (see Table 6.3).

Neurocardiogenic syncope is a type of autonomic dysfunction that is also referred to as **vasodepressor syncope**, **vasovagal syncope**, and **reflex syncope**. Potential mechanisms include:

1. The first response is primary bradycardia, sometimes to the extreme of sinus arrest or even brief asystole, with subsequent hypotension. This is known as the cardioinhibitory response.
2. The second is a primary vasodepressor response that is characterized by hypotension with the heart rate being relatively preserved.
3. The third is mixed and is the most common response that features *simultaneous* hypotension and bradycardia.

The common pathway producing the heart rate and blood pressure responses and cerebral hypoperfusion is the Bezold-Jarisch reflex (Fig. 6.1). For most children and adolescents, **prodromal warning signs** herald the impending syncopal episode and can, after the first episode, allow the child enough time to prevent fainting by sitting with the head between the knees or by lying supine.

The physiologic mechanisms of neurocardiogenic syncope have been demonstrated with head-up tilt-table testing. **Tilt-table testing** can be performed with or without invasive blood pressure monitoring. The goal is to reproduce the patient's symptoms under close monitoring. Various tilt angles and durations have been described, as has the use of isoproterenol as a provocative stimulus.

If the history suggests the diagnosis of neurocardiogenic syncope with normal physical examination findings and a normal electrocardiogram (ECG), treatment may be empirically started (Tables 6.6 and 6.7). The first line of treatment is education and counseling. Most patients will eventually outgrow neurocardiogenic syncope. Patients should maintain hydration and increase dietary salt if there are not any contraindications. Patients should be counseled to avoid situations that precipitate an event and taught to abort an event by lying down.

If the patient fails conservative therapies, pharmacologic treatments may be tried. Physicians have used fludrocortisone with increased salt intake, β-adrenergic blockers, and midodrine which has had promising results. None of these medications has demonstrated consistent benefit to treat neurocardiogenic syncope.

ORTHOSTATIC SYNCOPE

Conditions that produce **hypotension** (orthostatic or supine) frequently produce syncope or presyncope. Cardiac function and structure are usually normal before the episode; during the predisposing illness, cardiac filling pressures are often reduced because of reduced venous return from hypovolemia or decreased peripheral vascular resistance (peripheral pooling of blood). Dehydration from diarrhea and vomiting, hyperthermia, hyperpyrexia, heat exhaustion, polyuria (diabetes mellitus) or poor intake from anorexia, together with the systemic effects of the primary illness, may produce orthostatic or true hypotension and syncope. In these conditions, dizziness, hypotension,

TABLE 6.2 Noncardiac Causes of Syncope-Like Events

Reflex Vasodepressor Syncope
Neurocardiogenic (vasovagal)
Emotion (seeing blood)
Pain (needle phobia)

Miscellaneous Situational Reflex
Tussive
Sneeze
Exercise/post-exercise
Swallowing
Stretching
Defecation
Micturition
Valsalva (increased intrathoracic pressure)
Breath holding spells

Systemic Illness
Hypoglycemia
Anemia
Infection
Hypovolemia, dehydration
Adrenal insufficiency
Narcolepsy/cataplexy
Pulmonary embolism
Ruptured ectopic pregnancy

Central Nervous System
Seizure (atonic, absence, myoclonic-astatic)
Stroke/transient ischemic attack
Subarachnoid hemorrhage

Dysautonomia

Basilar Artery Migraine

Drug Effects
β-Blocking agents
Vasodilating agents
Opiates
Sedatives
Drugs prolonging QT interval
Diuretics
Anticonvulsant agents
Antihistamines
Antidepressant agents
Anxiolytic agents
Drugs of abuse
Insulin, oral hypoglycemic agents
Carbon monoxide

Other Etiologies
Carotid sinus sensitivity
Subclavian steal
Panic attack/anxiety
Conversion disorder

From Van Hare GF. Syncope. In: Kliegman RM, Stanton BF, St. Geme JW III, Schor NF, eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:514.

TABLE 6.3 Causes of Cardiovascular Syncope: Potentially Fatal if Unrecognized

1. Arrhythmias
   - A. Bradyarrhythmias
     - a. Sinus node dysfunction (especially in patients with congenital heart defects)
     - b. AV block (congenital or acquired)
     - c. Kearns-Sayre syndrome
     - d. Pacemaker malfunction
   - B. Tachyarrhythmias
     - a. Supraventricular
       1. Wolff-Parkinson-White syndrome
       2. Supraventricular tachycardia/atrial arrhythmias (especially in patients with congenital heart defects)
     - b. Ventricular: ventricular tachycardia/torsades/ventricular fibrillation
       1. Channelopathies
          - a. Long QT syndrome
          - b. Catecholaminergic polymorphic ventricular tachycardia
          - c. Brugada syndrome
          - d. Short QT syndrome
       2. Drug induced
       3. Idiopathic
          - a. Ventricular fibrillation
          - b. Outflow tract
2. Structural/functional heart disease
   - A. Cardiomyopathy
     - a. Hypertrophic cardiomyopathy
     - b. Dilated cardiomyopathy
     - c. Arrythmogenic right ventricular dysplasia
   - B. Coronary anomalies
     - a. Anomalous origin
     - b. Kawasaki disease
   - C. Valvar aortic mitral or pulmonary stenosis
   - D. Arrhythmogenic right ventricular dysplasia
   - E. Acute myocarditis
   - F. Congenital heart disease (repaired and unrepaired)
   - G. Pulmonary hypertension, pulmonary embolus
   - H. Aortic dissection (Marfan syndrome)
   - I. Cardiac masses
   - J. Eisenmenger syndrome

From MacNeill E, Vashist S. Approach to syncope and altered mental status. *Pediatr Clin N Am*. 2013;60:1083-1106.

or syncope occurs rapidly when the patient assumes an upright position (seconds). Prolonged bed rest, combined with poor fluid intake during an illness, may also result in syncope or presyncope when the child arises to leave the bed. In most of these situations, fluid administration is sufficient to restore intravascular volume and venous return to alleviate postural or supine hypotension.

POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME (POTS)

Postural orthostatic tachycardia syndrome is characterized by recurrent and chronic symptoms of orthostatic intolerance, exercise intolerance, light headedness, fatigue, sweating, tremor, anxiety, and presyncope when upright. The syndrome may be secondary to autonomic dysfunction. Symptoms are improved with lying down. Criteria to diagnose POTS include symptoms that have lasted greater than 6

(See *Nelson Textbook of Pediatrics*, p. 516.)

TABLE 6.4 Clinical Features Suggesting Specific Causes of Syncope

Diagnostic Consideration
Neurocardiogenic
Symptoms after prolonged motionless standing, sudden unexpected pain, fear, or unpleasant sight, sound, or smell
Syncope in a well-trained athlete after exertion (without heart disease)
Situational syncope during or immediately after micturition, cough, swallowing, or defecation
Syncope with throat or facial pain (glossopharyngeal or trigeminal neuralgia)
Organic Heart Disease (e.g., Coronary Artery Disease, Aortic Stenosis, Primary Arrhythmia, Obstructive Hypertrophic Cardiomyopathy, Pulmonary Hypertension)
Brief loss of consciousness, no prodrome, history of heart disease
Syncope with exertion
Family history of sudden death
Neurologic
Seizures: confusion for >5 min after regaining consciousness
Transient ischemic attack, subclavian steal, basilar migraine: syncope associated with vertigo, dysarthria, diplopia, arm exercise
Migraine: syncope associated with antecedent headaches
Other Vascular
Carotid sinus: syncope with head rotation or pressure on the carotid sinus (as in tumors, shaving, tight collars)
Orthostatic hypotension: syncope immediately on standing
Subclavian steal or aortic dissection: differences in blood pressure or pulse between the two arms
Drug Induced
Patient is taking a medication that may lead to long QT syndrome, orthostasis, or bradycardia
Psychiatric Illness
Frequent syncope, somatic complaints, no heart disease

Modified from Kapoor WN. Syncope. *N Engl J Med.* 2000;343:1856-1862.

TABLE 6.5 Comparison of Clinical Features of Syncope and Seizures

Features	Syncope	Seizures
Relation to posture	Common	No
Time of day	Diurnal	Diurnal or nocturnal
Precipitating factors	Emotion, injury, pain, crowds, heat, exercise, fear, dehydration, coughing, micturition	Sleep loss, drug/alcohol withdrawal
Skin color	Pallor	Cyanosis or normal
Diaphoresis	Common	Rare
Aura or premonitory symptoms	Long	Brief
Convulsion	Rare, brief	Common
Other abnormal movements	Minor twitching	Rhythmic jerks
Injury	Rare	Common (with convulsive seizures)
Urinary incontinence	Rare	Common
Tongue biting	No	Can occur with convulsive seizures
Postictal confusion	Rare	Common
Postictal headache	No	Common
Focal neurologic signs	No	Occasional
Cardiovascular signs	Common (cardiac syncope)	No
Abnormal findings on EEG	Rare (generalized slowing may occur during the event)	Common

From Bruni J. Episodic impairment of consciousness. In: Daroff RB, Jankovic JM, Mazziotta JC, Pomeroy SL, eds. *Bradley's Neurology in Clinical Practice*. 7th ed. Philadelphia: Elsevier; 2016:9.

months, heart rate that increases by at least 40 beats/min, if <18 years or 30 beats/min if >18 years, after assuming a standing from supine position for at least 10 minutes, symptoms worsen with standing and improve with recumbence, and the absence of other overt causes of orthostatic intolerance.

A detailed history of orthostatic intolerance may identify symptoms of headache, fatigue, sleep disorder, weakness, hyperventilation, shaking, sweating, anxiety, dizziness, and presyncope. An evaluation for POTS may include a complete blood count, glucose, electrolytes, and thyroid function. Cardiac evaluation should include an ECG. A tilt-table test may be helpful to demonstrate the effects of orthostatic stress (increased heart rate).

There is no specific treatment for POTS. Medications that may aggravate symptoms of POTS should be avoided including antihypertensive agents, sedatives, and many other psychiatric medications. Patients should avoid aggravating factors, such as dehydration, extreme heat, and alcohol. Nonpharmacologic treatment includes aerobic exercise, compressive stockings, and increased fluid and salt intake. Pharmacologic treatment should be tailored to the variant the patient exhibits.

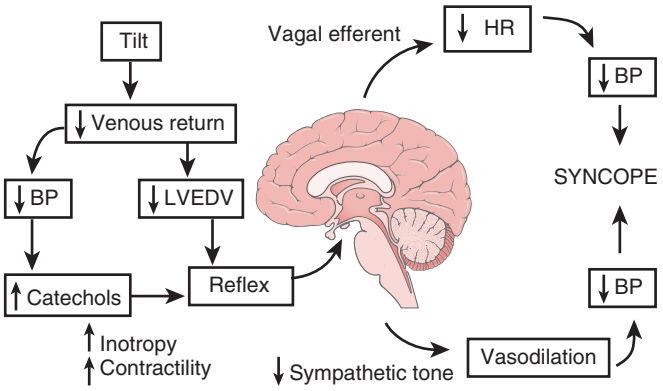


FIGURE 6.1 Tilt-table testing: the Bezold-Jarisch reflex. BP, blood pressure; HR, heart rate; LVEDV, left ventricular end-diastolic volume.

TABLE 6.6 Nonpharmacologic Treatment of Neurocardiogenic Syncope

- Education, counseling, and reassurance
- Avoid precipitating or triggering factors
- Increase water and salt intake
  - 1.5-2.5 L of water daily
  - At least 2-5 g of salt daily
- Isometric counter-pressure maneuvers
  - Leg crossing
  - Buttock tensing
  - Squatting
- Head-up sleeping
- Abdominal binders, thigh-high or below knee elastic compression stockings (20-30 mm Hg pressure)
- Psychological counseling

From Moodley M. Clinical approach to syncope in children. *Sem Pediatr Neurol.* 2013;20:12-17.

TABLE 6.7 Pharmacologic Treatment of Neurocardiogenic Syncope

β-Adrenergic Antagonists
Atenolol 1-2 mg/kg/day
Esmolol
Metoprolol 1-2 mg/kg/day
Nadolol
Propranolol 0.5-4 mg/kg/day

α-Adrenergic Agonists
Ephedrine
Methylphenidate 5-10 mg tid
Midodrine 2.5-10 mg tid
Pseudoephedrine 60 mg bid

Anticholinergics
Disopyramide 10-15 mg/kg/day
Hyoscine
Propantheline
Scopolamine

Selective Serotonin Receptor Reuptake Inhibitors
Fluoxetine 10-20 mg/day
Sertraline 25-50 mg/day

Mineralocorticoids
Fludrocortisone 0.1-0.3 mg/day

From Moodley M. Clinical approach to syncope in children. *Sem Pediatr Neurol.* 2013;20:12-17.

CARDIAC SYNCOPE/SUDDEN CARDIAC DEATH

A variety of cardiac conditions can result in hypotension and syncope (Tables 6.8 and 6.9; see Table 6.3). Dysrhythmias are common and are usually silent between episodes (see Table 6.8). Supraventricular tachycardia, ventricular tachycardia, and heart block are the most common types of dysrhythmia and may be primary or may result from medications or illicit drugs. Any form of acquired heart block carries a high mortality rate (Fig. 6.2). A common cause of acquired heart block is Lyme disease. Heart block may necessitate temporary or permanent electronic pacing to maintain cardiac output.

Lead II

FIGURE 6.2 Congenital complete atrioventricular (AV) block. The ventricular rate is regular at 53 beats/min. The atrial rate is somewhat variable, from 65-95 beats/min, and completely dissociated from the ventricle. The QRS morphology is normal, which is common in congenital complete AV block. (From Van Hare GF. AV block. In: Kliegman RM, Stanton BF, St. Geme III JW, Schor NF, eds. *Nelson Textbook of Pediatrics.* 20th ed. Philadelphia: Elsevier; 2016:2260.)

Primary cardiac conduction abnormalities that may result in syncope include Wolff-Parkinson-White syndrome, long QT syndromes, and catecholamine-sensitive ventricular tachycardia. **Wolfe-Parkinson-White syndrome** is characterized by a *short PR interval*, preexcitation seen as a widened QRS duration and a delta wave on the proximal portion of the QRS. The delta wave represents the presence of accessory electrical tissue from atria to ventricle, with rapid antegrade conduction causing excitation of ventricular tissue before atrioventricular node–His bundle stimulation. If that pathway can conduct in the retrograde manner, a reentrant circuit is created, causing a narrow QRS complex tachycardia. This greatly shortens the diastolic ventricular filling time and results in diminished left ventricular end-diastolic volume, with subsequently decreased stroke volume and decreased cardiac output. Although the tachycardia is rarely sufficiently fast to result in syncope, some children have profound hypotension and a rapid loss of consciousness. In adults, a similar mechanism results from atrial flutter or fibrillation if the ventricular response rate is fast.

Long QT syndromes are inherited (usually autosomal dominant) abnormalities in the electrical recovery (repolarization) of the heart (Fig. 6.3). Prolongation of the repolarization phase results in the risk of simultaneous depolarization, the "R-on-T" phenomenon, which causes disorganized ventricular electrical stimulation characterized by **torsades de pointes** (coarse ventricular tachycardia), a potentially lethal dysrhythmia (Fig. 6.4). There may be a family history of sudden cardiac death. Family studies with the same mutation have demonstrated that affected patients may not always have a long QT interval on ECG as defined for the syndrome, but an increased QT interval may become evident with exercise or during catecholamine infusion. Long QT syndromes may be responsible for some of the incidents of sudden infant death syndrome and drowning. Although additional genetic forms have been described, most mutations for prolonged QT involve either a sodium channel or potassium channel (Table 6.10). Genotype may predict the patient's presentation with LQT1 events associated with stress, while LQT3 may be associated with sleep. Long QT syndromes may present as a syncopal episode, seizures, palpitations, or presyncope. Diagnosing long QT is based on clinical history and ECG findings of a prolonged rate-corrected QT interval. Genetic testing may identify approximately 75% of patients. Acquired prolongation of the QT interval may also be seen in electrolyte abnormalities (hyperkalemia) and with a variety of medications (Table 6.11). A drug history and toxicology screen may be warranted if there is any question of QT prolongation.

Patients who have undergone **corrective or palliative surgery** for congenital cardiac disease are at risk for both early and late onset dysrhythmias that might result in syncope. Sinus node disease

(See *Nelson Textbook of Pediatrics*, p. 2261.)

TABLE 6.8 Primary Electrical Abnormalities: Features Electrocardiogram, and Treatment

Primary Electrical Abnormalities	Features	ECG	Treatment
LQTS: Romano-Ward, Jervell–Lange-Nielsen, acquired	Familial genetic disorder Ion channel mutations Presents in torsades de pointes Romano-Ward is MC inherited LQTS Jervell–Lange-Nielsen has congenital deafness	Prolonged QT measured from the onset of the Q wave to the end of the T wave in lead II Varies with heart rate but >0.44 in men, >0.46 in children and women for HR 50-90/min is prolonged Torsades de pointes can occur Can deteriorate from polymorphic ventricular tachycardia to ventricular fibrillation	β Blocker therapy Recommendations on exercise intensity by a cardiologist ICD if β blockers fail
Brugada syndrome	Inherited autosomal dominant arrhythmogenic syndrome characterized by life-threatening ventricular arrhythmias Genetic mutations in *SCN5A* and 13 other genes	ECG abnormalities are from repolarization and depolarization abnormalities Coved-type ST segment elevations in the right precordial leads J wave amplitude ≥2 mm followed by a negative T wave	Placement of ICD
Wolff-Parkinson White	Owing to ≥1 reentrant pathways inducing SVT or atrial fibrillation Up to 14% associated with malignant tachycardias Malignant arrhythmias from short reentrant pathway repolarization or multiple pathways	Short PR interval Delta waves present	Undergo EPT and ablation
Dilated cardiomyopathy: ventricular tachycardia/fibrillation	Cardiac dilation and systolic dysfunction Inherited or acquired Lamin AC gene mutations a common cause of DCM and SCD	Marked LVH Poor R wave progression Left atrial enlargement Right axis deviation	Permanent pacemaker and ICD placement
Catecholamine-exercise: ventricular tachycardia	Ventricular ectopy induced by exercise or emotional stress Mutation in gene that encodes Ca-mediated sarcoplasmic fibers Lethal in 30-50% if left untreated	Pre-exercise ECG is usually normal, stress testing recommended ECG with exercise Nonsustained wide ventricular tachycardia	β Blocker therapy Recommendations on exercise intensity by a cardiologist ICD if β blockers fail

DCM, dilated cardiomyopathy; ECG, electrocardiograph; EPT, electrophysiologic testing; HR, heart rate; ICD, implantable cardioverter defibrillator; LQTS, long QT syndrome; LVH, left ventricular hypertrophy; MC, most common; SCD, sudden cardiac death; SVT, supraventricular tachycardia. From Ellison S. Sudden cardiac death in adolescents. *Prim Care Clin Office Pract.* 2015;42:57-76.

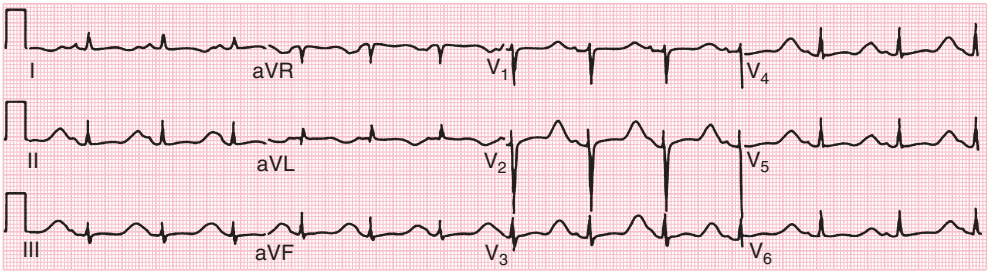


FIGURE 6.3 An electrocardiogram showing a QT interval of 640 milliseconds in a patient with LQT1 syndrome, with the terminal portion of the T wave merging with the P wave. (From Garan H. Ventricular arrhythmias. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 25th ed. Philadelphia: Elsevier; 2016:373.)

TABLE 6.9 Potential Causes of Sudden Death in Infants, Children, and Adolescents

SIDS and SIDS "Mimics"
SIDS
Long QT syndromes*
Inborn errors of metabolism
Child abuse
Myocarditis
Ductal-dependent congenital heart disease

Corrected or Unoperated Congenital Heart Disease
Aortic stenosis
Tetralogy of Fallot
Transposition of great vessels (postoperative atrial switch)
Mitral valve prolapse
Hypoplastic left-heart syndrome
Eisenmenger syndrome

Coronary Arterial Disease
Anomalous origin*
Anomalous tract (tunneled)
Kawasaki disease
Periarteritis
Arterial dissection
Marfan syndrome (rupture of aorta)
Myocardial infarction

Myocardial Disease
Myocarditis
Hypertrophic cardiomyopathy*
Dilated cardiomyopathy
Arrhythmogenic right ventricular dysplasia
Lyme carditis

Conduction System Abnormality/Arrhythmia
Long QT syndromes*
Brugada syndrome
Proarrhythmic drugs
Preexcitation syndromes
Heart block
Commotio cordis
Idiopathic ventricular fibrillation
Arrhythmogenic right ventricular dysplasia
Catecholaminergic polymorphic ventricular tachycardia
Heart tumor (myxoma, rhabdomyoma)

Miscellaneous
Pulmonary hypertension
Pulmonary embolism
Heat stroke
Cocaine and other stimulant drugs or medications
Anorexia nervosa
Electrolyte disturbances

*Common.
SIDS, sudden infant death syndrome.
From Van Hare GF. Sudden death. In: Kliegman RM, Stanton BF, St. Geme JW III, Schor NF, eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:2262.

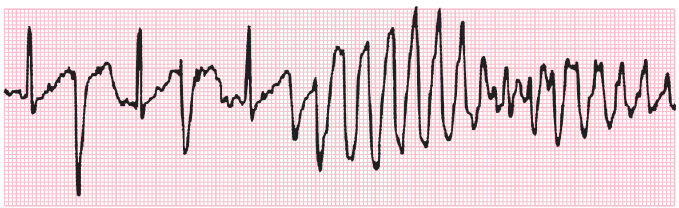


FIGURE 6.4 Episode of torsades de pointes in a patient with long QT syndrome. (From Van Hare GF. Sudden Death. In: Kliegman RM, Stanton BF, St. Geme JW III, Schor NF eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia, Elsevier; 2016:2262.)

(in patients undergoing atrial surgery) may result in tachycardia-bradycardia episodes that can be associated with hypotension. Ventricular dysrhythmias are particularly common after repair of tetralogy of Fallot, double-outlet right ventricle, truncus arteriosus, and pulmonary atresia involving right ventriculotomy with subsequent ventricular scar formation.

Uncorrected structural heart disease is a relatively rare cause of a sudden decrease in cardiac output. However, **hypertrophic cardiomyopathies** can result in obstruction of left ventricular outflow with resultant high transmural pressure and secondary cardiac ischemia, which can be fatal. This type of obstruction is exacerbated by high sympathetic tone, which causes increased contractility and is a frequent mechanism of syncope associated with exercise in competitive athletes. The presence of an outflow tract murmur in the setting of syncope, especially if there is a positive family history, warrants evaluation with *both* electrocardiography and echocardiography. Any condition that impedes left ventricular outflow (valvular aortic stenosis or subaortic stenosis), left ventricular inflow or filling (mitral stenosis or pericardial tamponade), or blood flow through the pulmonary vasculature (primary or secondary pulmonary hypertension) may also result in syncope. In almost all cases, characteristic physical findings lead the clinician to the diagnosis. Pulmonary hypertension may be associated with cyanosis, in which case there is cerebral hypoxia resulting from right-to-left shunting, as well as decreased left ventricular output resulting from poor transpulmonary flow and decreased left ventricular filling.

Other rare causes of cardiac syncope are thoracic masses and intracardiac tumors or masses, coronary artery abnormalities, and inflammatory cardiac diseases (myocarditis). Masses or tumors, such as myxomas, fibromas, and rhabdomyomas, tend to produce paroxysmal symptoms, which are often associated with position changes, especially from the recumbent position. **Coronary artery anomalies** are usually not accompanied by signs of ischemia. Rather, the most

TABLE 6.10 Inherited Channel Mutations in Long QT Syndromes

	Chromosome	Gene	Protein	Ion Current Affected	Trigger	Special Features/ Occurrence
LQTS Type						
1	11p15.5	*KCNQ1*	KvLQT1 (Kv7.1)	I_{Ks}	Exercise (swimming), emotion	42-54%
2	7q35-36	*KCNH2*	HERG (Kv11.1)	I_{Kr}	Rest, emotion, exercise (acoustic, postpartum), surprise (sudden loud noise)	35-45%
3	3p24-21	*SCN5A*	Nav1.5	I_{Na}	Rest, sleep, emotion	1.7-8%; high lethality
4	4q24-27	*ANK2*	Ankyrin-B	I_{Na-K}, I_{Na-Ca}, I_{Na}	Exercise	<1%
5	21q22	*KCNE1*	MinK	I_{Ks}	Exercise, emotion	<1%
6	21q22	*KCNE2*	MiRP1	I_{Kr}	Rest, exercise	<1%
7	17q23	*KCNJ2*	Kir2.1	I_{K1}	Rest, exercise	Periodic paralysis, dysmorphic feature
8	12p13.3	*CACNA1C*	Cav1.2	I_{Ca}	Exercise, emotion	Rare, syndactyly
9	3p25.3	*CAV3*	Caveolin-3	I_{Na}	Nonexertional, sleep	Rare
10	11q23.3	*SCN4B*	NaVβ4	I_{Na}	Exercise, postpartum	<0.1%
11	7q21-22	*AKAP9*	Yotiao	I_{Ks}	Poorly characterized	<1%
12	2q11.2	*SNTA1*	Syntrophin α1	I_{Na}	Poorly characterized	<1%
13	11q24	*KCNJ5*	Kir3.4	K_{Ir}	Poorly characterized	<1%

From Morita H, Wu J, Zipes DP. The QT syndromes: Long and short. *Lancet.* 2008;372:750-762.

TABLE 6.11 Drugs That Prolong the QT Interval and Produce Torsades de Pointes

Drugs Commonly Involved	Other Drugs
Disopyramide	Amiodarone
Dofetilide	Arsenic trioxide
Ibutilide	Cisapride
Procainamide	Calcium channel blockers: lidoflazine (not marketed in the United States)
Quinidine	Antiinfective agents: clarithromycin, erythromycin, halofantrine, pentamidine, quinoline-class antibiotics
Sotalol	Antiemetic agents: domperidone, droperidol
Bepridil	Antipsychotic agents: chlorpromazine, halperidol, mesoridazine, thioridazine, pimozide
	Methadone

From Roden D. Drug-induced prolongation of the QT interval. *N Engl J Med.* 2004;350:1013-1022.

common manifestation is syncope or sudden cardiac death from compression of the anomalous left main coronary artery as it courses between the pulmonary outflow and the aortic root (Fig. 6.5). This usually occurs in a competitive athlete whose hypertrophied heart responds to catecholamine stimulation during activity and inadvertently compresses the anomalous coronary artery. Inflammatory conditions, such as heart block associated with Lyme disease and ventricular tachycardia associated with myocarditis or pericarditis, predispose to dysrhythmias.

Cardiac syncopal episodes can be accompanied by brief tonic-clonic seizure activity known as **Stokes-Adams syndrome**. The seizure activity appears 10-20 seconds after the onset of asystole and is usually of short duration with no subsequent postictal phase. This may explain why many children with cardiac syncope frequently see a neurologist.

Sudden cardiac death is discussed with cardiac causes of syncope because cardiac causes of syncope may also produce sudden death (see Table 6.3). Sudden cardiac arrest or death is defined as the abrupt and unexpected loss of heart function. Structural causes include valvular aortic stenosis, coronary artery anomalies, cardiomyopathies, and myocarditis. Cardiac arrhythmias associated with sudden death include Wolff-Parkinson-White syndrome and prolonged QT syndrome. A less common cause is **commotio cordis** resulting from non-penetrating blunt trauma to the chest. Warning events or symptoms may not always be evident prior to sudden cardiac death; if it presents, patients may complain of episodes of dizziness, lightheadedness, presyncope, syncope, dyspnea, or palpitations. Other relevant history may include fatigue, unexplained seizure, or chest pain. It is important for the physician to perform a detailed history and physical examination to look for warning signs of cardiovascular disease in the patient *and* family (Table 6.12). Key elements of the physical examination should include measurement of blood pressure, a complete cardiovascular exam with attention to heart rate, rhythm, murmurs, pulses, and signs of Marfan syndrome.

NEUROLOGIC CAUSES OF SYNCOPE-LIKE EPISODES

Primary neurologic causes of syncope are more unusual in otherwise healthy children and adolescents than in adults. Seizures must be considered if there is a history of an aural prodrome, focal or generalized tonic-clonic activity, and a prolonged postictal phase of lethargy or confusion (see Tables 6.4 and 6.5). Prolonged post-event lethargy is unusual with more common causes of syncope if the vital signs have returned to normal. Seizures are a common cause of loss of consciousness in the recumbent patient. Seizures are often accompanied by tachycardia and normal or elevated blood pressure. A premonitory

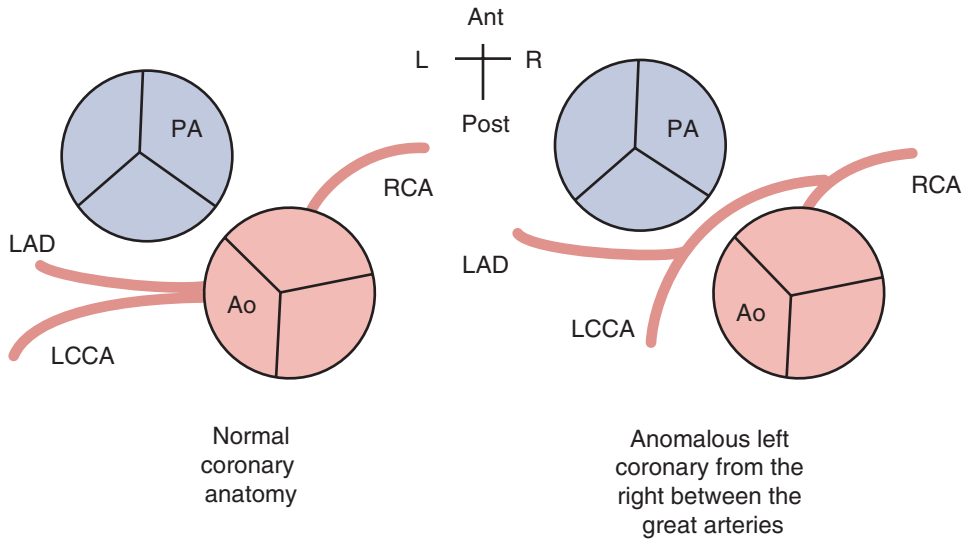


FIGURE 6.5 Coronary artery anomalies associated with sudden cardiac death. Ant, anterior; Ao, aorta; L, left; LAD, left anterior descending coronary artery; LCCA, left circumflex coronary artery; PA, pulmonary artery; Post, posterior; R, right; RCA, right coronary artery.

TABLE 6.12 Pediatric Sudden Cardiac Death Risk Assessment*

Patient History Questions:

Tell Me About Any of These in Your Child… Yes or No

Has your child fainted or passed out during or after exercise, emotion, or startle?
Has your child ever had extreme shortness of breath and/or discomfort, pain, or pressure in his or her chest during exercise?
Has your child had extreme fatigue associated with exercise (different from other children)?
Has a doctor ever ordered a test for your child's heart?
Has your child ever been diagnosed with an unexplained seizure disorder? Or exercise-induced asthma not well controlled with medication?

Family History Questions:

Tell Me About Any of These in Your Family…

Are there any family members who had a sudden, unexpected, unexplained death before the age of 50 (including SIDS, car crash, drowning, others) or near-drowning?
Are there any family members who died suddenly of "heart problems" before the age of 50?
Are there any family members who have had unexplained fainting or seizures?
Are there any relatives with certain conditions, such as:

- Enlarged heart: hypertrophic cardiomyopathy
- Dilated cardiomyopathy
- Heart rhythm problems: Long QT syndrome
- Short QT syndrome
- Brugada syndrome
- Catecholaminergic ventricular tachycardia
- Arrhythmogenic right ventricular cardiomyopathy
- Marfan syndrome (aortic rupture)
- Heart attack, age 50 or younger
- Pacemaker or implanted defibrillator
- Deaf at birth (congenital deafness)

Please Explain More About Any "Yes" Answers.

*Ask these questions (or have parents complete for your review) at periodic times during well-child visits (neonatal, preschool, before or during middle school, and before or during high school).
From Campell R, Berger S, Ackerman M, et al. Policy statement pediatric sudden cardiac arrest. *AAP Pediatr*. 2012;e1094-e1102.

aura may herald vertebrobasilar vascular spasm, which appears to occur when syncope is with **basilar type migraines**. There may be a history of unilateral visual changes; the loss of consciousness usually has a somewhat longer onset and duration. The patient frequently complains of headache after regaining consciousness. Basilar type migraine or migraine affecting the vertebrobasilar circulation can cause dizziness, vertigo, ataxia, confusion, and headache. There is often a positive family history of migraines.

METABOLIC CAUSES OF SYNCOPE

Hypoglycemia should always be included as a cause of syncope, but it is rare in children and adolescents except in patients with insulin-dependent diabetes or inborn errors of glucose or glycogen metabolism (see Chapter 44). With hypoglycemia, the patient feels weak, hungry, sweaty, agitated, confused, and eventually experiences altered mental status. Onset is gradual, and the patient remains hemodynamically stable, although tachycardia may be evident. Ingestion of oral hypoglycemic agents may exceed the body's normal glucose homeostasis, resulting in hypoglycemia.

PSYCHIATRIC CAUSES OF SYNCOPE

Patients with a history of panic attacks may become syncopal secondary to hyperventilation. The mechanism is not completely understood, but may involve the reaction of cerebral blood flow in response to hypocapnia and respiratory alkalosis. Tetany or paresthesias may be present in some patients. The history of the episode is critical and witnesses are especially helpful. The patient frequently relates a feeling of suffocation, smothering, shortness of breath, or chest tightness. In retrospect, the patient may also admit to numbness and tingling of the extremities and visual changes. Hyperventilation and hypocapnia may be detected during a tilt-table test by measuring end-tidal CO_2.

A psychiatric cause of syncope (or pseudosyncope) is a diagnosis of exclusion. The patient is usually an adolescent and frequently has episodes in the presence of an audience. The patient is unusually calm in describing the episodes and relates details that may indicate no loss of consciousness. During the episode, there are no associated hemodynamic changes and no pallor, sweating, or respiratory changes. Typically, the patient falls gracefully and gently without injury. The key is to define what secondary gain the patient attains through the factitious disorder.

EVALUATION OF THE SYNCOPAL CHILD

◆ History

The history of the event is the critical information for most patients (see Table 6.4). A detailed account of what the patient felt immediately before losing consciousness, what the patient was doing, what the posture or position was, how the patient looked, how long the episode lasted and associated signs or symptoms direct the diagnostic work-up. A thorough and detailed family history is necessary to discover risk for sudden death, dysrhythmia, heart disease, seizures, and metabolic disorders. The medication history, including over the counter, prescribed, and illicit drugs, as well as any accessible medication of other family members should be gathered.

◆ Physical Examination

Any person who has a syncopal episode should undergo a thorough physical examination, with special attention to the cardiovascular and neurologic systems. The examination should include obtaining vital signs with the patient supine and after standing for 5-10 minutes. Upon careful auscultation, the presence of an outflow tract murmur radiating to the neck, an abnormally loud second heart sound, or the presence of a long decrescendo diastolic murmur at the apex leads to more involved diagnostic testing. In most cases, patients with a history of syncope have normal physical findings at the time of the examination.

◆ Diagnostic Tests

Because the child or adolescent who has had a syncopal episode is often evaluated hours or days after the episode, testing serum glucose, and electrolytes or urine toxicology screening is usually of no value. *All patients presenting with syncope need an ECG* (Fig. 6.6). The ECG should be inspected for the rhythm, with special attention to non-sinus rhythms and bradycardia. Measurements of the intervals should be performed manually regardless of any preprogrammed measurements printed on the ECG. Abnormalities of the PR, QRS, or QT/corrected QT (QTc) interval imply an underlying conduction abnormality. The P wave, QRS, and T wave amplitudes may indicate chamber enlargement or hypertrophy, each of which carries an increased risk for dysrhythmia. In the patient who also has a history of **palpitations** associated with syncope, long-term cardiac monitoring, with or without a subsequent patient-activated cardiac event recorder monitor, may help capture the cardiac rhythm when the patient is symptomatic. If a heart murmur is appreciated, if there is a family history of sudden death or cardiomyopathy, or if the ECG is at all questionable, a cardiology consultation should be obtained, and two-dimensional, Doppler, and color-flow echocardiography should be performed. If the syncopal event is associated with exercise, echocardiography is critical; if the results are normal, a graded treadmill exercise stress test should be performed with full ECG and blood pressure monitoring. Patients with primary dysrhythmias may require cardiac catheterization and electrophysiologic testing.

Patients exhibiting prolonged loss of consciousness, seizure activity, and a postictal phase of lethargy or confusion should be referred for neurologic consultation and electroencephalography. Without this history, the reported positive yield of electroencephalography is less than 1 in 300 studies. Likewise, neuroimaging studies generally have an exceptionally low yield in the absence of abnormality upon physical examination (see Fig. 6.6).

SUMMARY AND RED FLAGS

Hypotension, both supine and orthostatic, is a major red flag, as are associated palpitations, exertional symptoms, or chest pain (Tables 6.13 and 6.14); participation in gym class or sports must be restricted until a complete diagnostic work-up is completed. Additional red flags include syncope while supine, a positive family history, prolonged loss of consciousness, prolonged seizures, prolonged postevent neurologic signs, and abrupt onset with no prodrome. Laboratory tests, except for the ECG which is mandatory, are generally of limited value unless guided by pertinent findings in the history and physical examination. The ECG allows screening for Wolfe-Parkinson-White syndrome, heart block, and long QT syndrome as well as hypertrophic cardiomyopathies and myocarditis. The most common identifiable etiology in an otherwise healthy child or adolescent is neurocardiogenic syncope, usually a benign and transient condition.

VERTIGO

The characteristic description of vertigo is the illusion of **motion** usually described as spinning or whirling. The perception of motion may be internal ("My head is [or eyes are] spinning") or external ("The

(See *Nelson Textbook of Pediatrics*, p. 3069.)

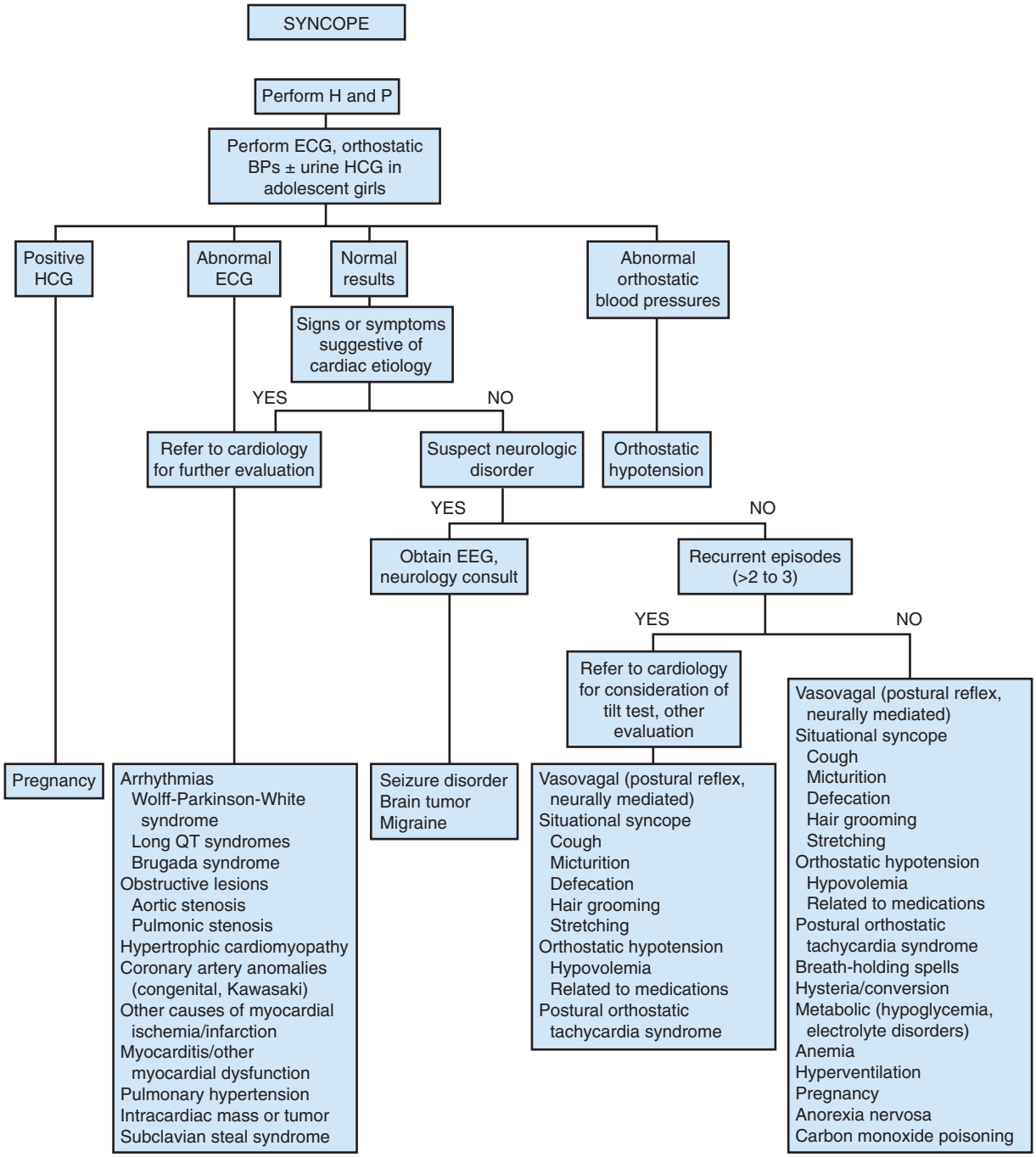


FIGURE 6.6 Syncope algorithm. BP, blood pressure; ECG, electrocardiography; EEG, electroencephalography; H, history; HCG, human chorionic gonadotropin; P, physical examination. (From Pomeranz A, Sabnis S, Busey SL, Kliegman RM, eds. *Pediatric Decision-Making Strategies*. Philadelphia: Elsevier; 2016:59.)

room is spinning or moving"). The sensation is usually rotatory, but it can be linear ("It feels like the swaying of a boat").

Obtaining an accurate description from younger children is difficult. Using terms that the child may understand such as "sliding" or "swinging" may be helpful. The patient's description is critical although potentially vague; further questioning may lead to the rather discrete differential diagnosis of vertigo.

The presence of associated symptoms may help locate the pathology to a central or peripheral cause of vertigo (Tables 6.15, 6.16, and 6.17). Fortunately, peripheral causes of vertigo are more common. Spontaneous **nystagmus** and abnormal head positions are symptoms associated more with peripheral causes of vertigo along with nausea, vomiting, sweating, faintness, and fright. Peripheral vertigo results in stimulation of the autonomic nervous system with resultant intense nausea, vomiting, pallor, and diaphoresis. If the dizziness occurs with abrupt changes in the position of the head, peripheral causes of vertigo should be suspected. Peripheral vertigo can be caused by the following: middle ear infections, paroxysmal positional vertigo, labyrinthitis, vestibular neuronitis, Ménière disease, or trauma (see Table 6.16).

Patients suffering from acute ongoing peripheral vertigo appear very ill and very uncomfortable. Because middle ear infection can cause peripheral vertigo, some children seen with otitis media and

TABLE 6.13 "Red Flags" in the Evaluation of Patients with Syncope

Syncope with activity or exercise or supine	History of cardiac surgery
Syncope not associated with prolonged standing	History of Kawasaki disease
Syncope precipitated by loud noise or extreme emotion	Implanted pacemaker
Absence of presyncope or lightheadedness	Abnormal physical examination
Family history of syncope, drowning, sudden death, familial ventriclar arrhythmia syndromes, cardiomyopathy	Murmur Gallop rhythm Loud and single second heart sound Systolic click Increased apical impulse (tachycardia) Irregular rhythm Hypo- or hypertension Clubbing Cyanosis
Syncope requiring CPR	
Injury with syncope	
Anemia	
Other cardiac symptoms	
Chest pain	
Dyspnea	
Palpitations	

From Van Hare GF. Syncope. In: Kliegman RM, Stanton BF, St. Geme JW III, Schor NF, eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:515.

TABLE 6.14 Summary of Clinical Recommendations for Transient Loss of Consciousness

Topic	Recommendations
Initial assessment	Detailed history, especially from witnesses Full clinical examination 12-lead ECG
Uncomplicated faints	Suggestive features include: Posture: occurrence during prolonged standing or previous similar episodes avoided by lying down Provoking factors, such as pain or a medical procedure Prodromal symptoms, such as sweating or feeling warm or hot before TLoC Further investigation and specialist referral are not needed.
Epilepsy	Suggestive features are a bitten tongue; head turning to one side during TLoC; no memory of abnormal behavior that occurred before, during, or after TLoC; unusual posturing; prolonged limb jerking; confusion after the event; or prodromal déjà vu or jamais vu. If features of epilepsy are present, arrange for early review by an epilepsy specialist. Do not arrange for EEG before neurologic assessment. Note that brief seizure-like activity often occurs during syncope, including uncomplicated faints. Do not suspect epilepsy unless suggestive features are present. Arrange for cardiovascular assessment if the cause of TLoC is unclear.
Urgent specialist referral	Give immediate treatment for clinically urgent problems (such as complete AV block or severe bleeding). Arrange for urgent specialist cardiovascular assessment for patients at risk for a severe adverse event (such as those with long QT interval, cardiac arrhythmia, or structural heart disease).
Further cardiovascular assessment	Focus on specific disorders that may cause TLoC, such as orthostatic hypotension, the carotid sinus syndrome, structural heart disease, or cardiac arrhythmia. Assessment should include repeated history, clinical examination, and 12-lead ECG. For suspected cardiac arrhythmia or unexplained TLoC, use ambulatory ECG for further assessment: Very frequent episodes: use 24- to 48-hr Holter monitoring. Moderately frequent episodes: use external event monitoring. Infrequent episodes: use an implantable event recorder.

AV, atrioventricular; ECG, electrocardiography; EEG, electroencephalogram; TLoC, transient loss of consciousness.
Modified from Cooper PN, et al. Synopsis of the National Institute for Health and Clinical Excellence Guideline for management of transient loss of consciousness. *Ann Intern Med*. 2011;155:543-549.

vomiting may in fact have peripheral vertigo and secondary vomiting.

A more indolent course, change in consciousness or behavior or seizures may indicate a central origin of vertigo (see Table 6.17). Underlying causes of central vestibular dysfunction include acute vascular ischemic or thromboembolic events, acute demyelinating diseases, pharmacologic vertigo (alcohol, barbiturates, benzodiazepines), more indolent causes, including tumors of the brainstem or cerebellum and chronic demyelinating diseases or trauma (see Table 6.17).

EVALUATION OF THE PATIENT WITH VERTIGO

◆ History

A careful, detailed description of the prodrome and the actual symptoms, including timing, duration, associated symptoms, preceding infections (especially of the upper respiratory tract, such as otitis media or sinusitis), medications, and a history of trauma must be documented. A past, personal, or family history of vertigo or any other neurologic condition is important.

TABLE 6.15 Differences Between Peripheral and Central Vestibular Dysfunctions

Symptom/Sign	Peripheral	Central
Severity of vertigo	Marked Nausea and vomiting common	Often mild
Nystagmus	Bilateral Unidirectional Rotatory/horizontal Never vertical Fast phase usually opposite to side of lesion Improves with visual fixation	Bilateral or unilateral Bidirectional or unidirectional May be vertical Usually no change with visual fixation
	Begins within 2-10 seconds Fatigues with time Habituates	Begins immediately Persistent Reproducibly repetitive
Direction of environmental spin	Toward fast phase of nystagmus	Variable
Direction of past pointing	Toward slow phase of nystagmus	Variable
Tinnitus/deafness	Often present	Usually absent
Examples	Labyrinthitis Ménière disease Positional vertigo (see Table 6.16)	Multiple sclerosis Vertebrobasilar ischemia (see Table 6.17)

Modified from Reilly BM. *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991:191.

◆ Physical Examination

Special attention must be paid to the head, ears, eyes, nose, and throat examination. Good visualization of the tympanic membranes and of their mobility is necessary, along with testing both air and bony conduction with a tuning fork (Figs. 6.7 and 6.8). Visualization of the fundi is important. Testing of all the cranial nerves should be performed.

The neurologic examination must include an evaluation of the gait, a Romberg test, and an assessment of the visual fields and visual acuity (Fig. 6.9). In most children and adolescents, the physical examination results are normal with only subtle findings when the symptoms are provoked.

◆ Diagnostic Tests

The history and physical examination results direct the diagnostic work-up and indicate which tests need to be performed. Imaging studies important in the work-up of the vertiginous patient include computed tomography and magnetic resonance imaging. Both techniques allow visualization of the inner ear and the labyrinthine apparatus, as well as the brainstem and cerebellum. If an infectious cause is suspected, it may be useful to perform a lumbar puncture as long as increased intracranial pressure is not suspected. In the setting of trauma, the simple use of the pneumatic otoscope may allow the examiner to perform a "fistula test," reproducing or worsening the patient's symptoms because of an abnormal communication to the labyrinthine system. If hearing loss is a feature, audiometry and evoked response testing should be considered.

SUMMARY AND RED FLAGS

Vertigo is characterized by the perception of movement, particularly rotational movement, and can be a most distressing and incapacitating phenomenon. The history and examination should allow the examiner to distinguish between peripheral and central vestibular dysfunction.

In children and adolescents, peripheral vertigo is far more common than central vertigo. However, in certain at-risk populations, such as children with sickle cell disease, hemophilia, or congenital heart disease (especially children with right-to-left shunts or mixing lesions), and children receiving anticoagulation therapy, the central causes resulting from hemorrhagic and thromboembolic phenomena must be considered. Chronicity, persistence, vertical nystagmus, and signs of increased intracranial pressure are red flags. Because the diagnosis of vertigo requires that the patient be able to articulate the perception of movement, it is difficult to make this diagnosis in young children; the condition must be carefully distinguished from other movement impairments, especially disequilibrium.

DISEQUILIBRIUM

When a "dizzy" patient describes feeling unsteady on his or her feet, off balance, or uncoordinated, the patient is describing a disturbance in the body's equilibrium system. The fundamental complaint is difficulty in walking, not from weakness but from a feeling of lack of control.

Walking is a complex activity. The constant integration of visual, vestibular, and proprioceptive afferent information regarding the changing spatial orientation is performed by using all levels of the central nervous system: the cerebral cortex, cerebellum, brainstem, spinal cord, and peripheral neuromuscular system. These spatial data are then utilized by the efferent system, producing both voluntary and involuntary movements and spatial adjustments (Fig. 6.10). Disturbances in any of these pathways can result in difficulty with locomotion.

Disequilibrium, therefore, may result from any perceptual distortion of spatial orientation. The most common is visual impairment, to which any child who has played "Pin the Tail on the Donkey" or "Blind Man's Bluff" can attest. Humans depend heavily on visual perception to orient themselves in space. Vestibulocochlear dysfunction can also severely impair a person's ability to ambulate. Peripheral neuropathies affecting proprioceptive function impair the ability of the central nervous system to accurately perceive the position of the limbs with regard to one another and to either the ground or the body. Disorders causing diffuse damage to the integrative mechanism or cortical or cerebellar diseases can impair proprioception as well. Likewise, efferent motor disability produces impairment of locomotion by producing weakness or apraxias (Table 6.18).

TABLE 6.16 Peripheral Vestibulopathy

Syndrome	Usual Presentation	Typical Course	Hearing Loss?	Diagnosis
Benign paroxysmal positional vertigo	Paroxysmal, brief, purely positional vertigo	Often polyphasic illness with gradual improvement but intermittent brief recurrences for weeks/months Does not cause ongoing severe vertigo	No	History Nylen-Bárány maneuvers
Vestibular neuronitis	Acute-onset, severe vertigo, sometimes after viral respiratory infection	Severe ongoing vertigo for many hours or a few days Monophasic illness Resolves spontaneously No hearing loss	No	Clinical history Normal hearing Peripheral nystagmus Rapid (hours–days) resolution without recurrence
Infectious labyrinthitis	Usually, mild vertigo accompanying obvious sinusitis, otitis media, or serous otitis	Resolves over several days with resolution of otitis/sinusitis Very rarely: severe purulent labyrinthitis, mastoiditis, meningitis	No, unless conductive loss due to otitis associated	ENT examination: otitis media? serous otitis? sinusitis?
Toxic vestibulopathy	Vertigo and/or hearing loss associated with use of toxic drugs	Usually dose related and reversible after withdrawal or dose reduction of offending drug	Depends on drug, but sensorineural deafness is common with aminoglycosides, aspirin, loop diuretics, platinum; hearing is usually normal with alcohol and quinidine	Peripheral vertigo with or without hearing loss while/after patient takes vestibulotoxic drugs; most are reversible with discontinuation of drug
Cervicogenic vestibulopathy	Brief positional vertigo, associated with head and neck movements	Usually recurrent, brief, nondebilitating vertigo in patients with cervical spondylosis or other craniovertebral disease (rheumatoid arthritis, Klippel-Feil deformity)	No (but unrelated presbycusis common in this age group)	Typical history Nylen-Bárány maneuvers not consistent with benign positional vertigo Exclude: Vertebrobasilar ischemia Carotid sinus hypersensitivity
Cholesteatoma	Recurrent, often positional vertigo in patients with a history of chronic otitis, TM perforation, mastoiditis	Indolent progression of symptoms	Conductive	Usually visible (at superior border of tympanic membrane) on otoscope examination of ear
Otosclerosis	Progressive hearing loss, sometimes with intermittent vertigo	Indolent progressive hearing loss	Conductive	Family history Audiometry
Post-Traumatic				
Basilar (temporal bone) fracture	Severe vertigo, often with profound hearing loss immediately after head trauma	Gradual (days–weeks) resolution of vertigo; hearing loss, facial nerve injury often permanent	Often: sensorineural	Radiograph: fracture Hemotympanum? CSF otorrhea? Facial paresis?
Postconcussive	Ongoing, often mild/chronic vertigo after concussion, without fracture	Gradual resolution but often delayed for months–years	No	Persistent/chronic symptoms without evidence of other post-traumatic syndromes
Cupulolithiasis	Classic benign positional vertigo, but after head trauma	Same as for benign positional vertigo	No	Clinical history Nylen-Bárány maneuvers Exclude fistulas
Perilymphatic fistula	Trauma may be remote or indirect (swimming, diving injuries) Usually, positional vertigo, recurrent; or mild persistent vertigo	Post-traumatic vertigo that does not improve over time	Often: mixed or sensorineural	Clinical history Positive fistula test Valsalva maneuver: symptoms worsen?
Whiplash	Positional vertigo, worse with neck extension or turning, after deceleration neck injury	Gradual but slow improvement with resolution of neck symptoms	Usually none	Clinical history Exclude fractures and fistulas
Ossicular disruption	Hearing loss, acute vertigo, following head/facial trauma	Gradual (days) resolution of vertigo; hearing loss persists	Conductive	Clinical history Audiometry Exclude fistulas

CSF, cerebrospinal fluid; ENT, ear–nose–throat; TM, tympanic membrane.

Modified from Reilly BM. *Practical Strategies in Outpatient Medicine.* 2nd ed. Philadelphia: WB Saunders; 1991:196-197.

TABLE 6.17 Central Vertigo

Cause	Clinical Clues	Diagnosis
Vertebrobasilar ischemia	Known (suspected) vascular disease: hypertensive, diabetic Almost always accompanied by brainstem symptoms and signs: diplopia, dysarthria, dysesthesias, motor weakness	TIA: clinical history Stroke: neurologic examination CT scan may be unreliable MRI more sensitive Angiography?
Cerebellar hemorrhage	Hypertensive, anticoagulated, posttraumatic Sudden headache: diplopia, ataxia usually more prominent than vertigo	CT scan
Cerebellopontine angle tumors (acoustic neuroma)	Hearing loss, tinnitus much more prominent than vertigo Mild disequilibrium Early: normal neurologic examination, except sensorineural hearing loss Later: cranial nerves V and VII abnormal; papilledema?	Audiometry: retrocochlear, sensorineural hearing loss CT scan, MRI Internal audiometry canal tomography ENG, ABER
Multiple sclerosis	Optic neuritis Internuclear ophthalmoplegia Spastic paraparesis/incontinence Vertigo first isolated symptom in only 10% of cases	Multiplicity of symptoms and signs dissociated in time and space MRI scanning CSF: oligoclonal bands
Drug toxicity	Alcohol, sedatives, tranquilizers, opiates, anticonvulsants	Discontinue drug
Basilar migraine	Vertigo part of headache syndrome Usually positive family history	Clinical history
Vertiginous (temporal lobe) epilepsy	Vertigo as aura prior to loss of consciousness Very rare	Clinical history Exclude other diagnoses EEG
Cranial neuropathy	Many types, all uncommon: Herpes zoster: external ear/palate skin lesions and cranial nerve VIII symptoms Postinfectious: after viral syndromes: polyneuritis and/or cerebellitis and/or encephalitis Chronic meningitis: syphilis, tuberculosis, sarcoid, carcinomatous Vasculitis: Cogan syndrome, polyangiitis with granulomatosis, temporal arteritis, syphilis Head and neck carcinoma Vascular compression syndromes	
Others: Heredofamilial disorders (Friedreich ataxia, spinocerebellar degeneration, olivopontocerebellar degeneration) Cerebellar degeneration (alcohol, cancer) Tumor of brainstem, cerebellum Syrinx cervical cord Post-traumatic concussion		

ABER, auditory brainstem-evoked response; CT, computed tomography; CSF, cerebrospinal fluid; EEG, electroencephalography; ENG, electronystagmography; MRI, magnetic resonance imaging; TIA, transient ischemic attack.
Modified from Reilly BM. *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991:200.

The history is critical for patients complaining of dizziness or difficulty ambulating. For children, this includes a detailed developmental history, because the differential diagnosis varies significantly for children who were walking and then stop and for those who do not achieve that milestone. For younger children, it may be very difficult to determine whether refusal or reluctance to walk is related to imbalance, pain, or weakness. Nausea and vomiting are usually associated with vertigo but tend to be rare with disequilibrium. Nausea and vomiting may accompany a viral illness that results in an **acute cerebellar ataxia** and thus, may precede the onset of disequilibrium. If nausea is simultaneous with the disequilibrium, drug or alcohol intoxication must be considered. Morning nausea or vomiting can be seen with increased **intracranial pressure**, as in hydrocephalus and posterior fossa tumors. Any history of head trauma, especially in toddlers, and any history of congenital heart disease with the potential for paradoxical embolization, including septic emboli resulting in brain abscess, must be considered.

It is important to distinguish acute intermittent ataxia from more chronic or progressive forms (Tables 6.19 and 6.20). Drugs and **postviral cerebellitis** are common causes of acute sudden-onset ataxia. Varicella-associated postinfectious acute cerebellar ataxia usually comes after the infection, but in rare instances, it may occur before or during chickenpox. Its nature is benign. **Metabolic hereditary disorders** may cause intermittent symptoms provoked by fever, as in maple syrup urine disease, ataxia-telangiectasia, Hartnup disease, Refsum disease, pyruvate decarboxylase deficiency, abetalipoproteinemia, biotinidase deficiency, and some enzyme deficiencies. These must be distinguished from hypothyroidism, demyelinating disorders, muscular dystrophies, and neoplasms of the posterior fossa, brainstem, and spinal cord. **Paraneoplastic effects** of neuroblastoma produce ataxia,

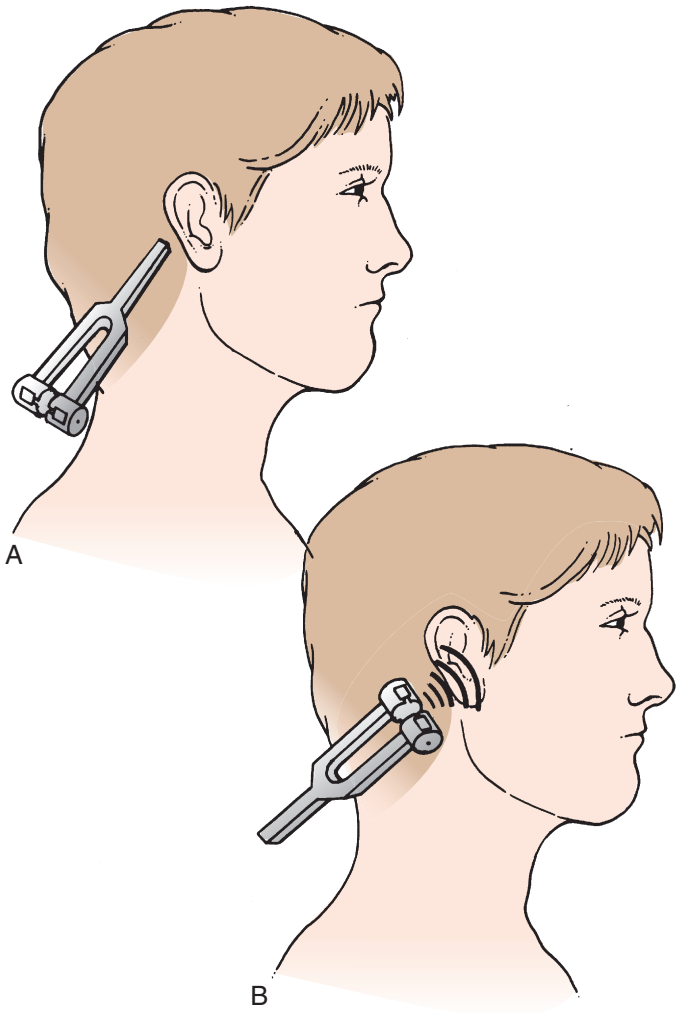


FIGURE 6.7 The Rinne test. The tuning fork is first placed on the mastoid process *(A)*. When the sound can no longer be heard, the tuning fork is placed in front of the external auditory meatus *(B)*. Normally, air conduction is better than bone conduction. (From Swartz MH. *Textbook of Physical Diagnosis: History and Examination*. Philadelphia: WB Saunders; 1989:175.)

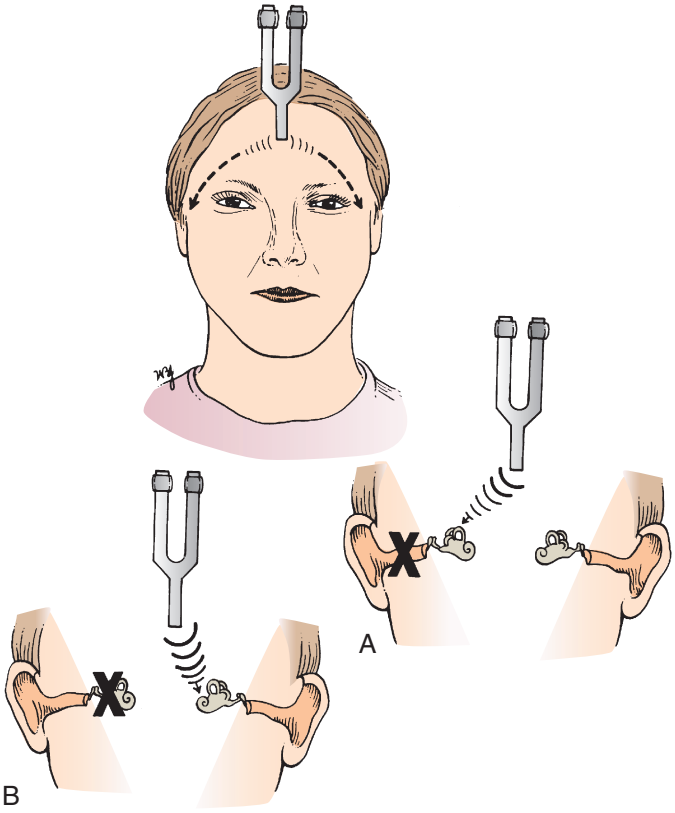


FIGURE 6.8 The Weber test. When a vibrating tuning fork is placed on the center of the forehead, the sound is normally heard in the center without lateralization to either side *(top)*. *A,* In the presence of a conductive hearing loss, the sound is heard on the side of the conductive loss. *B,* In the presence of a sensorineural loss, the sound is better heard on the opposite (unaffected) side. (From Swartz MH. *Textbook of Physical Diagnosis: History and Examination*. Philadelphia: WB Saunders; 1989:175.)

opsoclonus, and myoclonus. The Miller Fisher variant of **Guillain-Barre syndrome** produces ataxia, ophthalmoplegia, and areflexia.

Progressive ataxias have a poorer prognosis. Age at onset can be used to distinguish some causes: posterior fossa tumors and neuroblastoma generally occur within the first decade, Friedreich ataxia and Duchenne muscular dystrophy during the late first to second decades, and multiple sclerosis and diabetic peripheral neuropathy in the second decade.

Observation of the child's gait is an important component of the physical examination. Sufficient room should be found to allow the child to initiate walking, to proceed in a straight line for 10-20 paces and to turn and return. The normal child, older than 2-3 years, initiates walking without hesitation and steps smoothly with a consistent stride length and height and a narrow base. The arms should swing freely and rhythmically, alternating with the feet and there should be little sway in the trunk. When the child stops, there should be no hesitation again and no wavering or compensation. The observer should practice watching children walk normally to develop a sense for each part of the complex motion.

One of the most common gait abnormalities in children is the **wide-based gait**. Careful observation of toddlers at various stages of development familiarizes the observer with the transition from the wide-based, lurching steps of a 12-month-old to the smooth, sure, rhythmic stride of children older than 2-3 years. Excessive trunk sway is typical of cerebellar ataxia. Waddling tends to be caused by proximal muscle weakness with a forward leaning, stiff appearance. It is important to distinguish an unsteady gait with irregular steps from a limp or a sensory deficit resulting in a high step with a slapping foot plant.

In a toddler, passive and active range of motion exercises should be performed to ensure the observer that there is no joint or muscle pain. Reflexes, including the Babinski sign, should be carefully tested. Testing the sensory system in a toddler, especially proprioception, vibration, and two-point discrimination, can be a challenge. The Romberg test may also be difficult for younger children.

EVALUATION OF THE PATIENT WITH DISEQUILIBRIUM

◆ History

A detailed developmental history, especially for a younger child, is obtained. The family history should also be complete. The examiner should check for prodromal illnesses, especially viral (varicella) in nature:

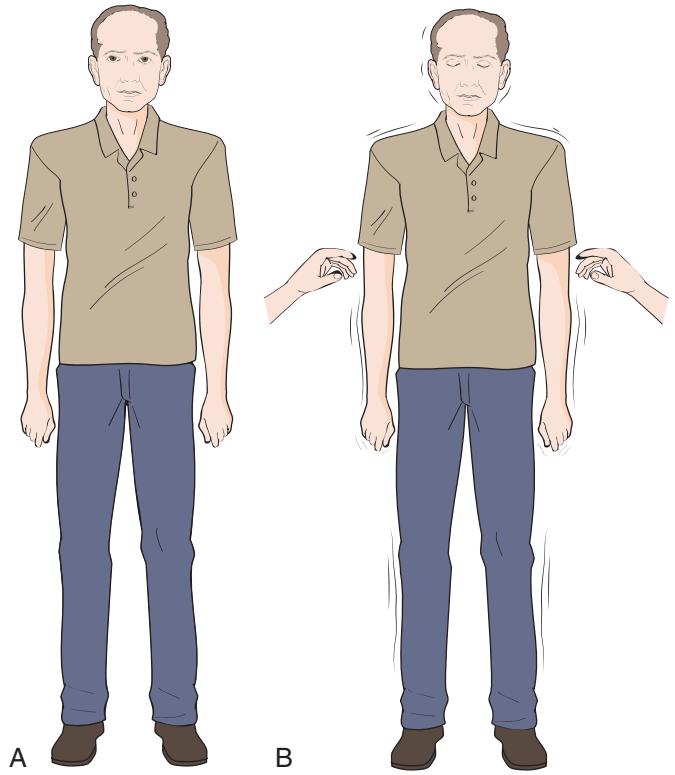


FIGURE 6.9 The Romberg test. The patient stands upright, feet together, arms at sides. The examiner should stand next to the patient. The test is performed in two stages: with the patient's eyes open and then with the eyes closed. Even a normal person may experience mild subjective disequilibrium and may "waver" with the eyes closed. Thus, the Romberg test can sometimes stimulate the feeling of disequilibrium. *A,* With the eyes open, the patient can stand unsupported without difficulty. *B,* With the eyes closed, the patient loses his or her balance. This test result suggests peripheral neuropathy or vestibular dysfunction or both. Cerebellar disease more often results in an inability to maintain posture with the eyes either open or closed. (From Reilly BM. *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991:168.)

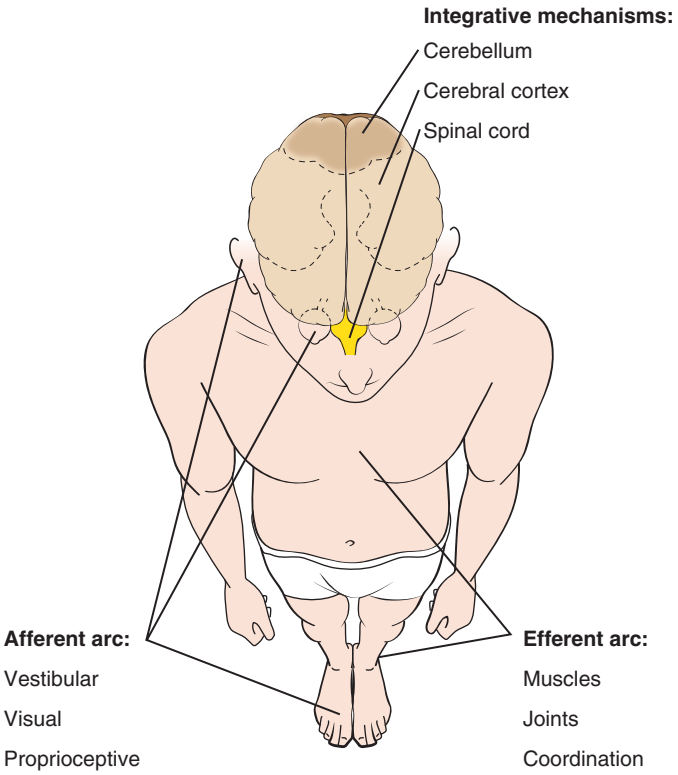


FIGURE 6.10 The afferent, integrative, and efferent components of the equilibrium system. (From Reilly BM. *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991:166.)

Is there any history of trauma?
What is the character of the disability?
Does the child feel unsteady standing, starting to walk, stopping or turning?
How do the parents characterize the child's gait?
Are there associated symptoms, such as nausea, vomiting, pain, or vertigo?
Does the child take or have access to any medications or drugs?
Is the disequilibrium intermittent or constant?
Are there any other medical conditions?

◆ Physical Examination

A thorough general physical examination should precede a very detailed neuromuscular examination. The presence of a goiter, cutaneous lesions of neurofibromatosis or tuberous sclerosis may point to a diagnosis immediately. The neuromuscular examination should proceed from head to toe in an organized and systematic manner. Muscle tone, bulk, and symmetry of the face, trunk and extremities are important. Cranial nerves should be examined, as should the sensory system. During the motor examination, the physician should isolate muscle groups and joints by observing the gait more than once before assessing overall function. The Romberg test should be performed in all patients old enough to cooperate, as should the lateralizing cerebellar tests, such as the finger-to-nose and rapid, alternating movements. Attention to detail in the history and physical examination findings usually yields a diagnosis.

◆ Diagnostic Tests

Other than for drug ingestion, obvious peripheral neuropathies or myopathies, focal extremity infections, or varicella-associated cerebellar ataxia, magnetic resonance imaging is the principal diagnostic test for children and adolescents with disequilibrium. Metabolic tests and thyroid function tests are indicated by either history or physical findings. Especially in younger children, imaging is necessary to rule out the posterior fossa tumors and demyelinating diseases. The lumbar puncture and analysis of the cerebrospinal fluid may also be indicated in cases preceded by a viral or infectious prodrome. When weakness is associated with the disequilibrium, there may be a place for electromyography and nerve conduction studies.

SUMMARY AND RED FLAGS

Ataxia can be seen in children at any age; it may portend serious pathologic processes, including posterior fossa tumors, leukodystrophies, metabolic disorders, and familial-hereditary disorders. The history must be obtained carefully, with attention to developmental milestones, family history, and specifics of prodromal illnesses (chickenpox), associated symptoms, and a description of the gait. The physical examination must also be detailed and methodical, with special emphasis on the neuromuscular examination. Imaging studies of the central nervous system are usually required, especially for younger children, in whom the possibility of neoplasms is the greatest.

TABLE 6.18 Disequilibrium

Cause	Clues	Gait/Romberg Test Result
Most Common		
Multiple sensory deficits	Visual impairment? Hearing/vestibular dysfunction? Neuropathy? Spondylosis/degenerative joint disease? Neuropathy? Weakness?	Timid: slow, short-stepped, apprehensive Remarkably improved with sensory assist (cane, companion) Romberg: normal or sensory
Hyperventilation/anxiety disorders	Young, healthy, anxious patient with *episodic "spells"* of disequilibrium *or* Constant, chronic, elusive disequilibrium with or without obvious medical/psychosocial stress	Usually normal gait Romberg: normal *or* "Nonphysiologic"
Vestibular disorders	*Chronic* unilateral vestibulopathy may cause ongoing disequilibrium: Ménière disease, cholesteatoma, fistula, acoustic neuroma, drug-induced vestibulopathy	Usually normal gait May veer to side of vestibular lesion Romberg: sensory
Drug induced	Central nervous system agents: tranquilizers, barbiturates, sedatives, alcohol, H_2 blockers, β blockers, calcium agents, indomethacin Vestibulotoxic agents: aspirin, loop diuretics, aminoglycosides, quinidine	Timid and/or ataxic gait Romberg: normal or cerebellar Romberg: sensory or normal
Alcoholic	Heavy alcohol abuse may cause cerebellar and/or sensory degeneration Nystagmus uncommon	Ataxic gait Romberg: cerebellar or sensory
Painful ambulation	Arthritis? Claudication? Pain is limiting factor!	Limping? Waddling? Normal gait? Romberg: usually normal
Fear of falling	Normal examination No apraxia or ataxia Rarely, phobic	Timid gait Romberg: often cerebellar but fluctuates, inorganic
Less Common		
Hypothyroidism	Weight gain or poor growth, cold intolerance, hoarseness, fatigue	Usually normal gait Severe: ataxic gait
Hypoglycemia	Episodic	Romberg: usually normal
Apraxia	Usually diffuse cortical dysfunction or frontal lobe disease Usually apraxic in execution of other skilled movements (e.g., combing hair, brushing teeth)	Apraxic gait Romberg: normal
Peripheral disease	Diabetes, alcoholism, pernicious anemia Only very severe (proprioceptive) neuropathy causes gait disorder	Sensory gait: footdrop and/or circus clown Romberg: sensory
Cerebellar disease (nonalcoholic)	See text	Ataxic gait Romberg: cerebellar
Spasticity	Multiple sclerosis, spinal cord tumor/trauma Legs: weak, hyperreflexic, clonus Often bowel/bladder dysfunction	Spastic, scissors gait Romberg: often normal
Normal-pressure hydrocephalus	Urinary incontinence Cognitive impairment Gait disturbance	Ataxic/apraxic
Hemiplegia	Prior cerebrovascular accident Hemiparesis on neurologic examination	Hemiplegic gait Romberg: often normal (if able to perform at all)
Proximal myopathy	Severe bilateral proximal leg weakness: hip disease, muscular dystrophy, myositis, etc.	Waddling gait Romberg: normal
Hysterical	Unpredictable, intermittent or bizarre "Secondary gain"	Gait varies: sometimes normal, timid, limping, apraxic Romberg: often cerebellar, but fluctuates, inorganic

CNS, central nervous system; CSF, cerebrospinal fluid.
Modified from Reilly BM. *Practical Strategies in Outpatient Medicine.* 2nd ed. Philadelphia: WB Saunders; 1991:172-173.

TABLE 6.19 Acute or Recurrent Ataxia

- Brain tumor
- Conversion reaction
- Drug ingestion
- Encephalitis (brainstem)
- Genetic disorders
  - Dominant recurrent ataxia
  - Episodic ataxia type 1
  - Episodic ataxia type 2
  - Hartnup disease
  - Maple syrup urine disease
  - Pyruvate dehydrogenase deficiency
- Migraine
  - Basilar
  - Benign paroxysmal vertigo
- Postinfectious/immune
  - Acute disseminated encephalomyelitis
  - Acute postinfectious cerebellitis (varicella)
  - Miller Fisher syndrome
  - Multiple sclerosis
  - Myoclonic encephalopathy/neuroblastoma
- Pseudoataxia (epileptic)
- Trauma
  - Hematoma
  - Postconcussion
  - Vertebrobasilar occlusion
- Vascular disorders
  - Cerebellar hemorrhage
  - Kawasaki disease

From Augustine E, Mink J. Movement disorders. In: Kliegman R, Stanton B, Schor N, et al, eds. *Nelson Textbook of Pediatrics.* 19th ed. Philadelphia: Elsevier; 2011:2053-2055.

TABLE 6.20 Chronic or Progressive Ataxia

Brain Tumors
- Cerebellar astrocytoma
- Cerebellar hemangioblastoma (von Hippel–Landau disease)
- Ependymoma
- Medulloblastoma
- Supratentorial tumors

Congenital Malformations
- Basilar impression
- Cerebellar aplasias
- Cerebellar hemisphere aplasia
- Dandy-Walker malformation
- Vernal aplasia
- Chiari malformation

Hereditary Ataxias
- Autosomal dominant inheritance
- Autosomal recessive inheritance
  - Abetalipoproteinemia
  - Ataxia-telangiectasia
  - Ataxia without oculomotor apraxia
  - Ataxia with episodic dystonia
  - Friedreich ataxia
  - Hartnup disease
  - Juvenile GM_2 gangliosidosis
  - Juvenile sulfatide lipidoses
  - Maple syrup urine disease
  - Marinesco-Sjögren syndrome
  - Pyruvate dehydrogenase deficiency
  - Ramsay Hunt syndrome
  - Refsum disease (HSMN IV)
  - Respiratory chain disorders

X-Linked Inheritance
- Adrenoleukodystrophy
- Leber optic neuropathy
- With adult-onset dementia
- With deafness
- With deafness and loss of vision

From Augustine E, Mink J. Movement disorders. In: Kliegman R, Stanton B, Schor N, et al, eds. *Nelson Textbook of Pediatrics.* 19th ed. Philadelphia: Elsevier; 2011:2053-2055.

LIGHTHEADEDNESS

Lightheadedness is the most difficult to characterize without using the term "dizzy." The lightheaded patient's description is vague and nonspecific. Terms such as "woozy," "spaced-out," "dreamy," "giddy," or "drugged" are frequently used. The key for the clinician is to elicit an adequate description from the patient to rule out vertigo, disequilibrium, and presyncope. The differential diagnosis for lightheadedness is then rather short in comparison with the other "dizziness" conditions (Fig. 6.11). It is often difficult to distinguish lightheadedness from presyncope.

In the patient who complains of lightheadedness, voluntary hyperventilation may reproduce his or her symptoms. Voluntary hyperventilation in normal subjects produces a variety of symptoms (Table 6.21). This test is predictive only if the patient's symptoms are precisely reproduced, and all other investigation results are negative.

Lightheadedness that is episodic frequently follows a pattern related to the underlying psychogenic disorder: phobic disorders, posttraumatic stress syndrome, panic attacks, and anxiety disorders. Such situational anxieties, phobias, or panic attacks may occur with or without hyperventilation. Careful history taking is the key to recognizing the pattern. If the history is that of constant lightheadedness ("always there"), the origin is almost always psychogenic. This is a **somatization** generally of anxiety disorder or depression. The clinician must nonetheless remain cautious with predictable episodes because postural episodes, drug-related episodes, and perimenstrual episodes can follow a pattern and represent physiologic abnormalities that predispose to lightheadedness.

Especially if the episodes of lightheadedness are unpredictable, the clinician is advised to consider a broader differential diagnosis. Severe anemia, low cardiac output, thyroid disease, and some medications may produce occasional lightheadedness. Of greater concern are episodes of lightheadedness associated with other symptoms, especially chest pain, seizures, confusion, and visual or auditory changes. Likewise, exertional lightheadedness must be pursued to definitively rule out a cardiac dysrhythmia.

If hyperventilation reproduces the patient's symptoms, it is not the diagnosis in and of itself. Hyperventilation is a feature of many psychogenic syndromes and may be acute or chronic. Part of the performance of the hyperventilation should be educating the patient to the feelings and the scenario leading to the hyperventilation reaction. Even young children can then be trained to regulate their breathing to avoid the symptoms. However, this does not address the underlying cause of

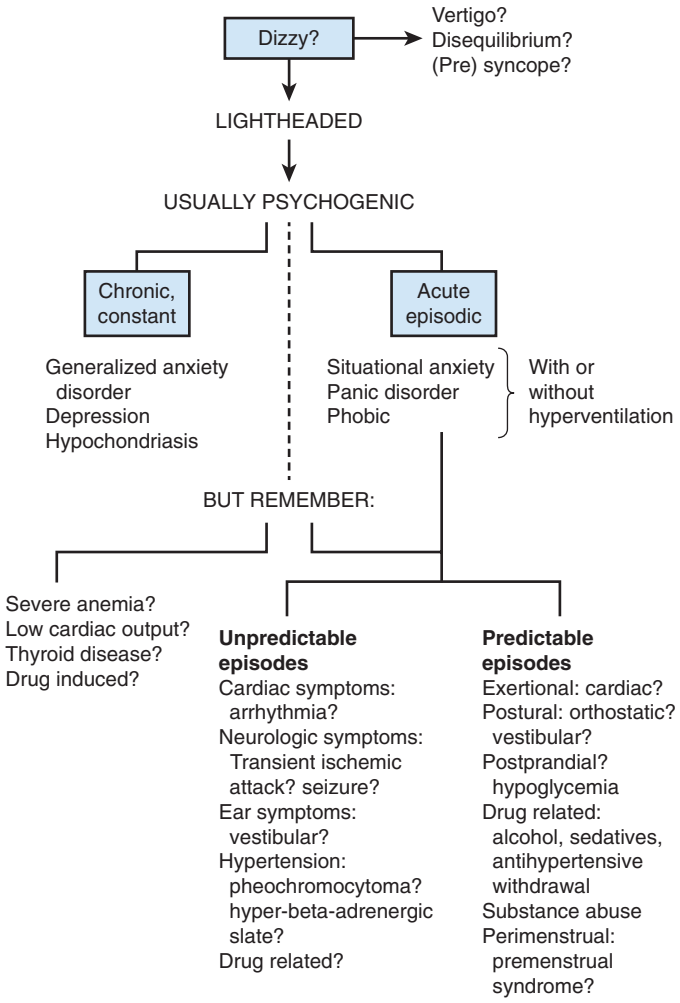


FIGURE 6.11 Evaluation for lightheadedness (From Reilly BM. *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991:206.)

the hyperventilation reaction; that requires patient, nonjudgmental, longer term counseling, and careful categorization of the underlying disorder. The clinician should not hesitate to consult a psychiatrist to facilitate this process as well as treat the definitive psychogenic disorder.

EVALUATION OF THE PATIENT WITH LIGHTHEADEDNESS

◆ History

The examiner should listen for descriptions suggesting vertigo, disequilibrium, or presyncope and should establish whether there is any pattern to the occurrence of the feeling of lightheadedness. The child, parents, or siblings are asked about associated symptoms, such as diaphoresis, hyperpnea, pallor or flushing, headache, and chest pain. After the more serious physiologic disorders are ruled out by history, physical examination, or diagnostic testing, psychogenic disorders should be pursued.

◆ Physical Examination

After a thorough general physical examination, including examination of the fundi, a full, detailed neurologic examination should be performed. In addition to allowing primary cardiac, endocrine, or neurologic disorders to be ruled out, the examination allows the clinician to gain the confidence of the patient and demonstrates the physician's concern about the patient's complaints. The patient should be given feedback, reassurance, and information about the purpose of various maneuvers in the physical examination.

TABLE 6.21 Symptoms Associated with Hyperventilation

General
Fatigue
Diffuse weakness
Insomnia
Nightmares
Headache
"Feel cold"
Sweats

Cardiovascular
Palpitations
Tachycardia
Precordial pain
Raynaud phenomenon

Respiratory
Shortness of breath
Chest pain
Sighing respirations
Yawning
"Can't get deep breath"
Paroxysmal nocturnal dyspnea
Unexplained cough
Dry mouth

Musculoskeletal
Muscle spasm
Tremors
Twitching
Tetany

Neurologic
Dizziness
Paresthesias (especially distal)
Unsteadiness
Impaired memory and/or concentration
Slurred speech
Blurred vision

Gastrointestinal
Globus hystericus
Mouth dryness
Dysphagia
Bloating
Belching/flatulence
Abdominal pain

Psychic
Tension
Anxiety
Depression
Apprehension

From Reilly BM. *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991:208.

◆ Diagnostic Tests

Diagnostic testing is directed by the history and physical examination findings. In the setting of lightheadedness, tests are generally done to rule out potentially serious cardiovascular and neurologic conditions.

SUMMARY AND RED FLAGS

Lightheadedness must be distinguished from vertigo, disequilibrium, and presyncope. Frequently, the patient's description of the sensation is vague and uncertain. A pattern of the appearance of the symptoms may suggest an underlying cause. The coexistence of any other symptoms must be carefully sought. Physical findings are generally normal, including the neurologic examination; specific attention is given to cerebellar, vestibular, and sensory function. Voluntary hyperventilation in the supine position frequently reproduces the patient's lightheadedness. Hyperventilation may be acute or chronic and is a symptom itself, rarely a diagnosis.

Treatment must address the underlying psychogenic cause in order to be successful.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

General

Alboni P, Brignole M, Menozzi C, et al. Diagnostic value of history in patients with syncope with or without heart disease. *J Am Coll Cardiol*. 2001;37:1921-1928.

Johnsrude CL. Current approach to pediatric syncope. *Pediatr Cardiol*. 2000;21:522-531.

Narchi H. The child who passes out. *Pediatr Rev*. 2000;21:384-388.

Paris Y, Toro-Salazar OH, Gauthier NS, et al. Regional implementation of a pediatric cardiology syncope algorithm using SCAMPS methodology. *J Am Heart Assoc*. 2016;5(2). pii: e002931. doi:10.1161/JAHA.115.002931.

Post R, Dickerson L. Dizziness: a diagnostic approach. *Am Fam Physician*. 2010;82:361-368.

Scammell TE. Narcolepsy. *N Engl J Med*. 2013;373(27):2654-2662.

Tanel RE. Putting the bite into the pediatric syncope evaluation. *Pediatr Case Rev*. 2001;1:3-18.

Willis J. Syncope. *Pediatr Rev*. 2000;21:201-204.

Syncope

Agarwal AK, Garg R, Sarkar P. Postural orthostatic tachycardia syndrome. *Postgrad Med J*. 2007;83:478-480.

Berger S, Dhala A, Friedberg D. Sudden cardiac death in infants, children, and adolescents. *Pediatr Cardiol*. 1999;46:221-234.

Bradley T, Dixon J, Easthope R. Unexplained fainting, near drowning and unusual seizures in childhood: Screening for long QT syndrome in New Zealand families. *N Z Med J*. 1999;112:299-302.

Campell R, Berger S, Ackerman M, et al. Policy statement pediatric sudden cardiac arrest. *Peds*. 2012;e1094-e1102.

DiMario FJ Jr. Prospective study of children with cyanotic and pallid breath-holding spells. *Pediatrics*. 2001;107:265-269.

Eirís-Pual J, Rodríguez-Nunez A, Fernandez-Martínez N, et al. Usefulness of the head-upright tilt test for distinguishing syncope and epilepsy in children. *Epilepsia*. 2001;42:709-713.

Ellison S. Sudden cardiac death in adolescents. *Prim Care*. 2015;42:57-76.

Jacob G, Costa F, Shannon JR, et al. The neuropathic postural tachycardia syndrome. *N Engl J Med*. 2000;343:1008-1014.

Kouakam C, Vaksmann G, Pachy E, et al. Long-term follow up of children and adolescents with syncope. *Eur Heart J*. 2001;22:1618-1625.

Lahat H, Eldar M, Levy-Nissenbaum E, et al. Autosomal recessive catecholamine- or exercise-induced polymorphic ventricular tachycardia. *Circulation*. 2001;103:2822-2827.

MacNeil E, Vashist S. Approach to syncope and altered mental status. *Pediatr Clin North Am*. 2013;60:1083-1106.

Moodley M. Clinical approach to syncope in children. *Semin Pediatr Neurol*. 2013;20:12-17.

Pfammatter JP, Paul T. Idiopathic ventricular tachycardia in infancy and childhood. *J Am Coll Cardiol*. 1999;33:2067-2072.

Pomeranz A, Busey S, Sabnis S. Behrman R, Kliegman R, eds. *Pediatric Decision-Making Strategies*. Philadelphia: Saunders; 2002:58-61.

Priori SG, Napolitano C, Gioedano U, et al. Brugada syndrome and sudden cardiac death in children. *Lancet*. 2000;355:808-809.

Ritter S, Tani LY, Etheridge SP, et al. What is the yield of screening echocardiography in pediatric syncope? *Pediatrics*. 2000;105:E58.

Roden D. Drug-induced prolongation of the QT interval. *N Engl J Med*. 2004;350:1013-1022.

Rodríguez-Nunez A, Fernandez-Cebrian S, Perez-Munuzuri A, et al. Cerebral syncope in children. *J Pediatr*. 2000;136:542-544.

Salim MA, Ware LE, Barnard M, et al. Syncope recurrence in children: Relation to tilt-test results. *Pediatrics*. 1998;102:924-926.

Satish R. Postural tachycardia syndrome. *Circulation*. 2013;127:2336-2342.

Shalev Y, Gal R, Tchou PJ, et al. Echocardiographic demonstration of decreased left ventricular dimensions and vigorous myocardial contraction during syncope induced by head-up tilt test. *J Am Coll Cardiol*. 1991;18:746-751.

Sutton R. Clinical classification of syncope. *Prog Cardiovasc Dis*. 2013;55:339-344.

Thilenius OG, Quinones JA, Husanyi TS, et al. Tilt test for diagnosis of unexplained syncope in pediatric patients. *Pediatrics*. 1991;87: 334-338.

Van Hare G, Long Q. T syndromes. In: Kliegman R, Stanton B, Schor N, et al., eds. *Nelson Textbook of Pediatrics*. 19th ed. Philadelphia: Elsevier Saunders; 2011:1616-1618.

Vertigo

Bower C, Cotton R. The spectrum of vertigo in children. *Arch Otolaryngol Head Neck Surg*. 1995;121:911-915.

Dunn DW, Snyder H. Benign positional vertigo of childhood. *Am J Dis Child*. 1976;176:1099.

Froehling DA, Bowen JM, Mohr DN, et al. The canalith repositioning procedure for the treatment of benign paroxysmal positional vertigo: A randomized trial. *Mayo Clin Proc*. 2000;75:695-700.

Hotson JR. Clinical detection of acute vestibulocerebellar disorders. *West J Med*. 1984;140:910-913.

Katsarkas A, Kirkham TH. Paroxysmal positional vertigo: A study of 255 cases. *J Otolaryngol*. 1978;7:320-330.

Weisleder P, Fife TD. Dizziness and headache: A common association in children and adolescents. *J Child Neurol*. 2001;16:727-730.

Disequilibrium

Augustine E, Mink J, et al. Movement disorders. In: Kliegman R, Stanton B, Schor N, eds. *Nelson Textbook of Pediatrics*. 19th ed. Philadelphia: Elsevier Saunders; 2011:2053-2055.

DeAngelis C. Ataxia. *Pediatr Rev*. 1995;16:114-115.

Dinolfo EA, Adam HM. Evaluation of ataxia. *Pediatr Rev*. 2001;22:177-178.

Dreyfus PM, Oshtory M, Gardner ED, et al. Cerebellar ataxia: Anatomical, physiological and clinical implications. *West J Med*. 1978;128:499-511.

Kinast M, Levin HS, Rothner AD, et al. Cerebellar ataxia, opsoclonus and occult neural crest tumor. *Am J Dis Child*. 1980;134:1057-1059.

Lightheadedness

Magarian GJ. Hyperventilation syndromes: Infrequently recognized common expressions of anxiety and stress. *Medicine (Baltimore)*. 1982;61:219-236.

Naschitz JE, Hardoff D, Bystritzki I, et al. The role of the capnography head-up tilt test in the diagnosis of syncope in children and adolescents. *Pediatrics*. 1998;101:E6.

Tiwari S, Bakris GL. Psychogenic vertigo: A review. *Postgrad Med*. 1981;70:69-77.

7

Chest Pain

Julie M. Kolinski

Chest pain can be the presenting complaint for a child feeling chest tightness, burning, pressure, stabbing sensations, palpitations, or heartburn. This can make quickly discerning an etiology difficult, particularly in young children who are not able to verbalize precise symptoms. Chest pain as a symptom affects equal numbers of girls and boys and children under and over 12 years of age. Diagnostically, children younger than 12 years with chest pain are more likely to have cardiorespiratory etiologies for their pain; whereas, adolescents are more likely to have musculoskeletal or psychogenic etiologies.

The general public has been adequately educated on the significant morbidity and mortality that chest pain can imply in adults in the form of cardiac ischemia. Therefore, when children complain of chest pain, it can provide significant anxiety for patients, families, and providers. Due to this anxiety, cardiology consultation is often sought. Unlike adults, underlying cardiac pathology is rare in children with chest pain. Only 4-6% of children without known congenital heart disease are found to have a cardiac etiology. The challenge for the medical care provider is to distinguish chest pain as a commonly benign pediatric complaint from significant cardiac disease, limit unnecessary evaluation, and provide adequate reassurance for an anxious patient and family.

Due to the rarity of cardiac pathology as the cause for chest pain, it is difficult to develop evidence-based guidelines for evaluation, and the implication of a misdiagnosis of a serious disorder is high. Chest pain caused by noncardiac causes may be the combination of multiple diagnoses, leaving medical providers seeking to "rule out" life-threatening cardiac causes of chest pain. The evaluation, if nonconclusive, can leave patients and families without precise answers. Most final diagnoses of noncardiac chest pain represent clinical impressions rather than confirmed diagnoses; between 20 and 45% of pediatric cases of chest pain are labeled idiopathic. The lack of a defined etiology or the presence of multiple causes for a particular patient can heighten worry, anxiety and subsequent morbidity, which is reflected in missed days of school, reduced exercise, and psychologic distress. Furthermore, chest pain can become a chronic condition in the pediatric population; up to 45-69% of patients have been noted to have persistent symptoms with 19% of patients reporting symptoms lasting for more than 3 years.

Overall, if medical providers methodically approach a child or adolescent's complaint of chest pain, they can provide thoughtful diagnostic evaluations that not only discover serious cardiac pathology if present but also reassure families when a noncardiac etiology is suspected.

CAUSES OF CHEST PAIN

The most common causes of chest pain in descending frequency include idiopathic, musculoskeletal, pulmonary, psychogenic, gastrointestinal, and cardiac diagnoses (Table 7.1). A differential diagnosis of pediatric chest pain is listed in Table 7.2. The etiology of chest pain in the absence of cardiac pathology can be multifactorial and includes multiple items on this list.

APPROACH TO THE PATIENT WITH CHEST PAIN

A practical approach to chest pain first requires a detailed history and physical examination. An awareness of indicators (red flags) and prioritization that may suggest serious disease and necessitate immediate treatment are essential (Table 7.3 and Table 7.4). *In particular, children and adolescents who have chest pain or syncope that is exertional should be taken seriously, particularly if there is a family history of sudden death.* Children rarely come in complaining of "shortness of breath on exertion" or "palpitations." Instead, children should be asked if they keep up with their same-age peers when participating in activities, if they finish last in races, or whether they have to pause in the middle of a flight of stairs. If concerned for palpitations, a provider can ask if a child's heart ever skips a beat or seems to do flip flops or somersaults in their chest. If red flags are not present but a potentially serious noncardiac etiology of chest pain is suspected, a continued investigation of the pain itself is necessary to make a diagnosis; it can also serve as a therapeutic intervention. A deliberate, orderly, and complete approach to the clinical evaluation often calms an anxious child and family.

A complete history and physical examination usually with an electrocardiogram (ECG) used to diagnose chest pain allows medical providers to avoid missing life-threatening cardiac pathology. Further testing has been debated when this evaluation indicates a noncardiac diagnosis as the vast majority of patients with a cardiac cause of chest pain have had suggestive symptoms (exertional chest pain, concerning family history findings, abnormal examination findings, and/or abnormal ECG findings), which appropriately lead to further investigation. The considerable anxiety generated among patients, families, and even providers in regard to this symptom can promote evaluations that are extensive, costly, and often low yield.

◆ History

The goal of a thorough history of a patient with chest pain is to determine if the etiology is life threatening, a manifestation of a chronic condition with possible serious complications, a specific acute cause or multiple acute and/or chronic causes. Although chest pain affects children and adolescents of all ages equally, the age of a child can assist in diagnosis. Adolescents are more likely to have musculoskeletal or psychogenic causes of chest pain, while younger children have more respiratory disorders and vague complaints.

One possible approach includes a stepwise, directed history that includes:

(See *Nelson Textbook of Pediatrics,* p. 2155.)

TABLE 7.1 Causes of Chest Pain in Children and Adolescents by Frequency of Causes

Idiopathic	12-85%
Musculoskeletal	15-31%
Pulmonary	12-21%
Psychiatric	5-17%
Gastrointestinal	5-7%
Cardiac	4-6%
Other	4-21%

- Description of pain (Table 7.5)
- Assessment for red-flag symptoms, including targeted family history
- Medication review
- Review of known illnesses
- Review of systems including psychosocial evaluation

Eliciting the basics of the chest pain's duration, quality, propensity to radiate, severity, and timing is essential. Details that have been noted to be particularly helpful include duration, aggravating and relieving factors, and associated symptoms. Severe pain that lasts only a few seconds up to 1 or 2 minutes is often from the chest wall, but chest pain that persists longer is more likely to be organic in nature. Aggravating and alleviating factors can include position changes that accompany the pain from pericarditis or onset after eating spicy foods in gastroesophageal reflux. The character and location of the pain in pediatric patients are less helpful in the diagnostic evaluation due to often vague descriptions; nonetheless, medical providers should continue to obtain this information to understand the whole picture. Providers should remember that children often complain of chest pain when the pain is in a different place, such as the epigastrium or flank. Finally, it is important to determine whether or not the chest pain has had an impact on the child's activity.

Red-flag symptoms (see Table 7.3) are high-yield, must-know characteristics of a child or adolescent's chest pain. Oftentimes, after a patient's complete description of the pain, a medical provider will already know the answers to multiple red-flag symptoms, such as when the pain occurs, if it wakes the patient from sleep, and if it is associated with syncope. A targeted family history includes asking about inherited conditions such as familial hypercholesterolemia, hypertrophic cardiomyopathy, asthma, and Marfan syndrome. It also can provide information regarding relatives with adult-onset cardiac illnesses associated with chest pain, such as heart failure or ischemia, which may be providing added anxiety for the family.

Medications that the child may already be taking are important to consider. Some medications have specific links to etiologies of chest pain, such as tetracyclines with erosive esophagitis or oral contraceptives with pulmonary embolism. Other illicit medications such as cocaine and other sympathomimetic agents (such as amphetamines, synthetic marijuana) have been associated with chest pain. A child's known underlying illnesses and surrounding medical complaints discovered in a review of systems can complete the clinical picture for medical providers. The presence of joint pain or rash could suggest collagen vascular disease or the presence of increased drooling could represent an esophageal foreign body.

A full psychosocial review should be performed on each patient to ensure that details of personal stressors and behaviors emerge. It is useful to learn about these aspects of the child's chest pain from

TABLE 7.2 Differential Diagnosis of Pediatric Chest Pain

Musculoskeletal
Trauma (accidental, abuse)
Exercise, overuse injury (strain)
Costochondritis
Tietze syndrome
Precordial catch syndrome
Slipping rib syndrome
Fibromyalgia
Spinal cord or nerve root compression

Pulmonary
Asthma
Pneumonia
Pleurisy
Cough
Pneumothorax, pneumomediastinum
Pulmonary embolism
Tumor
Foreign body

Psychiatric
Hyperventilation
Anxiety
Panic disorder

Gastrointestinal
Achalasia
Gastroesophageal reflux
Esophageal foreign body including pill esophagitis
Esophageal spasm
Esophageal rupture
Cholecystitis
Subdiaphragmatic abscess
Perihepatitis (Fitz-Hugh–Curtis syndrome)
Peptic ulcer disease
Pancreatitis

Cardiac
Hypertrophic cardiomyopathy
Aortic stenosis
Mitral valve prolapse
Dilated cardiomyopathy
Pericarditis
Myocarditis
Endocarditis
Idiopathic ventricular tachycardia
Exercise-induced ventricular tachycardia
Wolff-Parkinson-White syndrome
Aortic dissection
Pulmonary hypertension
Ischemia (anomalous coronary artery, systemic lupus erythematosus, post heart transplant, Kawasaki disease, sympathomimetic drugs, hypercholesterolemia)

Other
Herpes zoster (cutaneous)
Sickle cell anemia vasoocclusive crisis (rib infarction)
Primary or metastatic cancer
Splenic rupture
Drug-related: cigarette smoking, cocaine use, sympathomimetic use, tetracycline ingestion
Anorexia nervosa
Breast-related disease

TABLE 7.3 Red Flags That Increase the Likelihood of a Cardiac Cause for Chest Pain

- Sudden onset of severe pain
- Pain occurs with exercise
- Exertional syncope
- Pain that awakes the patient from sleep
- Palpitations and/or dysrhythmias
- Family history of sudden death, young onset ischemic heart disease, inherited arrhythmias such as long QT syndrome or Brugada syndrome, deep vein thrombosis or pulmonary embolism
- Cyanosis
- Personal past or current history of congenital heart disease
- Personal history of connective tissue disease, hypercoagulable or hypercholesterolemic state, systemic lupus erythematosus, Kawasaki disease, sickle cell anemia, Marfan syndrome, cystic fibrosis, Ehlers-Danlos syndrome
- Personal history of cocaine, huffing, and/or amphetamine use

the child and the parent/family separately. Make sure to interview the patient alone if the child is older or an adolescent. It is difficult for children to discuss areas of difficulty, such as family relationships, school difficulties or concerns about physical development, with family present. It is useful to ask "What are you concerned that this pain is caused by?" of both the patient and the family. This question frequently gives information about overriding fears and concerns that can help medical providers know how to appropriately reassure the family in the likely event that the chest pain has a benign, noncardiac etiology.

Musculoskeletal

Musculoskeletal chest wall pain is perhaps the most identifiable cause of chest pain due to its association with localized tenderness elicited by specific manipulation of the thorax (Fig. 7.1). Pain can involve the ribs, costochondral junctions, costal cartilages, intercostal muscles, sternum, clavicle, or spine. The pain is often worse with movement, coughing, and inspiration. In considering musculoskeletal etiologies, thoroughly consider any trauma to the chest wall. Both contusion and rib fracture can be particularly painful with exquisite tenderness on palpation and pain on inspiration. Table 7.6 highlights common causes of musculoskeletal chest pain.

In general, chest wall pain can result from the strain of any muscle group present in the chest; however, multiple syndromes have been described in relation to specific patterns of muscular pain (Fig. 7.2). Some of these syndromes include pectoral syndrome (pain in a band across the anterior parasternal chest wall on the right or the left), coracoid syndrome (pain at the site of the pectoralis minor muscle with tenderness at its insertion onto the coracoid process), and xiphoid process syndrome (pain over the xiphoid process).

Respiratory

Respiratory causes of chest pain are often diagnosed through use of history and general appearance of the patient (Table 7.7). Some of these causes can require urgent evaluation and treatment. In a patient with sudden, significant chest pain, medical providers should consider acute pneumothorax or acute pulmonary embolism (along with acute pericarditis, myocarditis, or aortic dissection—discussed in cardiac etiologies of chest pain). Asthma or reactive airway disease is more likely in a patient with audible wheezing and cough. Notably, patients with chest pain from undiagnosed causes after complete evaluation

TABLE 7.4 Categorization and Prioritization of Chest Discomfort

Category 1: Does the Complaint Indicate Life-Threatening Emergency, Such As…

- Acute ischemic heart disease
- Aortic dissection
- Pulmonary embolism
- Spontaneous pneumothorax/pneumomediastinum
- Acute arrhythmia

Indicators:

- Acute onset
- Severe pain
- High or low blood pressure
- Significant tachycardia
- Cyanosis
- Loss of consciousness
- Pleuritic-type pain

Category 2: Does the Complaint Indicate a Chronic Condition That Might Result in Serious Complications, Such As…

- Aortic stenosis
- Pulmonary hypertension
- Coronary disease
- Hypertrophic cardiomyopathy
- Marfan syndrome
- Nonbenign cardiac arrhythmias, such as Wolf-Parkinson-White syndrome, long QT syndrome, ventricular arrhythmias

Indicators:

- Recurrent intermittent discomfort, especially with exercise
- History of syncope
- Family history of heart disease
- Heart murmur

Category 3: Does the Complaint Indicate Specific Acute Causes, Such As…

- Asthma
- Pericarditis
- Pneumonia
- Pleural effusion
- Herpes zoster
- Chest wall injury
- Hyperventilation

Indicators:

- Acute onset
- Fever
- Associated signs and symptoms of lung disease, such as cough or dyspnea

Category 4: Does the Complaint Indicate Specific Chronic Causes, Such As…

- Gastroesophageal reflux disease
- Fibromyalgia
- Panic disorder

Indicators:

- Chronic intermittent symptoms
- Other gastrointestinal symptoms
- Psychosocial indicators such as school absences, mood symptoms, family problems

have a greater likelihood than normal control subjects to have abnormal results on methacholine challenges and exercise testing, indicating reactive airway disease is a more common etiology of chest pain than providers realize. Finally, pneumonia and respiratory infections are the most common causes of chest pain when it presents with fever.

Psychogenic/Idiopathic

Psychogenic causes of chest pain are more common in adolescents than in children under the age of 12. Patients with psychogenic etiologies of chest pain may also have additional physiologic causes of pain; psychologic risk factors can amplify the clinical presentation of chest pain. Psychologic forms of chest pain are typically recurrent with particular stressors. Children and adolescents may have a history of anxiety and/or stressful life events that are not easily apparent but can have a large impact on their perception of pain. Many psychologic factors, such as anxiety, depression, and psychosomatic features often coexist. Patients with psychogenic causes of chest pain are the most likely to have other somatic symptoms, including breathlessness, fatigue, nervousness, near-syncope, and palpitations. These patients also often demonstrate more bodily worries, more limitation of general activity, and more school absences. The most common etiologies of psychogenic chest pain are hyperventilation and underlying psychiatric illness, such as anxiety, depression, or somatoform disorders (conversion or somatization).

Hyperventilation, most often in the setting of a **panic attack**, is characterized by rapid breathing accompanied with dyspnea and anxiety to the degree that systemic symptoms result, such as paresthesias, dizziness/lightheadedness, palpitations, and confusion (Table 7.8). This can occur as an acute one-time episode or can represent an underlying panic disorder if recurrent. These symptoms are manifestations of physiologic phenomena caused by hypocapnic respiratory alkalosis, chest muscle strain from use of accessory muscles, tachycardia and arrhythmias, spasm of the diaphragm, and gastric distention caused by aerophagia (Fig. 7.3). Typically, the patient's chest pain complaint will include sharp, nonradiating pain over the left precordium. It is the easiest to diagnose when these symptoms arise without exertion. However, it is often difficult to differentiate hyperventilation from asthma as both diagnoses can include dyspnea, chest tightness, cough during exercise, and symptoms characteristic of bronchospasm.

TABLE 7.5 Historical Features of Chest Pain That Are Essential to Its Assessment

Duration of pain (how long present but also duration of each episode)
Acuteness of onset
Severity of pain (use scale of 1-10)
Associated symptoms
Precipitating and ameliorating factors
Quality of pain (pleuritic, sharp, dull)
Location of pain
Limitation of activities by pain
Radiation of pain
Time of day that pain occurs
Recent activity, injury, and stresses
Full psychosocial review, including behaviors
Medical history
Family medical history

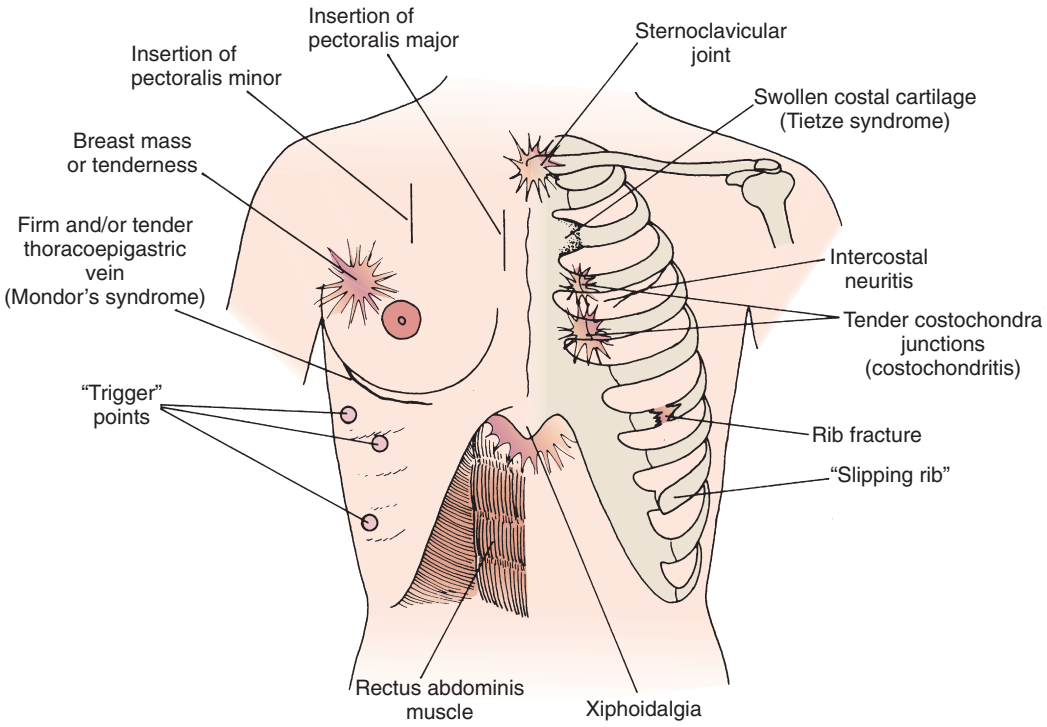


FIGURE 7.1 Palpable and/or visible abnormalities of the chest wall that may be found in different chest wall syndromes. In addition, various proximal abdominal causes of chest pain, such as disease of the gallbladder, liver, stomach, pancreas, or subdiaphragmatic space must be considered. (From Reilly BM. Chest pain. In: *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991.)

TABLE 7.6 Causes of Musculoskeletal Chest Pain

Signs and Symptoms	Diagnosis
Aching pain after new or intense exercise or repetitive coughing Can appear up to 2 days later Pain reproduced by range of motion testing or palpation	Muscular strain
Sharp, anterior pain over costochondral junctions Exacerbated by deep breathing 1st through 5th ribs are most common	Costochondritis
Sharp, localized pain at one costochondral junction Area is swollen, ± warm, erythematous bulbous or fusiform 1-4 cm mass 2nd or 3rd costochondral junction is most common Age predominance in adolescents and early twenties	Tietze syndrome
Pain and increased mobility of 8th, 9th, or 10th ribs (which are not attached to the sternum), resulting in impingement of superior intercostal nerve Intermittent sharp pain in chest or upper abdomen Brought on by exertion, especially sudden upward and anterior movement ("hooking maneuver"; see Fig. 7.2) Can have popping sensation at onset of pain Caused by trauma or dislocation of these ribs	Slipping rib syndrome (lower rib pain syndrome)
Brief (30 sec–3 min), nonradiating, sharp pain in the left parasternal area or cardiac apex ("Texidor twinge") Occurs at rest or with mild activity Exacerbated with inspiration and alleviated by shallow breathing or straightened position Related to poor posture	Precordial catch syndrome
Pain over both anterior chest and back Spasm in muscles innervated by nerve root causes pain No midline spine bony tenderness History of vertigo, headache, pain after prolonged recumbence or straining	Spinal cord or nerve root compression, typically lower cervical or upper thoracic spine
Chronic aching and stiffness Multiple points of tenderness on palpation of muscle with minimal pressure Associated with fatigue and sleep disturbance	Fibromyalgia

Hyperventilation can also occur concurrently with costochondritis or asthma, further complicating diagnosis.

Anxiety, depression, and somatiform disorders can cause episodic chest pain with or without hyperventilation. Within anxiety disorders, chest pain and other symptoms are typically temporally related to stressful situations. Anxiety-related psychogenic chest pain is 4 times as likely to occur in a patient with a family history of chest pain (often an adult with a history of cardiac ischemia), and the pain is often fleeting and vague in its description.

Gastrointestinal

Esophagitis (reflux, infectious, eosinophilic) and esophageal motility disorders (diffuse esophageal spasm, achalasia) can cause chest pain in both adults and children. Esophagitis is characterized by symptoms typical of "heartburn," a substernal burning sensation that is exacerbated by eating or position changes, specifically lying supine. However, heartburn is less common in children with esophagitis than adults. More commonly, children will have the presence of epigastric tenderness on exam. In fact, epigastric tenderness is one of the best indicators of a gastrointestinal etiology of pain in a child. Often, a trial of H_2-blocking agents or proton pump inhibitors helps diagnostically and therapeutically in the evaluation of esophagitis. Motility disorders of the esophagus cause chest pain that lasts from only a few seconds to several hours. The pain is nonexertional but can be exacerbated by bending forward. Achalasia classically causes dysphagia, nocturnal regurgitation, and chest pain. It can occur at any age and the chest pain is variably associated with the diagnosis (19-95% of the time). Eosinophilic esophagitis can cause chest pain secondary to esophageal inflammation, dysmotility, and reflux. Other notable gastrointestinal disorders can also cause chest pain including esophageal foreign body, gastric and duodenal ulcers, cholecystitis, pancreatitis, hepatitis, and infections of the subdiaphragmatic space. Esophageal rupture is a rare cause of chest pain; it has been described in patients with bulimia nervosa or after surgical repair of a tracheoesophageal fistula.

Other

Other causes of chest pain are diverse and variable. Patients with herpes zoster often experience chest pain *prior* to the typical vesicular rash over a unilateral dermatome. These patients can continue to have burning chest pain for weeks to months. Breast-related causes of chest pain can occur in both males and females. Females may complain of throbbing or burning chest pain caused by fibrocystic disease, fibroadenoma, swelling with menstruation, mastitis, or pregnancy. Gynecomastia in males can lead to unilateral or bilateral chest pain. Substance abuse of tobacco and/or cocaine in addition to other sympathomimetic substances can also cause chest pain. Other medications, such as tetracyclines, iron, or nonsteroidal antiinflammatory agents, can cause pill-induced esophagitis. Foreign bodies in the airways and/or esophagus can be unusual causes of chest discomfort; these diagnoses are typically evident due to other symptoms such as dysphagia, drooling, choking, stridor, or dyspnea. Neoplastic diseases such as mediastinal tumors or lymphomas can also manifest primarily as chest pain.

In addition, certain underlying disease processes have clinical courses that can manifest as chest pain. In patients with sickle cell anemia, chest pain can be secondary to acute chest syndrome and rib or pulmonary infarction. Long-term complications of Kawasaki disease include coronary artery stenosis and coronary artery aneurysm, both of which can present as chest pain. Patients with these cardiac complications of Kawasaki disease often have associated symptoms of fatigue, shortness of breath, and diaphoresis. Patients with Marfan syndrome are at high risk for dissecting aortic aneurysm, as are patients with Turner syndrome, type IV Ehlers-Danlos syndrome, and homocystinuria. A dissecting aortic aneurysm will often have the history of a sharp, sudden onset of chest pain with radiation to the back. Rheumatic fever is an acquired condition that can present with the major manifestations of carditis, which may include tachycardia out of proportion to degree of fever, mitral regurgitation or aortic regurgitation, and signs of pericarditis or heart failure. Chest pain also can be present before the onset of lower spinal symptoms in ankylosing spondylitis, a disease of the sacroiliac joints with variable involvement in the thoracic and cervical spine. A phenomenon that can occur with any cardiac procedure is postpericardiotomy syndrome, which includes fever, chest pain, and an audible friction rub approximately 1-2 weeks post-surgery.

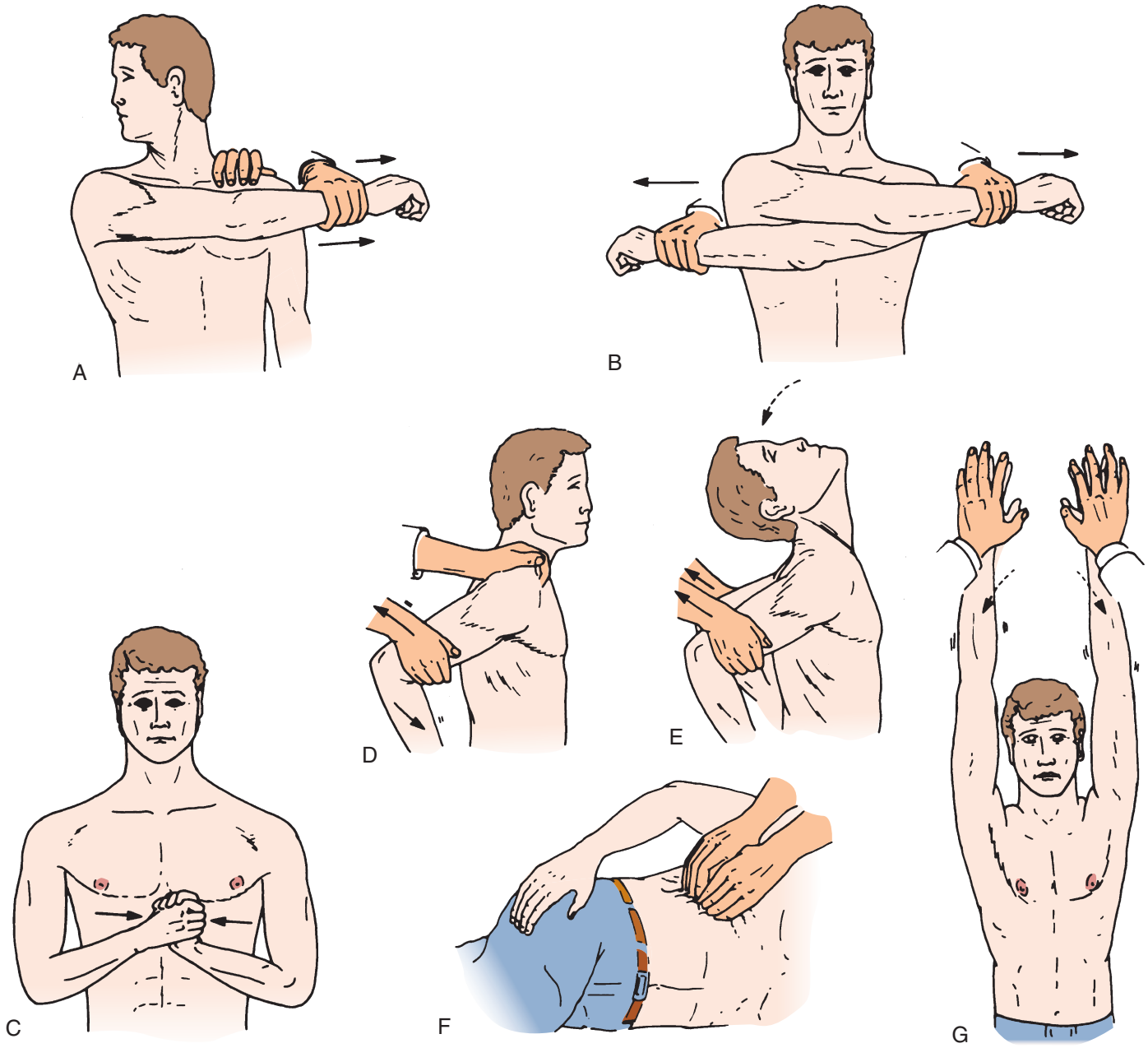


FIGURE 7.2 Chest wall maneuvers. *A, B,* The "scissors" maneuver. The patient's arm is adducted across the anterior chest, and the examiner pulls the patient's hand beyond the contralateral shoulder *(A)*. When both arms are tested together, traction is applied to both *(B)*; the patient turns the head to either side, and the arms form a "scissors." Pain originating in the scapula, thoracic spine, pectoral muscles, or ribs and intercostal structures is often precipitated by the scissors maneuver. *C*, The "hedge clipper" maneuver. The pectoralis major muscles are stressed by the patient's pressing the palms forcefully together with the elbows flexed anterior to the chest. The pectoral muscles are thus more clearly defined, and pain is often appreciated within the muscles or at their insertion in the upper parasternal area (see Fig. 7.1). *D*, The "racing dive" maneuver. The pectoralis minor muscles are stressed by forcefully resisting the patient's attempt to throw forward the shoulder and upper arm from an initial position behind (dorsal to) the chest wall. The attempted arm motion is that of flinging the arm and hand forward, as a swim racer would when beginning a racing dive. The examiner resists this forward arm and shoulder motion. *E*, The "crowing rooster" maneuver. The patient hyperextends the neck while the examiner lifts both of the patient's arms backward and superiorly. Pain originating in the cervical spine or anterior chest wall or both is often thus reproduced. *F*, The "hooking" maneuver. With the patient supine, the examiner stands at the patient's side, facing the patient's feet. The examiner then "hooks" his or her fingers around the lower costal margin of the patient's rib cage and pulls anteriorly (ventrally) and superiorly (cephalad). This maneuver may elicit pain when costochondritis or traumatic rib injuries involve the lower rib cage, when the upper rectus abdominis muscle is torn, or when a "slipping rib" is the problem. *G*, The "high ten" maneuver. The patient raises both hands overhead, elbows extended, and then presses forward with the hands against resistance offered by the examiner. Pain originating in the anterior rib cage, thoracic spine, or pectoral muscles may be elicited here. (*A*, *B*, and *G* from Reilly BM. Chest pain. In: *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991.)

TABLE 7.7 Respiratory Causes of Chest Pain

Signs and Symptoms	Diagnosis
Unilateral pain associated with severe dyspnea Can have radiation to ipsilateral shoulder Degree of pain does not correlate to extent of pneumothorax Risk factors include tall and thin body habitus, asthma, cystic fibrosis, inhalation of cocaine/marijuana	Pneumothorax, primary or secondary
Sudden pain, dyspnea, tachycardia ± hypoxia Pain is pressure-like or pleuritic Can have hemoptysis (rare) Risk factors include central venous catheter, trauma, malignancy, immobilization, oral contraceptive use, recent abortion or surgery, hypercoagulable state ECG with sinus tachycardia, right heart strain	Pulmonary embolism
Wheeze, ± shortness of breath, ± cough If exercise-induced, can cause chest pain in absence of wheeze	Asthma, reactive airway disease
Fever, cough ± sputum production Midsternal or parasternal pain that can be diffuse Pain exacerbated by deep breathing, coughing, straining	Pneumonia with pleurisy

TABLE 7.8 Type and Incidence of System Involvement During Hyperventilation in Children

System	Percentage of Cases
Cardiovascular	
Chest pain	86
Palpitation	74
Pallor	72
Cold extremities	42
Respiratory	
Deep, sighing respirations	100
Dyspnea, breathlessness	68
Neurologic	
Numbness	66
Dizziness	58
Tingling	34
Loss of consciousness	22
Musculoskeletal	
Aches and pains	38
Limping	20
Tetany	10
Gastrointestinal	
Dry mouth	52
Abdominal bloating and pain	40
Belching	26

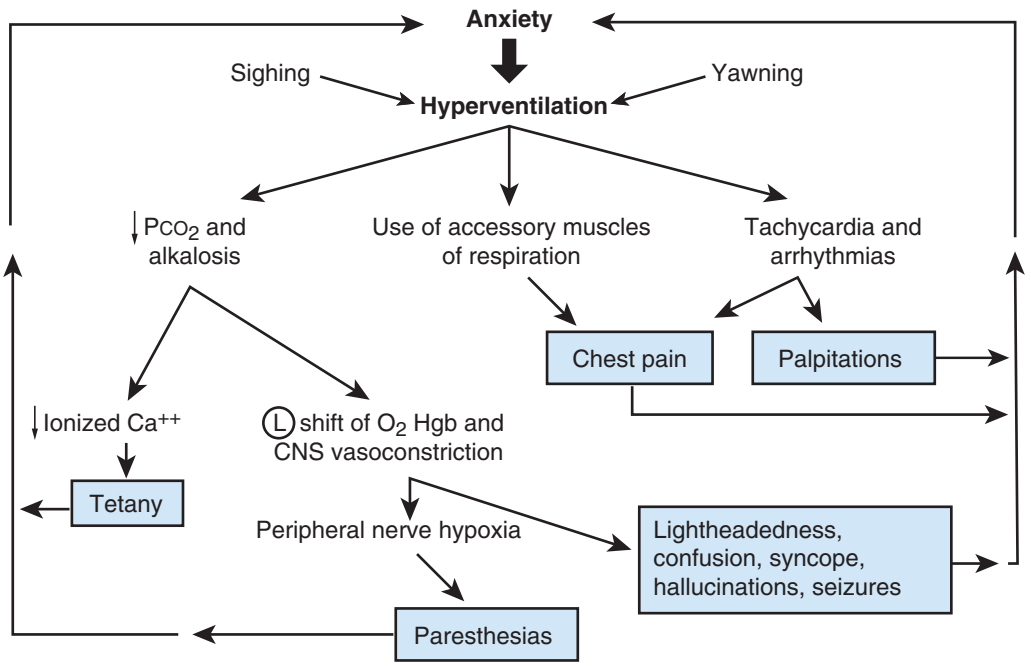


FIGURE 7.3 Pathophysiologic mechanisms of hyperventilation. CNS, central nervous system; Hgb, hemoglobin; P_{CO_2}, carbon dioxide pressure; O_2 Hgb, oxyhemoglobin dissociation curve. (From Herman SP, Stickler GB, Lucas AR. Hyperventilation syndrome in children and adolescents: Long-term follow-up. *Pediatrics*. 1981;67:183-187.)

Cardiac

Although cardiac disease is a rare cause of chest pain, there is potential for dangerous morbidity and mortality if left undiagnosed. One of the foremost concerns of families with children who have chest pain is whether or not their child is having a heart attack, although this is extremely uncommon. Etiologies of chest pain due to cardiac disease include arrhythmias, ischemia, structural abnormalities, and pericardial or myocardial disorders (Tables 7.9, 7.10, and 7.11). Arrhythmias are the most common, whereas patients with myocarditis or myocardial infarction are often the most acutely ill. Heart disease is more commonly found in adolescents than in younger children who complain of chest pain, and adolescents represent the largest group of patients between 1 and 21 years of age who die suddenly of cardiac causes.

Supraventricular and ventricular tachyarrhythmias can put adolescents at risk for sudden death. Supraventricular tachycardia (SVT), a narrow complex tachycardia, is the most common arrhythmia in children. Patients with pre-excitation, accessory pathways that cause an arrhythmia such as Wolff-Parkinson-White syndrome are at the highest risk for SVT. Ventricular tachycardia is a wide complex tachycardia that is often associated with mitral valve prolapse, viral myocarditis, or long QT syndrome. Chest pain caused by an arrhythmia is typically associated with palpitations and/or dyspnea but not necessarily with exercise. The pain is caused by an imbalance of myocardial oxygen supply and demand, subendocardial wall stress, and diminished diastolic coronary perfusion. The pain itself is typically intermittent as most arrhythmias are inherently sporadic in their onset and resolution.

Chest pain that increases during physical exertion or other stress and is relieved by rest, is often poorly localized to the substernal area, and can radiate to the left arm and/or jaw is secondary to a cardiac etiology. This pain is often referred to as anginal and can be secondary to ischemia, although ischemia is not common in children or adolescents. Other conditions that can cause anginal chest pain in children are listed in Table 7.9. Any sign of anginal chest pain should prompt investigation of obstructive, structural cardiac abnormalities and anomalies of the coronary arteries. Associated presyncope, syncope, and/or palpitations with these symptoms should significantly raise a provider's suspicion for underlying cardiac disease, and a complete physical examination with an electrocardiogram is essential for further diagnostic evaluation.

Structural abnormalities lead to chest pain through altered cardiac output, which can lead to syncope or death. Tables 7.10 and 7.12 review the signs, symptoms, and electrocardiogram findings of the structural cardiac abnormalities that can cause chest pain.

TABLE 7.9 Causes of Pediatric Anginal Chest Pain

Aortic stenosis
Hypertrophic cardiomyopathy
Coronary artery thrombosis
Anomalous coronary artery location or anatomy
Coronary vasospasm
Mitral valve prolapse

Modified from Place R, Vezzetti R. Pediatric and adolescent chest pain. *Pediatr Emerg Med Pract.* 2007;4:1-28.

TABLE 7.10 Structural Cardiac Abnormalities that Can Cause Chest Pain

Signs and Symptoms	ECG	Diagnosis
Chest pain with associated dyspnea is brought on by exercise Patient history of syncope, presyncope Seen in adolescence due to rapid growth of left ventricle in puberty Crescendo-decrescendo systolic ejection murmur from outflow tract gradient	Prominent septal Q wave, left ventricular hypertrophy, left axis deviation	Hypertrophic cardiomyopathy
Chest pain is brought on intermittently Patient history of tiring easily, exertional dyspnea +/– syncope, cool extremities Signs of right heart failure is a late finding High-pitched, early diastolic decrescendo murmur (pulmonary regurgitation)	Right ventricular hypertrophy	Pulmonary Hypertension (often secondary to pulmonary stenosis or Eisenmenger complex)
Chest pain is brought on with exercise Patient history of syncope at late stages Harsh crescendo-decrescendo systolic murmur radiating to carotid arteries +/– thrill	Left ventricular strain	Aortic stenosis
Chest pain that is vague, non-exertional, but most children are asymptomatic Patient history of postural hypotension, palpitations, or syncope Late to mid-systolic click preceding a systolic murmur	Normal, T-wave abnormalities or prominent U waves	Mitral valve prolapse
Chest pain that is acute, present on anterior or posterior chest that can migrate to arms, abdomen and legs Patient history may include Marfan syndrome, Ehrlos-Danlos syndrome, previously healthy weight-lifting athletes High-pitched early diastolic decrescendo murmur (aortic regurgitation)	Normal, can have low QRS voltages	Aortic dissection
Chest pain may be present but unclear due to patient age (for example, symptoms occur at 2-3 mo of age) Patient history of poor feeding, diaphoresis, tachycardia, irritability Signs of heart failure can be present	Anterolateral myocardial infarction pattern with Q waves and ST changes	Anomalous left coronary artery from pulmonary artery

TABLE 7.11 Etiology of Pericarditis and Pericardial Effusion

Idiopathic (Presumed Viral)

Infectious Agents

Bacterial: Group A streptococci, *Staphylococcus aureus*, pneumococci, meningococci,* *Haemophilus influenzae*,* *Salmonella* species, *Mycoplasma pneumoniae, Borrelia burgdorferi, Mycobacterium tuberculosis*, rickettsiae, tularemia

Viral†: Coxsackievirus (group A, B), echovirus, mumps, influenza, Epstein-Barr virus, cytomegalovirus, herpes simplex, herpes zoster, hepatitis B virus

Fungal: *Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis, Cryptococcus neoformans, Candida* species, *Aspergillus* species

Parasitic: *Toxoplasma gondii, Entamoeba histolytica*, schistosomes

Collagen Vascular–Inflammatory and Granulomatous Diseases

Rheumatic fever
Systemic lupus erythematosus (idiopathic and drug induced)
Juvenile idiopathic arthritis (JIA)
Kawasaki disease
Scleroderma
Mixed connective tissue disease
Reactive arthritis
Inflammatory bowel disease
Granulomatosis with polyangiitis
Dermatomyositis
Behçet syndrome
Sarcoidosis
Vasculitis
Familial Mediterranean fever
Serum sickness
Stevens-Johnson syndrome

Traumatic

Cardiac contusion (blunt trauma)
Penetrating trauma
Postpericardiotomy syndrome
Radiation

Contiguous Spread

Pleural disease
Pneumonia
Aortic aneurysm (dissecting)

Metabolic

Hypothyroidism
Uremia
Gaucher disease
Fabry disease
Chylopericardium

Neoplastic

Primary
Contiguous (lymphoma)
Metastatic
Infiltrative (leukemia)

Others

Drug reaction
Pancreatitis
Post–myocardial infarction
Thalassemia
Central venous catheter perforation
Heart failure
Hemorrhage (coagulopathy)
Chylous
Biliary-pericardial fistula

*Infectious or immune complex.
†Common (viral pericarditis or myopericarditis is probably the most common cause of acute pericarditis in a previously normal host).

Acute pericarditis causes substernal chest pain that is sharp, stabbing and aggravated by deep inspiration, coughing, or straining. Typical pericarditis pain is improved by being in the sitting position, and patients will avoid lying supine. There are many causes of pericarditis and/or pericardial effusion (see Table 7.11). Idiopathic or viral pericarditis has a preceding or accompanying flulike illness with myalgias, arthralgias, and fever. Evaluation for acute pericarditis includes physical examination during which a 3 component pericardial rub (atrial systole, ventricular systole, diastolic filling) may be present on auscultation. Of note, this rub may disappear with the development of pericardial effusion. Electrocardiogram findings of acute pericarditis go through a 4-stage evolution. Stage 1, the most classic stage for diagnosis (Fig. 7.4), may reveal diffuse PR depressions with upright P waves followed by J-point ST elevations. The ST elevations noted in pericarditis are referred to as J-point elevations due to their upsloping "J" shape. Subsequently, stage 2 shows descent of the J-point elevations followed by stage 3 with T wave inversions. Stage 4 then shows restitution back to the child's baseline ECG. These J-point ST elevations are markedly different from ST elevations caused by cardiac ischemia, which are more dome-shaped (see Fig. 7.4). In pericarditis, in order to clarify the amount of pericardial fluid present and whether or not there is ventricular dysfunction, an echocardiogram is performed.

Acute myocarditis often is caused by or follows viral infections. Symptoms of acute myocarditis include lethargy, pallor, low-grade fever, anorexia, chest or abdominal pain, and signs of congestive heart failure. ECG abnormalities tend to be diffuse and nonspecific, and complications of myocarditis include arrhythmias and conduction blocks. Patients with myocarditis have the propensity to become severely ill and often require inpatient or even intensive care hospitalization.

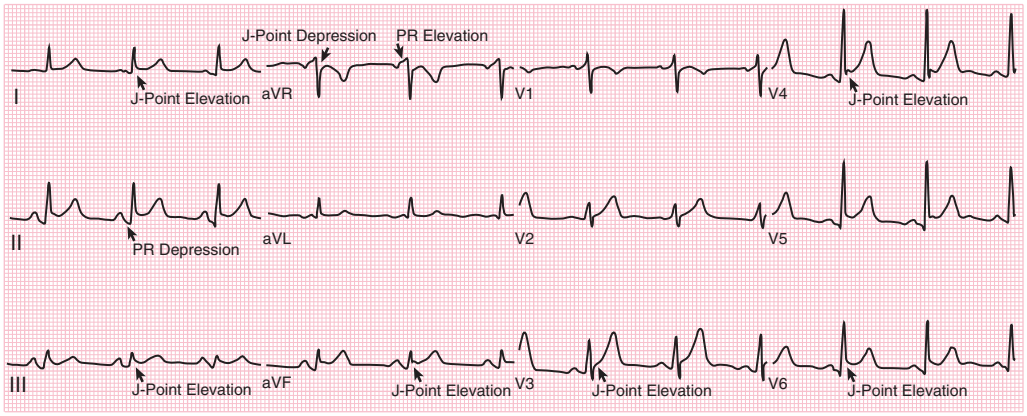
◆ Physical Examination

A physical examination can often confirm a medical provider's suspicion of a particular diagnosis or diagnoses, especially when it comes to the complaint of chest pain. The cardiovascular assessment of children requires patience, thoroughness, and flexibility to adapt to children who may not desire you to examine them. All physical examinations for the complaint of chest pain should start with observing the child for general states of distress, pain with breathing, and interaction with parents. Vital signs can indicate the presence of pain by revealing signs of tachycardia and tachypnea, and can provide information regarding potential serious medical illness, including fever, hypoxia, or hypotension. Blood pressures should be obtained in upper and lower extremities, monitoring closely for a gradient between extremities. All

TABLE 7.12 Systolic Murmurs Important in the Diagnosis of Chest Pain

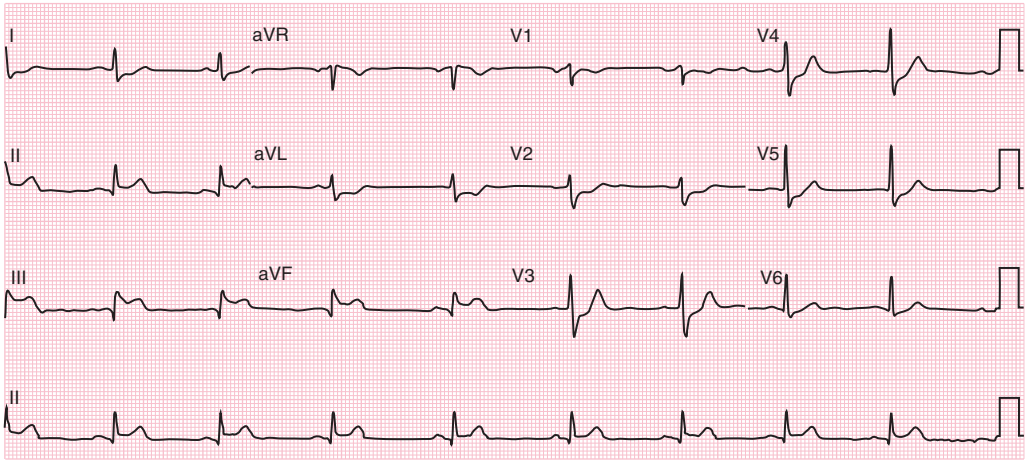
Innocent ejection murmur	Loudest left sternal border at base, 1-3 intensity, peaks early in systole; no click, gallop, heave, or diastolic murmur	Diminishes with standing and Valsalva maneuver
Valvular aortic stenosis	*Mild:* Similar to innocent murmur but ejection click is possible *Severe:* Loudest over right second intercostal space, peaks late in systole; delayed carotid upstroke, thrill present; left ventricular heave; audible S_4 gallop; aortic insufficiency murmur may also be present	
Hypertrophic cardiomyopathy	Loudest over left second intercostal space, peaks in midsystole; carotid upstroke brisk or bisferiens; no diastolic murmur	Increases with standing or Valsalva maneuver; decreases on squatting
Pulmonic stenosis	*Mild:* Similar to innocent murmur but ejection click is possible *Severe:* Loudest over left second intercostal space; loud, widely split S_2; thrill present; right ventricular heave; ejection click at left second intercostal space	
Mitral valve prolapse	Loudest at left sternal border and apex; mid- to late-systolic murmur; click precedes murmur	Increases with standing after squatting and during expiration

Pericarditis



A

Infarction



B

FIGURE 7.4 A, Acute pericarditis. Note diffuse J-point ST elevations and near ubiquitous PR segment depressions. *B*, Acute ST elevation myocardial infarction: Note dome-shaped, sometimes referred to as "tombstone shaped," ST elevations in leads II, III, and aVF with reciprocal ST depressions in leads I, aVL, and V_1-V_5 consistent with an acute inferior wall myocardial infarction. (*A* from Spodick DH. Acute pericarditis: current concepts and practice. *JAMA*. 2003;289:1150-153; *B* from Hwang C, Levis JT. ECG diagnosis: ST-elevation myocardial infarction. *Perm J*. 2014;18:e133.)

vital signs should be evaluated in the context of reference ranges for a child's age and height.

A helpful physical exam finding is elicitation of chest wall tenderness upon palpation of the thorax, which is pathognomonic for chest wall pain (see Fig. 7.1). Therefore, medical providers are encouraged to palpate over the chest including the ribs, intercostal areas, sternum, xiphoid, manubrium, axilla, clavicles, epigastric area, spinous processes, and paraspinal areas. Chest wall maneuvers can also be performed in order to better understand what muscle group is causing the pain (see Fig. 7.2).

Palpation of the chest wall should be performed to identify the point of maximal intensity and to determine if there is a cardiac heave or thrill. Palpation of the abdomen should be done for tenderness and organomegaly. Both distal and proximal pulses should be felt for equality and caliber. After palpation, percussion should be done. Dullness to percussion can suggest consolidation, effusion, or atelectasis, whereas hyperresonance to percussion can suggest pneumothorax or asthma.

Every medical provider should allow ample time for auscultation of the lungs and heart. Medical providers should follow a constant, systemic procedure for listening to heart sounds. Heart sounds include S_1-S_4. S_1 is caused by mitral and tricuspid valve closure, and S_2 is caused by aortic and pulmonary valve closure. The sounds caused by these valves opening are not heard in healthy individuals. Because the left-sided valves close before the right-sided valves, the S_2 heart sound can be physiologically split into the aortic valve and then the pulmonic valve closing during inspiration. S_3 and S_4 are harder to understand and hear. S_3 is a result of the deceleration of blood at the end of early rapid filling of the ventricles. An S_3 is normal in children with hyperdynamic circulations (such as athletes) and thin chest walls (of note, in adults an S_3 is always abnormal). An S_4 is a result of deceleration of blood at the end of late rapid filling of the ventricles. Audible S_4 sounds are always abnormal, no matter what age the patient is. Therefore, a gallop rhythm (3 heart sounds) can be normal or abnormal.

Subsequently, medical providers must listen to what occurs between S_1 and S_2. A mid-systolic click is often an indicator of the mitral valve prolapsing into the left atrium. It can be a single click or series of clicks. Then, the medical provider should listen for heart murmurs. Heart murmurs can provide additional clinical evidence for potential cardiac causes of chest pain. Listening for heart murmurs should be performed with the patient supine, sitting, standing, squatting, and standing after squatting. Many murmurs increase in intensity with decreased ventricular filling or decreased afterload (standing, release of Valsalva, squatting); however, hypertrophic cardiomyopathy's murmur does the opposite. It increases in intensity with the Valsalva maneuver and decreases with squatting. Of note, all diastolic murmurs or murmurs grade 3/6 or higher should be further evaluated with an echocardiogram. The presence of a gallop rhythm or a friction rub can make an immediate cardiac diagnosis. A pericardial friction rub is a scratchy, high-pitched, to-and-fro sound caused by the inflamed pericardial surfaces rubbing together during cardiac motion and that is loudest when the patient is upright and leaning forward.

Electrocardiogram

An electrocardiogram may be helpful if there is a suggestive history and/or physical examination for potential cardiac disease. In the absence of a suggestive history and physical, the yield of an electrocardiogram is considered low as it may be normal in patients with structural heart disease or arrhythmias. Regardless, because of its relatively low cost and noninvasive nature, electrocardiograms should be performed in the evaluation of chest pain if there are any concerns discovered in the history assessment or physical examination. After a medical provider obtains an ECG, there are a few important principles to keep in mind. ECG findings are age-specific (for example, infants have a right ventricular-dominant ECGs and T waves are usually inverted), arrhythmias are often not found on routine ECGs, and provider should be careful in using the "machine" read in regard to myocardial infarction, pericarditis, or long QT syndrome (the computer is prone to overdiagnosis).

◆ Further Diagnostic Testing

One of the biggest challenges for primary care providers is when to refer to a cardiology subspecialist. Cardiac consultation is reasonable for any child with red-flag symptoms, specifically chest pain associated with exertion, syncope with exertion, chest pain with concurrent palpitations, abnormal findings on cardiac examination or ECG, a history of cardiac surgery/intervention, or a high-risk family history. If a patient has chest pain with concurrent fever or signs of hemodynamic instability, the child should be referred to the emergency department for further evaluation for myocarditis.

When the previous evaluation results in a positive screening result, echocardiogram is the diagnostic test of choice for further assessment. However, of note, referral to a cardiologist is generally more cost-effective than obtaining an echocardiogram without a cardiologist. An echocardiogram should be obtained urgently if there are signs of cardiac tamponade (hypotension, tachycardia, pulsus paradoxus) or poor cardiac output. It is also useful if mitral valve prolapse, valvular heart disease, hypertrophic cardiomyopathy, septal defects, endocarditis, or pericarditis is suspected.

Other diagnostic modalities can include chest radiographs, exercise stress tests, and Holter monitors. A chest radiograph is helpful if there is a clinical finding that needs further investigation, such as a history of trauma or fever. Other than pulmonary disease, a chest radiograph can note cardiomegaly or pneumothoraces. Regardless, a chest radiograph in the absence of febrile illness or trauma has not been shown to be largely beneficial as the likelihood of finding bone or intrathoracic abnormalities in the absence of these features is low. Exercise stress tests should be reserved for anginal cardiac pain in the setting of other normal testing. Due to the difficulty of determining anginal chest pain in the pediatric population, there has been an increased frequency of exercise stress tests ordered. However, medical providers should remember that in the setting of chest pain with a normal echocardiogram evaluation, an exercise stress test has low yield. A 24-hour Holter monitor or a 30-day loop recorder only should be utilized if an arrhythmia is suspected but the resting electrocardiogram is normal. Testing for other underlying abnormalities as the cause of noncardiac chest pain can include pulmonary function testing and/or methacholine challenge testing as well as esophageal manometry testing.

Laboratory testing for biochemical markers of cardiac damage is used extensively in the adult population, primarily to diagnose and assist in management of acute myocardial infarction. In pediatrics, they are not often utilized. Biochemical markers include the MB isoenzyme of creatine kinase (CK-MB) and troponin T. In adults, the MB isoenzyme of creatine kinase often is only measured if the troponin T is found to be elevated. Troponin T is a protein present in high concentrations in the myocardium but not in other tissues and is released rapidly after myocardial injury in direct proportion to the extent of injury. Troponin T has a high specificity and a low sensitivity for myocardial injury; therefore false positives often occur, especially in pediatrics where the prevalence of myocardial ischemia and injury is extremely low. In general, nonischemic causes for elevated troponin have not been well studied in children. Multiple studies have noted that troponin T shows elevation in postoperative cardiac surgery patients and in diagnoses of myocarditis. Cut off values have not been well

defined; however, low-level troponin T elevations can signify serious disease in children, as opposed to adults where these small elevations would be considered insignificant. Selective use of the troponin assay may be useful in conjunction with the presence of ECG abnormalities. Additional studies in pediatrics are continually ongoing regarding the potential usefulness of cardiac biochemical markers in diseases with muscle breakdown such as Duchenne muscular dystrophy or in determining subtle cardiac dysfunction after convulsive seizures.

◆ Treatment

Medical providers should refer patients to cardiology specialists if cardiac etiologies are still a concern after thorough history, physical, and necessary ancillary studies such as electrocardiograms. Unfortunately, a precise diagnosis is not made in a high percentage of cases. It is up to the medical provider to carefully deal with uncertainty, not over-test or over-refer, and provide ongoing care that minimizes anxiety. Most importantly, if a noncardiac etiology is the highest consideration, medical providers should thoughtfully provide extensive reassurance that includes a symptomatic treatment approach and a plan for appropriate follow-up. It is of the utmost importance that providers provide this reassurance and follow-up to avoid a chronic course of chest pain with potential disability. Of note, families should be specifically asked about school absenteeism so that recommendations for returning to school can be given. Treatment plans should be tailored to both the most likely diagnosis and the patient's individual concerns. Musculoskeletal chest pain can be treated with heat, anti-inflammatory medications, or specific exercises. Respiratory causes of chest pain require aggressive therapies for the underlying cause, most frequently reactive airway disease. Psychogenic causes of chest pain are perhaps the hardest to treat, often requiring consultation with behavioral pediatricians, counselors, and/or psychologists. Primary care providers can start this treatment by having their patients keep pain diaries to help facilitate follow-up discussions. Gastrointestinal causes of chest pain can be diagnosed and treated with a trial of H_2-blocking agents or proton pump inhibitors in addition to reflux precautionary behaviors such as avoiding foods that worsen the symptoms, not eating close to bedtime, and elevating the head of the bed at night.

Overall, because etiologies of chest pain are so often multifactorial and require ongoing evaluation and treatment, the primary care physician must stay actively involved in the patient's care over time.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Alehan F, Erol I, Cemil T, et al. Elevated CK-MB mass and plasma brain-type natriuretic peptide concentrations following convulsive seizures in children and adolescents: Possible evidence of subtle cardiac dysfunction. *Epilepsia*. 2009;50:755-760.

Angoff GH, Kane DA, Giddins N, et al. Regional implementation of a pediatric cardiology chest pain guideline using SCAMPs methodology. *Pediatrics*. 2013;132:e1-e8.

Archer TP, Qualman SJ, Mazzaferri EL. Chest pain and dyspnea in a 17-year-old smoker. *Hosp Pract (Off Ed)*. 1998;33:97-98.

Brown JL, Hirsh DA, Mahle WT. Use of troponin as a screen for chest pain in the pediatric emergency department. *Pediatr Cardiol*. 2012;33:337-342.

Cartaya Blanco C, Bandler Parekh J. In brief: Pericarditis. *Pediatr Rev*. 2010;31:83-84.

Collins SA, Griksaitis MJ, Legg JP. 15-minute consultation: A structured approach to the assessment of chest pain in a child. *Arch Dis Child Educ Pract Ed*. 2014;99:122-126.

Danduran MJ, Earing MG, Sheridan DC, et al. Chest pain: characteristics of children/adolescents. *Pediatr Cardiol*. 2008;29:775-781.

Driscoll DJ, Glicklich LB, Gallen WJ. Chest pain in children: a prospective study. *Pediatrics*. 1976;57:648-651.

Drossner DM, Hirsh DA, Sturm JJ, et al. Cardiac disease in pediatric patients presenting to a pediatric ED with chest pain. *Am J Emerg Med*. 2011;29:632-638.

Friedm Schonlein an KG, Alexander ME. Chest pain and syncope in children: a practical approach to the diagnosis of cardiac disease. *J Pediatr*. 2013;163:896-901.

Geggel RL. Conditions leading to pediatric cardiology consultations in a tertiary academic hospital. *Pediatrics*. 2004;114:409-417.

Hallagan LF, Dawson PA, Eljaiek LF. Pediatric chest pain: Case report of a malignant cause. *Am J Emerg Med*. 1992;10:43-45.

Haworth SG. The management of pulmonary hypertension in children. *Arch Dis Child*. 2008;93:620-625.

Hwang C, Levis JT. ECG diagnosis: ST-elevation myocardial infarction. *Perm J*. 2014;18:e133.

Kane DA, Fulton DR, Saleeb S, et al. Needles in hay: chest pain as the presenting symptom in children with serious underlying cardiac pathology. *Congenit Heart Dis*. 2010;5:366-373.

Kocis KC. Chest pain in pediatrics. *Pediatr Clin North Am*. 1999;46:189-203.

Kronick-Mest C. Postpericardiotomy syndrome: etiology, manifestations and interventions. *Heart Lung*. 1989;18:192-198.

Kyle WB, Macicek SL, Lindle KA, et al. Limited utility of exercise stress tests in the evaluation of children with chest pain. *Congenit Heart Dis*. 2012;7:455-459.

Lam JC, Tobias SC. Follow-up survey of children and adolescents with chest pain. *South Med J*. 2001;94:921-924.

Leung A, Robson W, Cho H. Chest pain in children. *Can Fam Physician*. 1996;4:23-33.

Lipshultz SE, Nader Rifai SE, Lipsitz SR, et al. Predictive value of cardiac troponin T in pediatric patients at risk for myocardial injury. *Circulation*. 1997;96:2641-2648.

Loiselle KA, Lee JL, Gilleland J, et al. Factors associated with healthcare utilization among children with noncardiac chest pain and innocent heart murmurs. *J Pediatr Psychol*. 2012;37:817-825.

Owens TR. Chest pain in the adolescent. *Adolesc Med*. 2001;12:95-104.

Place R, Vezzetti R. Pediatric and adolescent chest pain. *Pediatr Emerg Med Pract*. 2007;4:1-26.

Pomeranz AJ, Busey SL, Sabnis S, et al. Chest Pain. *Pediatric Decision-Making Strategies*. 16th ed. To Accompany Nelson Textbook of Pediatrics. 2002:52-57.

Reddy SR, Singh HR. Chest pain in children and adolescents. *Pediatr Rev*. 2010;31:e1-e10.

Roodpeyma S, Sadeghian N. Acute pericarditis in childhood. A 10-year experience. *Pediatr Cardiol*. 2000;21:363-367.

Rowe BH, Dulberg CS, Peterson RG, et al. Characteristics of children presenting with chest pain to a pediatric emergency department. *Can Med Assoc J*. 1990;143:388-394.

Sabri MR, Ghavanini AA, Haghighat M, et al. Chest pain in children and adolescents: epigastric tenderness as a guide to reduce unnecessary work-up. *Pediatr Cardiol*. 2003;24:3-5.

Saleeb SF, Li WY V, Warren SZ, et al. Effectiveness of screening for life-threatening chest pain in children. *Pediatrics*. 2011;124:e1062-e1068.

Selbst SM, Ruddy RM, Clark BJ, et al. Pediatric chest pain: a prospective study. *Pediatrics*. 1988;82:319-323.

Snyder CS, Fenier AL, Friedman RA, et al. The emergency department versus the computer: which is the better electrocardiographer? *Pediatr Cardiol*. 2003;24:364-368.

Soongswang J, Durongpisitkul K, Nana A, et al. Cardiac troponin T: a marker in the diagnosis of acute myocarditis in children. *Pediatr Cardiol*. 2005;26:45-49.

Spodick DH. Acute pericarditis: current concepts and practice. *JAMA*. 2003;289:1150-1153.

Swenson JM, Fischer DR, Miller AS, et al. Are chest radiographs and electrocardiograms still valuable in evaluating new pediatric patients with heart murmurs or chest pain? *Pediatrics*. 1997;98:1-3.

Thull-Freedman J. Evaluation of chest pain in the pediatric patient. *Med Clin North Am*. 2010;94:327-347.

Wiens L, Sabath R, Ewing L, et al. Chest pain in otherwise healthy children and adolescents is frequently caused by exercise-induced asthma. *Pediatrics*. 1992;90:350-353.

8

Murmurs

Andrew N. Pelech

Most heart murmurs are normal or innocent, and must be distinguished from pathologic murmurs of congenital or acquired cardiac diseases. Whereas less than 1% of the population has structural congenital cardiac disease, as many as 85% of the population has a heart murmur sometime during childhood. The causes of cardiac murmurs are often influenced by the age of the patient at presentation (Table 8.1). The causes of congenital heart disease are varied and include genetic disorders, syndrome complexes (Table 8.2), metabolic disorders, and teratogenesis. The causes of acquired heart diseases in children include rheumatic fever, endocarditis, and cardiac injury caused by systemic illnesses.

THORAX

Knowing the location of the heart chambers and valves within the thorax helps in the interpretation of heart sounds (Fig. 8.1). The left atrium is located posteriorly, close to the spine. The right atrium and right ventricle are located anteriorly, immediately beneath the sternum. The outflow tract of the right ventricle, which contains the pulmonary valve, rises to the left of the sternum. The parts of the left side of the heart that are close to the chest wall include the left ventricular apex and the ascending aorta as it passes up to the right of the sternum. In other areas, lung tissue lies between the heart and chest wall. This may diminish or distort the intensity of heart sounds.

ORIGINS OF THE HEART SOUNDS

Normal heart sounds originate from vibrations of heart valves when they close and from heart chambers when they fill or contract rapidly. The amount of pressure that forces the valve closure influences the intensity of a heart sound. Other mechanical factors such as valve stiffness, thickness, and excursion have less effect on sound intensity.

Cardiac murmurs are the direct result of blood-flow turbulence. The amount of turbulence and consequently the intensity of a cardiac murmur is directly proportional to both the pressure difference or gradient across a narrowing or defect and the blood flow or volume moving across the site.

As sound radiates from its source, sound intensity diminishes with the square of the distance. Consequently, heart sounds should be loudest near the point of origin. However, other factors influence this relationship. Sound passage through the body is affected by the transmission characteristics of the tissues. Fat has a more pronounced dampening effect on higher frequencies than does more dense tissue such as bone. If the difference in tissue density is significant—for example, between the heart and lungs—more sound energy is lost. Only the loudest sounds may be heard when lung tissue is positioned between the heart and chest wall.

In contrast to intensity, the frequency of a cardiac murmur is proportional to pressure difference or gradient across a narrowing alone.

CARDIAC CYCLE

Cardiac sounds and murmurs that arise from turbulence or vibrations within the heart and vascular system may be innocent or pathologic. It is important to understand the timing of events in the cardiac cycle as a prerequisite to understanding heart murmurs. The relationship between the normal heart cycle and that of the heart sounds is noted in Fig. 8.2.

The cardiac cycle begins with **atrial systole**, the sequential activation and contraction of the 2 thin-walled upper chambers. Atrial systole is followed by the delayed contraction of the more powerful lower chambers, termed **ventricular systole**. Ventricular systole has 3 phases:

1. Isovolumic contraction: the short period of early contraction when the pressure builds within the ventricle but has yet to rise sufficiently to permit ejection
2. Ventricular ejection: when the ventricles eject blood to the body (via the aorta) and to the lungs (via the pulmonary artery)
3. Isovolumic relaxation: the period of ventricular relaxation when ejection ceases and pressure falls within the ventricles

During ventricular contraction, the atria relax (**atrial diastole**) and receive venous return from both the body and the lungs. Then, in **ventricular diastole**, the lower chambers relax, allowing initial passive filling of the thick-walled ventricles and emptying of the atria. Later, during the terminal period of ventricular relaxation, the atria contract. This atrial systole augments ventricular filling just before the onset of the next ventricular contraction.

The sequence of contractions generates pressure and blood flow through the heart. The relationship of blood volume, pressure, and flow determines opening and closing of heart valves and generates characteristic heart sounds and murmurs.

CHANGES IN THE CIRCULATION AT BIRTH

An understanding of the fetal, transitional, and neonatal adaptations of the circulation is important in the evaluation of the pediatric cardiovascular system, because many organic heart diseases are evident in association with the circulatory changes occurring at birth. The majority of significant structural congenital heart disease is recognized in the first few weeks of life. The age at recognition or referral often dictates the nature of the cardiac anomaly and the urgency with which assessment is necessary.

In the fetus (Fig. 8.3), oxygen is derived from the placenta and returns via the umbilical vein and through the ductus venosus to enter the inferior vena cava and right atrium. Preferentially, flow is directed across the foramen ovale to enter the left atrium and, subsequently, the left ventricle. Deoxygenated blood returning from the superior vena cava and upper body segment is preferentially directed by the flap of the eustachian valve to enter the right ventricle and then, via the ductus arteriosus, to enter the descending aorta to return via the umbilical

TABLE 8.1 Causes of Heart Murmurs

Neonate*	Infant	Older Child
Transient patency of the ductus arteriosus	Congenital heart disease (L→R shunt or R→L shunt)†	Congenital valvular obstruction
Peripheral pulmonic stenosis	Ejection murmurs (normal)	Ejection murmurs (normal)
Cyanotic congenital heart disease	Anemia	Repaired congenital heart disease
Congenital valvular obstruction	Arteriovenous malformation	Anemia
Arteriovenous malformation (CNS, hepatic, pulmonary)	Infective endocarditis	Mitral valve prolapse
Anemia	Kawasaki disease	Venous hum
Asphyxia-related myocardial ischemia (transient TI or MI)	Hunter syndrome	Bacterial endocarditis
	Hurler syndrome	Rheumatic fever
	Fabry syndrome	Marfan syndrome
		Prosthetic valves
		Obstructive (hypertrophic) cardiomyopathy (subaortic stenosis)
		Carotid or abdominal bruit
		Tumor (atrial myxoma)
		Thyrotoxicosis
		Systemic lupus erythematosus
		Pericardial friction rub

*Common causes of congenital heart disease in low-birth-weight infants include PDA, VSD, tetralogy of Fallot, coarctation of the aorta–interrupted aortic arch, hypoplastic left heart syndrome, heterotaxy, and dextrotransposition of the great arteries, in that order. Common causes of congenital heart disease in term infants include VSD, dextrotransposition of the great arteries, tetralogy of Fallot, coarctation of the aorta, pulmonary stenosis, hypoplastic left heart syndrome, and PDA; other causes represent a smaller percentage.
†The relative percentages of congenital heart lesions are VSD (25-30%); ASD (6-8%); PDA (6-8%); coarctation of aorta (5-7%); tetralogy of Fallot (5-7%); pulmonary valve stenosis (5-7%); aortic valve stenosis (5-7%); dextrotransposition of great arteries (3-5%); and hypoplastic left ventricle, truncus arteriosus, total anomalous venous return, tricuspid atresia, single ventricle, and double-outlet right ventricle representing 1-3% each. Other and more complex lesions (forms of heterotaxy) together represent 5-10% of all lesions.
ASD, atrial septal defect; CNS, central nervous system; L, left; MI, mitral insufficiency; PDA, patent ductus arteriosus; R, right; TI, tricuspid insufficiency; VSD, ventricular septal defect.

arteries to the placenta. The pressures within both ventricles are essentially equal, inasmuch as both chambers pump to the systemic circulation. However, in utero, the right ventricle does the majority of the work, pumping 66% of the combined cardiac output. At transition (see Fig. 8.3), with the first breath, pulmonary arterial resistance begins to fall as the lungs begin the process of respiration. Pulmonary venous return to the left atrium closes the flap of the foramen ovale. Through mechanical and chemical mechanisms, the ductus arteriosus begins to close. In the normal full-term infant, this is accomplished by 10-15 hours after birth. Intermittent right-to-left atrial level shunting through the foramen ovale may occur, particularly if pulmonary vascular resistance fails to drop. In addition, structural cardiac abnormalities necessitating patency of the ductus arteriosus for maintenance of either pulmonary blood flow (pulmonary atresia) or systemic blood flow (hypoplastic left heart syndrome) most often manifest within the first few days of life. Thus, the time when a pediatric patient presents for evaluation is influenced by the spectrum of heart diseases. Ductus-dependent abnormalities, such as pulmonary atresia, transposition of the great arteries, coarctation of the aorta, hypoplastic left heart syndrome, or significant outflow obstructions (e.g., critical aortic valve stenosis) manifest in the first few days after birth. In the absence of an associated anomaly, hemodynamically significant ventricular septal defects (VSDs) seldom manifest before 2-4 weeks after birth. Atrial septal defects (ASDs) are seldom symptomatic in infancy.

NORMAL INTRACARDIAC PRESSURES

In the child after birth and successful transition, resistance to flow in the pulmonary circuit is much lower than in the systemic circuit. Therefore, the pressures in the right-sided chambers are lower than those in the left-sided chambers. The higher values (see Fig. 8.3) reflect pressures during ventricular systole in a normal heart. Pressure in the great vessels during systole is identical to that in the corresponding ventricles. This changes if there is outflow obstruction. In ventricular diastole, the semilunar valves (aortic and pulmonary) close. Resistance to blood flow in the vascular bed determines the diastolic pressures in the great arteries. The thin-walled atria generate much lower pressures than do the ventricles, both during the phase of passive atrial filling (**v wave**) and during atrial contraction (**a wave**). Only the mean (m) or average atrial pressure is shown in Fig. 8.3. During ventricular relaxation, the diastolic pressures are lower than those in the atria, enabling filling. Knowledge of the cardiac cycle is important in understanding the more complicated hemodynamics and flow patterns of specific cardiac abnormalities.

PEDIATRIC CARDIOVASCULAR EVALUATION

◆ History

Historical assessment of the pediatric patient referred for evaluation of a cardiac murmur should include questions about the family history, the pregnancy, and perinatal course, in addition to questions about symptoms of cardiovascular disease. An index of exercise or play capacity should be sought, as should an assessment of growth and development. The presence of congenital abnormalities of other major organ systems is associated with structural cardiac problems in as many as 25% of patients.

Structural heart disease is frequently seen in association with recognizable syndromes (see Table 8.2). Children with clearly definable chromosomal disorders known to have a significant incidence of structural cardiac abnormalities, such as Down or Turner syndromes, are usually

(See *Nelson Textbook of Pediatrics,* p. 2799.)

TABLE 8.2 Syndromes or Syndrome Complexes Associated with Congenital Heart Disease

Syndrome	Dominant Cardiac Defect
Alagille (arteriohepatic dysplasia)	Peripheral pulmonary stenosis
Asplenia	Complex cyanotic heart disease, anomalous veins, pulmonary atresia
Carpenter	Patent ductus arteriosus, ventricular septal defect
Cat eye	Total anomalous pulmonary venous return
Char	Patent ductus arteriosus
CHARGE	Ventricular, atrioventricular, and atrial septal defects
de Lange	Tetralogy of Fallot, ventricular septal defect
Down (Trisomy 21)	Artioventricular septal defects, ventricular septal defect, patent ductus arteriosus
Ellis–van Creveld	Single atrium, endocardial cushion defects
Fanconi	Patent ductus arteriosus, ventricular septal defect
Fetal alcohol	Ventricular septal defect, atrial septal defect, tetralogy of Fallot
Fragile X	Mitral valve prolapse, aortic root dilation
Goldenhar	Tetralogy of Fallot
Holt-Oram	Atrial or ventricular septal defect
Hydantoin/phenytoin embryopathy	Atrial or ventricular septal defect, coarctation of aorta
Infant of diabetic mother	Hypertrophic cardiomyopathy, ventricular septal defect
Laurence-Moon	Tetralogy of Fallot, ventricular septal defect
Marfan	Aortic root dissection, mitral valve prolapse
Mulibrey nanism	Pericardial thickening, constrictive pericarditis
Multiple lentigines (LEOPARD)	Pulmonary stenosis
Noonan	Pulmonic stenosis (dysplastic valve), atrial septal defect
PHACE	Coarctation of aorta, ventricular septal defect, patent ductus arteriosus
Pierre Robin	Coarctation of aorta
Polycystic kidney disease	Mitral valve prolapse
Polysplenia	Complex acyanotic lesions, azygos continuation
Rubella	Patent ductus arteriosus, peripheral pulmonary stenosis
Rubinstein-Taybi	Patent ductus arteriosus
Scimitar	Hypoplasia of the right lung, anomalous pulmonary drainage
Smith-Lemli-Opitz	Ventricular septal defect, patent ductus arteriosus
Thrombocytopenia–absent radius (TAR)	Atrial septal defect, tetralogy of Fallot, ventricular septal defect
Trisomy D	Ventricular septal defect, patent ductus arteriosus, atrial septal defect
Trisomy E	Ventricular septal defect, patent ductus arteriosus, atrial septal defect
Turner	Coarctation of aorta, bicuspid aortic valve
VACTERL (VATER)	Ventricular septal defect, tetralogy of Fallot
Valproate	Coarctation of aorta, hypoplastic left heart syndrome
Velocardiofacial	Ventricular septal defect, right aortic arch
Williams (7q11.23 deletion)	Supravalvular aortic stenosis, peripheral pulmonary stenosis
Wolf-Hirschhorn	Atrial septal defect, ventricular septal defect
22q11.2 deletion syndrome	Tetralogy of Fallot, interrupted aortic arch, ventricular septal defect, truncus arteriosus

CHARGE, coloboma, heart disease, atresia choanae, retarded growth and development or central nervous system anomalies, genital hypoplasia, and ear anomalies and/or deafness; LEOPARD, lentigines, electrocardiographic conduction defects, ocular hypertelorism, pulmonary stenosis, abnormalities of the genitals, retarded growth, deafness; PHACE, posterior fossa malformations, hemangiomas, arterial anomalies, coarctation of aorta, and eye abnormalities; VACTERL, vertebral abnormalities, anal atresia, cardiac abnormalities, tracheoesophageal fistula and/or esophageal atresia, renal agenesis and dysplasia, and limb defects; VATER, vertebral defects, imperforate anus, tracheoesophageal fistula, and radial and renal dysplasia.

referred for further diagnostic evaluation. Family history of sudden unexplained death, rheumatic fever, sudden infant death syndrome, or a structural cardiac abnormality in a first-degree relative may be relevant. Hypertrophic cardiomyopathy in a first-degree relative is associated with a high incidence of inheritance, and this condition is sufficiently subtle that echocardiographic screening is mandatory.

A maternal history of gestational diabetes mellitus may be associated with a transient hypertrophic cardiomyopathy in as many as 30% of infants of these mothers, as well as with definable congenital structural abnormalities. Additional relevant pregnancy history may include the presence of chronic or acute maternal illness, congenital infections, or medication use, any of which may be associated with significant

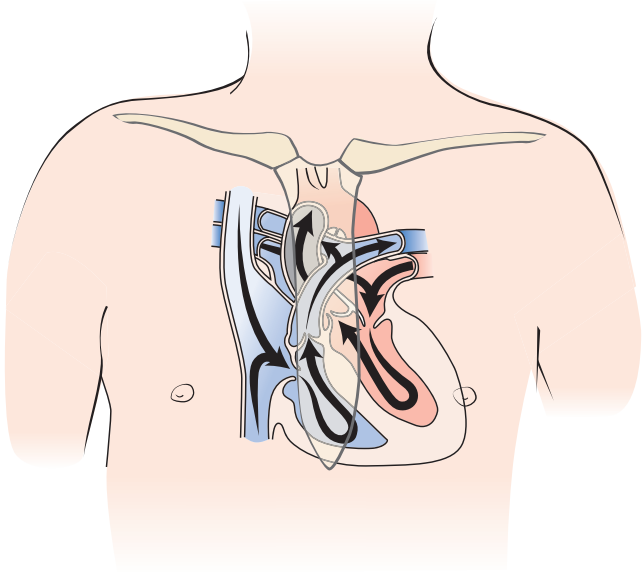


FIGURE 8.1 Location of the heart within the thorax. The right atrium and right ventricle lie immediately beneath the sternum. The left atrium lies posteriorly against the spine. The left ventricle extends laterally toward the chest wall, whereas the left ventricular outflow tract extends to the right side of the sternum, going upward toward the cardiac base.

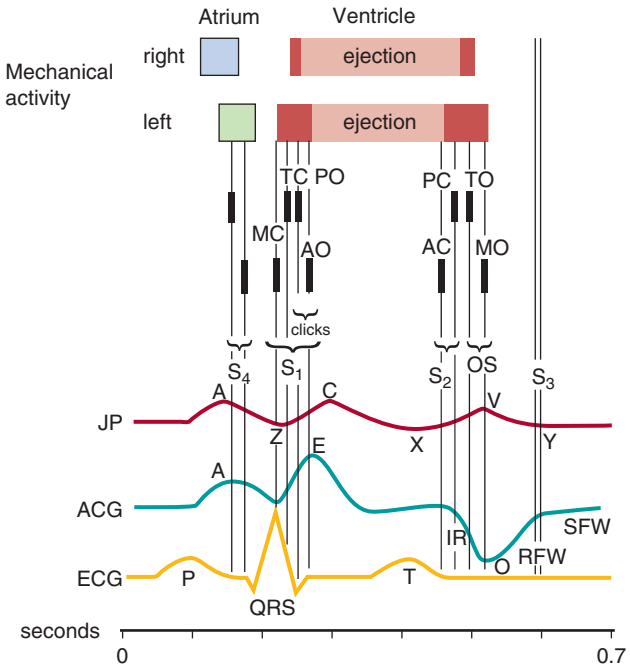


FIGURE 8.2 The cardiac cycle. Relationship among electrical and mechanical events, valvular motion, heart sounds (S_1, S_2, S_3, and S_4), the jugular pulse wave (JP), and the apexcardiogram (ACG). AC and AO, aortic component and opening; ECG, electrocardiogram; IR, isovolumic (isochronic) relaxation wave; MC and MO, mitral component and opening; O, opening of mitral valve; OS, opening snap of atrioventricular valves; PC and PO, pulmonic component and opening; RFW, rapid-filling wave; SFW, slow-filling wave; TC and TO, tricuspid component and opening. (From Tilkian AG, Conover MB. *Understanding Heart Sounds and Murmurs: With an Introduction to Lung Sounds*. 3rd ed. Philadelphia: WB Saunders; 1993.)

structural heart disease. Unexplained fever, lethargy, a history of intravenous drug use, or additional symptoms arising after recent dental work should arouse suspicion of possible endocarditis.

SYMPTOMS AND SIGNS OF HEART DISEASE

The general health of a child with a suspected cardiac malformation is important. Particularly relevant are the rate of growth, development, and history of past illnesses. Although symptoms of **failure to thrive** are nonspecific, patterns of growth reflect duration and severity of the disease and effectiveness of treatment (see Chapter 9). In an infant, feeding difficulties are often the first evidence of congestive heart failure. Feeding problems are common manifestations of cardiac disease and may be evidenced as disinterest, excessive fatigue, long feeding duration, diaphoresis, tachypnea, dyspnea, or a change in the pattern of respiration. It is important to obtain a measure of caloric intake by quantitating the number and/or volume of feedings. Some index of **exertional tolerance** should be sought in all children as an index of cardiovascular fitness and a sign of functional capability. This index should be age relevant and, in an infant, might include assessment of the vigor and duration of feeding and the time period of interactive play. In a toddler, the index might include ability to keep up with peers, climb stairs, or walk for extended periods. In an older child, a comparison with peer sporting interactions, level of function in physical education, and an index of aerobic ability should be sought.

Respiratory rates should be assessed in the quiet infant (Table 8.3). The rate and pattern of breathing should be assessed for a full minute, because rates may vary considerably with activity and feeding. **Tachypnea** may occur as a consequence of increased pulmonary blood flow. With increasing pulmonary congestion, particularly obstruction to pulmonary venous drainage, dyspnea is manifested as an anxious look with grunting, flaring of the alae nasi, and intercostal, suprasternal, and subcostal retractions. Cardiac asthma or exercise-inducible reactive airway disease may occur as a consequence of passive or active pulmonary congestion (see Chapter 3). Compression of airways by plethoric vessels may contribute to the stasis of secretions and atelectasis, which predisposes to respiratory tract infections.

Cyanosis in association with a cardiac murmur suggests a structural lesion with restriction to pulmonary blood flow (Table 8.4). Cyanosis, or a blue discoloration of the skin and mucous membranes, is a consequence of reduced hemoglobin (>5 g/dL), and is evident in one third of infants with potentially lethal congenital heart disease. Central cyanosis is distinguished from acrocyanosis or peripheral cyanosis by involvement of the warm mucous membranes, including the tongue and buccal mucosa. Acrocyanosis or peripheral cyanosis is generally confined to the perioral and perinasal regions, extremities, or nail beds and occurs in the child who is cold, vasoconstricted, or at rest. A distinctive feature is that central cyanosis generally worsens with activity and increasing cardiac output, whereas acrocyanosis generally improves or resolves with increased activity.

◆ Physical Examination

Overall Appearance

Height and weight should be measured and plotted on a growth chart. An assessment of the child's overall growth, appearance, and state of distress serves as a guide to the urgency of further investigation and management. The sick infant often appears anxious, fretful, diaphoretic, pale, or breathless and is seldom consolable. Observe for cyanosis, pallor, digital clubbing, an abnormal pattern of respiration, and possible dysmorphic features, which may suggest specific structural cardiac anomalies.

(See *Nelson Textbook of Pediatrics,* p. 2261.)

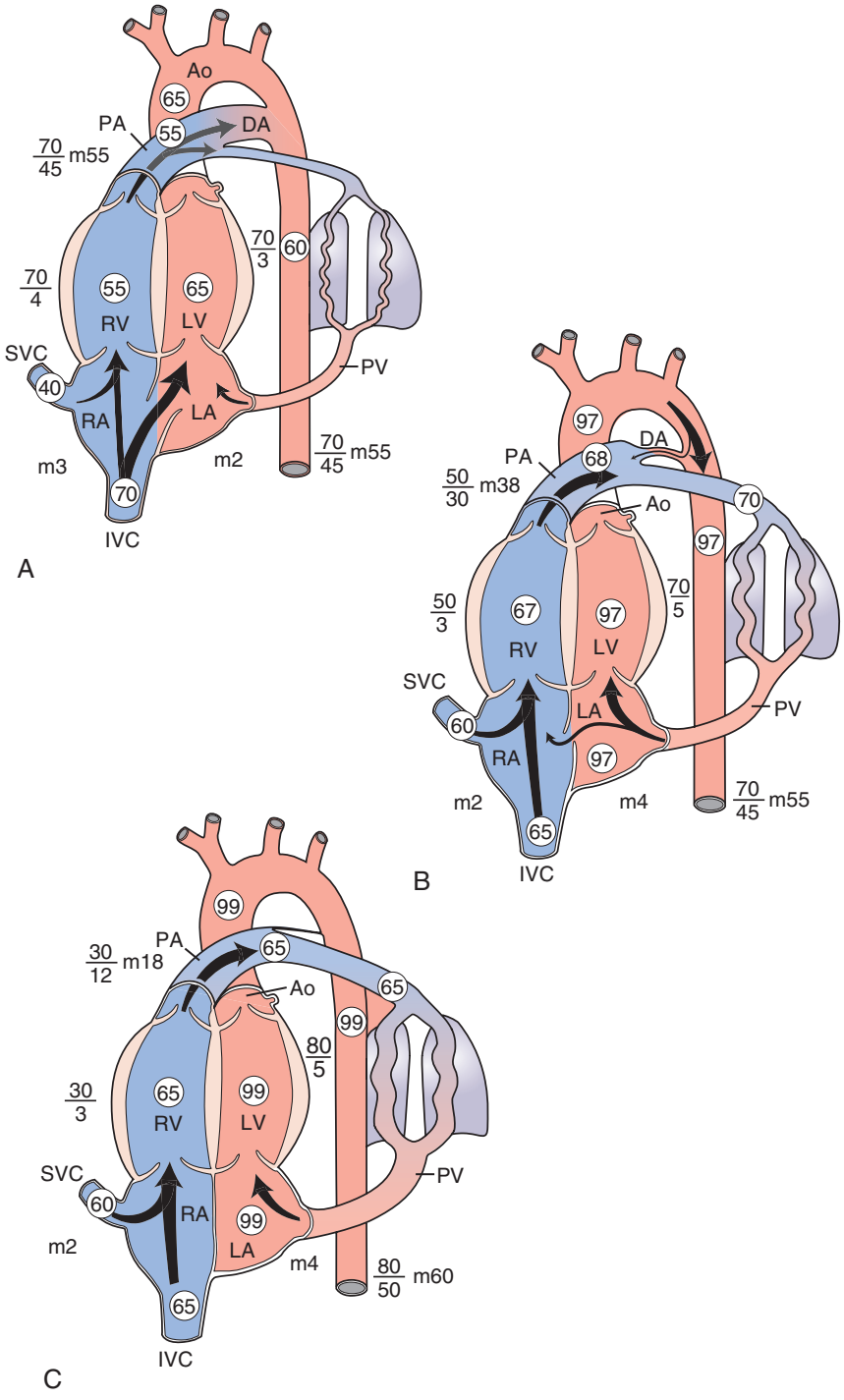


FIGURE 8.3 Fetal (A), transitional (B), and neonatal (C) circulations. The course of the circulation in the heart and great arteries of the late-gestation fetal lamb, within a few hours of delivery and as a newborn, are presented. The figures in the circles within the chambers and vessels represent percent oxygen saturation. The numbers alongside the chambers and vessels are pressures in mm Hg related to amniotic fluid pressure as zero. Ao, aorta; DA, ductus arteriosus; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; m, mean; PA, pulmonary artery; PV, pulmonary vein; RA, right atrium; RV, right ventricle; SVC, superior vena cava. (Modified from Rudolph AM. Chapters 2 and 3. In: *Congenital Disease of the Heart*. Chicago: Year Book Medical; 1974.)

Vital Signs

Normal resting heart rates and respiratory rate values for age are presented in Table 8.3. Blood pressure should be measured manually using an appropriately-sized cuff. Every child should have a comparison of upper and lower blood pressures on at least one occasion. The lower limb systolic blood pressure is normally 10 mm Hg higher than the upper limb pressure in older children. On occasion, the subclavian arteries may arise aberrantly beyond the site of ductal ligament insertion. Therefore, both upper limb pressures should be measured and compared with the lower limb pressure. Normal values for blood pressure in children are presented in Fig. 8.4.

TABLE 8.3 Normal Values of Respiratory and Heart Rates in Infants and Children

	AGE				
	Birth-6 Weeks	6 Weeks-2 Years	2-6 Years	6-10 Years	Older Than 10 Years
Respiratory rate	45-60/min	40/min	30/min	25/min	20/min
Heart rate	125 ± 30/min	115 ± 25/min	100 ± 20/min	90 ± 15/min	85 ± 15/min

TABLE 8.4 Categories of Cyanotic Heart Lesions in the Neonate

Group	Heart Size	Pulmonary Blood Flow	Low Cardiac Output	Respiratory Distress	Examples
I	Small	Reduced	No	None	Hypoplastic RV with pulmonary atresia Hypoplastic RV with tricuspid atresia Tetralogy of Fallot (severe)
II	Small or slight cardiomegaly	Increased	No	Moderate	Transposition of great arteries with intact ventricular septum
III	Large	Increased	Yes	Yes	Complicated coarctation of aorta with VSD, hypoplastic LV
IV	Small	Pulmonary venous congestion	Yes	Yes	Obstructed total anomalous pulmonary veins

LV, left ventricle; RV, right ventricle; VSD, ventricular septal defect.
Modified from Gillette PC. The cardiovascular system. In: Behrman RE, Kliegman RM, eds. *Nelson Essentials of Pediatrics*. 2nd ed. Philadelphia: WB Saunders; 1994:503.

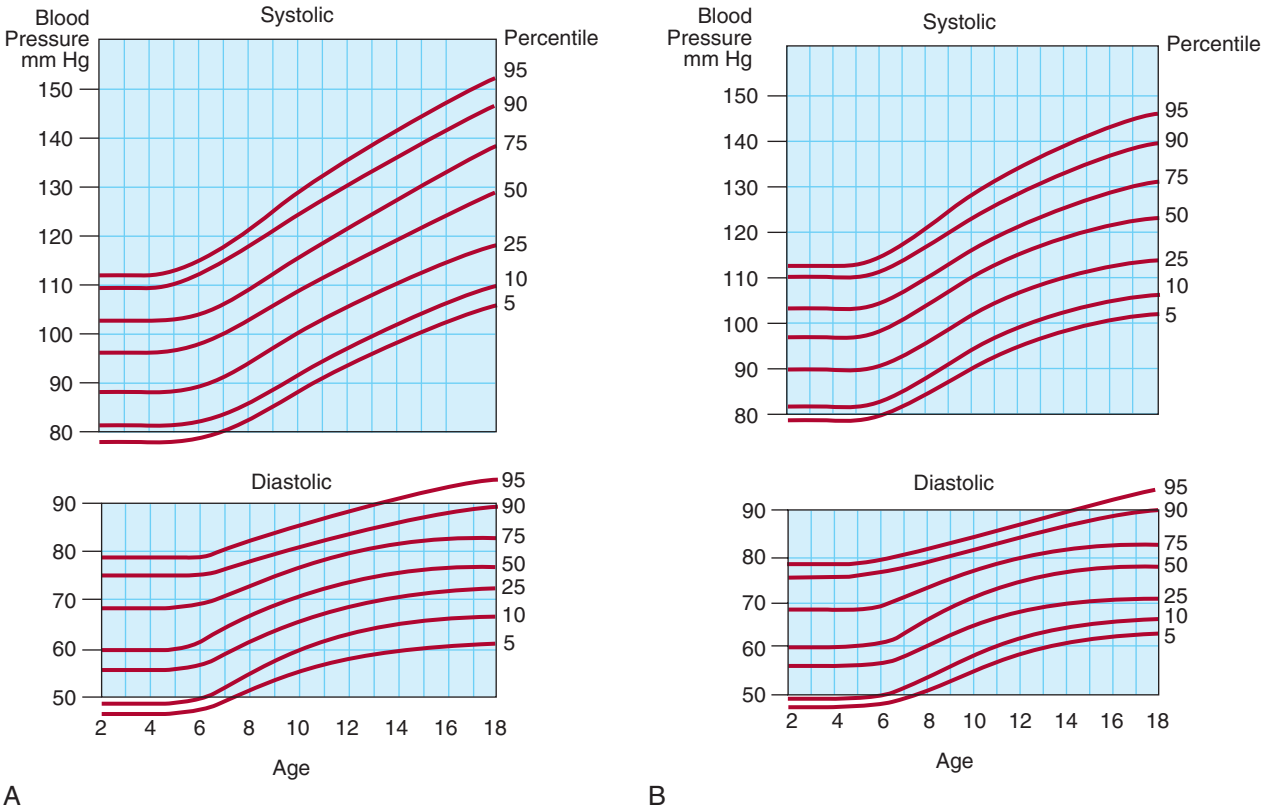


FIGURE 8.4 Normal blood pressure percentiles for boys *(A)* and girls *(B)*, aged 2-18 years. The Korotkoff IV sound is used for diastolic blood pressure. (Modified from the National Heart, Lung, and Blood Institute. Report of the second task force on blood pressure control in children, 1987. *Pediatrics* 1987;79:1.)

Respiratory Assessment

Respiratory distress may suggest cardiac disease. In addition to noting the rate, depth, and effort of respiration, the inspection should include observation for evidence of air trapping, increased chest diameter, or the presence of subcostal Harrison sulci as an indication of chronic upper airway obstruction. An allergic malar facies may also suggest upper airway obstructive disease with predisposition to hypercapnia and pulmonary hypertension. Although crackles in the lungs in infants and even young children usually indicate infection, pulmonary edema should also be a consideration.

CARDIOVASCULAR ASSESSMENT

Arterial Examination

Pulses should be assessed for rate, rhythm, volume, and character. The dynamic character of the pulse may provide information about the cardiac output. A clinical index of cardiac output includes the warmth of the digits and measured capillary refill time. This is obtained by blanching the nail beds or digits and estimating the time to full reperfusion, which is normally less than 2 seconds. Initially, the radial and brachial pulses should be assessed simultaneously in the upper limb. By palpating the pulse at 2 sites and altering the pressure applied by the palpating fingers, a more accurate assessment of the rate of rise, volume, and contour may be obtained. Assessment of the femoral pulse requires that the infant be quiet. Palpating parallel to the inguinal crease and allowing the leg to continue to flex is generally more effective than extending the leg. Blood pressures in the arm and leg should be assessed, and the radial and femoral pulses should be palpated simultaneously. Whenever possible, the radial pulse should be brought in close apposition to the femoral pulse to compare for any delay. This enables a more accurate appreciation of any temporal delay and enables more accurate detection of the presence of **coarctation of the aorta**. The presence of a palpable femoral pulse is by itself an inadequate screen for coarctation because a widely patent ductus arteriosus (PDA) or collateral vessels (particularly in the older patient) may provide delayed perfusion. Previous arterial instrumentation, injury, or congenital variability may account for reduction in palpable peripheral pulses.

Venous Examination

In infants and young children, the liver character and size offer more reliable indicators of right atrial pressure and systemic congestion than does the jugular venous pressure. The position, size, and consistency of the liver should be assessed. The character of the normal liver margin is generally likened to that of the cartilage of the external pinna, and the margin should be sharp and angulated. In the newborn, the liver may be normally palpable at 1.5-2.5 cm below the right costal margin in the midclavicular line. This distance decreases to approximately 1-2 cm by 1 year of age and remains just palpable until school-entrance age. In the presence of congestive heart failure, the liver enlarges and distends downward. The congested liver margin becomes rounded and firm and is often more difficult to feel. An enlarged liver may be tender, and aggressive palpation may cause discomfort and tensing of the abdominal musculature, making accurate assessment difficult. A transverse liver is suggestive of a **heterotaxy syndrome** with abnormal abdominal organ location (situs abnormalities) and complex congenital heart lesions. The spleen should always be sought; enlargement suggests endocarditis in the patient with a heart murmur. Splenic enlargement in association with congestive heart failure is unusual (see Chapter 17).

Precordial Examination

Inspection of the chest may suggest the presence of a precordial bulge of long-standing right ventricular volume overload. The examiner's entire palm and hand should be warmed and then fully applied to the patient's chest wall to maximize ability to detect thrills or heaves. Whereas the examiner's fingertips are best utilized to localize an abnormality, the palmar surface of the metacarpals and first phalanges are more sensitive for the detection of low-frequency events. The fingertips should be used to localize the most lateral displacement of the apical impulse. In patients of all ages, the apical impulse should be confined to one intercostal interspace and would be described as localized; however, if the apical impulse is equally dynamic in 2 or more interspaces then it is best described as diffuse. In the neonate, a right ventricular impulse may be felt close to the sternum. Later in life, the same degree of parasternal activity is likely to suggest pulmonary hypertension, right-sided heart volume overload, or right ventricular outflow obstruction. The lateral displacement of the apex, normally located in the midclavicular line, should be compared to existing landmarks. A dynamic or thrusting character to an apical impulse may be detected in association with an elevated cardiac output or various forms of obstruction to left ventricular outflow. On occasion, an apical filling impulse, coinciding with an audible S_3, may be normally palpable, particularly in the adolescent or athlete with a relative bradycardia and increased stroke volume.

A **thrill** is a palpable murmur and should be sought in the precordial and suprasternal areas. The palmar surface of the examiner's hand is most sensitive in detection of a thrill; however, only the tips of the digits fit in the patient's suprasternal notch. A palpable second heart sound (S_2), indicative of a significant level of pulmonary hypertension, may be detected as a sharp or distinctive impulse in the pulmonary outflow.

Auscultation

Thorough auscultation in the cooperative patient may take as long as 5-10 minutes and should include listening in the principal areas of the precordial auscultation (tricuspid, pulmonary, mitral, and aortic) with both the bell and diaphragm of the stethoscope, with the patient in the supine, sitting, and standing positions. These 4 areas serve as a guide to auscultation of the heart (Fig. 8.5). These are the optimal sites for listening to sounds that arise within the chambers and great vessels:

1. The tricuspid area is represented by the fourth and fifth intercostal spaces along the left sternal edge but extends to the right of the sternum as well as downward to the subxiphisternal area.
2. The pulmonary area is the second intercostal space along the left sternal border. Murmurs that are best heard in this area may also extend to the left infraclavicular area and often lower, along the left sternal edge to the third intercostal space.
3. The mitral area involves the region of the cardiac apex and generally is at the fifth intercostal space in the midclavicular line. This area may also extend medially to the left sternal edge and laterally to the region of the axilla.
4. The aortic area, although centered at the second right intercostal space, may extend to the suprasternal area, to the neck, and inferiorly to the third left intercostal space. The margins of these areas are ill defined, and auscultation should not be limited to these sites and may extend to the axillae, neck, back, or infraclavicular areas.

A step-by-step auscultation—first for heart sounds, subsequently for systolic murmurs, and then separately for diastolic murmurs—is essential. The ability to clearly characterize the S_2 is perhaps more crucial than for any other sound; the effects of respiration are important. The components of the S_2 in childhood are normally split with

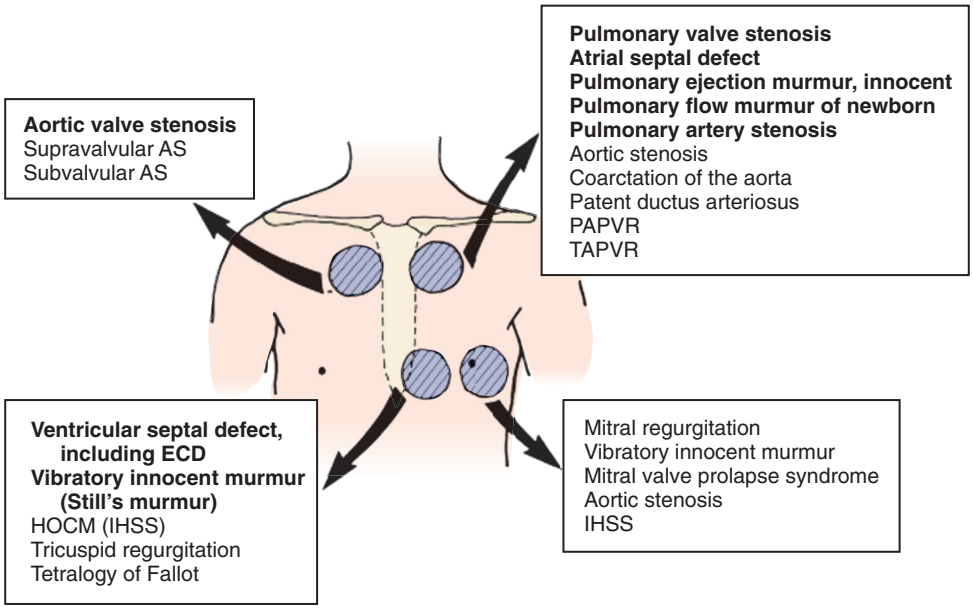


FIGURE 8.5 Diagram showing systolic murmurs audible at various locations. Less common conditions are shown in smaller type. AS, aortic stenosis; ECD, endocardial cushion defect; HOCM, hypertrophic obstructive cardiomyopathy; IHSS, idiopathic hypertrophic subaortic stenosis; PAPVR, partial anomalous pulmonary venous return; TAPVR, total anomalous pulmonary venous return. (From Park MK. *Park's Pediatric Cardiology for Practitioners*. 6th ed. Philadelphia: Elsevier; 2014:33, Figure 2-12.)

inspiration and become single on expiration. A loud pulmonary closure sound should suggest the possibility of pulmonary artery hypertension. The S_2 may be widely split and/or fixed in association with right ventricular volume overload or delayed right ventricular conduction. Normal inspiratory splitting of the S_2 should be sought and established in all patients. As timing may be difficult in the infant with a rapid respiratory rate, the presence of splitting at any time during the respiratory cycle may be accepted as normal.

The right ventricle is normally just beneath the sternum. This proximity generally makes sounds emanating from the right heart louder and less diffuse. In addition, right heart sounds and murmurs are more influenced by the effects of respiration.

Heart Sounds

First direct the examination to the normal heart sounds in sequence. Appreciate the effects of inspiration and expiration on the heart sounds. Then address additional heart sounds and murmurs. Describe any variability that occurs with a change of body position.

First Heart Sound

The first heart sound (S_1) (see Fig. 8.2) arises from closure of the atrioventricular (mitral and tricuspid) valves in early isovolumic ventricular contraction and, consequently, is best heard in the tricuspid and mitral valve areas. Mitral valve closure occurs slightly in advance of tricuspid valve closure, and, on rare occasion, near the lower-left sternal edge 2 components (splitting) of the S_1 may be heard. There is usually a single sound. The S_1 is most easily heard when the heart rate is slow because the interval between the S_1 and S_2 is shorter than the interval between the S_2 and subsequent S_1. The intensity of the S_1 is influenced by the position of the atrioventricular valve at the onset of ventricular contraction.

Second Heart Sound

Shortly after the onset of ventricular contraction, the semilunar valves (aortic and pulmonary) open and permit ventricular ejection. This opening does not usually generate any sound. The atrioventricular valves remain tightly closed during ventricular ejection. As ventricular ejection nears completion, the pressure begins to fall within the ventricles, and the semilunar valves snap closed. This prevents regurgitation from the aorta and pulmonary artery back into the heart. The closure of the semilunar valves generates the S_2 (see Fig. 8.2). The S_2 usually consists of a louder and earlier aortic valve closure sound (A_2), followed by a later and quieter pulmonary valve closure sound (P_2). Normal physiologic splitting or variability is appreciated most easily in the pulmonary area during or near the end of inspiration. During expiration, the aortic and pulmonary valves close almost synchronously and produce a single or narrowly split S_2. Normal splitting of S_2 is caused by (1) increased right-sided heart filling during inspiration because of increased blood volume returning via the venae cavae; and (2) diminished left-sided heart filling because blood is retained within the small blood vessels of the lungs when the thorax expands. During inspiration, when the right ventricle is filled more than the left, it takes slightly longer to empty. This causes the noticeable inspiratory delay in P_2 in relation to A_2. *Splitting of the S_2 during inspiration is a normal finding and should be sought in all patients.*

The aortic and pulmonary pressure in diastole closes the semilunar valves. Many forms of congenital or acquired heart disease have an impact on the pulmonary circulation and, consequently, often affect the S_2. Thus, the higher the pulmonary artery diastolic pressure, the more intense and earlier the P_2 is. Pulmonary hypertension in children is suggested when the P_2 is palpable, loud, and narrowly split or cannot be separated from A_2. If the P_2 is audible outside of the pulmonary area, particularly at the apex, then pulmonary hypertension is likely. A single or narrow split S_2 may also be noted in patients with severe pulmonic or aortic valve stenosis, tetralogy of Fallot, truncus arteriosus, pulmonary atresia, hypoplastic left heart syndrome, tricuspid valve atresia, or Eisenmenger syndrome with a VSD. In the presence of moderate to severe pulmonic stenosis, there is low pulmonary artery diastolic pressure. The pulmonary valve closure is therefore delayed and of decreased intensity and is occasionally inaudible.

The S_2 may be widely split and/or fixed in association with right ventricular volume overload or delayed right ventricular conduction.

Third Heart Sound

The third heart sound (S_3) (see Fig. 8.2), which is of very low frequency, occurs about a third of the way into diastole, at the time of the most rapid filling of the ventricles. It is most likely caused by sudden tension of the ventricles, enough to produce sound vibrations within the myocardial wall. Vibrations in the atrioventricular valve itself, as well as in the chordae, may also contribute to the sound. The amplitude of S_3 increases with an increased ventricular filling rate. When heard at the apex, S_3 is considered left ventricular in origin, and when heard at the lower left sternal border, S_3 is likely to be right ventricular in origin. An apical S_3 of soft to moderate intensity is readily heard in most children and young adults. An S_3 in association with tachycardia is termed a **gallop** and may be caused by lesions associated with left or right ventricular diastolic overload or diminished ventricular compliance.

Fourth Heart Sound

The fourth heart sound (S_4) (see Fig. 8.2) is also of low frequency and can be both left-sided and right-sided in origin. It occurs with atrial contraction against a high resistance and is therefore heard just before S_1. It is more difficult to hear than S_3, particularly in children, in whom the PR interval is usually shorter than that in the adult. The S_4 is thought to be caused by a forceful atrial contraction against a poorly compliant left ventricle (e.g., as in diastolic overload). The sound is readily heard in adults with significant chronic hypertension or left ventricular cardiomyopathy and, except for its timing, sounds much like an S_3. In a young baby with total anomalous pulmonary venous return, low pulmonary vascular resistance, and significantly increased right ventricular and pulmonary blood flow, a loud right ventricular S_4 (as well as S_3) may be heard as part of a quadruple rhythm at the lower left sternal border. An intermittent S_4 may be heard in children with complete atrioventricular block. Whereas an S_3 may be heard in a normal adolescent and can be physiologic, the S_4 only occurs in a pathologic condition.

Ejection Click

An audible ejection click (see Fig. 8.2) is abnormal and is either related to the hemodynamics associated with a dilated root of the aorta (**aortic ejection click**) or a dilated root of the pulmonary artery (**pulmonary ejection click**) or the effects of a thickened and immobile semilunar valve. The sound is sharp and of very high frequency. The pulmonary ejection click is best heard at the upper-left sternal border, whereas the aortic ejection click is usually best heard at the apex. It may also be heard at the upper-right sternal border, but if so, it is always louder at the apex or the lower-left sternal border. The click arises either from sudden tension of the semilunar valve or from sudden distention with lateral pressure at the root of the aorta or pulmonary artery. The sound is present in aortic or pulmonary valve stenosis. In such cases, the rapid movement of the stenotic valve is suddenly checked. An aortic ejection click may be heard in the presence of a normal aortic valve (as in severe tetralogy of Fallot with a large aortic root); a pulmonary ejection click may be heard with a normal pulmonic valve (as in Eisenmenger syndrome with a large pulmonary root). The aortic ejection click, best heard at the apex, does not vary with respirations. However, the pulmonary ejection click, best heard at the upper-left sternal border, is better heard on expiration than inspiration.

An ejection click or a sharp sound present at the upper-left sternal border, louder with expiration or heard only on expiration, is characteristic of **pulmonary valve stenosis**. The ejection click follows the period of isovolumic contraction and occurs as a consequence of restricted semilunar (aortic or pulmonary) valve excursion at the onset of ventricular ejection. When the ejection sound occurs at the upper-right sternal border or at the apex, a bicuspid or stenotic aortic valve disease is suggested. In contrast to ejection clicks, right-sided cardiac murmurs are accentuated with inspiration. Left-sided heart auscultatory abnormalities vary little with the respiratory cycle.

In the case of the aortic ejection click, the sound is usually well separated from S_1. However, the pulmonary ejection click is usually closer to S_1 than is an aortic click. In some moderate to severe cases, the pulmonary ejection click occurs at the same time as S_1. If one perceives a split S_1, one is most likely hearing an ejection click as the causes of a true split S_1 are very rare.

Opening Snap

The opening snap, present only in rheumatic mitral valve stenosis when the anteromedial leaflet is immobile, is heard early in diastole, usually above the apex, and is of medium frequency. Because the leaflets are fused, the downward movement of the opening valve is suddenly checked, resulting in the opening snap. This sound is often confused with an S_3. The frequency is somewhat higher and the timing is earlier than those of an S_3. The opening snap and the S_3, although similar in timing, can never occur together in the same patient.

Non-Ejection Click

Non-ejection clicks are heard at the apex and occur one third to half of the way between S_1 and S_2. Thus, they are commonly called **mid-systolic clicks**. The sounds are of medium to high frequency. The sound is caused by the sudden tensing of the posterior mitral valve leaflet as it prolapses into the left atrium; in rare cases, there may be multiple mid-systolic clicks. The clicks may be loud, but they may also be soft and easily missed.

CLASSIFICATION OF CARDIAC MURMURS

Heart murmurs are the consequence of turbulent blood flow. Turbulence may arise as a result of

- high flow through abnormal or normal valves
- normal flow through narrow or stenotic valves or vessels
- backward or regurgitant flow through incompetent leaky valves
- flow through congenital or surgical communications
- anemia with high flows and discrete decreased blood viscosity

Not all cardiac murmurs indicate heart problems.

The clinician should be able to determine and describe the following seven characteristics of heart murmurs:

1. Timing: the relative position within the cardiac cycle relative to S_1 and S_2
2. Intensity or loudness: murmurs are graded as
   - grade I: heard only with intense concentration
   - grade II: faint but heard immediately
   - grade III: easily heard, of intermediate intensity
   - grade IV: easily heard and associated with a thrill (a palpable vibration on the chest wall)
   - grade V: very loud, with a thrill present, and audible with only the edge of the stethoscope on the chest wall
   - grade VI: audible with the stethoscope off the chest wall
3. Location: on the chest wall with regard to
   - area where the sound is loudest (point of maximal intensity)
   - area over which the sound is audible (extent of radiation)
4. Shape: to include the duration (the length of the murmur from beginning to end) and configuration (the dynamic changing nature of the murmur)

5. Pitch: the frequency range of the murmur, generally described as low, medium, or high—pitched
6. Quality: aspect that relates to the presence of harmonics and the overtones
7. Physiologic effects: of different positions, manipulations, or maneuvers

PEDIATRIC MURMUR EVALUATION

After the neonatal period, an innocent murmur may be detected at some time in the majority of children before school age. The clinical diagnosis of a normal ejection or innocent murmur should only occur in the setting of an otherwise normal history, physical examination, and appearance (Table 8.5 and Fig. 8.6).

Thorough auscultation in the cooperative patient should include listening in the principal areas (tricuspid, pulmonary, mitral, and aortic) of the precordium with both the bell and diaphragm of the stethoscope and with the patient in the supine, sitting, and standing positions.

SYSTOLIC MURMURS

Systolic murmurs begin with or follow the S_1 and end before the S_2 (Fig. 8.7).

Holosystolic murmurs, beginning abruptly with S_1 and continuing at the same intensity to S_2, are graphically shown as a rectangle. This murmur begins during the period of isovolumic contraction and thus occurs when there is a regurgitant atrioventricular valve (tricuspid or mitral) or in association with a VSD.

Ejection murmurs are crescendo-decrescendo or diamond-shaped murmurs that may arise from narrowing of the semilunar valves or outflow tracts. The rising-and-falling nature of the murmur reflects the periods of low flow at the beginning and end of ventricular systole.

Innocent murmurs are almost exclusively ejection systolic in nature (see Table 8.5). They are generally soft, are never associated with a palpable thrill, and are subject to considerable variation with positioning changes.

Early systolic murmurs start abruptly with S_1 but taper and disappear before the S_2 and are exclusively associated with small muscular VSDs.

Mid-systolic to late-systolic murmurs begin midway through systole and are often heard in association with the mid-systolic clicks and insufficiency of mitral valve prolapse.

DIASTOLIC MURMURS

Diastole, the period between closure of the semilunar valves (S_2) and subsequent closure of the atrioventricular valves (S_1), is normally silent because of relatively low flow through large valve orifices. Regurgitation of the semilunar valves, stenosis of the atrioventricular valves, or increased flow across the atrioventricular valves all cause turbulence and may produce diastolic heart murmurs (Fig. 8.8).

Early diastolic murmurs are decrescendo in nature and arise from either aortic or pulmonary valve insufficiency (regurgitation).

Mid-diastolic murmurs are diamond-shaped and occur because of either (1) increased flow across the normal tricuspid or mitral valve or (2) normal flow across an obstructed or stenotic tricuspid or mitral valve.

Late diastolic or crescendo murmurs are created by stenotic or narrowed atrioventricular valves and occur during atrial contraction.

CONTINUOUS MURMURS

Flow through vessels, channels, or communications beyond the semilunar valves is not confined to either systole and/or diastole. Thus, there may be turbulent flow throughout some or all of the cardiac cycle (Fig. 8.9). The resulting murmur that extends beyond the S_2 has been classically termed "continuous." The continuous murmur can be heard through part or all of diastole. Continuous murmurs are generally pathologic; the venous hum is an exception.

TABLE 8.5 Common Innocent Heart Murmurs in Children

Type (Timing)	Description of Murmur	Age Group
Classic vibratory murmur (Still murmur) (systolic)	Maximal at MLSB or between LLSB and apex Grade 2 to 3/6 Low-frequency vibratory, "twanging string," groaning, squeaking, or musical	3–6 yr Occasionally in infancy
Pulmonary ejection murmur (systolic)	Maximal at ULSB Early to mid-systolic Grade 1-3/6 in intensity Blowing in quality	8–14 yr
Pulmonary flow murmur of newborn (systolic)	Maximal at ULSB Transmits well to the left and right chest, axilla, and back Grade 1-2/6 in intensity	Premature and full-term newborns Usually disappears by 3–6 mo of age
Venous hum (continuous)	Maximal at right (or left) supraclavicular and infraclavicular areas Grade 1-3/6 in intensity Inaudible in the supine position Intensity changes with rotation of the head and compression of the jugular vein	3–6 yr
Carotid bruit (systolic)	Right supraclavicular area and over the carotids Grade 2-3/6 in intensity Occasional thrill over a carotid	Any age

LLSB, lower left sternal border; MLSB, mid-left sternal border; ULSB, upper left sternal border.
From Park MK. *Park's Pediatric Cardiology for Practitioners*. 6th ed, Philadelphia: Elsevier/Saunders; 2014:36, Table 2-8.

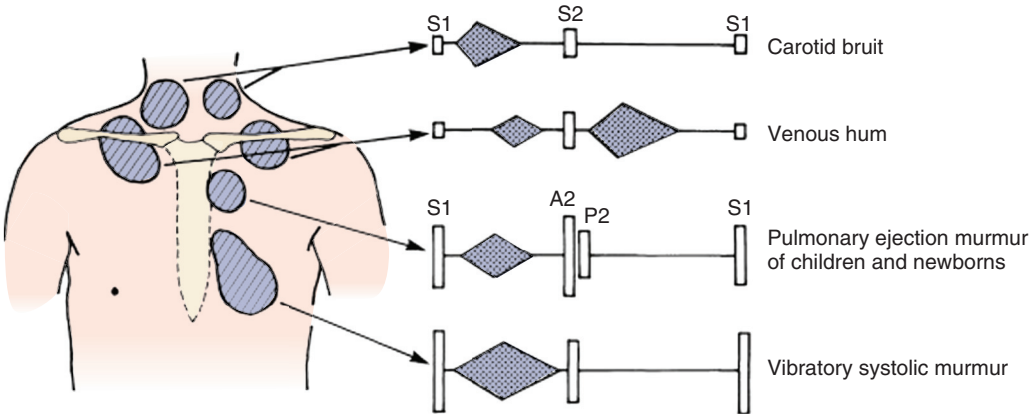


FIGURE 8.6 Diagram of innocent heart murmurs in children. (From Park MK. *Park's Pediatric Cardiology for Practitioners*. 6th ed. Philadelphia: Elsevier; 2014:37, Figure 2-14.)

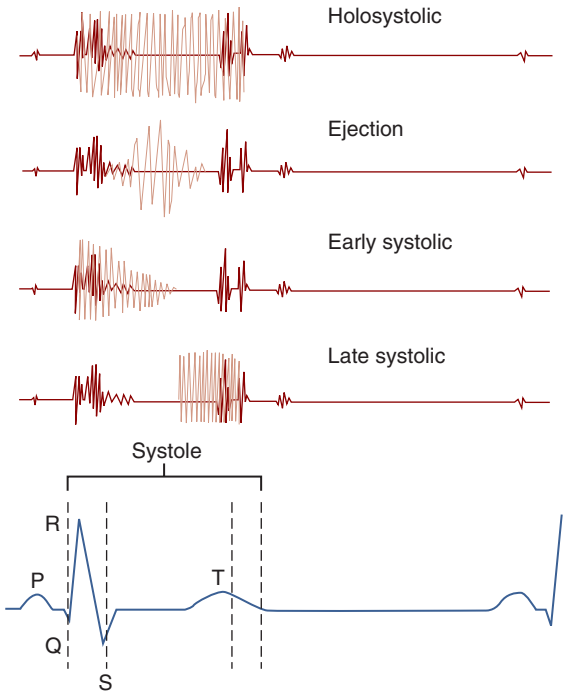


FIGURE 8.7 Four types of systolic heart murmurs. The holosystolic or pansystolic murmur begins abruptly with the first heart sound (S_1) and proceeds at the same intensity to the second heart sound (S_2). The ejection systolic or crescendo-decrescendo murmur begins with the onset of volume ejection from the heart. As the flow increases, the murmur varies both in intensity and frequency and subsequently tapers as the period of ejection ceases, before the S_2. The early systolic murmur begins, as does the holosystolic murmur, abruptly with S_1 but terminates in mid-systole with the cessation of shunt flow. The late systolic murmur begins well after S_1, commencing in mid- to late systole in association with the development of valve insufficiency and proceeds at this intensity to S_2. (From Pelech AN. The cardiac murmur. *Pediatr Clin North Am.* 1998;45:107-122.)

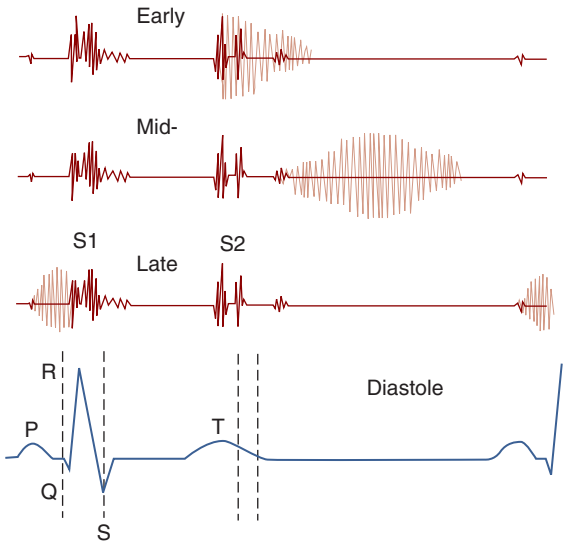


FIGURE 8.8 Diastolic murmurs. The early diastolic or decrescendo murmur occurs in association with closure of the semilunar valves (second heart sound) and tapers through part or all of diastole. The mid-diastolic murmur rises and falls in intensity with atrial volume entering the ventricle. The late systolic or crescendo diastolic murmur occurs late in diastole with atrial contraction, before systole, and ascends to the first heart sound. (From Pelech AN. The cardiac murmur. *Pediatr Clin North Am.* 1998;45:107-122.)

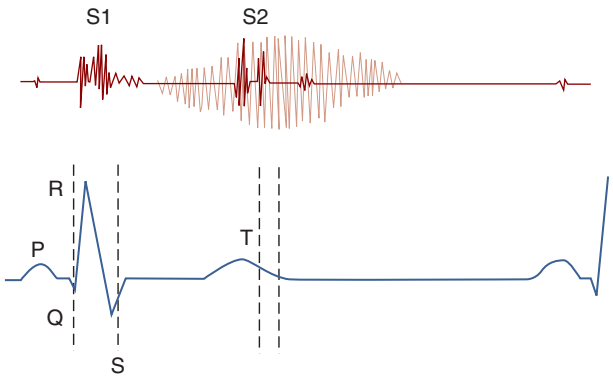


FIGURE 8.9 Continuous murmur. The continuous murmur begins in systole and proceeds up to and through the second heart sound, proceeding through part or all of diastole. (From Pelech AN. The cardiac murmur. *Pediatr Clin North Am.* 1998;45:107-122.)

MURMURS IN CHILDREN WITH NORMAL HEARTS

"Innocent" murmurs occur in the absence of structural or physiologic cardiac disease. Innocent murmurs have been called functional, benign, innocuous, or physiologic but are perhaps best termed normal to accurately convey to parents the favorable impression and outcome that should accompany the diagnosis. After the neonatal period, a normal murmur may be detected in the majority of children at some time before school age.

The normal murmurs of childhood are composed of five systolic and two continuous types but are never solely diastolic (see Table 8.5 and Fig. 8.6). The intensity or loudness of the murmur is grade III or less and consequently is never associated with a palpable thrill. The majority of all murmurs, both innocent and organic, are accentuated by fever, anemia, or increased cardiac output.

Vibratory Still Murmur

The most common innocent murmur in children is the vibratory systolic murmur described by Sir George Still. The murmur is typically audible in children between ages 2 and 6 years, but may be present as late as adolescence or as early as infancy. The murmur is low to medium in pitch, confined to early systole, generally grade II (range I-III), and heard maximally at the lower-left sternal edge and extending to the apex. The murmur is loudest when the patient is in the supine position and often changes in character, pitch, and intensity with upright positioning.

The most characteristic feature of the murmur is its vibratory, musical, harmonious quality described as a twanging sound, very like that made by twanging a piece of tense string. The quality of the murmur can thus never be described as "noisy" or "rough." Quite characteristically, the intensity of the murmur diminishes and the pitch changes with upright positioning; it seldom disappears entirely.

The origins of the murmur are obscure and have been ascribed to vibration of the pulmonary valves during systolic ejection, vibrations arising from the shift in blood mass in the dynamically contracting ventricle, physiologic narrowing of the left ventricular outflow tract, and the presence of ventricular false tendons or bridging bands. Phonocardiographic recordings have shown the innocent murmur to arise from either the right ventricular or left ventricular outflow tracts.

Pulmonary Flow Murmur

An innocent pulmonary outflow tract murmur may be heard in children, adolescents, and young adults. The murmur is a crescendo-decrescendo, loudest in early- to mid-peaking ejection systolic murmur confined to the second and third interspaces at the left sternal border. It is of low intensity (grades II-III) and transmits to the pulmonary area. It is rough and dissonant without the vibratory musical quality of the Still murmur. The murmur is best heard in the supine position and is exaggerated by the presence of a pectus excavatum, a straight back, or kyphoscoliosis, which results in compression or approximation of the right ventricular outflow tract to the chest wall. The murmur is augmented in full exhalation while the patient is supine, rarely resulting in the perception of a palpable thrill, and is diminished by upright positioning and held inspiration.

The murmur of an ASD is attributable to increased flow through the pulmonary outflow tract and may be indistinguishable from the innocent pulmonary flow murmur. However, the hyperdynamic right ventricular impulse, wide splitting of the pulmonary component of the S_2, and presence of a mid-diastolic flow rumble should enable distinction.

The murmur of pulmonary valve stenosis may be distinguished from the innocent pulmonary flow murmur by the frequent presence of a systolic thrill, higher pitch, longer duration, and/or presence of an ejection click. The presence of an ejection click signifies improper opening of a semilunar valve and is usually of pathologic origin. In pulmonary stenosis, the S_2 may be widely split and the P_2, when audible, is of diminished intensity.

Peripheral Pulmonary Arterial Stenosis Murmur

A common murmur heard frequently in newborns and in infants younger than 1 year is the audible turbulence of peripheral branch pulmonary arterial stenosis, angulation, or narrowing. These ejection character murmurs are typically grade I or II, are low to moderate in pitch, begin in early to middle systole, and extend up to and occasionally just after the S_2. These murmurs are most often present in normal newborns but may be associated with viral lower respiratory tract infections and reactive airway disease in older infants. In the fetus, the pulmonary trunk is a relatively dilated, domed structure because it receives the majority of combined cardiac output from the high-pressure right ventricle. Right and left pulmonary artery branches arise from this major trunk as comparatively small lateral branches that receive little intrauterine flow because of high pulmonary artery resistance. When the lungs expand at birth, the relative disparity transiently persists. The branches also arise at comparatively sharp angles from the main pulmonary trunk, accounting for turbulence and a recognized physiologic drop in pressure from the main trunk to the proximal branch pulmonary arteries. In association with a respiratory tract infection, regional vascular reactivity and pulmonary blood flow redistribution may account for the reappearance of the murmur after the neonatal period.

The murmurs are often best heard peripherally in the axillae and back with both regional and temporal variability. Because of the rapid respiratory rate of infants, similar sound frequency composition of breath sounds, and peripheral location of the murmurs, these murmurs are often overlooked. They are often most evident in the recovery phase of a respiratory illness. Of importance is that the murmur of peripheral branch stenosis changes with heart rate variability, increasing in intensity with heart rate slowing as the stroke volume increases and, conversely, diminishing with tachycardia and reduction in stroke volume.

The normal peripheral branch stenosis murmur may be indistinguishable from the peripheral murmur of significant stenosis of the branch pulmonary vessels seen in Williams or rubella syndrome or from accompanying hypoplasia or narrowing of the pulmonary arteries. Murmurs of significant anatomic narrowing may be distinguished by their higher pitch and extension after the S_2 in children after the first few months of life. The pulmonary flow murmur of an ASD may mimic this murmur but is not heard in this age group. Proximal pulmonary valve or right ventricular outflow obstruction may also closely resemble this murmur, but these obstructions are often of louder intensity, possibly associated with an ejection click, and heard maximally lower along the left sternal border.

Supraclavicular or Brachiocephalic Systolic Murmur

A supraclavicular systolic crescendo-decrescendo murmur may be heard in children and young adults. This systolic murmur is audible maximally above the clavicles and radiates to the neck but may be present to a lesser degree on the superior chest. The murmur is low to medium in pitch, of abrupt onset, brief, and maximal in the first half or two thirds of systole. High pitch or extension into diastole is unusual and suggests significant vascular obstruction.

The murmur is present in both supine and sitting positions but varies with hyperextension of the shoulders. The shoulders can be hyperextended with the elbows brought behind the back until the shoulder girdle is taut. When this maneuver is done rapidly, the

murmur diminishes or disappears altogether. Supraclavicular systolic murmurs are thought to originate from the major brachiocephalic vessels as they arise from the aorta.

Aortic Systolic Murmur or "Athlete's Murmur"

Innocent systolic flow murmurs may arise from the outflow tract in older children and young adults. The murmurs are ejection in character, confined to systole, and audible maximally in the aortic area. In children, these murmurs may arise secondarily to extreme anxiety, anemia, hyperthyroidism, fever, or any condition of increased systemic cardiac output.

In trained athletes, slower heart rates with increased stroke volume may give rise to short crescendo-decrescendo murmurs of low to medium pitch. Physical examination may suggest a relatively displaced thrusting apex and a physiologic S_3.

These murmurs must be distinguished from the systolic murmur of hypertrophic cardiomyopathy obstructions of the left ventricular outflow tract. The presence of a family history for hypertrophic cardiomyopathy or a family history of unexplained death in a young individual, particularly if associated with activity, is suggestive of hypertrophic cardiomyopathy. A systolic murmur that gets louder with performance of the Valsalva maneuver is considered almost diagnostic of hypertrophic cardiomyopathy with systolic anterior motion of the mitral valve. A reduction in venous return results in closer apposition of the septum and mitral valve and dynamic narrowing of the left ventricular outflow tract. In contrast, rapid squatting improves venous return; the left ventricular chamber size is enlarged, the mitral valve and septum are farther apart, and the murmur of hypertrophic cardiomyopathy gets softer. It is often difficult to be certain of the cause of this type of aortic murmur, and further investigations may be indicated.

Normal Continuous Murmurs

Venous Hum

The most common type of continuous murmur heard in children is the innocent cervical venous hum, which is most audible on the low anterior part of the neck just lateral to the sternocleidomastoid muscle but often extends to the infraclavicular area of the anterior chest wall. The murmur is generally louder on the right than on the left, is louder when the patient is sitting than when lying down, and is accentuated in diastole. Intensity varies from faint to grade III. Patients are occasionally aware of a loud hum. The murmur is quite variable in character, always low pitched and often described as rumbling, roaring, or whirring.

The venous hum is best accentuated or elicited with the patient in a sitting position and looking away from the examiner. The murmur often resolves or changes in character with lying down and may be eliminated or diminished by gentle compression of the jugular vein or turning the head toward the side of the murmur. The murmur is thought to arise from turbulence at the confluence of flow as the internal jugular and subclavian veins enter the thoracic inlet or perhaps from angulation of the internal jugular vein as it courses over the transverse process of the atlas.

Mammary Arterial Soufflé

The mammary arterial soufflé occurs most frequently late in pregnancy and in lactating women but may occur in rare cases in adolescence. The murmur arises in systole but may extend well into diastole, being audible maximally on the anterior chest wall over the breast. There is usually a distinct gap between the S_1 and the origin of the murmur; this gap is thought to relate to the delayed arrival of cardiac stroke volume at the peripheral vasculature. The murmur is generally high pitched and has an unusual superficial character but may vary considerably from day to day. Firm pressure with the stethoscope or digit pressure on the chest wall occasionally abolishes the murmur. The murmur is thought to be arterial in origin, arising from the plethoric vessels of the chest wall. The murmur must be distinguished from the continuous high-pitched murmur of an arteriovenous fistula or a PDA. Characteristically, the mammary arterial soufflé varies significantly from day to day, is present in a most distinctive patient population, and resolves with termination of lactation.

PHYSICAL EXAMINATION OF COMMON LESIONS WITH LEFT-TO-RIGHT SHUNT

Atrial Septal Defects

The most common form of ASD (Fig. 8.10) is the ostium secundum defect in the floor of the fossa ovalis. Blood flow through an ASD in

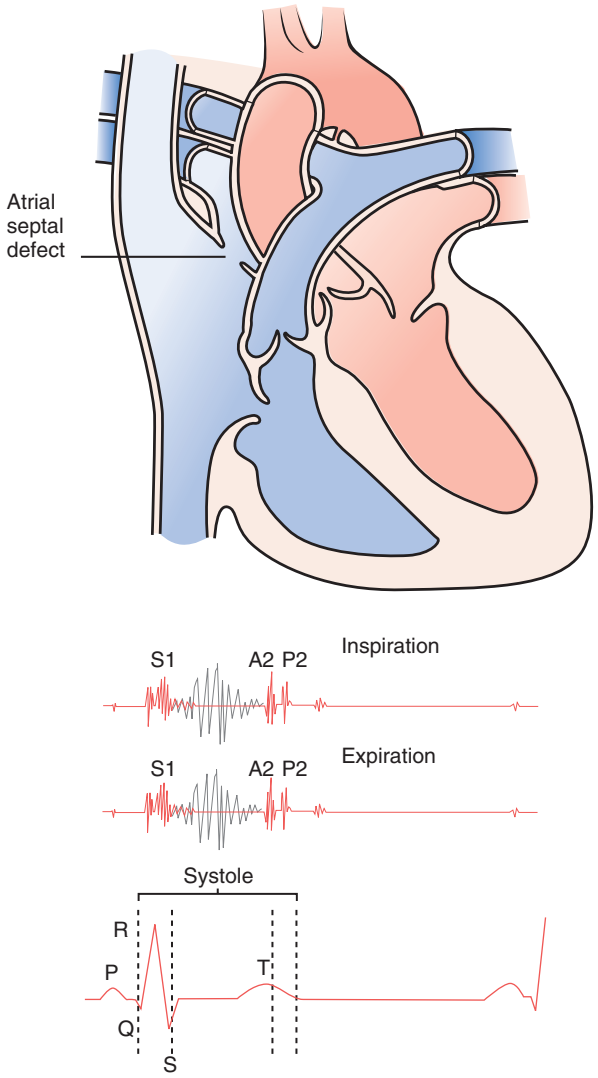


FIGURE 8.10 Atrial septal defects. The most common type of defect, the secundum atrial septal defect, is shown. Characteristically, in association with a large left-to-right shunt, wide and fixed splitting of the second heart sound occurs. The murmur is that of increased flow through the right ventricular outflow tract. The shunt flow through the defect, which occurs at low pressure, is inaudible.

the low-pressure atria is inaudible. The auscultatory findings in ASD are related to the consequences of increased blood volume that enters the right side of the heart. The right ventricular volume overload is associated with right ventricular overactivity and a right ventricular parasternal tap.

The right atrium and ventricle receive the blood returning from the body plus the blood shunted from left to right through the ASD. This causes a prolongation of right-sided heart emptying. The P_2 of the S_2 is often widely split and fixed (no respiratory variation).

Two types of murmur may be audible:

1. The typical pulmonary flow murmur is ejection systolic in character, generally of low intensity (grade II or III), and of low pitch. The crescendo-decrescendo murmur begins shortly after the S_1 and ends well before the S_2.
2. In patients with a large atrial shunt, there is typically a well-localized, low-pitched mid-diastolic flow rumble in the tricuspid area because of increased flow across the tricuspid valve.

ASDs may lead to pulmonary hypertension in the second and third decades of life. Treatment is surgical or by device closure during cardiac catheterization.

PATENT DUCTUS ARTERIOSUS

In this condition, the connection between the aorta and pulmonary artery that exists prenatally remains open after birth (Fig. 8.11).

The amount of shunt flow is dependent not only on the size of the ductus communication but also on the differential resistances of the systemic and pulmonary circulations. In some children, the PDA may produce significant left-sided heart volume overload and signs of high-output congestive heart failure.

The peripheral pulses associated with significant diastolic runoff to the pulmonary vascular area are bounding. Palpation may reveal a thrill in systole at the upper-left sternal edge (when the murmur is grade IV or greater); an abnormal left ventricular impulse; and, if the left-to-right shunt is large, a hyperdynamic and displaced apical impulse. The majority of patients have an asymptomatic murmur.

Premature infants often have persistence of ductal patency after birth. Initially, in the presence of neonatal lung disease and elevated pulmonary vascular resistance, the shunt volume is not large. After the lung disease improves, the presence of a PDA becomes apparent through the detection of a cardiac murmur and bounding pulses. Preterm infants with a PDA may show signs of heart failure, pulmonary edema, a hyperdynamic precordium, and difficulty in weaning from the ventilator. Treatment in preterm infants includes intravenous indomethacin or ibuprofen and fluid restriction; if these measures are unsuccessful, surgical ligation is generally indicated.

The PDA causes a continuous machine-like murmur, best heard in the pulmonary area. The murmur is generally high pitched, peaks in late systole, and continues well through the S_2. If the PDA is large, a mid-diastolic flow rumble may be heard at the apex because of relative mitral valve stenosis. Beyond the neonatal period, treatment is surgical ligation or device closure during cardiac catheterization.

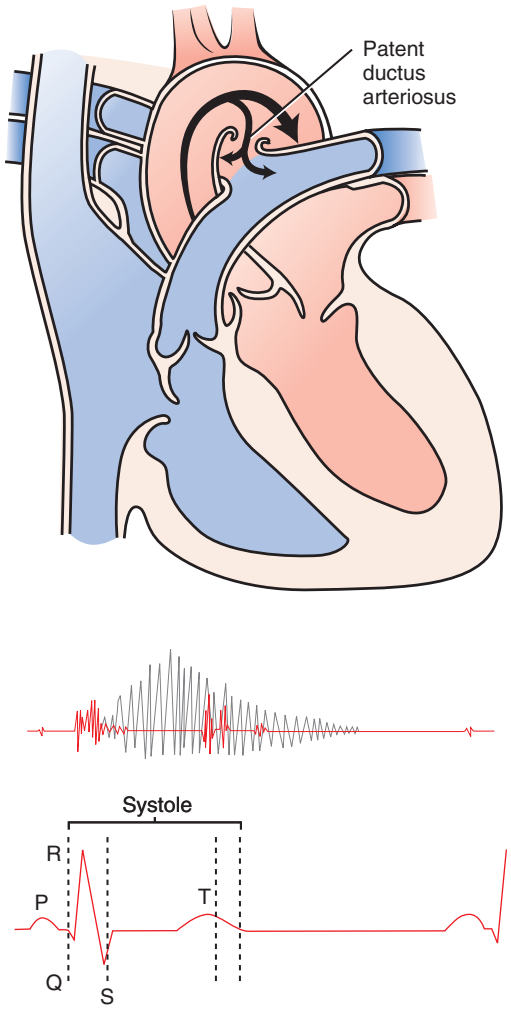


FIGURE 8.11 The patent ductus arteriosus consists of residual patency of a fetal communication between the two great arteries. Because the shunt occurs outside the heart, the murmur is continuous and high pitched if the defect is restrictive and the pulmonary artery pressures are low.

VENTRICULAR SEPTAL DEFECTS

These common developmental communications between the two ventricles (Fig. 8.12) may be classified as

- perimembranous
- muscular
- atrioventricular or inlet
- subarterial or outlet

The acoustic findings depend on five factors:

1. Size
2. Location
3. Shunt or defect flow
4. Pulmonary hypertension
5. Associated anomalies

All of these factors need to be addressed in the clinical description of a VSD.

The VSD (Fig. 8.13) causes a left-to-right shunt or, in rare cases, a right-to-left shunt, depending on the resistance to the flow of blood leaving the ventricles. The turbulence and thus the intensity of the murmur are directly proportional to the flow and pressure difference between the ventricles.

Size

A moderate-sized VSD that is restrictive (i.e., a pressure difference exists between the ventricles) causes a harsh blowing holosystolic murmur, which is often very loud and frequently associated with a palpable thrill.

The very restrictive or small VSD creates a high-pitched systolic murmur and causes little or no physiologic disturbance. Muscular

(See *Nelson Textbook of Pediatrics,* Fig. 426-6.)

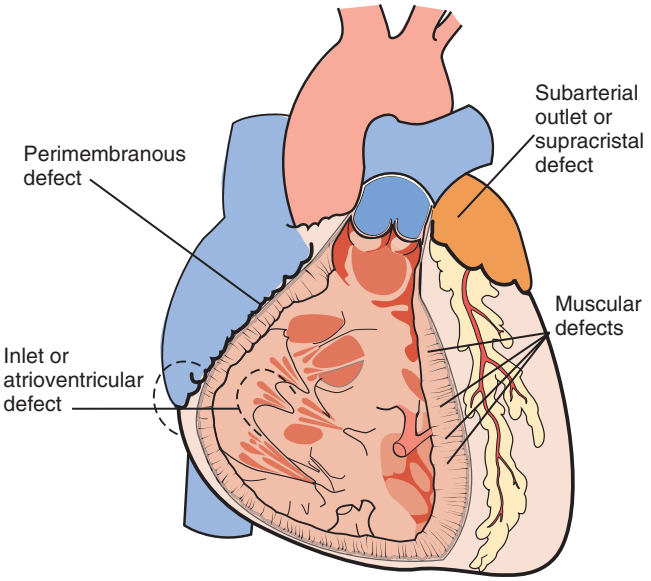


FIGURE 8.12 Anatomic types of ventricular septal defects. The 4 types of defects of the ventricular septum are shown. The most common type is the muscular defect, which commonly occurs in the anterior trabecular area of the septum. The perimembranous (often called membranous) defect occurs in the regions of the pars membranacea, or the embryonic bulboventricular foramina. The subarterial outlet, or supracristal defect, extends to the fibrous ring of the semilunar valves. The inlet or atrioventricular septal defect is that of the atrioventricular canal or embryonic atrioventricularis communis.

defects may close in mid-systole, which then abruptly stops shunt flow and the murmur before S_2.

In an unrestrictive or large VSD, no pressure difference exists between the two ventricles. This results in less turbulence and therefore a reduced intensity of the murmur.

Location

The perimembranous defect is best heard at the left sternal edge in the third left intercostal space. Muscular defects are heard variably from the sternal edge to the apex. Outlet or subarterial defects are best heard higher along the sternum.

Shunt Flow

If the volume of flow through the VSD (shunt flow) is large (i.e., more than 2-3 times normal ventricular outflow), a low-pitched, mid-diastolic flow rumble may be heard in the mitral area. The extra volume of blood returning from the pulmonary circulation to the left side of the heart creates this murmur of "relative" (not true anatomic) mitral valve stenosis.

Pulmonary Hypertension

High pressure in the pulmonary artery limits left-to-right shunt flow and murmur intensity. The pulmonary closure sound is louder and is either narrowly split or single.

Associated Anomalies

Frequently there are anomalies associated with a VSD, such as right- or left-sided heart outflow obstruction or aortic insufficiency. This may affect the character of the murmur.

Of importance is that the VSD murmur begins very early with the onset of left ventricular contraction, which may precede right ventricular contraction because the left ventricle is activated earlier. The

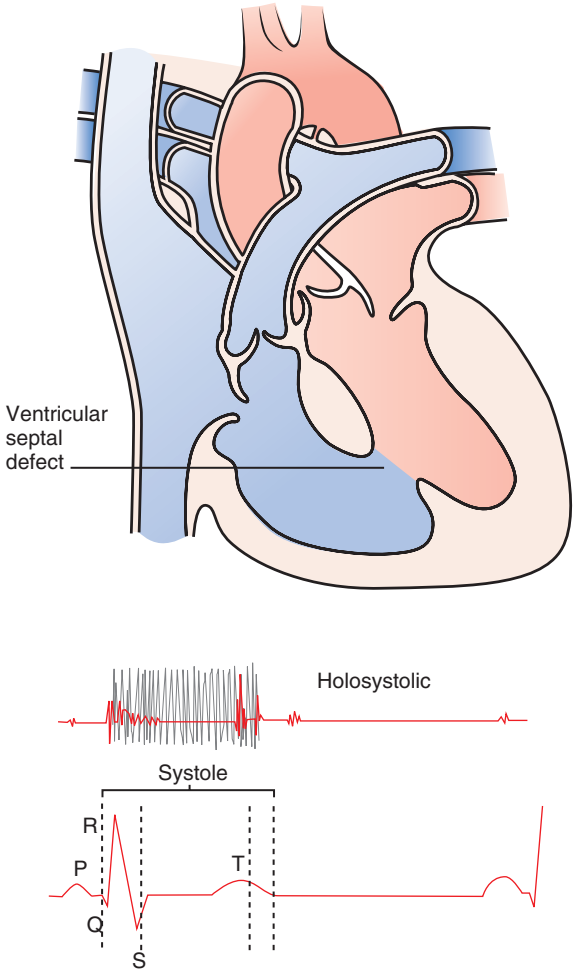


FIGURE 8.13 Ventricular septal defects. A ventricular septal defect is a communication between the high-pressure left ventricle and the lower-pressure right ventricle. The shunt flow begins with the onset of ventricular contraction before the period of ejection (isovolumic contraction) and consequently gives rise to a holosystolic murmur that obscures the first and often the second heart sounds. The murmur is high pitched if the defect is restrictive, and the right-sided heart pressures are low; however, the murmur may be low pitched or even inaudible if the defect is large or if the pulmonary artery pressures are high, as occurs in the newborn.

murmur commences during the period of isovolumic contraction and, if it is loud (grade III or greater), often obscures the S_1. Blood is ejected from the left ventricle to the right ventricle throughout systole, giving rise to a classical full-length, or "holosystolic," murmur. On occasion, VSD murmurs may not be full length. This may occur in a small muscular VSD that coapts or closes in mid-systole or, in rare cases, in the presence of heart failure with diminished systolic function.

Analysis of the S_2 in VSD is important and, in conjunction with precordial palpation, enables estimation of the pulmonary artery pressure. The larger the defect, the higher the pulmonary artery pressure and the earlier and louder the P_2 are. Thus, the split of S_2 may become very narrow, or the S_2 may even become single, a finding of great concern. In large defects, a balance exists between delayed P_2, caused by large pulmonary blood flow, and early P_2 caused by high pulmonary artery pressure. The wider the split of S_2, the less the concern is, because pulmonary vascular resistance is then likely to be low.

The intensity or loudness of a murmur relates to the combination of both flow and gradient across the defect. Pitch or frequency relates

to gradient alone. Thus, very small defects with small left-to-right shunt flow may have a soft, high-pitched murmur. In moderate-sized defects, the murmur is loud, often associated with a palpable thrill. In large defects with no restriction between the right and left ventricle, the murmur is low pitched and less intense as the pulmonary artery and right-sided heart pressures equate with the left-sided heart pressure.

In many children, the VSD spontaneously closes, as noted, and the murmur becomes softer and softer until it disappears with defect closure. In patients who develop increased pulmonary vascular resistance and a reduction in shunt flow and who are at risk for progressing to **Eisenmenger syndrome** (irreversible pulmonary vascular disease and cyanosis with right-to-left ventricular level shunt), the murmur also becomes quieter. Thus, a diminishing VSD murmur may be evolving into either a good or bad outcome. The treatment of a VSD includes management of heart failure and surgery.

COMPLETE ATRIOVENTRICULAR SEPTAL DEFECTS

There is great variation in the anatomy of atrioventricular septal defects (AVSDs). AVSDs (Fig. 8.14) occur in complete, partial, and intermediate forms. In the complete AVSD, the intracardiac defect extends between both the atria and ventricles. The atrial or ventricular extent of the defect may be the primary level of shunt flow; consequently, the defect may manifest primarily as either an ASD or VSD. Often the defects are large and unrestrictive. In addition, a common accompaniment of AVSD is a cleft in the left-sided atrioventricular valve, which may cause varying degrees of valve insufficiency. Approximately half of the children born with **Down syndrome** have congenital heart disease, the most common abnormality of which is complete AVSD. Maturation of the pulmonary arteries and small muscular arteries is delayed in children with Down syndrome, and elevated pulmonary vascular resistance early in life is common. Therefore, the lesion may be missed early in life because signs of congestive heart failure may not occur. It is recommended that all children with Down syndrome undergo echocardiographic evaluation. In patients with complete AVSDs, the electrocardiogram demonstrates an abnormally counterclockwise superior vector due to displacement of the AV node. If this finding is present, an echocardiogram should be obtained. Intermediate or partial AVSDs are less likely associated with Down syndrome.

In the partial form of AVSD, absence of the lower part of the interatrial septum, the **ostium primum**, is the major component of the abnormality. In such patients, the manifestation and examination are similar to those described for a secundum type of ASD. Often, mitral regurgitation is present and is apparent as an apical holosystolic murmur that obscures S_1. If the amount of mitral valve insufficiency is large, a mid-diastolic flow rumble of increased filling may be heard.

The manifestation and consequently the clinical signs in patients with AVSD vary considerably, depending on the patient's age, pulmonary vascular resistance, size and level of the defects, amount of valve insufficiency, and ventricular function. Patients with an AVSD often manifest the signs of congestive heart failure early in infancy. Surgical repair provides definitive treatment.

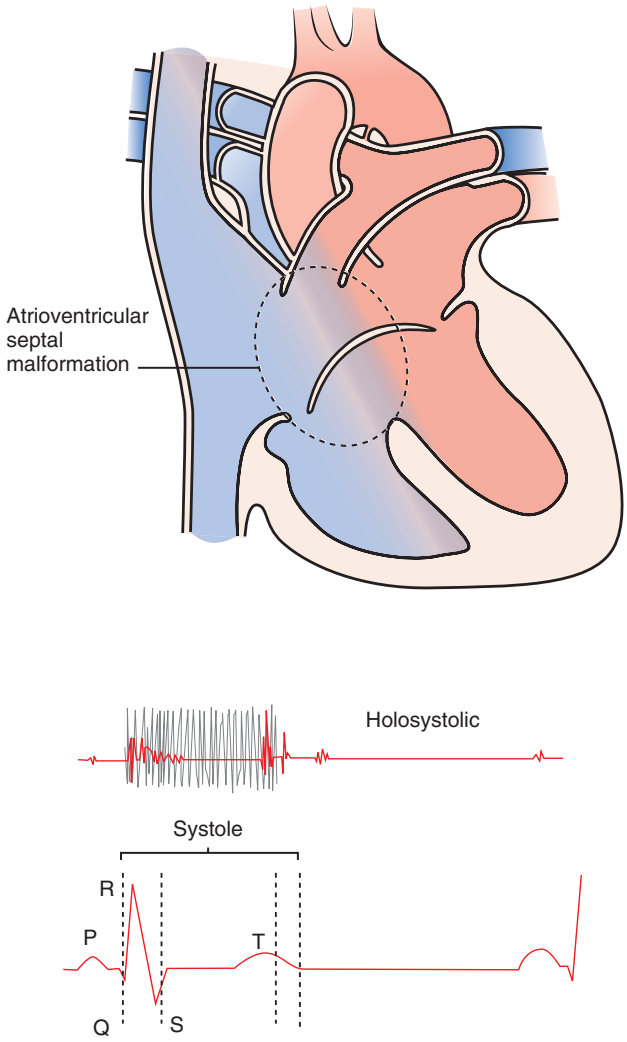


FIGURE 8.14 Complete atrioventricular septal malformation. The atrioventricular septal malformations vary markedly between a large atrial component with a restrictive ventricular communication to a large unrestrictive inlet ventricular septal defect. Consequently, their clinical manifestations also vary from that of an atrial septal defect to that of an unrestrictive ventricular septal defect.

PHYSICAL EXAMINATION OF COMMON LESIONS WITH RIGHT-TO-LEFT SHUNT: CYANOSIS

Tetralogy of Fallot

The tetralogy (Fig. 8.15) has 4 anatomic features:

1. VSD
2. Pulmonary stenosis
3. Dextroposition or rightward position of the aorta
4. Right ventricular hypertrophy

The functional significance of this anomaly is related to the degree of right ventricular outflow tract obstruction. There is a harsh ejection systolic murmur, heard best in the pulmonary area but also widely transmitted through the chest. The right ventricular outflow obstruction is most frequently a combination of muscular, annular, and valvular narrowing. Consequently, the P_2 is soft, delayed and is often inaudible. The VSD is typically large and unrestrictive. The prominent systolic murmur in tetralogy of Fallot is therefore not caused by the septal defect.

Patients with tetralogy of Fallot may present with moderate to severe degrees of right ventricular outflow obstruction, right-to-left ventricular level shunting, and varying degrees of cyanosis. Alternatively, the outflow obstruction may be mild, providing a predominant left-to-right shunt and causing the "acyanotic" or "pink" form of tetralogy of Fallot. In these patients, the degree of outflow obstruction becomes progressive; bidirectional flow develops and, finally, a dominant right-to-left shunt emerges.

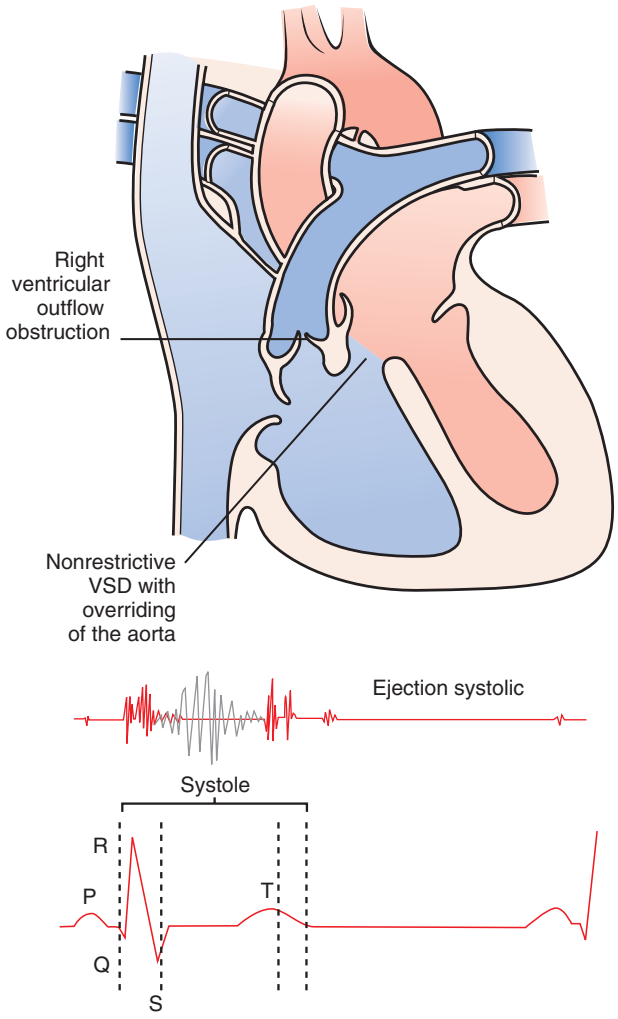


FIGURE 8.15 Tetralogy of Fallot. The 4 anatomic malformations seen in association with tetralogy of Fallot include an unrestrictive perimembranous ventricular septal defect (VSD), overriding of the aorta, right ventricular hypertrophy, and an obstructive right ventricular outflow tract. The cardiac murmur in tetralogy, a harsh loud ejection systolic murmur, arises from the turbulence generated in the right-sided heart outflow. Because the VSD is unrestrictive and the right- and left-sided heart pressures are equal, the VSD generates no sound. The pulmonary closure sound is often soft or inaudible.

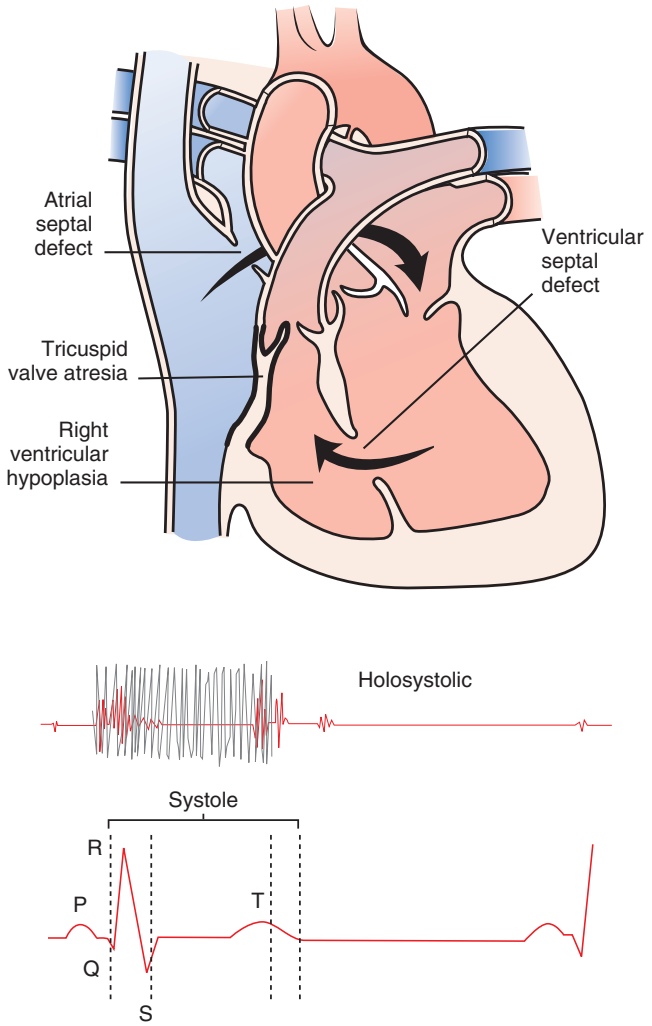


FIGURE 8.16 Tricuspid valve atresia. In this condition, the murmur most often detected is a holosystolic murmur of a communicating ventricular septal defect or an ejection systolic murmur related to an obstructing pulmonary outflow.

One aspect of tetralogy physiology is the variable degree of desaturation that may occur as a consequence of the reactive nature of the right ventricular outflow obstruction. The sudden development of severe reactive obstruction in response to temperature, fever, illness, dehydration, or intense crying may precipitate a **hypercyanotic** or **tetralogy spell**. Either increased infundibular reactivity or decreased systemic vascular resistance is responsible for the diminished pulmonary blood flow. This life-threatening event manifests as profound cyanosis, tachypnea, and dyspnea, progressing to acidosis, unconsciousness, and death. During a spell, the outflow tract murmur disappears with the diminution in pulmonary blood flow.

Tetralogy of Fallot is a consequence of developmental anterior displacement of the conal or outlet septum and failure to adjoin with the muscular trabecular interventricular septum. Because conal tissue is needed for closure of the membranous ventricular septum, the anterior displacement and hypoplasia of the conus results in a VSD, which is characteristically unrestrictive. The aorta extends more to the right, which results in overriding of the aorta.

In cases in which there is a predominant left-to-right shunt, the murmur is a long, loud ejection systolic murmur and may overwhelm and obscure the S_1. The murmur extends up the left sternal border (pulmonary area) and throughout both lung fields. The right ventricle is at systemic pressure, and the pitch of the murmur is quite high. There is a right ventricular parasternal impulse and often a palpable thrill in the pulmonary outflow region.

In cyanotic tetralogy of Fallot, the loudness or intensity of the murmur diminishes as the pulmonary blood flow decreases. The systolic murmur remains high pitched, harsh, and ejection in shape. The S_1 remains loud or normal; the S_2 is single.

In the most severe form of tetralogy, pulmonary atresia with VSD, there is no pulmonary outflow murmur at all. Definitive corrective treatment of tetralogy of Fallot is surgical.

TRICUSPID VALVE ATRESIA

In tricuspid valve atresia (Fig. 8.16), the tricuspid valve does not develop, and in its place there may be an imperforate membrane or a

thick muscle wedge. The right ventricle is usually very small; the left ventricle compensates and is large. A dynamic diffuse left ventricular cardiac impulse is palpable. All systemic venous blood returning to the right atrium must pass across at atrial septal level to enter the left atrium and then the left ventricle. Pulmonary blood flow occurs most often as a consequence of a VSD or, in rare cases, is dependent on the ductus arteriosus. The electrocardiogram reveals an abnormally superior left axis. Examination reveals a VSD murmur. The softer and shorter the murmur, the less the pulmonary blood flow is, so that, just as in tetralogy of Fallot, the softer the murmur, the more severe the cyanosis is. If there is enough pulmonary blood flow, both P_2 and A_2 may be heard. Palliative surgery is required.

PULMONARY ATRESIA WITH INTACT VENTRICULAR SEPTUM

There are two forms of pulmonary valve atresia. The first is pulmonary atresia with VSD and generally a long fibrous or muscular outflow atresia, which is the most severe malformation on the spectrum of tetralogy of Fallot. The second form occurs in association with an intact interventricular septum (Fig. 8.17), and right-sided heart hypoplasia is usually then present.

The cardiac impulse in hypoplastic right ventricle with pulmonary atresia may be right ventricular even though the dominant ventricle is the left. In contrast to tricuspid valve atresia, a VSD is not part of this lesion. The source of the pulmonary blood flow in the neonate is a ductus arteriosus with left-to-right shunt. A murmur from this ductus may be audible. There is a single S_2 (aortic closure). On occasion, there is tricuspid valve regurgitation, which may be confused with a VSD murmur. The murmur is high pitched, because the right ventricular pressures are very high. The electrocardiogram helps differentiate tricuspid valve and pulmonary atresia. In both disorders, left ventricular hypertrophy is present, but in pulmonary atresia, there is a normal inferior vector. Echocardiography confirms the diagnosis. There is usually profound cyanosis.

Intravenous prostaglandin therapy is required to ensure ductal patency and pulmonary blood flow in the neonatal period. Surgical repair is usually palliative.

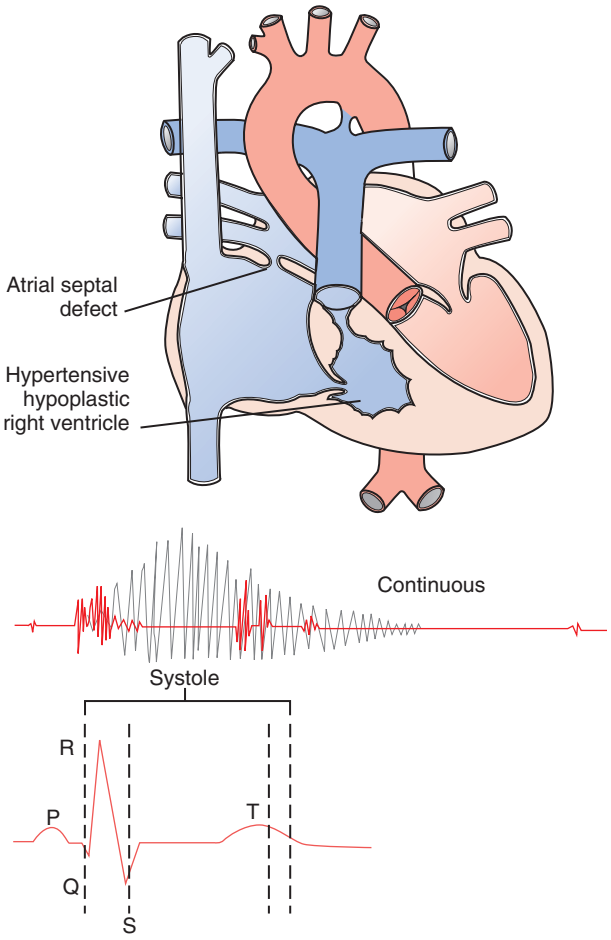


FIGURE 8.17 Pulmonary atresia with intact septum. Characteristically, the defect manifests in the cyanotic neonate. Most often, a continuous murmur of a patent ductus arteriosus is audible. Less often, a high-pitched murmur of tricuspid valve insufficiency may be heard.

TRANSPOSITION OF THE GREAT ARTERIES

In transposition of the great arteries (Fig. 8.18), the aorta arises from the morphologic right ventricle, and the pulmonary artery arises from the morphologic left ventricle. In transposition of the great arteries, desaturated systemic venous blood returns to the right atrium, passes to the right ventricle, and is returned to the aorta and thus to the systemic circulation. Any oxygenation occurring in this setting is the result of mixing of blood with the pulmonary circulation at the ductal, atrial, or ventricular level.

Transposition of the great arteries with an intact ventricular septum manifests in the neonatal period with profound cyanosis in an infant

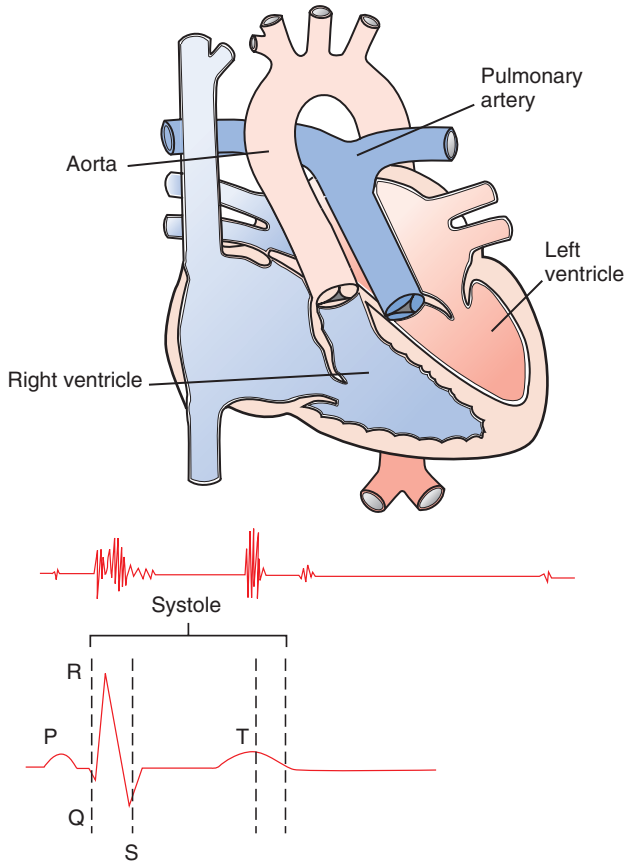


FIGURE 8.18 Transposition of the great arteries. The aorta in this condition arises anteriorly, giving rise to a loud, single second heart sound. Many profoundly cyanotic full-term newborns with no audible murmur have transposition of the great arteries.

whose saturations do not improve with oxygen administration; this is the so-called **hyperoxia test**. There is a pronounced right ventricular impulse, and the A_2 is loud because it is anterior. There may be a faint soft short ejection murmur that is audible along the left sternal border as a result of increased pulmonary blood flow. However, there are often no murmurs. Heart failure is not expected. The P_2 is often not heard.

If there is a VSD, the patient may not present in the neonatal period. The minimal cyanosis may be difficult to detect. Such infants usually become ill at 2-3 weeks of age as a result of congestive heart failure rather than hypoxia. The examination findings are very different, because both ventricles are very hyperdynamic. The heart is large; there is often a palpable thrill and a loud systolic murmur.

Treatment consists of corrective surgical switching of the great vessels.

HYPOPLASTIC LEFT HEART SYNDROME

Hypoplastic left heart syndrome (Fig. 8.19) consists of varying degrees of left-sided heart (mitral valve, left ventricle, aortic valve, or arch) hypoplasia or atresia such that the left ventricle cannot support the systemic circulation. In the first day or two after birth, the neonate may not be recognized as being ill if the ductus arteriosus remains open and the right ventricular output contributes to the systemic output. When the ductus begins to close, perfusion deteriorates, the pulses are diminished, acidosis develops, and death ensues.

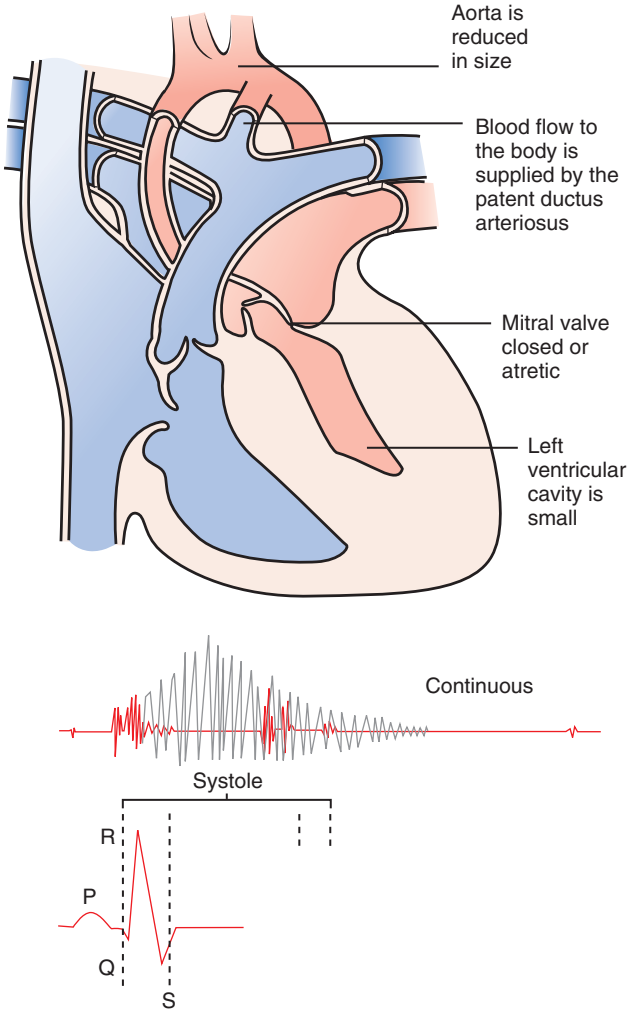


FIGURE 8.19 Hypoplastic left heart syndrome. In this condition, the systemic circulation is supplied from the right ventricle via the ductus arteriosus. The continuous murmur of ductal flow that may be heard is generally low pitched as a result of equal pulmonary and aortic pressures.

The affected infant is often tachypneic, gray, and poorly perfused. There may be considerable pulmonary blood flow and a dynamic right ventricle impulse. An ejection systolic murmur may be audible in the pulmonary area. The heart function may be very poor, and the precordial and auscultatory examination findings may be quiet. A significantly restrictive ASD may cause profound pulmonary venous congestion and poor oxygenation.

After intravenous prostaglandin E_1 has been given, causing opening of the ductus arteriosus, a reasonable systemic output and palpable pulses should return.

Treatment includes the staged Norwood palliative repair to single-ventricle Fontan operation or heart transplantation.

PHYSICAL EXAMINATION OF COMMON LESIONS WITH SIMPLE OBSTRUCTION

In areas of obstruction, the gradient or pressure difference across an obstruction relates to the severity of the narrowing, the flow across the narrowing, and the pressure able to be generated (i.e., the cardiac function).

PULMONARY VALVE STENOSIS

The hemodynamic abnormality in pulmonary valve stenosis (Fig. 8.20) is attributable to increased pressure within a right ventricle that is attempting to eject through a narrowed or obstructed valve. The more severe the stenosis, the higher the intraventricular pressure is until cardiac failure occurs.

This condition is characterized by an ejection systolic murmur, heard best in the pulmonary area. The murmur is diamond-shaped. With increasing valvular obstruction, the murmur becomes louder and higher pitched and peaks later in systole. The P_2 is very helpful because the more severe the pulmonary valve stenosis, the more delayed and less intense the P_2 is.

An ejection click, caused by abrupt arrest of leaflet excursion in early systole, frequently precedes the ejection systolic murmur. The more severe the pulmonary valve stenosis, the earlier and softer the pulmonary ejection click is. In other forms of right ventricular outflow obstruction, such as supravalvular stenosis and subvalvular stenosis, or in the setting of a dysplastic or malformed pulmonary valve, an ejection click is not audible.

In newborns with very severe critical pulmonic stenosis, cyanosis, and low cardiac output, the examination findings may be quite different. There may be no pulmonary ejection click, and the murmur may be very short, soft, or both.

Palpation in pulmonic valve stenosis may reveal a palpable thrill in the pulmonary area and an abnormal right ventricular impulse (except in mild cases).

Treatment is transcatheter balloon valve dilatation.

AORTIC VALVE STENOSIS

The hemodynamic impact of aortic valve stenosis (Fig. 8.21) is increased pressure in the left ventricle. The more severe the stenosis, the higher the left ventricular pressure is.

The apex beat is of a thrusting character and is not displaced in the absence of left-sided heart failure. Palpation, except in very mild cases,

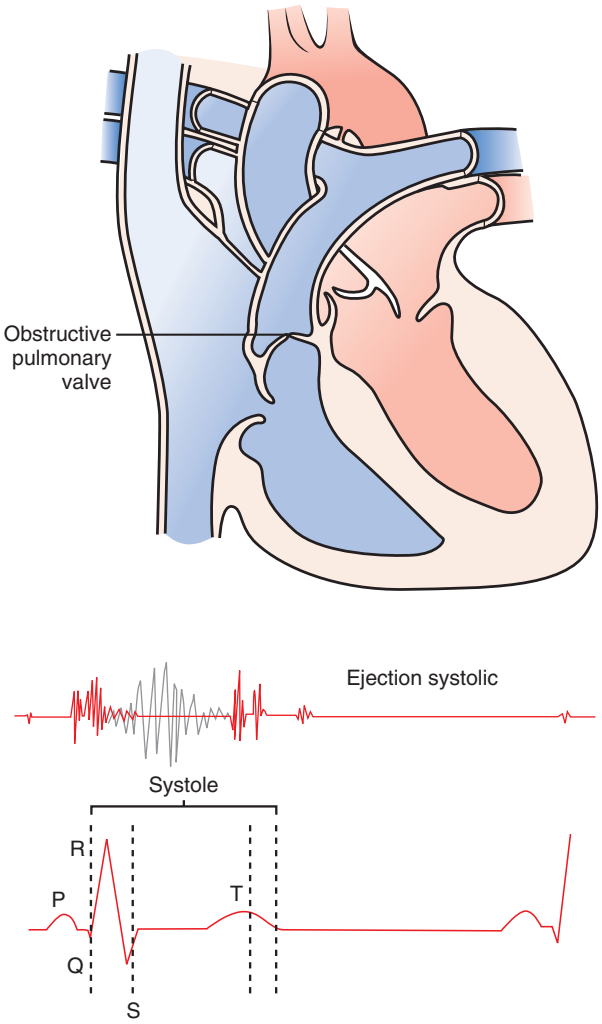


FIGURE 8.20 Pulmonary valve stenosis. Pulmonary valve stenosis gives rise to a rough ejection systolic murmur that is most prominent in the pulmonary area and radiates equally to both lung fields. The presence of an ejection click distinguishes valve obstruction from subvalvular or supravalvular stenosis.

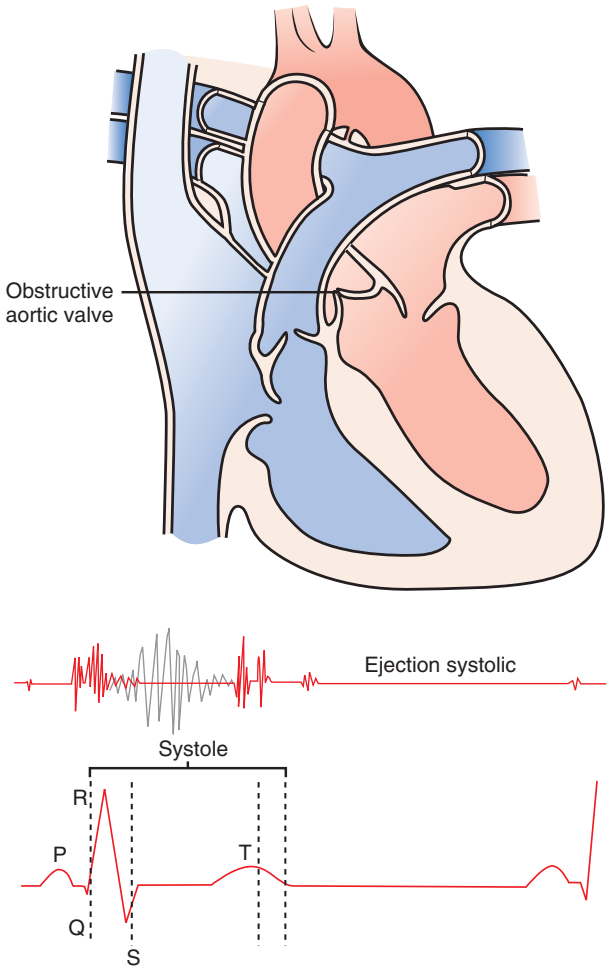


FIGURE 8.21 Aortic valve stenosis. The ejection systolic murmur from aortic valve stenosis is audible both at the apex and in the aortic area. The aortic area extends up to the carotid arteries. There is often a palpable thrill in the suprasternal notch. The pitch and peaking of the murmur allows estimate of the severity of stenosis. Note that a quiet and low-pitched murmur may suggest poor ventricular function and low output.

reveals a suprasternal notch thrill and often a carotid systolic thrill. If the murmur is grade IV or greater, a precordial thrill is also palpable at the upper-right sternal border (aortic area).

The murmur of aortic stenosis is a rough, harsh, diamond-shaped ejection systolic murmur. It is heard best in the aortic area but often extends into the neck and throughout the precordium.

A soft, short ejection murmur that peaks in systole indicates a mild degree of valve obstruction, whereas a loud, long, and late-peaking murmur, often associated with a palpable thrill, reflects more severe stenosis.

An ejection click often precedes the murmur and is heard best at the apex. The click intensity is inversely proportional to the severity of the valve narrowing. A loud aortic valve **ejection click** is often present in patients with a two-leaflet or bicuspid aortic valve even if there is no valve stenosis.

The splitting of the S_2 is normal. The paradoxical split, occurring when there is a large delay of A_2, is quite rare in children and young adults; it is seen in older people with calcific aortic valve stenosis and a failing left ventricle.

In newborns with severe or critical aortic stenosis and low cardiac output, the examination findings may be very different. There is often no aortic ejection click, and, strikingly, the murmur may be short, soft, or both. Significant heart failure and poor perfusion are present in such neonates.

Two other major types of aortic stenosis exist: subvalvular and supravalvular. Neither has an aortic ejection click. In **supravalvular aortic stenosis** (the major cardiac lesion associated with Williams syndrome), the murmur is usually in the aortic area, whereas in **subvalvular aortic stenosis**, the murmur position may extend to the left sternal border or the apex.

The **bicuspid aortic valve** is the most common of all congenital malformations of the heart, found in almost 2% of the general population. The normal aortic valve has three leaflets of equal size. The bicuspid valve has two functional leaflets, one generally larger than the other. The bicuspid aortic valve is often only mildly stenotic or is often unobstructed. The anomaly is recognized from the presence of an aortic ejection click. The ejection click is often mischaracterized as a split S_1, which is a very rare occurrence in children. Asymmetric stresses on the valve leaflets predispose to calcification, dysfunction, and deterioration after many years. The valve is also at risk for the development of infective endocarditis.

Treatment of severe aortic valve stenosis may include surgical or balloon valvotomy and often eventual valve replacement.

COARCTATION OF THE AORTA

Coarctation occurs in association with congenital cardiac anomalies or in isolation. There are fundamentally two forms of coarctation (Fig. 8.22). The more common form has been termed **juxtaductal or adult coarctation** and is typically a discrete area of aortic narrowing or indentation of ductal tissue in relationship to the ductus arteriosus or ligamentum. The second type of coarctation has been termed **infantile coarctation** and includes varying degrees of transverse and isthmic aortic arch hypoplasia.

The hemodynamic abnormality caused by a coarctation of the aorta is a high systolic pressure proximal to the area of narrowing, in the ascending aorta, the brachiocephalic vessels, and the left ventricle.

The diagnosis of coarctation of the aorta is made from recognition of systemic hypertension in the right arm and decreased arterial pulsation in the femoral arteries and the dorsalis pedis in comparison with that in the brachial arteries. The femoral pulses may be absent, or they may be diminished and delayed. In some cases, the left brachial pulse may be diminished as a result of involvement of the left subclavian artery in the site of narrowing. In rare cases, the right subclavian artery may arise aberrantly below the level of the coarctation, causing the pulse in this arm to be diminished. Therefore, brachial pulses must be felt on both sides and compared with the femoral pulses. The blood pressure must be obtained in both arms as well as in one leg. There is seldom any significant or consistent alteration in the heart sounds unless there is associated aortic valve disease. Up to 40% of patients with juxtaductal coarctation of the aorta have an associated bicuspid aortic valve, usually without stenosis. In these cases, there is an aortic ejection click. More complicated heart lesions, often unrestrictive VSDs or AVSDs, are often seen in association with isthmic arch hypoplasia.

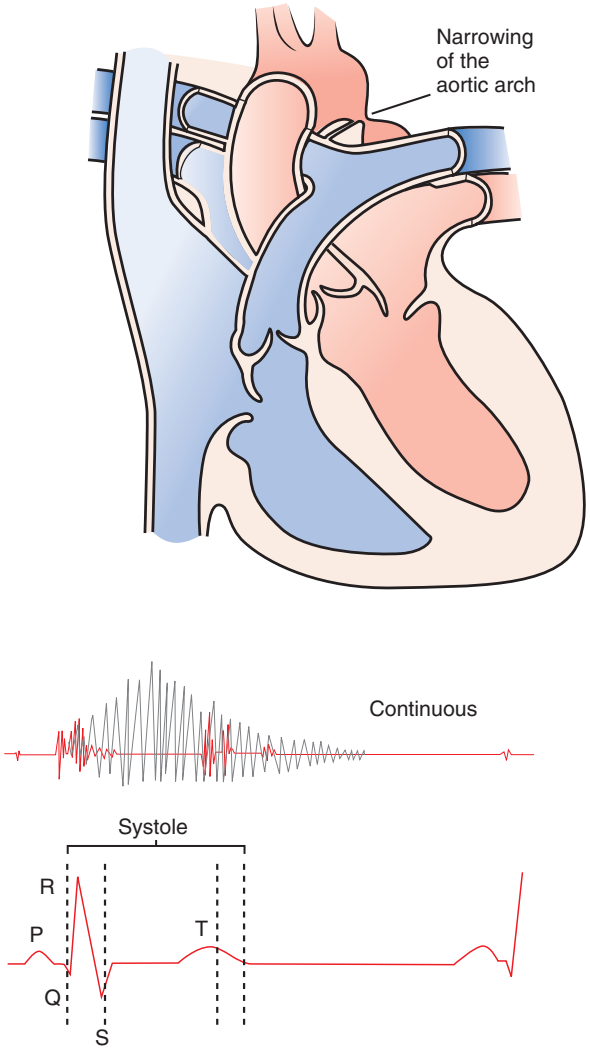


FIGURE 8.22 Coarctation of the aorta. The murmur of coarctation is often audible both anteriorly and posteriorly between the scapulae. It is a continuous murmur extending well into diastole.

The murmur of coarctation is of the ejection or continuous type, is rarely louder than grade III, starts well after S_1, and may peak late in systole or extend into diastole. The point of maximal cardiac activity is variable and is most often palpable in the fifth or sixth intercostal space, extending out to the axillary line. The murmur of coarctation extends to and is often loudest in the interscapular area posteriorly.

As with aortic stenosis and obstruction of the left-heart outflow, the newborn with coarctation may present with signs of low output and heart failure. Prostaglandins have proved useful in this circumstance, alleviating the obstruction by dilating reactive muscle in the aortic wall, which may have extended from the ductus or with opening of the ductus itself, enabling right-to-left ductal flow to the lower body and relieving associated pulmonary hypertension.

Treatment in the neonate is surgical. However, after infancy, aortic coarctation angioplasty with balloon or stent placement may be considered, as may surgery.

MITRAL VALVE STENOSIS

Congenital mitral valve stenosis (Fig. 8.23) is uncommon; when it occurs, it is usually in association with additional left-sided heart obstructive abnormalities, particularly coarctation of the aorta, which is termed the **Shone complex**. The most common type of significant stenosis is caused by a **single** or **"parachute" papillary muscle**. In its most severe form, it is part of the hypoplastic left ventricle syndrome, in which the valve is small, very stenotic, or atretic. In affected patients, cyanosis, heart failure, and poor perfusion are evident within the first few days after birth.

The leaflets in congenital stenosis are very immobile, and there is seldom the accentuation of the S_1 or an opening snap, which is characteristic of acquired or rheumatic mitral valve stenosis.

The murmur of mitral valve stenosis arises from the increased velocity of blood flow across the relatively immobile mitral leaflets during diastolic filling of the left ventricle. This causes a characteristic low-pitched mid-diastolic flow rumble best heard in the mitral area.

Rheumatic mitral valve stenosis is common in many areas of the world but is uncommon in the United States. As a consequence of mitral obstruction, the left atrial and pulmonary venous pressures are elevated. Often there is a reflex or secondary elevation of pulmonary artery pressures caused by thickening or constriction of small muscular pulmonary arteries. The features of pulmonary hypertension, including a prominent right ventricular tap, single loud or palpable S_2, and high-pitched pulmonary insufficiency may be apparent.

Excursion of the thickened leaflets often causes an early diastolic high-pitched opening snap before the onset of the murmur. In severe stenosis, strong atrial contraction late in diastole may create a late diastolic crescendo murmur. A loud S_1 is often heard in this condition.

(See *Nelson Textbook of Pediatrics,* p. 2208.)

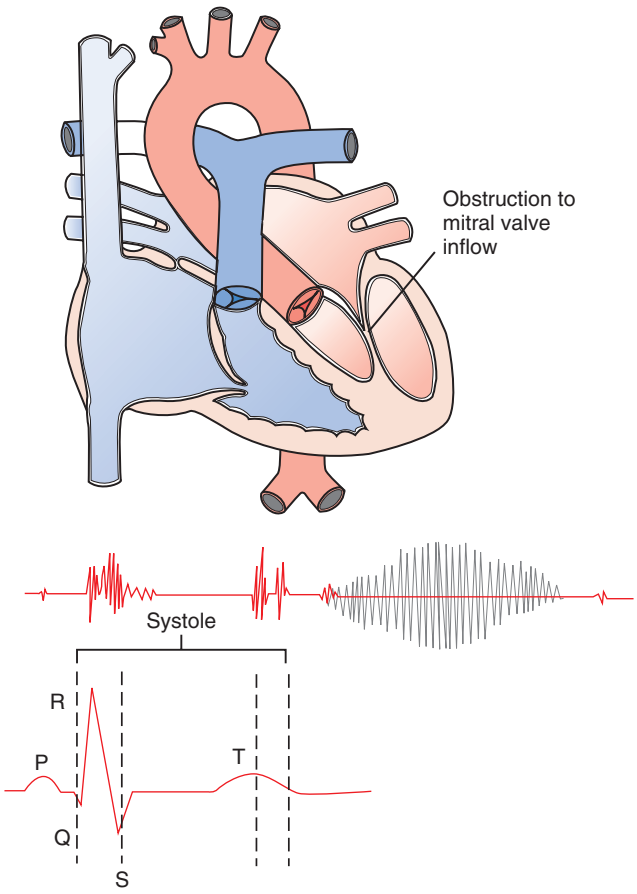


FIGURE 8.23 Mitral valve stenosis. The murmur of mitral valve stenosis occurs during the period of passive and active filling of the ventricle as turbulence occurs across the obstructive mitral valve. Pulmonary hypertension often arises as a consequence of the downstream obstruction.

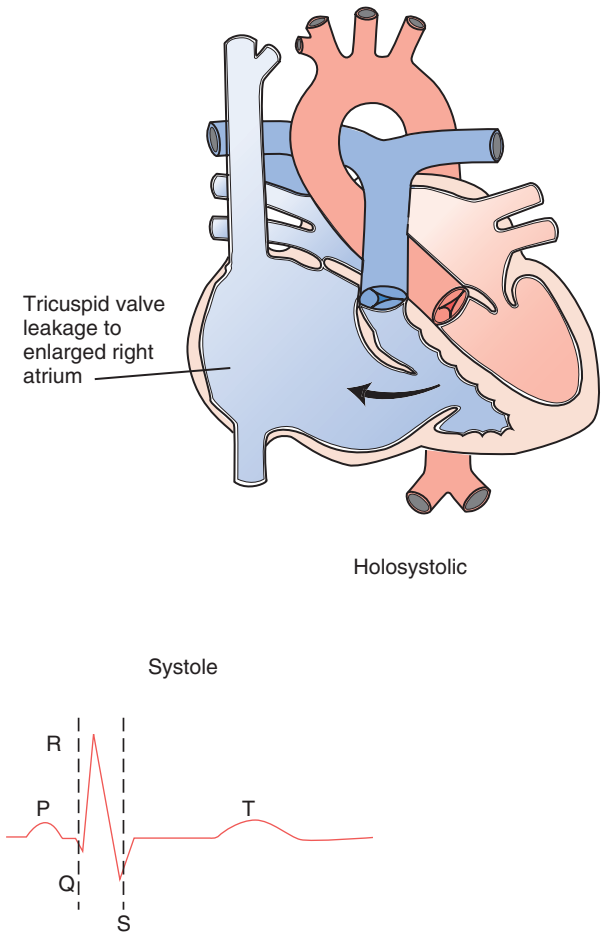


FIGURE 8.24 Tricuspid valve insufficiency. The holosystolic murmur of tricuspid valve insufficiency is low pitched in the absence of any pulmonary outflow obstruction. This makes tricuspid valve insufficiency very challenging to hear.

ATRIOVENTRICULAR VALVE AND SEMILUNAR VALVE INSUFFICIENCY

Tricuspid Valve Regurgitation

Tricuspid valve regurgitation (insufficiency) (Fig. 8.24) is uncommon in childhood in the absence of additional abnormalities. It may be a consequence of pulmonary artery hypertension, in which the high-pressure right ventricle contributes to a high-pitched holosystolic murmur at the lower-left or lower-right sternal border (tricuspid area).

Less often, tricuspid valve insufficiency may occur in association with a displaced and malformed tricuspid valve (**Ebstein anomaly**), in which case the pulmonary arterial and right ventricular pressures are not elevated, and the holosystolic murmur is low pitched. The features of right-sided cardiac murmurs vary much more with the respiratory cycle than do left-sided heart murmurs. There may be signs of right-sided heart failure: an enlarged pulsatile liver and, in the older child, a prominent V wave pulsation in the neck veins.

Mitral Valve Insufficiency

Mitral valve insufficiency (Fig. 8.25) is associated with a diffuse and dynamic apical impulse. If the volume of regurgitant flow is great, a bifid or double apical impulse of a palpable S_3 may be apparent.

The insufficiency jet of blood from the powerful left ventricle to the thin-walled left atrium causes a high-pitched blowing holosystolic murmur that has an abrupt onset. This murmur is heard best with the diaphragm of the stethoscope placed anteriorly in the mitral area. The systolic murmur radiates to the axillae.

The S_1 is usually of normal to increased intensity, but if the valve abnormality is rheumatic in origin, it may be sufficiently deformed that S_1 is quite soft. If the mitral regurgitation is quite significant, an S_3 filling sound is heard, often associated with a mid-diastolic flow rumble of "relative" mitral valve stenosis. Mitral valve insufficiency may be seen as a congenital lesion, in response to dilated annulus secondary to heart failure, during acute rheumatic fever, or as part of the mitral valve prolapse spectrum.

Mitral Valve Prolapse

This common condition of adolescents and young adults manifests as laxity of the mitral valve and results in slippage or displacement of the valve leaflets backward into the left atrium during systole (see Fig. 8.25).

The sudden tensing of the mitral valve often causes a mid-systolic click or sometimes multiple clicks that can be heard best in the mitral area. The click is frequently followed by a late high-pitched systolic murmur of mitral valve insufficiency. The timing of the click or clicks and the intensity of the murmur often vary with body position. When the patient is sitting up (and even more so during standing), the murmur gets louder or may be heard even when no murmur was heard

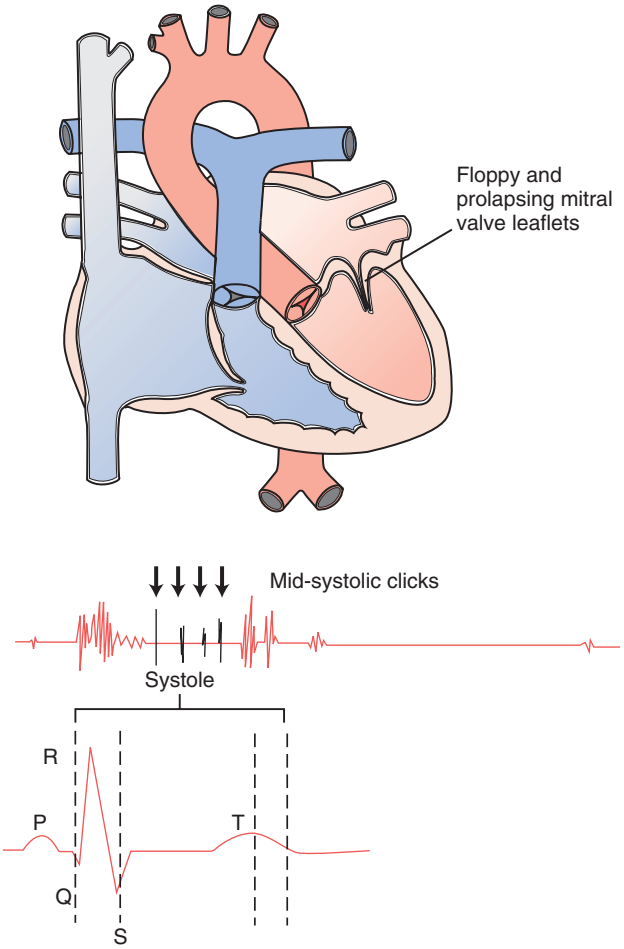


FIGURE 8.25 Mitral valve prolapse. The auscultatory examination findings can be very distinctive, with one or more sharp clicks being heard throughout systole. A late systolic high-pitched murmur may arise if mitral valve insufficiency occurs.

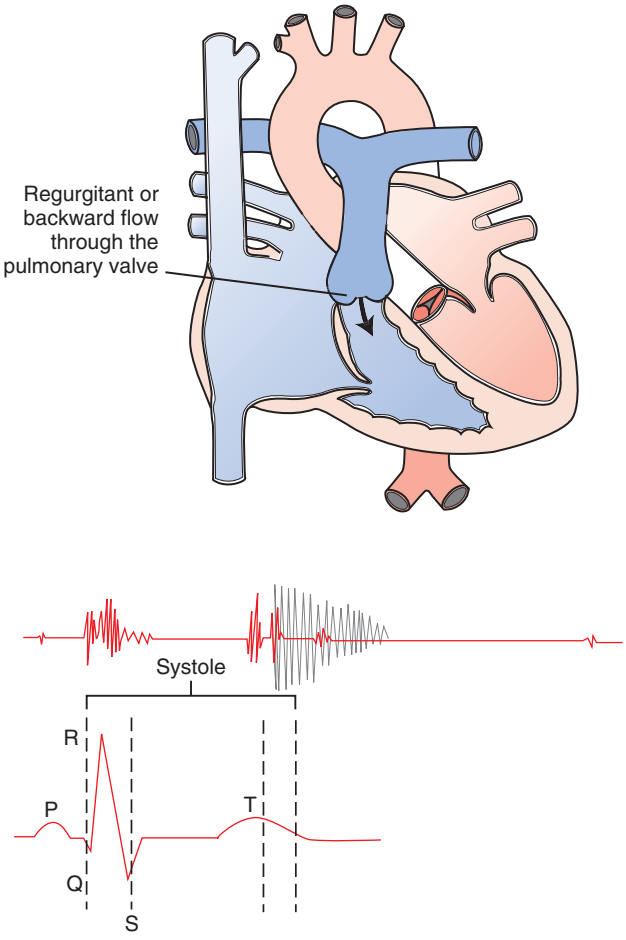


FIGURE 8.26 Pulmonary valve insufficiency. A low-pitched early diastolic murmur is heard just after the second heart sound. The murmur characteristically tapers into diastole.

when the patient was lying down. This is because the left ventricular architecture changes in the upright position. In rare cases, the position change may result in a late systolic murmur's becoming full length, although with late accentuation. The electrocardiogram often shows unusually anterior and superior T waves with prominent U waves, which suggests papillary muscle dysfunction.

Mitral valve prolapse does not usually progress in childhood, but it may be associated with supraventricular tachycardia, chest pain, and possibly endocarditis or cerebrovascular embolism. Ventricular tachycardia and fibrillation may occur in adults, but sudden cardiac death is very unusual during childhood and adolescence. Thickening of the valve, in addition to prolapse, increases the risk of these complications.

Pulmonary Valve Insufficiency

Pulmonary valve insufficiency (Fig. 8.26) rarely if ever occurs in isolation. Most often, congenital regurgitation of the pulmonic valve occurs in association with a pulmonary outflow obstruction such as in the **absent pulmonary valve syndrome**.

When the pulmonary arterial pressure is low, valve insufficiency is recognized by a very low- to medium-pitched early diastolic murmur that starts with P_2. This is heard best in the pulmonary area and extends for a short distance down the left sternal edge.

The more common types of pulmonary regurgitation are acquired, commonly after surgery for severe pulmonary valve stenosis, as occurs with tetralogy of Fallot, when the pulmonary outflow patch is placed and the valve leaflets are deficient or absent. Because no P_2 exists, the murmur often appears to start significantly after S_2. Because these patients often have surgically acquired right bundle branch block, the pulmonary valve closure would be well separated from aortic valve closure if the sound could be heard. The diastolic decrescendo murmur begins at that time.

Pulmonary hypertension, particularly when associated with a high pulmonary vascular resistance, is a common cause of secondary pulmonary insufficiency. Often, a pulmonary ejection click may be present because of the dilated pulmonary root. The S_2 is narrowly split or single because the high pulmonary artery diastolic pressure closes the valve early. A diastolic decrescendo murmur then begins with pulmonary valve closure and is high in frequency because the pulmonary artery pressure is high.

Aortic Valve Insufficiency

Congenital insufficiency of the aortic valve (Fig. 8.27) is rare and is usually mild and may not be audible. The valve may or may not be bicuspid. There is usually an aortic ejection click that is well separated from S_1, does not vary with respiration, and is usually best heard at the apex. The S_2 split is normal, although the A_2 may be loud and may have a "tambour" quality.

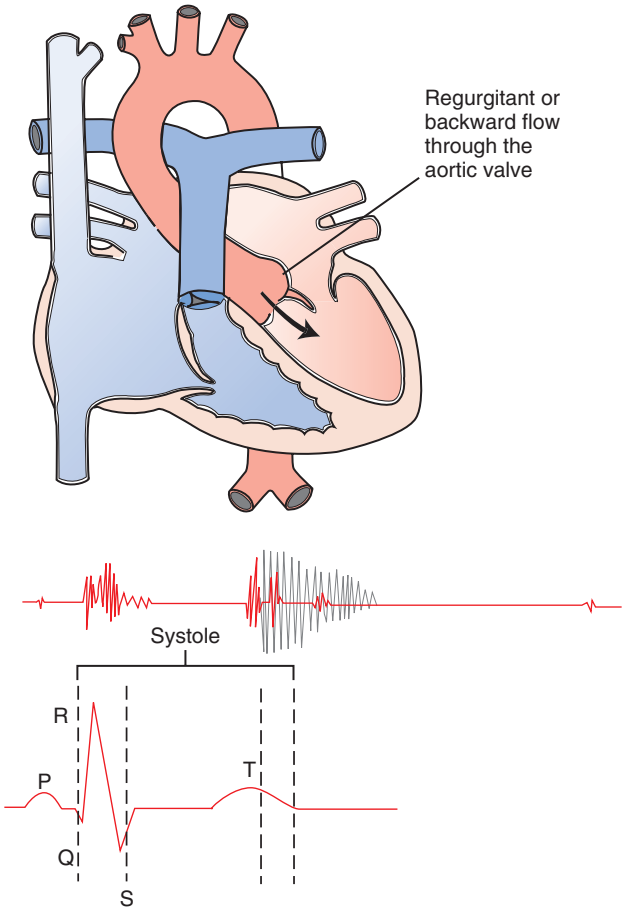


FIGURE 8.27 Aortic valve insufficiency. In contrast to the low-pressure murmur of pulmonary valve insufficiency (in the absence of pulmonary hypertension), the murmur of aortic valve insufficiency is high pitched and audible from the aortic area extending to the apex. The peripheral pulses and the intensity and length of the murmur provide clinical quantification of the magnitude of regurgitant flow.

After closure of the aortic valve (A_2), regurgitation of leakage at this site creates the high-pitched, early diastolic decrescendo murmur of aortic insufficiency. This murmur is heard best at the third left or right intercostal space while the patient is sitting. The pulse pressure is normal if the leak is mild.

The most common form of aortic insufficiency is acquired, most often as a consequence of severe **rheumatic carditis**, and can be present in both acute rheumatic fever and chronic rheumatic heart disease. In acute insufficiency, there is usually no aortic ejection click. The left ventricular impulse is abnormal and hyperdynamic, and a wide pulse pressure is present.

A long, low-frequency musical diastolic rumble beginning one-third of the time into diastole may occur, especially in the left lateral decubitus position in patients with significant valve insufficiency. This is called the **Austin Flint murmur**. It is believed to be related to regurgitant aortic flow passing across the anterior mitral valve and fluttering of the leaflet in conjunction with mitral valve inflow.

MISCELLANEOUS CARDIAC ANOMALIES

Pericardial Disease

Many infectious and noninfectious diseases may cause inflammation of the pericardial sac and surrounding structures. The presence of fluid in the pericardial sac may compromise cardiac filling and result in life-threatening impairment of cardiac output, "pericardial tamponade." The auscultatory findings in these cases often include friction rubs.

These variable sounds are high-pitched, superficial, and scratching noises. They occur in synchrony with cardiac movement and can be heard during the early period after myocardial infarction and most frequently after cardiac surgery (see Chapter 7).

PULMONARY HYPERTENSION

After the neonatal period, pressures in the pulmonary circulation are normally low (approximately 25 mm Hg systolic, or about one fourth of the pressure in the systemic circulation or aorta). Many diseases have profound effects on the pulmonary circulation and can elevate pressures within the pulmonary arteries. These include diseases of lung, pulmonary vasculature, heart, or liver; collagen vascular diseases; and obstruction of the upper airways.

One consistent physical finding detected in pulmonary hypertension is an active right ventricular parasternal tap with a distinctive, sharp palpable P_2. The P_2 is of increased intensity, and there is a single or narrowly split S_2. There may be no audible murmur; a high-pitched murmur of pulmonary valve insufficiency or a high-pitched systolic murmur of tricuspid valve insufficiency may be present.

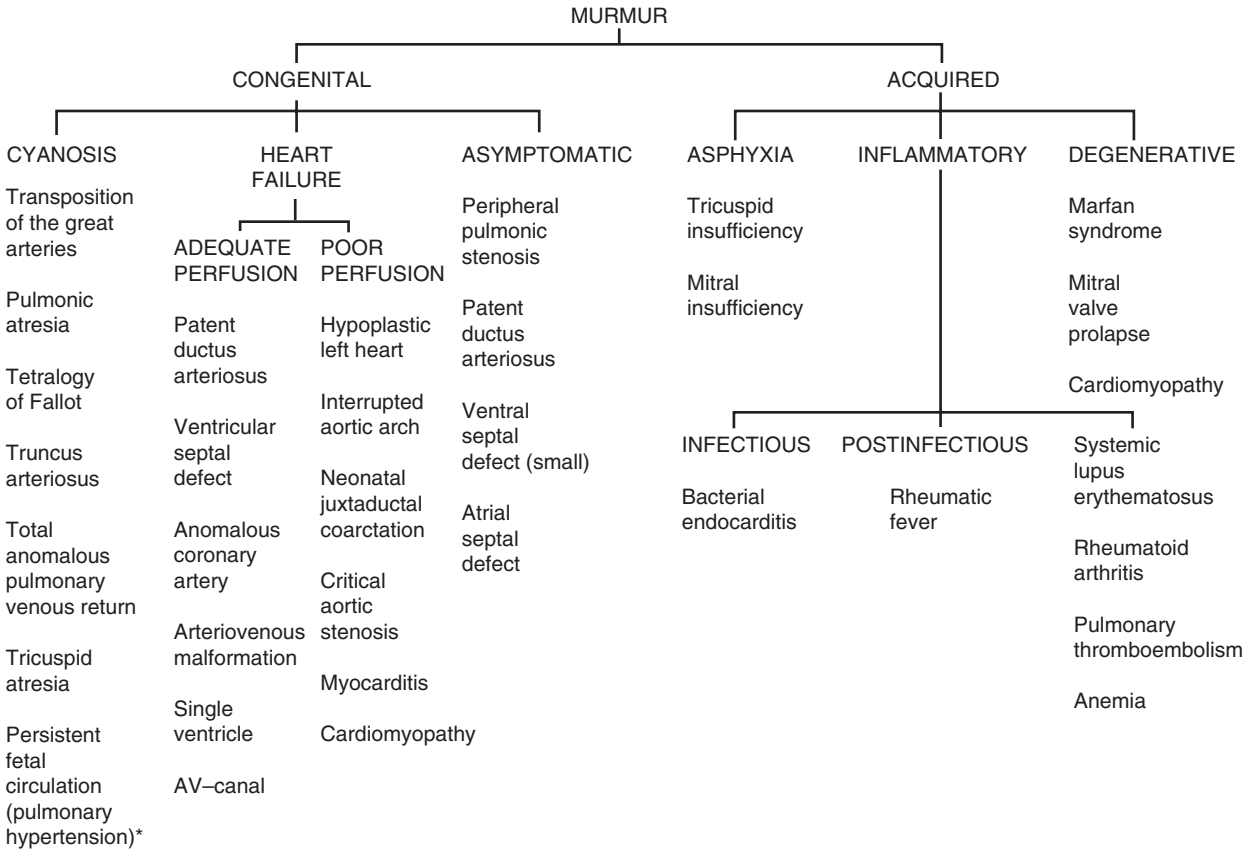
Recognition of pulmonary hypertension warrants a diligent search for the underlying cause. If the reason for the elevated pulmonary artery pressure remains unclear, the disorder is referred to as **primary pulmonary hypertension**. If an etiology can be found, the disorder is termed **secondary pulmonary hypertension**.

APPROACH TO CONGENITAL HEART DISEASE

Congenital heart disease may produce an asymptomatic murmur, heart failure, cyanosis, cyanosis with heart failure, or severe cardiogenic shock (Fig. 8.28). Malformations associated with profound and fixed cyanosis without heart failure are usually associated with right-sided obstructive lesions and a right-to-left shunt (e.g., pulmonary atresia, tetralogy of Fallot). Transposition of the great arteries with intact ventricular septum also manifests with profound and fixed hypoxia, with mild tachypnea, and with no heart failure. Malformations associated with cyanosis and heart failure have a large mixing lesion (single ventricle, truncus arteriosus, transposition plus a VSD), in which pulmonary oxygenated venous return mixes with desaturated systemic venous return before ejection to the systemic arterial circulation. In addition, obstructed total anomalous pulmonary veins may produce severe cyanosis, pulmonary venous engorgement, and pulmonary hypertension. Lesions associated with left-sided obstruction (critical aortic stenosis, interrupted aortic arch, hypoplastic left heart syndrome) produce significant cardiogenic shock, poor perfusion, and profound lactic acidosis.

The chest radiograph may provide helpful clues to the cause of the lesion, depending on the paucity (pulmonary atresia) or plethora (obstructed total anomalous pulmonary venous return) of the pulmonary vascular markings; the left- or right-sided (tetralogy of Fallot, truncus arteriosus) position of the aorta; the configuration of the heart (boot-shaped, as in tetralogy of Fallot; egg-shaped, as in transposition of the great arteries; or massive enlargement, as in Ebstein anomaly); or the side of the chest (risk of heart disease is higher with dextrocardia, especially if the stomach bubble is on the left side of the abdomen or if the liver is midline). The chest radiograph is of some help in distinguishing heart disease from congenital pneumonia, respiratory distress syndrome, pneumothorax, and congenital diaphragmatic hernia.

(See *Nelson Textbook of Pediatrics,* p. 2239.)



*Murmur represents tricuspid insufficiency (usually no murmur in persistent fetal circulation).

FIGURE 8.28 Algorithmic approach to the child with a heart murmur. AV, atrioventricular.

The electrocardiogram in infancy is of help in discriminating atrial and ventricular enlargement or hypertrophy and very helpful when there is an abnormal superior vector (complete atrioventricular canal, tricuspid atresia).

Two-dimensional real-time color Doppler echocardiography is most useful in identifying the anatomy of congenital heart lesions. The echocardiogram enables assessment of the 4 chambers, the interconnecting valves, the great arteries, the pulmonary venous return, and the anatomic relationships between these structures. Furthermore, color Doppler flow studies can determine the presence, direction, and magnitude of right-to-left or left-to-right shunts. Echocardiography has replaced cardiac catheterization for all but the most complex congenital heart lesions.

ACUTE RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

Rheumatic fever is a postinfectious, immunologically mediated inflammatory disease of the heart, joints, brain, and skin that is caused by group A streptococcus. Valvulitis, as manifested by specific and new heart murmurs, is often part of the initial clinical picture. The specific heart murmurs are 3: mitral regurgitation, aortic regurgitation, and the rare Carey-Coombs murmur, a mid-diastolic rumble at the apex. Pericarditis, usually associated with valvulitis, may produce a friction rub.

After the acute rheumatic fever has run its course, any remaining murmurs become part of chronic rheumatic heart disease. If the patient has continued permanent reliable penicillin prophylaxis, the severity of the mitral regurgitation often disappears; this happens less commonly with aortic regurgitation. The development of mitral valve stenosis is part of the natural history of severe repeated episodes of acute rheumatic fever. Pure aortic stenosis does not develop, although in the presence of long-standing rheumatic heart disease with severe aortic regurgitation, some aortic stenosis may be present. In some very severe cases, tricuspid valve regurgitation has been documented, but it is rare.

The diagnosis of acute rheumatic fever is suggested (although not definitively confirmed) by application of the revised Jones criteria, last edited in 2015 (Table 8.6). In addition, evidence of a group A streptococcal pharyngitis must be present, which may include a positive throat culture, positive streptococcal antigen or antistreptococcal antibody, or a history of prior episodes of rheumatic fever. In cases where carditis may be subclinical (no audible murmur), the diagnosis is supported by echocardiographic evidence of subclinical carditis (no audible murmur) by demonstrating significant mitral regurgitation with a regurgitant jet seen in 2 planes with chaotic flow and being holosystolic and extending 1 cm into the left atrium. Criteria for subclinical significant echocardiographic aortic regurgitation include its being seen in 2 imaging planes, being holodiastolic, and extending 1 cm into the ventricle (Table 8.7). The differential diagnosis is limited in the presence of carditis and arthritis (see Chapter 33) but includes systemic lupus erythematosus.

INFECTIVE ENDOCARDITIS

An acute or subacute infection of the cardiac valves produces infective endocarditis. Infection may involve a native, previously normal heart

TABLE 8.6 Guidelines for the Diagnosis of Initial or Recurrent Attack of Rheumatic Fever (Jones Criteria, Updated 2015)

Major Manifestations	Minor Manifestations	Supporting Evidence of Antecedent Group A Streptococcal Infection
Carditis	**Clinical Features**	Positive throat culture or rapid streptococcal antigen test
Polyarthritis	Arthralgia	Elevated or increasing streptococcal antibody titer
Erythema marginatum	Fever	
Subcutaneous nodules	**Laboratory Features**	
Chorea	Elevated acute-phase reactants: Erythrocyte sedimentation rate C-reactive protein	
	Prolonged P-R interval	

1. *Initial attack:* 2 major manifestations, or 1 major and 2 minor manifestations, plus evidence of recent GAS infection. *Recurrent attack:* 2 major, or 1 major and 2 minor, or 3 minor manifestations (the latter only in the Moderate/High-Risk population), plus evidence of recent GAS infection (see text).
2. Low-Risk population is defined as ARF incidence <2 per 100,000 school-age children per year, or all-age RHD prevalence of <1 per 1000 population. Moderate/High-Risk population is defined as ARF incidence >2 per 100,000 school-age children per year, or all-age RHD prevalence of >1 per 1000 population.
3. Carditis is now defined as clinical and/or subclinical (echocardiographic valvulitis).
4. Arthritis (major) refers only to polyarthritis in Low-Risk populations, but also to monoarthritis or polyarthralgia in Moderate/High-Risk populations.
5. Minor criteria for Moderate/High-Risk populations only include monoarthralgia (polyarthralgia for Low-Risk populations), fever of >38°C (>38.5°C in Low-Risk populations), ESR >30 mm/hr (>60 mm/hr in Low-Risk populations).

ARF, acute rheumatic fever; ESR, erythrocyte sedimentation rate; GAS, group A streptococci; RHD, rheumatic heart disease.
From Gewitz MH, Baltimore RS, Tani LY, et al. Revision of the Jones criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. *Circulation*. 2015.

TABLE 8.7 Echocardiographic Findings in Rheumatic Valvulitis

Pathologic Mitral Regurgitation (All 4 Met)	Pathologic Aortic Regurgitation (All 4 Met)
1. Seen in at least 2 views	1. Seen in at least 2 views
2. Jet length ≥2 cm in at least 1 view	2. Jet length ≥1 cm in at least 1 view
3. Peak velocity >3 meters/second	3. Peak velocity >3 meters/second
4. Pan-systolic jet in at least 1 envelope	4. Pan-diastolic jet in at least 1 envelope

From Shulman ST. Group A streptococcus. In: *Nelson Textbook of Pediatrics*. 20th ed. Elsevier; 2016.

valve, a valve or structure (e.g., PDA, VSD opposite an endocardial wall that is subjected to a jet stream) that is anomalous as a result of congenital heart disease, or a prosthetic device (e.g., valve, conduit, patch, graft, shunt, or pacemaker).

Endocarditis may affect congenital heart lesions (most commonly, tetralogy of Fallot, VSD, aortic stenosis, PDA, transposition of the great arteries), valves affected by rheumatic heart disease, and mitral valve prolapse. Endocarditis may develop in congenital heart anomalies in the unoperated and the postoperative state. Furthermore, up to 30% of cases of infective endocarditis occur on previously normal native valves.

Endocarditis is the result of a bacteremia, which in a normal host is usually transient, asymptomatic, and without sequelae. The presence of a damaged valve, a jet stream–injured endocardium, or a foreign body (e.g., central catheter, graft, shunt, or patch) creates a nidus of infection that permits the bacteria to bind, proliferate, and remain sequestered from normal host defense mechanisms. Transient and predisposing bacteremias occur during dental procedures that induce bleeding (even dental cleaning); tonsillectomy or adenoidectomy; intestinal (e.g., gall bladder), urinary (e.g., catheterization, dilatation), prostatic (e.g., cystoscopy), or respiratory surgery; esophageal manipulation (e.g., sclerotherapy, dilatation), incision and drainage of infected tissue; and gynecologic procedures (e.g., vaginal hysterectomy, vaginal delivery).

Bacterial vegetations grow and produce cardiovascular, embolic, or immune complex–mediated signs and symptoms (Table 8.8). Responsible bacteria are noted in Table 8.9; *Staphylococcus aureus*, α-hemolytic oral mucosa–derived streptococci, and enterococci are the dominant pathogens in native normal and unoperated anomalous valves. *Staphylococcus epidermidis* and *S. aureus* are common pathogens in the postoperative patient and in patients with prosthetic devices.

The definitive diagnosis of infective endocarditis includes recovery of a microorganism from culture or histologic study of a heart, an embolized vegetation, or an intracardiac abscess. Vegetations may be demonstrated by the sensitive technique of transesophageal echocardiography but are usually seen on transthoracic echocardiography. In the absence of direct definitive evidence, the following are important diagnostic factors: persistently positive blood cultures with a pathogen compatible with the diagnosis (see Table 8.9); echocardiographic evidence of an intracardiac mass, vegetations, perivalvular abscess, or new partial dehiscence of a prosthetic valve; and a new valvular murmur (regurgitation, or worsening or changing of a preexisting murmur).

TABLE 8.8 Manifestations of Infective Endocarditis

History
Prior congenital or rheumatic heart disease
Preceding dental, urinary, or intestinal procedure
Intravenous drug use
Central venous catheter
Prosthetic heart valve

Symptoms
Fever
Chills
Chest and back pain
Arthralgia/myalgia
Dyspnea
Malaise
Night sweats
Weight loss
CNS manifestations (stroke, seizures, headache, confusion)

Signs
Elevated temperature
Tachycardia
Embolic phenomena (Roth spots, petechiae, splinter nail bed hemorrhages, Osler nodes, CNS or ocular lesions)
Janeway lesions
New or changing murmur
Splenomegaly
Arthritis
Heart failure
Arrhythmias, heart block, conduction disturbances
Metastatic infection (arthritis, meningitis, mycotic arterial aneurysm, pericarditis, abscesses, septic pulmonary emboli)
Digital clubbing

Laboratory
Positive blood culture
Elevated erythrocyte sedimentation rate (may be low with heart or renal failure)
Elevated C-reactive protein level
Anemia
Leukocytosis
Immune complexes
Hypergammaglobulinemia
Hypocomplementemia
Cryoglobulinemia
Rheumatoid factor
Hematuria
Azotemia, high creatinine level (glomerulonephritis)
Echocardiographic evidence of valve vegetations, prosthetic valve dysfunction or leak, or myocardial abscess

CNS, central nervous system.
Modified from Behrman RE, ed. *Nelson Textbook of Pediatrics.* 14th ed. Philadelphia: WB Saunders; 1992.

TABLE 8.9 Bacterial Agents in Pediatric Infective Endocarditis

Common: Native Valve or Other Cardiac Lesions
Viridans group streptococci *(Streptococcus mutans, Streptococcus sanguinis, Streptococcus mitis)*
Staphylococcus aureus
Group D streptococci *(Streptococcus bovis)*
Enterococcus faecalis

Uncommon: Native Valve or Other Cardiac Lesions
Streptococcus pneumoniae
Haemophilus influenzae
Coagulase-negative staphylococci
Abiotrophia defectiva (nutritionally variant streptococcus)
Coxiella burnetii (Q fever)*
Neisseria gonorrhoeae
*Brucella**
*Chlamydia psittaci**
*Chlamydia trachomatis**
*Chlamydia pneumoniae**
*Legionella**
*Bartonella**
Tropheryma whipplei * (Whipple disease)
HACEK group†
*Streptobacillus moniliformis**
*Pasteurella multocida**
Campylobacter fetus
Culture negative (6% of cases)

Prosthetic Valve
Staphylococcus epidermidis
Staphylococcus aureus
Viridans group streptococci
Pseudomonas aeruginosa
Serratia marcescens
Diphtheroids
Legionella species*
HACEK group†
Fungi‡

*These fastidious bacteria plus some fungi may produce culture-negative endocarditis. Detection may require special media, incubation for more than 7 days, polymerase chain reaction on blood or valve for 16S rRNA (bacteria) or 18S rRNA (fungi), or serologic tests.
†The HACEK group includes *Haemophilus* species *(H. paraphrophilus, H. parainfluenzae, H. aphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species.
‡*Candida* species, *Aspergillus* species, *Pseudallescheria boydii, Histoplasma capsulatum.*
From Bernstein D. Infective endocarditis. In: *Nelson Textbook of Pediatrics.* 20th ed. Elsevier; 2016.

Blood cultures are helpful if 2 or more drawn 12 hours apart are positive or if a majority (e.g., 3 or 4) of separate cultures drawn in 1 hour are positive. More than 85% of first blood cultures are positive; the yield approaches 95% with the second blood culture. Sufficient blood must be inoculated into the media to detect the low-grade bacteremia of infective endocarditis; excessive blood inoculation may inhibit bacterial growth by continued activity of leukocytes unless the technique involves centrifugation lysis. The cultures should be incubated for more than the routine 72 hours (often 1-2 weeks), and the laboratory should be notified of the possible diagnosis so that laboratory personnel can enrich the media to encourage the growth of fastidious nutrient-dependent organisms.

Additional criteria for diagnosing infective endocarditis include fever, predisposing heart lesions and procedures (many patients have undergone no identifiable procedure), vascular phenomena (embolism, Janeway lesions, petechiae, septic pulmonary infarcts, intracranial hemorrhage), immune lesions (glomerulonephritis, Roth spots, Osler nodes), a suggestive but not definitive echocardiogram, and microbiologic criteria (positive blood culture but not as defined earlier; serologic evidence of active infection).

To prevent infective endocarditis, high-risk patients, procedures, and factors that predispose to bacteremia need to be identified (Table 8.10). Patients needing infective endocarditis prophylaxis include those with intracardiac foreign bodies (prosthetic valve, grafts), prior episodes of infective endocarditis, a heart transplant with abnormal valve function, and certain congenital heart abnormalities including the following: (1) cyanotic congenital heart disease that has not been fully repaired, including children who have had surgical shunts and conduits; (2) a congenital heart defect that has been repaired with prosthetic material or a device for the first 6 months after the repair procedure; and (3) repaired congenital heart disease with residual defects, such as persisting leaks or abnormal flow at or adjacent to a prosthetic patch or prosthetic device.

TABLE 8.10 2007 Statement of the American Heart Association (AHA): Cardiac Conditions Associated with the Highest Risk of an Adverse Outcome from Infective Endocarditis for Which Prophylaxis with Dental Procedures Is Reasonable

Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
Previous infective endocarditis
Congenital Heart Disease (CHD)*
Unrepaired cyanotic CHD, including palliative shunts and conduits
Completely repaired CHD with prosthetic material or device, whether placed by surgery or catheter intervention, during the 1-6 mo after the procedure†
Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch, or prosthetic device (which inhibits endothelialization)
Cardiac transplantation recipients who develop cardiac valvulopathy

*Except for the conditions listed here, antibiotic prophylaxis is no longer recommended by the AHA for any other form of CHD.
†Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 mo after the procedure.
From Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis. Guidelines from the American Heart Association. *Circulation.* 2007;116:1736-754.

SUMMARY AND RED FLAGS

Murmurs may be caused by cardiac or noncardiac lesions and may be congenital or acquired. Murmurs in the neonatal period are often transient, as a result of the changing hemodynamics of the transitional circulation between fetal and neonatal life, or as a result of the common occurrence of a small VSD, which usually closes in the first 1-5 years of life. Most murmurs at all ages are not caused by cardiac disease and are not associated with symptoms or increased risk for disease.

Red flags in the neonatal period include cyanosis or heart failure with or without the presence of other congenital anomalies or syndromes, such as trisomy 21. Such syndromes often manifest with multiple congenital anomalies, including those involving the cardiovascular, gastrointestinal, and central nervous systems. In the neonatal period, things not to miss include ductus-dependent lesions, in which systemic blood flow (as in interrupted aortic arch, hypoplastic left heart syndrome) or pulmonary blood flow (as in pulmonary atresia) is through the PDA. Sudden deterioration, cyanosis, or heart failure with increasing metabolic acidosis and a reduction in the murmur suggests closure of the ductus arteriosus. Another thing not to miss is the murmur associated with an arteriovenous malformation, such as the cerebral vein of Galen malformation, which manifests with heart failure and a cranial bruit. Finally, obstructed total anomalous venous return may be confused with persistent fetal circulation, and it may be difficult to establish the diagnosis. Total anomalous venous return is associated with fixed, profound cyanosis (PaO_2 <35 mm Hg), severe pulmonary venous congestion, and a small heart.

Acquired murmurs or symptomatic murmurs that change in quality should suggest acute or recurrent rheumatic fever, or infective endocarditis. Systemic symptoms and peripheral signs associated with these disorders are suggestive of the diagnosis. Arthritis (associated with rheumatic fever or endocarditis-induced immune complexes), fever, anemia, leukocytosis, cutaneous manifestations (erythema marginatum and subcutaneous nodules in rheumatic fever; Osler nodes, Janeway lesions, petechiae, and splinter hemorrhages in infective endocarditis), and evidence of prior infection (streptococcal antibodies) or current infection (positive blood cultures) help identify the nature of the acquired heart disease. Finally, heart murmurs in a normal heart may be caused by hemodynamic factors, such as severe anemia or thyrotoxicosis.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Introduction

Boneva RS, Botto LD, Moore CA, et al. Mortality associated with congenital heart defects in the United States: Trends and racial disparities, 1979-1997. *Circulation*. 2001;103:2376-2381.

Day INM, Wilson DI. Genetics and cardiovascular risk. *BMJ*. 2001;323:1409-1412.

Goldmuntz E. The epidemiology and genetics of congenital heart disease. *Clin Perinatol*. 2001;28:1-10.

Karl TR. Neonatal cardiac surgery: Anatomic, physiologic, and technical considerations. *Clin Perinatol*. 2001;28:159-185.

Origins of Heart Sounds

Glover DD, Murrah RL, Olsen CO, et al. Mechanical correlates of the third heart sound. *J Am Coll Cardiol*. 1992;19:450-457.

Nitta M, Ihenacho D, Hultgren HN. Prevalence and characteristics of the aortic ejection sound in adults. *Am J Cardiol*. 1988;61:142-145.

Shaver JA, O'Toole JD. The second heart sound: Newer concepts, part I: Normal and wide physiological splitting. *Mod Concepts Cardiovasc Dis*. 1977;46:7-17.

Tilkian AG, Conover MB. *Understanding Heart Sounds and Murmurs, With an Introduction to Lung Sounds*. 3rd ed. Philadelphia: WB Saunders; 1993.

Zoneraich S. Evaluation of century-old physical signs, S_3 and S_4, by modern technology. *J Am Coll Cardiol*. 1992;19:458-459.

Cardiovascular Assessment

Gessner IH. Evaluation of the infant and child with a heart murmur. In: Gessner IH, Victoria BE, eds. *Pediatric Cardiology: A Problem Oriented Approach*. Philadelphia: WB Saunders; 1993.

Liebman J. Diagnosis and management of heart murmurs in children. *Pediatr Rev*. 1982;3:321-329.

McNamara DG. Value and limitations of auscultation in the management of congenital heart disease. *Pediatr Clin North Am*. 1990;37:93-113.

Pelech AN. The cardiac murmur. *Pediatr Clin North Am*. 1998;45:107-122.

Poskitt EME. Failure to thrive in congenital heart disease. *Arch Dis Child*. 1993;68:158-160.

Silove ED. Assessment and management of congenital heart disease in the newborn by the district paediatrician. *Arch Dis Child*. 1994;70:F71-F74.

Murmurs in Children with Normal Hearts

Canent RV. Recognizing common innocent heart murmurs in infants and children. *Mo Med*. 1986;83:621-625.

Etchells E, Bell C, Robb K. Does this patient have an abnormal systolic murmur? *JAMA*. 1997;277:564-571.

Lembo N, Dell'Italia L, Crawford M, et al. Bedside diagnosis of systolic murmurs. *N Engl J Med*. 1988;318:1572-1578.

Rosenthal A. How to distinguish between innocent and pathologic murmurs in childhood. *Pediatr Clin North Am*. 1984;31:1229-1240.

Rosenthal A. Office maneuvers for evaluating children's heart murmurs. *Consultant*. 1986;26:147-160.

Stein PD, Sabbah HN. Aortic origin of innocent murmurs. *Am J Cardiol*. 1977;39:665-671.

Vibratory Still Murmur

Martins L, Van Zeller P, Roch-Goncalves F, et al. Morphology, prevalence and clinical significance of left ventricular false tendons in adults. *Acta Cardiol*. 1988;93:245.

Perry LW, Ruckman RN, Shapiro SR, et al. Left ventricular false tendons in children: Prevalence as detected by 2-dimensional echocardiography and clinical significance. *Am J Cardiol*. 1983;52:1264.

Shiekh MV, Lee WR, Mills RJ, et al. Musical murmurs: Clinical implications, long term prognosis, and echo-phonocardiographic features. *Am Heart J*. 1984;108:377-386.

Peripheral Pulmonary Arterial Stenosis

Danilowicz DA, Rudolph AM, Hoffman JI, et al. Physiologic pressure differences between the main and branch pulmonary arteries in infants. *Circulation*. 1972;45:410.

The Supraclavicular Murmur

Kawabori I, Stevenson JG, Dooley TK, et al. The significance of carotid bruits in children. *Am Heart J*. 1979;98:160.

Nelson WP, Hall RJ. The innocent supraclavicular arterial bruit—utility of shoulder maneuvers in its recognition. *N Engl J Med*. 1968;278:778.

Aortic Systolic Murmur

Stein PD, Sabbah HN. Aortic origin of innocent murmurs. *Am J Cardiol*. 1977;39:665.

Venous Hum

Cutforth R, Wiseman J, Sutherland RD. The genesis of the cervical venous hum. *Am Heart J*. 1970;80:488.

Potain SC. Des mouvements et des bruits qui se passent dans les veines jugulaires. *Bull Mem Soc Med Hop Paris*. 1867;4:3.

Mammary Arterial Soufflé

Tabatznik B, Randall TW, Hersch C. The mammary souffle of pregnancy and lactation. *Circulation*. 1960;22:1069.

Congenital Heart Disease

Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. *N Engl J Med*. 2000;342:256-263.

Driscoll DJ. Left-to-right shunt lesions. *Pediatr Clin North Am*. 1999;46:355-368.

Fedderly RT. Left ventricular outflow obstruction. *Pediatr Clin North Am*. 1999;46:369-384.

Grifka RG. Cyanotic congenital heart disease with increased pulmonary blood flow. *Pediatr Clin North Am*. 1999;46:405-425.

Karl TR. Neonatal cardiac surgery: Anatomic, physiologic, and technical considerations. *Clin Perinatol*. 2001;28:159-185.

Ovaert C, McCrindle BW, Nykanen D, et al. Balloon angioplasty of native coarctation: Clinical outcomes and predictors of success. *J Am Coll Cardiol*. 2000;35:988-996.

Pihkala J, Nykanen D, Freedom RM, et al. Interventional cardiac catheterization. *Pediatr Clin North Am*. 1999;46:441-464.

Thangaratinam S, Brown K, Zamora J, et al. Pulse oximetry screening for critical congenital heart defects in asymptomatic newborn babies: a systematic review and meta-analysis. *Lancet*. 2012;379:2459-2464.

Waldman JD, Wernly JA. Cyanotic congenital heart disease with decreased pulmonary blood flow in children. *Pediatr Clin North Am*. 1999;46:385-404.

Acute Rheumatic Fever and Rheumatic Heart Disease

Babu AN, Kymes SM, Carpenter Fryer SM. Eponyms and the diagnosis of aortic regurgitation: what says the evidence? *Ann Intern Med*. 2003;138:736-742.

Figueroa FE, Fernandez MS, Valdes P, et al. Prospective comparison of clinical and echocardiographic diagnosis of rheumatic carditis: Long term follow up of patients with subclinical disease. *Heart*. 2001;85:407-410.

Gewitz MH, Baltimore RS, et al. Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. *Circulation*. 2015;131:1806-1818.

Marcus RH, Sareli P, Pocock WA, et al. The spectrum of severe rheumatic mitral valve disease in a developing country. Correlations among clinical presentation, surgical pathologic findings, and hemodynamic sequelae. *Ann Intern Med*. 1994;120:177-183.

Stollerman GH. Variation in group A streptococci and the prevalence of rheumatic fever: A half-century vigil. *Ann Intern Med*. 1993;118:467-469.

Stollerman GH. Rheumatic fever in the 21st century. *Clin Infect Dis*. 2001;33:806-814.

Veasy LG. Time to take soundings in acute rheumatic fever. *Lancet*. 2001;357:1994-1995.

Veasy LG, Tani LY, Hill HR. Persistence of acute rheumatic fever in the intermountain area of the United States. *J Pediatr*. 1994;124:9-16.

Wald ER. Acute rheumatic fever. *Curr Probl Pediatr*. 1993;23:264-270.

Infective Endocarditis

Awadallah SM, Kavey REW, Byrum CJ, et al. The changing pattern of infective endocarditis in childhood. *Am J Cardiol*. 1991;68:90-94.

Baltimore RS. Infective endocarditis in children. *Pediatr Infect Dis J*. 1992;11:907-913.

Bayer AS, Ward JI, Ginzton LE, et al. Evaluation of new clinical criteria for the diagnosis of infective endocarditis. *Am J Med*. 1994;96:211-218.

Bouza E, Menasalvas A, Munoz P, et al. Infective endocarditis: A prospective study at the end of the twentieth century. *Medicine (Baltimore)*. 2001;80:298-307.

Brook MM. Pediatric bacterial endocarditis: Treatment and prophylaxis. *Pediatr Clin North Am*. 1999;46:275-287.

Carpenter JL. Perivalvular extension of infection in patients with infectious endocarditis. *Rev Infect Dis*. 1991;13:127-138.

Dajani AS, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis: Recommendations by the American Heart Association. *JAMA*. 1997;277:1794-1801.

Hansen D, Schmiegelow K, Jacobsen JR. Bacterial endocarditis in children: Trends in its diagnosis, course, and prognosis. *Pediatr Cardiol*. 1992;13:198-203.

Mylonakis E, Calerwood SB. Infective endocarditis in adults. *N Engl J Med*. 2001;345:1318-1330.

Saiman L, Prince A, Gersony WM. Pediatric infective endocarditis in the modern era. *J Pediatr*. 1993;122:847-853.

Tolan RW, Kleiman MB, Frank M, et al. Operative intervention in active endocarditis in children: Report of a series of cases and review. *Clin Infect Dis*. 1992;14:852-862.

Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association. A guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2007;116:1736-1754.

9

Failure to Thrive

Susan Feigelman and Virginia Keane

Calories from food provide energy for the body's maintenance functions of repair, regulation, metabolic functions, replacement of losses, and daily activity. Children have additional caloric requirements because they must also grow. Children under the age of 3 years whose caloric needs are not met do not grow according to published norms and are said to have failure to thrive (FTT) or growth faltering. FTT raises serious concerns. It is important to have a systematic, stepwise approach to the diagnosis and management of poor growth in young children and to follow growth over time.

The term **failure to thrive** is used to describe growth failure that accompanies many pathologic conditions as well as psychosocial causes. Differentiation between organic (biomedical) and nonorganic (psychosocial/environmental) is not always useful; children often have a combination of psychosocial and biomedical problems. Children with medical conditions will often have psychosocial issues related to eating and dysfunctional feeding patterns with caregivers. Children with primarily social or emotional issues around eating may develop medical consequences of undernutrition.

There is a poor yield from exhaustive laboratory evaluations of most children with FTT. Testing should be based on clues from the history and physical examination. Children with biomedical and/or psychosocial causes of FTT may or may not gain weight in institutional settings, and this short-term outcome is not always diagnostic.

The best diagnostic tool available to the clinician is a comprehensive history, including diet, family, growth (over time) and social histories, and a complete review of systems; and a complete physical examination. Further work-up should be directed by results from this initial evaluation.

NORMAL GROWTH

Newborns typically lose up to 10-12% of their birthweight during the first few days of life and regain this weight by the age of 2 weeks. Subsequently, they gain weight at a steady pace of about 1 oz per day for the first 3 months; gain at half to two thirds that rate for the next 3 months and half to two thirds again for the next 6 months. This results in a doubling of birthweight by the age of 4-6 months and a tripling before 1 year. Height and head circumference grow at similar well-defined rates. These three growth parameters should be plotted on appropriate growth charts and monitored for adherence to standard growth rates. Children grow in a stepwise manner, but on average their growth pattern follows the accepted curves (see Chapter 43). Online tools are available to assist with the determination of growth status (peditools.org).

Between the ages of 1 and 3 years, if caloric intake is normal, the child's growth adjusts to his/her genetic potential. Ultimate height is determined by additional factors, among them rates of bone maturity and pubertal development (see Chapter 43). Considerable energy from ingested food is required to achieve this growth. The energy balance can be described by the following equation, in which E equals energy:

$$E_{IN} = E_{OUT} + E_{growth} + E_{stored}$$

E_{OUT} is the sum of basal metabolic rate, energy expended in physical activity, and the energy needed for food digestion. Children should be in a positive energy balance for growth. Any imbalance in this energy equation (losing or using more calories than are ingested) results in abnormal growth patterns. Weight is usually affected first, followed by height and finally head circumference if the energy imbalance is severe and prolonged in young children.

DEFINITIONS

FTT is a sign, not a diagnosis. FTT is generally used to describe children younger than 2 or 3 years who meet any of the following criteria:

1. Growth under the third percentile on World Health Organization (WHO) weight for age growth charts (<3% = less than 3 standard deviations below mean)
2. Weight for height or body mass index (BMI) less than the 5th percentile
3. Growth patterns that have crossed two major percentiles downward on the weight for age charts within 6 months
4. Growth velocity less than normal for age

There are inherent problems with these definitions. Three percent of the population is at or below the 3rd percentile, and so those who are growing appropriately per their genetic potential must be differentiated from those with growth problems. The child who has been obese and is now approaching normal weight for height, crossing major weight percentiles in the process should not be considered a child with FTT. Some children are naturally slim. The clinician must exercise considerable judgment before raising the concern of poor growth.

Additional terms are used to describe children who are not growing well. A child has **wasting** if the weight for length or weight for height is below –2 standard deviations (or –2 z-scores which is equal to

(See *Nelson Textbook of Pediatrics,* p. 250.)

TABLE 9.1 Three Major Anthropologic Categories of Failure to Thrive

	Weight	Height	Head Circumference	Associated Diseases
Type I	Decreased	Decreased/normal	Normal	Malnutrition of organic or nonorganic etiology, usually secondary to intestinal, pancreatic, liver diseases or systemic illness or psychosocial factors
Type II	Decreased	Decreased	Normal	Endocrinopathies, bony dystrophy, constitutional short stature
Type III	Decreased	Decreased	Decreased	Chromosomal, metabolic disease, intrauterine and perinatal insults, severe malnutrition

From Shashidar H, Toila V. Failure to thrive. In: Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease.* 4th ed. Philadelphia: Elsevier; 2011:137.

<3 centile). **Stunting** is defined as a child whose height or length is less than −2 z-scores due to chronic undernutrition. In the third year of life, children are described as underweight if weight/age is <5% or if BMI is <5% or 10%. Short stature or microcephaly alone is not due to nutritional deficiencies (Table 9.1).

INTERPRETATION OF GROWTH CHARTS

The evaluation for any child who is not growing well includes a careful analysis of growth charts. A review of the growth pattern over time is the most useful. Measurements of length are the most susceptible to error; standard procedures should be used (see Chapter 43). Possible errors in weight, head circumference, date of birth, or plotting on the growth chart should all be considered. Once the correct data are available, the charts should be examined to answer the following questions:

- Are the measurements of length and weight proportionate?
- Has the head grown proportionately?
- How severe are the deficits of each measurement, relative to what is expected?
- When did the problem start and progress?
- Is the problem acute or chronic?
- What environmental factors were present at the start of this process (weaning, introduction of new foods)?

Although weight is usually the most readily available measurement, measurement of length is particularly critical, because it serves as the point of reference for other diagnostic considerations. The best way to obtain accurate length measurements is to use a specially calibrated length board with a fixed headpiece and a movable footpiece. In the absence of such a device, the examiner can use a table or desk with the infant's head pressed against the wall and a firm square box or thick textbook for the sliding footer. Measurements obtained with the infant lying on a mattress and marked with a pen on the sheet are not accurate (see Chapter 43).

The choice of growth curves is important. In the United States, the recommendation is to use the WHO charts from birth through the second year of life (http://www.cdc.gov/growthcharts/who_charts.htm) (see Chapter 43). Some children previously classified as FTT now fall into the normal range. Their health status may be worse than those classified as within normal range on both charts. The 2000 age- and gender-specific National Center for Health Statistics growth charts published by the Centers for Disease Control and Prevention combined data across geographic and ethnic populations and are appropriate to use for children over 24 months of age.

Conventions differ in whether to plot age in relation to actual birth date or to use corrected gestational age. Growth charts following children prenatally to infancy are available (see Fenton and Olsen at peditools.org). Beyond the equivalent of 40 weeks of gestation, standard charts can be used, keeping in mind that premature infants may not catch up on all parameters for 2 or 3 years.

TABLE 9.2 Classification of Degree of Malnutrition

BMI z-Score	Weight for Length Percentile	Weight Deficit (for Current Length)	Degree/Risk of Malnutrition
0	50%	90–100%	Normal
−1	2.4–15.9%	80–90%	Mild
−2	0.2–2.3%	70–80%	Moderate
−3	<0.2%	<70%	Severe

Because infants with FTT no longer follow their growth curves, the usual convention of expressing growth measurements in relation to normal percentiles is not always useful. Researchers use weight/length or BMI z-scores to better define and assess degree of malnutrition (Table 9.2).

Some conventions classify the severity of wasting or "malnutrition" by the weight deficit for the current length. Loss of about 40% of expected weight for length (actual weight divided by expected weight for length <60%) is the extreme of wasting that is compatible with survival. Therefore, 80-90% actual weight divided by expected weight for length corresponds to mild, 70-80% is moderate, and 60-70% is severe. These calculations are critical for planning nutritional rehabilitation and therefore essential to the overall diagnostic and treatment processes.

It is important to note the following points:

1. Infants and toddlers who are short in proportion to weight should be considered to have primary growth problems, including various endocrine and skeletal disorders (see Chapter 43) (see Table 9.1).
2. Infants who have had inadequate caloric intake will be abnormally thin. If the problem developed at some time after birth, weight will drop off before changes in length or head circumference.
3. Infants with disproportionately small heads may have primary neurologic problems affecting brain growth because head growth is the last to be affected by malnutrition and is not characteristic of primary skeletal growth problems (see Table 9.1). An alternative diagnosis is craniosynostosis, or early closure of skull growth plates.

Several examples of how these patterns may be interpreted are presented in Figs. 9.1 to 9.4. Growth charts adjusted for abnormal head size (micro- or macrocephaly) are not available. This factor becomes of relatively less importance as the child ages, but during infancy may significantly affect the weight percentile and requires clinical judgment to assess.

Disease-specific growth charts have been developed for certain populations (e.g., trisomy 21, skeletal dysplasias). Their use is most

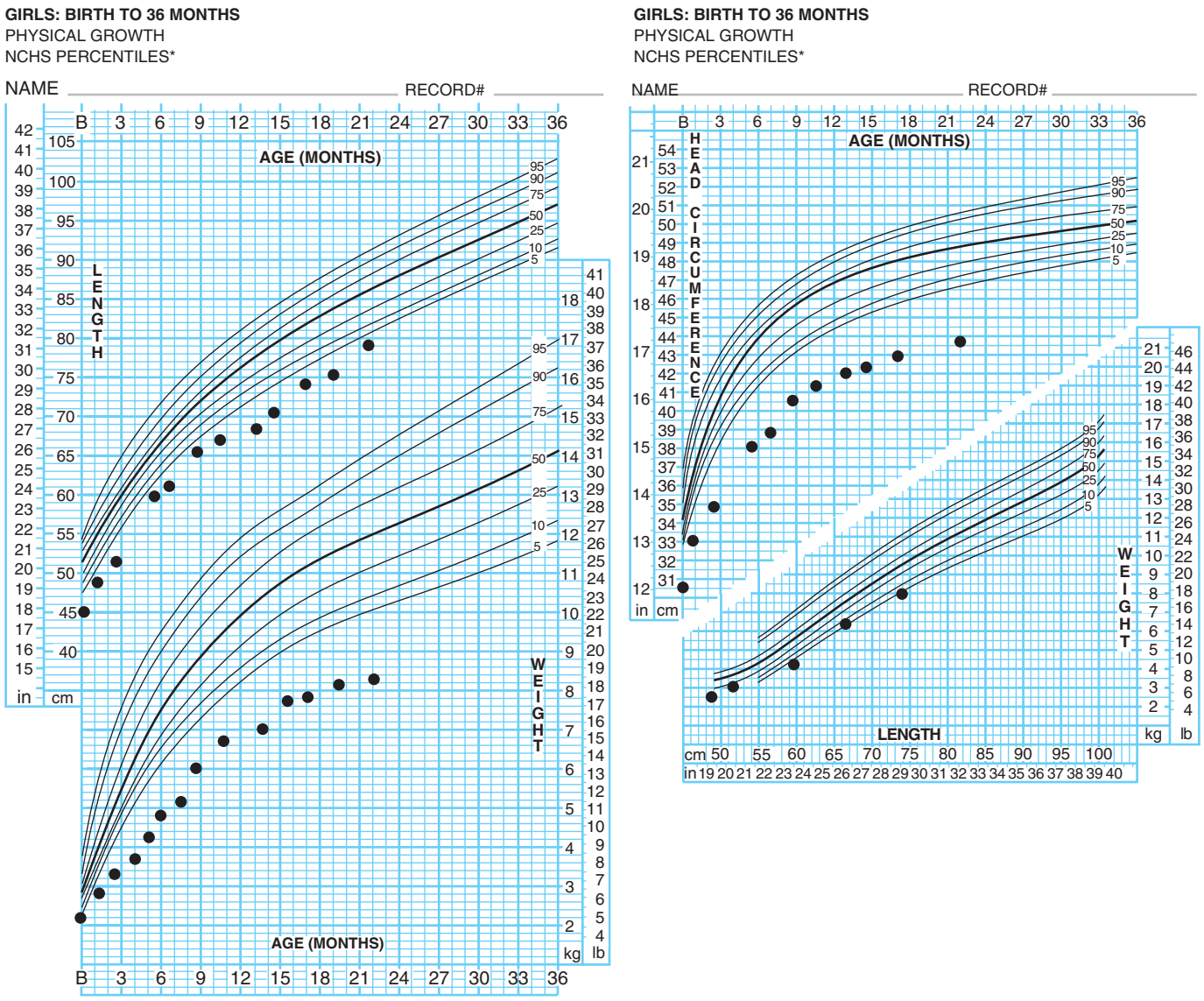


FIGURE 9.1 Growth curve of an infant girl with unexplained chronic failure to thrive, which affected weight and head growth more than length, which suggested an organic disorder. Intrauterine growth restriction without postnatal catch-up growth is demonstrated (see Chapter 43). (Modified from National Center for Health Statistics: NCHS growth charts. *Monthly Vital Statistics Report.* 1976;25:76-1120. Rockville, MD: Health Resources Administration, June 1976. Data from The Fels Research Institute, Yellow Springs, Ohio. Copyright 1976, Ross Laboratories.)

appropriate for conditions that affect muscle and bone development (e.g., Russell-Silver syndrome). Any other disease -specific charts should be used in conjunction with the WHO charts.

EPIDEMIOLOGY

FTT is found in all populations, but has a higher prevalence among children of low socioeconomic status compared to those in higher socioeconomic groups. FTT accounts for up to 5% of all hospitalizations; up to 10% of children may have FTT at some point in time. Most affected children with nutritional problems present before the age of 3 years.

CLINICAL PRESENTATION

Parents often voice concerns about their young child's weight gain. They may complain that their child is a picky eater or seems not to drink enough formula, or they worry that breast milk supply is inadequate. Very commonly, parents complain that their child is not as big as a similar-aged child or a sibling at that age. Many such children are growing normally. Plotting the child's growth and reviewing it with the parent is usually reassuring, or it may serve to confirm the parents' concerns. When families raise concerns about growth, regardless of whether a problem exists, the child and the weight have already become a focus of concern for that family. Often parents have already put a great deal of effort into changing the child's eating patterns. The child's real or perceived weight or appetite problem may cause intrafamily conflict. In this setting, conversations about the child's growth may carry a high emotional charge.

However, it is often the physician who is first to raise concerns. These suspicions can be confirmed by carefully plotting the growth parameters. The clinician must then prioritize the clinical issues and decide whether the FTT should be addressed immediately or deferred

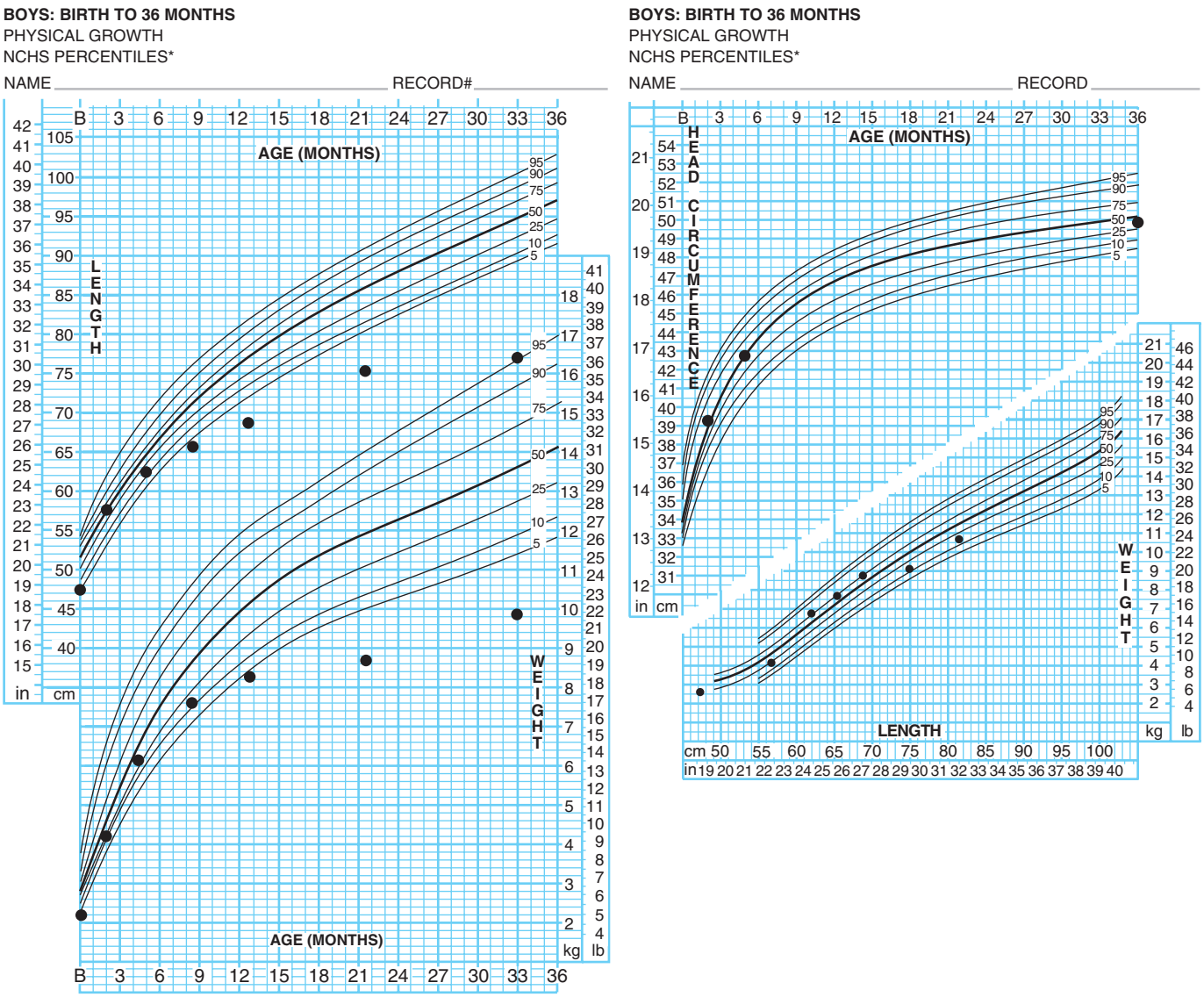


FIGURE 9.2 Growth curve of an infant boy with untreated growth hormone deficiency. Note that weight and length remain proportionate, whereas head growth is less affected. (Modified from National Center for Health Statistics: NCHS growth charts. *Monthly Vital Statistics Report*. 1976;25:76-1120. Rockville, MD: Health Resources Administration, June 1976. Data from The Fels Research Institute, Yellow Springs, Ohio. Copyright 1976, Ross Laboratories.)

for evaluation and management at another time in the very near future. In rare cases, the growth failure is so severe (child is <60% of ideal body weight for height) that immediate hospitalization must be instituted to begin nutritional rehabilitation. In this case, the evaluation can take place over several days, while therapeutic nutritional interventions are ongoing.

APPROACH TO DETERMINING ETIOLOGY

Clinicians need to have a broad approach to determining etiology of FTT for each child. Many children with FTT, particularly those with chronic diseases, have a mixed pattern of increased needs or losses attributable to organic causes, along with environmental causes leading to calorie deprivation.

There are several growth conditions that result in smaller than normal size but that are not due to calorie insufficiency. Children with constitutional delay usually grow normally over the first year, but weight and height decelerate to near or below the 5th percentile followed by growth at normal rates along their new curve (see Chapter 43). The symmetric deceleration of height and weight is a clue that the child does not have calorie insufficiency. Infants who are born small for gestational age and are *symmetrically* small are believed to have a reduced number of somatic cells in relation to their normal-sized peers as a result of an early intrauterine event. Infants who are *asymmetrically* small for gestational age, with sparing of the head circumference and possibly length, suffered a late intrauterine event, such as poor maternal nutrition or placental insufficiency. These infants often eat voraciously and experience catch-up growth early in life. Children with genetic short stature have short height for age with appropriate low weight.

Children with FTT caused by calorie insufficiency typically have decreased weight gain, at first with sparing of height and head circumference (wasting). Long-standing calorie insufficiency results in height deceleration (stunting). Height or length is the best predictor of

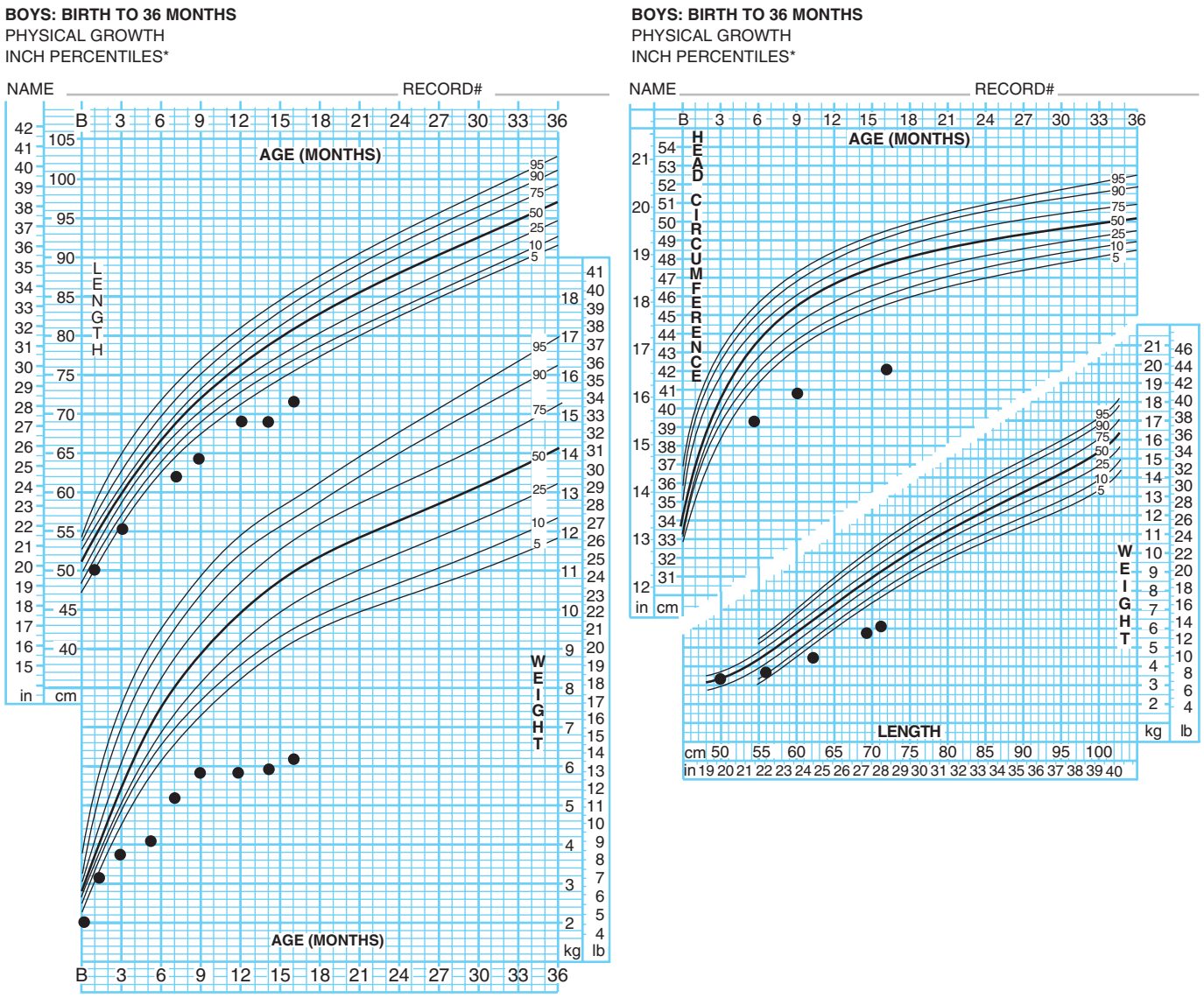


FIGURE 9.3 Growth curve of an infant boy with severely impaired head growth, poor weight gain, and less impairment of length. Most obvious is the marked microcephaly associated with developmental delay, suggestive of an underlying neurologic disorder. (Modified from National Center for Health Statistics: NCHS growth charts. *Monthly Vital Statistics Report*. 1976:25:76-1120. Rockville, MD: Health Resources Administration, June 1976. Data from The Fels Research Institute, Yellow Springs, Ohio. Copyright 1976, Ross Laboratories.)

chronic malnutrition. Only in the worst, long-standing cases is head growth decreased. This typical pattern suggests calorie insufficiency and informs the clinician of the chronicity of the problem.

There are several approaches to the differential diagnosis. The functional approach determines whether there is a problem with increased calorie requirement or utilization, inadequate calorie intake, or increased calorie loss (Table 9.3). The systems approach focuses on the identification of the organ system or systems that might be responsible for the poor growth. A careful history can point the clinician toward a particular system to consider for further diagnostic evaluation (Table 9.4).

Another approach is to consider the age at onset, the child's developmental level, and the conditions likely to manifest at that stage of development. The causes of prenatal growth problems include environmental toxins, maternal drug and alcohol use, prenatal infection, congenital syndromes, placental insufficiency, and poor prenatal nutrition. Poor growth immediately after birth can be associated with maternal postpartum depression, bonding and attachment disorders, incorrect formula preparation, failure to establish breast-feeding, and congenital anomalies or metabolic conditions. In children older than 9 months, issues of separation and autonomy may result in power struggles over eating resulting in insufficient intake. For toddlers, poor food choices (empty calories found in juice drinks and snack foods), dysfunctional feeding interaction (restriction of self-feeding or lack of structure around meals), and distraction (chaotic home environment, television and electronic devices) may interfere with adequate food intake.

◆ History

The history is the most important part of the evaluation of the child with FTT and guides the evaluation.

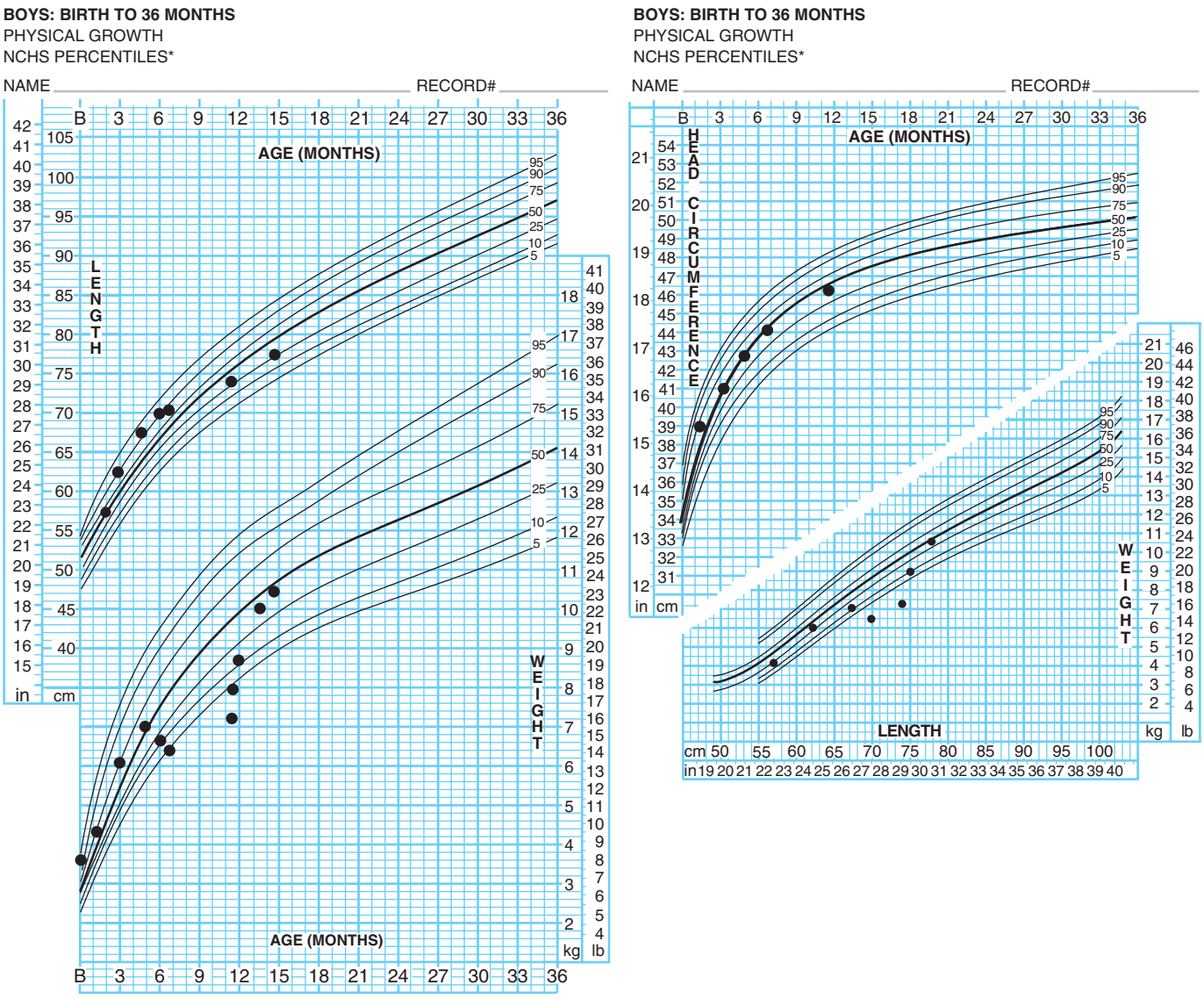


FIGURE 9.4 Growth curve of an infant boy with acute weight loss and catch-up weight gain. Before the age of $4^1/_2$ months, there was normal growth while he was breast-feeding. After a change to an inadequate weaning diet, severe weight loss developed, but less impairment of length occurred. Head size was not affected. An acute episode of diarrhea led to multiple dietary changes that resulted in further weight loss. With a proper diet history, nutritional rehabilitation with a balanced diet resolved this child's problem. This may also be a pattern of a child with celiac disease. (Modified from National Center for Health Statistics: NCHS growth charts. *Monthly Vital Statistics Report*. 1976:25:76-1120. Rockville, MD: Health Resources Administration, June 1976. Data from The Fels Research Institute, Yellow Springs, Ohio. Copyright 1976, Ross Laboratories.)

History of the Present Illness

If poor growth is first noted by the clinician, the clinician should identify whether the family perceives a problem. What is the family members' perception of the child's food intake? When, if ever, did they first notice a problem? What changes have they made to address the problem? Asking these questions in a nonjudgmental manner will reassure the family that the clinician regards them as partners in the task of improving the child's growth.

A detailed feeding history should start with infant feeding; dietary sources and growth patterns should be chronologically reviewed. Was the child breast- or formula-fed? If breast-fed, were there any problems with milk sufficiency? How did each parent feel about breast-feeding? Did the mother feel emotionally supported in her choice to breast-feed? If the child was formula-fed, what was the formula; how was it mixed; was there ever any reason to change formula? Was feeding a pleasurable or a difficult experience for the parent and child? These questions may give insight into early parent-child interaction problems.

If the child is beyond infancy, when and how were solid foods introduced? Were there any specific food refusals that might indicate an allergy or intolerance? How did the child accept solids? What are the child's food preferences? When did the child start to self-feed? Where does the child eat? Is there a high chair or secure place to eat? Are there family meals, or does the child eat alone? What is going on in the immediate environment when the child is eating? These

TABLE 9.3 Differential Diagnosis by Functional Category

Excessive Calorie Needs
Diabetes mellitus
Cystic fibrosis
Chronic respiratory or cardiovascular disease
Hyperthyroidism
Cerebral palsy/spasticity
Chronic infection or inflammatory diseases

Inadequate Calorie Intake
Family education and mental health: maternal depression, psychosis, substance abuse, lack of parental knowledge of child nutrition needs
Parent-child interaction: parental emotional distance, parental anxiety, mealtime distractions (i.e., television), lack of family mealtime, overindulgent or overcontrolling parent, parental inability to read hunger, and satiety cues
Poor food choices: allows grazing, excessive juice intake
Child factors: neuromuscular disease, poor oral/motor coordination, chronic disease with easy tiring, and failure to complete meals, difficult temperament, hyperactivity, inability to display hunger cues
Economic factors: family not able to afford adequate food, diluting formula, early conversion from formula to cow's milk
Food aversion: impaired swallowing, oropharyngeal or esophageal inflammation, anorexia causing conditions, psychosocial factors

Increased Calorie Loss/Failure to Incorporate Ingested Calories
Diabetes mellitus
Malabsorption syndromes (celiac disease, lactose intolerance, cystic fibrosis, other causes of pancreatic insufficiency, chronic cholestasis)
Metabolic disorders
Chronic diarrhea including IPEX and IPEX-like syndromes
Gastroesophageal reflux and other conditions with chronic vomiting, eosinophilic gastroenteritis
Short gut syndrome

IPEX, immune dysregulation polyendocrinopathy enteropathy X-linked.

questions can reveal dysfunctional eating behaviors that can affect the child's intake.

Questions about unusual eating habits or pica may indicate nutritional deficiencies, such as iron deficiency (Table 9.5). Children with difficult temperaments may have problematic eating behaviors.

Does the child have difficulty taking or manipulating food in the mouth? Is there frequent choking on food? Does the child drool? Is there food refusal or aversion suggesting **dysphagia**? If the response to any of these questions is confirmatory, consider difficulty with oral motor control. This is common among children with neurologic problems.

What is the child's usual daily pattern of activity? Who prepares the food and feeds the child? Is there more than one caregiver? Do the parents know what other caregivers feed the child, or if the child has vomited or defecated while in the care of another adult? Is there a difference in how the child eats or eliminates when the child is with the parents in comparison to other caretakers?

A careful *dietary* history is imperative. The 24-hour recall is standard, although some authorities question its validity. The clinician asks the parent to remember everything the child ate in the past 24 hours and whether that was a typical day. It is helpful to start with the present and work backward. Alternatively, the parent may keep a 3-day food diary. The diary should be structured so that the type of food, quantity, method of preparation, and amount eaten are recorded; beverages should be included. The caregiver should receive prior instruction regarding how to estimate portions and to include only what the child actually eats.

Diet review is a good opportunity to explore parental beliefs about food and the feeding of children (e.g., children must drink water, they need lots of milk, juice is good for them, fat should be restricted to prevent obesity and heart disease). It may be useful to explore parent assumptions about food based on their own experiences or beliefs. The parent who sees the child as vulnerable may be overanxious and rigid about food intake. Cultural norms may dictate certain food choices, which may not provide optimal nutrition. Vegetarian diets may provide insufficient protein, vitamin B_{12}, and iron. Rice and almond milks have inadequate protein for young children. Some parents may substitute goat's milk or rice milk for cow's milk–based nutrition. Goat's milk is deficient in folate while rice milk is extremely low in protein and has caused severe protein deficiency.

Medical History

The prenatal and perinatal history begins with the mother's age, general health, and parity. Was this pregnancy planned? What was the mother's reaction to the pregnancy? How did the father and other family members react? Was mother emotionally prepared for a child? Did the mother have any emotional problems during or before her pregnancy? What was her alcohol, tobacco, and drug intake during pregnancy? When did she start prenatal care? Did she have sufficient visits to monitor the pregnancy? How much weight did she gain? Were there any complications during the pregnancy? Was prenatal testing for sexually transmitted and other infections obtained, and what were the results? Was she hoping for a boy or a girl?

The perinatal history includes problems with labor, method of delivery, and the newborn's growth parameters at birth (i.e., appropriate [AGA], small [SGA], or large [LGA] for gestational age). Is this an SGA infant who needs extra calories for catch-up growth or a newborn with intrauterine growth restriction who is small in all growth parameters? Did the baby have any problems in the nursery? A nursery stay more than 2-3 days may indicate a problem with the newborn. Did the baby have feeding problems after birth? Was breast-feeding begun immediately?

The child's medical history should be reviewed for chronic conditions and recurrent, acute conditions, such as recurrent emesis, diarrhea, constipation, neurologic symptoms, or recurrent infections. Hospitalizations, surgical procedures, medications, and allergies should be explored. Immunization status should be ascertained. It is essential to document neurodevelopmental progress, because motor or cognitive delays could be associated with neurologic dysfunction that increases calorie requirements and/or decreases feeding efficiency.

Family History

The clinician should ascertain the growth of siblings and other family members. Are there patterns of growth in the family that might result in a child growing less than expected in the early years? What, if any, differences do the parents notice between this child and their other children? What were the growth patterns and ultimate sizes of the parents and grandparents? What was the age at menarche and puberty in parents and siblings? Creating a two-generation genogram that includes the height and weight of each family member may provide clues to the growth potential of the patient. Plotting the mean parental height on the child's height curve will help to predict ultimate stature.

Is there any history of heart, renal, or gastrointestinal disease in the family? Have there been any early childhood deaths? Is there any sickle

TABLE 9.4 Failure to Thrive: Differential Diagnosis by System

Psychosocial/Behavioral
Inadequate diet because of poverty/food insufficiency, errors in food preparation
Poor parenting skills (lack of knowledge of sufficient diet)
Child/parent interaction problems (autonomy struggles, coercive feeding)
Food refusal/aversion/dysphagia
Parental cognitive or mental health problems (depression)
Child abuse or neglect

Neurologic
Oral motor dysfunction (dysautonomia, brainstem lesion, cerebral palsy, Chiari malformation)
Spasticity
Developmental delay
Increased intracranial pressure
Diencephalic syndrome

Renal
Urinary tract infection
Renal tubular acidosis
Renal failure

Endocrine
Diabetes mellitus
Hypothyroidism/hyperthyroidism
Growth hormone deficiency
Adrenal insufficiency

Genetic/Metabolic/Congenital
Cystic fibrosis
Sickle cell disease
Inborn errors of metabolism (organic acidosis, hyperammonemia, storage disease)
Fetal alcohol syndrome
Skeletal dysplasias
Chromosomal disorders
Multiple congenital anomaly syndromes (VATER, CHARGE)

Gastrointestinal
Pyloric stenosis
Gastroesophageal reflux
Eosinophilic esophagitis
Malrotation
Malabsorption syndromes
Celiac disease
Milk intolerance: lactose, protein
Pancreatic insufficiency syndromes
Chronic cholestasis
Inflammatory bowel disease
Chronic congenital diarrhea states including IPEX
Pseudoobstruction

Cardiac
Cyanotic heart lesions
Congestive heart failure

Pulmonary/Respiratory
Severe asthma
Cystic fibrosis; bronchiectasis
Chronic respiratory failure
Bronchopulmonary dysplasia
Adenoid/tonsillar hypertrophy
Obstructive sleep apnea

Miscellaneous
Autoimmune diseases
Autoinflammatory–recurrent fever syndromes
Malignancy
Primary immunodeficiency
Transplantation

Infections
Perinatal infection
Occult/chronic infections
Parasitic infestation
Tuberculosis
Human immunodeficiency virus

CHARGE, coloboma, heart disease, choanal atresia, retarded growth and retarded development and/or central nervous system anomalies, genital hypoplasia, and ear anomalies and/or deafness; IPEX, immune dysregulation polyendocrinopathy enteropathy X-linked; VATER, vertebral defects, imperforate anus, tracheoesophageal fistula, and radial and renal dysplasia.

cell disease or other anemic condition? Are there any family members with genetic or metabolic conditions? Is there a family history of mental illness that might affect the child or the caretakers? Is there consanguinity?

Social History

Many cases of FTT do not have a primary medical etiology, and thus the social history is vital. The examiner should start with the family constellation and who takes care of the child. What is the relationship of the adults in the household, and how do they get along? Are the parents working, and if they work simultaneously, who cares for the child? Are food stores accessible? Do the parents have adequate storage, refrigeration, and food preparation space? Are there adequate eating facilities and implements? Are there siblings who might eat the child's food? Is the child enrolled in the Women, Infants, and Children (WIC) program? Families should be screened for food insecurity. What is the cultural context of food selection and eating behavior?

More difficult social issues must be approached carefully, with a statement to the family that all patients with this problem are asked these routine questions. Is there any substance abuse in the home that might result in use of food money for tobacco, alcohol, or drugs? Have the child protection authorities ever been involved with the family?

Is the child in group daycare, or has the family traveled to an area where a chronic infection such as a parasite might have been acquired? Although the social history can be the most revealing part of the history, it can be the most difficult to elicit. Often the clinician must establish trust with the family before they can reveal the source of their inability to meet their child's nutritional needs.

Review of Systems

A thorough review of systems can help to reveal organic conditions. A few areas merit special attention: Are there sources of calorie loss? Does the child vomit or spit up frequently? What is the stool pattern and quality? What is the pattern and frequency of urination? Does

TABLE 9.5 Characteristics of Mineral Deficiencies

Mineral	Function	Manifestations of Deficiency	Comments	Sources
Iron	Heme-containing macromolecules (e.g., hemoglobin, cytochrome, myoglobin)	Anemia, spoon nails, reduced muscle and mental performance	History of pica, cow's milk, gastrointestinal bleeding, excessive milk in diet	Liver, eggs, grains
Copper	Redox reactions (e.g., cytochrome oxidase)	Hypochromic anemia, neutropenia, osteoporosis, hypotonia, hypoproteinemia, poor growth	Inborn error, Menkes kinky hair syndrome, occipital horn syndrome, long term TPN	Liver, oysters, meat, nuts, grains, legumes, chocolate
Zinc	Metalloenzymes (e.g., alkaline phosphatase, carbonic anhydrase, DNA polymerase; wound healing)	Acrodermatitis enteropathica; poor growth, acro-perioral-perianal rash, alopecia, delayed sexual development, hypogeusia, infection	Protein-calorie malnutrition; weaning; malabsorption syndrome	Meat, grains, cheese, nuts
Selenium	Prevents oxidative damage	Keshan cardiomyopathy in China, poor growth	Endemic areas; long-term TPN	Meat, vegetables
Chromium	Insulin cofactor	Poor weight gain, glucose intolerance, neuropathy	Protein-calorie malnutrition, long-term TPN	Yeast, breads
Fluoride	Strengthens dental enamel	Caries	Supplementation during tooth growth, narrow therapeutic range, fluorosis may cause staining of the teeth	Seafood, supplemented water
Iodine	Thyroxine, triiodothyronine production	Simple endemic goiter Myxedematous cretinism: congenital hypothyroidism Neurologic cretinism: mental retardation, deafness, spasticity, normal T_4 level at birth	Endemic in New Guinea, the Congo; endemic in Great Lakes area before iodized salt available	Seafood, iodized salt, most food in nonendemic areas

T_4, thyroxine; TPN, total parenteral nutrition.
From Tershakovec AM. Stallings VA. Pediatric nutrition and nutritional disorders. In: Behrman RE, Kliegman RM, eds. *Nelson Essentials of Pediatrics*, 2nd ed. Philadelphia: WB Saunders; 1994:81.

urination seem excessive or inadequate? Affirmative answers may indicate a gastrointestinal, metabolic, or renal problem. Are there sources of increased calorie need? Has the child been sick? Has the child had fevers? Does the child tire when feeding? Is there decreased activity?

Constitutional: The examiner should ask whether there are any fevers, night sweats, or changes in activity. Assess sleep hygiene, amount of sleep, and whether sleep is disrupted by snoring or awakenings.

Gastrointestinal: The examiner should inquire about choking, swallowing, dysphagia, vomiting, and spitting up. Night waking and coughing may indicate reflux. Diarrhea, constipation, abdominal pain, distention, or discomfort may indicate organic disease. Pocketing food, or retaining food in the mouth, may indicate oral-motor dysfunction that impedes adequate intake.

Cardiopulmonary: The examiner should ask about coughing, wheezing, night waking, shortness of breath, exercise intolerance, and early tiring during feeding.

Renal: The examiner should inquire about dysuria, hematuria, increased urinary frequency or volume, secondary enuresis, and urine that seems unusually dilute.

◆ Physical Examination

The examination should start with accurate measurements of height or length, weight, and head circumference; these parameters should be plotted on a standard growth curve. Weight for height or BMI (if >2 years of age) should also be plotted. Historical events should be obtained and plotted to identify patterns of growth.

As part of a complete physical examination, the following signs should be sought:

General: degree of emaciation, state of fat distribution and muscle mass, dysmorphic features, vital signs (including blood pressure)

Head, eyes, ears, nose, and throat: fontanel size, evidence of chronic ear infections, allergic stigmata, patency of upper airway

Cardiorespiratory: respiratory effort, lower airway sounds, cardiac sounds, pulses, edema

Gastrointestinal: organomegaly, abdominal distention, rectal fissures or prolapse

Genitourinary: renal masses, Tanner staging

Musculoskeletal: joint swelling, bone deformities

Skin: hydration, evidence of chronic inflammation, bruising or scarring, rashes, hair quality and distribution, nails

Lymph nodes: local vs. generalized (see Chapter 36)

Neurologic: muscle volume, tone (hypo or hypertonic), strength, coordination, swallowing and drooling, assessment of development and interaction with the examiner.

Abnormalities associated with pathologic biomedical conditions should prompt a search for a specific diagnosis (see Table 9.4). On occasion, growth failure as well as other physical findings can be associated with specific nutrient deficiencies (Table 9.6; see Table 9.5).

◆ Laboratory Evaluation

Almost any serious chronic illness may result in FTT; therefore the examiner must have a broad diagnostic screening approach and simultaneously consider the more likely possibility that nonmedical

(See *Nelson Textbook of Pediatrics,* p. 343.)

TABLE 9.6 Characteristics of Vitamin Deficiencies

Vitamin	Function	Manifestations of Deficiency	Comments	Sources
Water-Soluble				
Thiamine (B_1)	Coenzyme in ketoacid decarboxylation (e.g., pyruvate →acetyl-CoA transketolase reaction)	Beri-beri: polyneuropathy, calf tenderness, heart failure, edema, ophthalmoplegia	Inborn errors of lactate metabolism; boiling milk destroys B_1	Liver, meat, milk, cereals, nuts, legumes
Riboflavin (B_2)	FAD coenzyme in oxidation-reduction reactions	Anorexia, mucositis, anemia, cheilosis, nasolabial seborrhea	Photosensitizer	Milk, cheese, liver, meat, eggs, whole grains, green leafy vegetables
Niacin (B_3)	NAD coenzyme in oxidation-reduction reactions	Pellagra: photosensitivity, dermatitis, dementia, diarrhea, death	Tryptophan is a precursor	Meat, fish, liver, whole grains, green leafy vegetables
Pyridoxine (B_6)	Cofactor in amino acid metabolism	Seizures, hyperacusis, microcytic anemia, nasolabial seborrhea, neuropathy	Dependency state; deficiency secondary to drugs	Meat, liver, whole grains, peanuts, soybeans
Pantothenic acid	Coenzyme A in Krebs cycle	None reported	—	Meat, vegetables
Biotin	Cofactor in carboxylase reactions of amino acids	Alopecia, dermatitis, hypotonia, death	Bowel resection, inborn errors of metabolism, and ingestion of raw eggs	Yeast, meats; made by intestinal flora
B_{12}	Coenzyme for 5-methyl-tetrahydrofolate formation; DNA synthesis	Megaloblastic anemia, peripheral neuropathy, posterior lateral column disease, vitiligo	Vegans; fish tapeworm; transcobalamin or intrinsic factor deficiencies	Meat, fish, cheese, eggs
Folate	DNA synthesis	Megaloblastic anemia	Goat milk deficient; drug antagonists; heat inactivates	Liver, greens, vegetables, cereals, cheese
Ascorbic acid (C)	Reducing agent; collagen metabolism	Scurvy: irritability, purpura, bleeding gums, periosteal hemorrhage, aching bones	May improve tyrosine metabolism in preterm infants	Citrus fruits, green vegetables; cooking destroys it
Fat-Soluble				
A	Epithelial cell integrity; vision	Night blindness, xerophthalmia, Bitot spots, follicular hyperkeratosis, poor growth	Common with protein-calorie malnutrition; malabsorption	Liver, milk, eggs, green and yellow vegetables, fruits
D	Maintains serum calcium, phosphorus levels	Rickets: reduced bone mineralization, poor growth	Prohormone of 25- and 1,25-vitamin D; malabsorption	Fortified milk, cheese, liver
E	Antioxidant	Hemolysis in preterm infants; areflexia, ataxia, ophthalmoplegia	May benefit patients with G6PD deficiency; malabsorption	Seeds, vegetables, germ oils, green leafy vegetables
K	Posttranslation carboxylation of clotting factors II, VII, IX, and X and proteins C, S	Prolonged prothrombin time; hemorrhage; elevated PIVKA (protein induced in vitamin K absence)	Malabsorption; breast-fed infants	Liver, green vegetables; made by intestinal flora

FAD, flavin adenine dinucleotide; G6PD, glucose-6-phosphate dehydrogenase; NAD, nicotinamide adenine dinucleotide.
Modified from Tershakovec A, Stallings VA. Pediatric nutrition and nutritional disorders. In: Behrman RE, Kliegman RM, eds. *Nelson Essentials of Pediatrics*. 2nd ed. Philadelphia: WB Saunders; 1994:74.

processes are the cause. In most cases of chronic "organic" illness, there is likely some indication in the history, physical examination, or selected diagnostic screening tests (Table 9.7). The few cases of organic FTT not detected by these screening tests may become evident when the infant does not respond to nutritional rehabilitation. If, however, the examiner attempts to pursue every conceivable diagnostic test for organic causes of FTT before implementing vigorous nutritional rehabilitation, he or she is likely to run out of time, patience, and resources and to come to no conclusion. Some unusual cases may take months or years before a diagnosis is made.

The choice of the appropriate initial laboratory tests may include several general screening tests (complete blood count, urinalysis, serum electrolyte levels, blood urea nitrogen level) to detect treatable conditions. A complete blood cell count can reveal clinically inapparent anemia, which, although usually secondary to the poor nutritional state, can sometimes contribute to the poor dietary intake or suggest anemia of chronic disease. A urinalysis and urine culture can reveal evidence of an occult urinary tract infection or renal tubular acidosis. An erythrocyte sedimentation rate or C-reactive protein may provide evidence of chronic inflammation or infection. The examiner may need to test for celiac disease, in which poor weight gain may be the only symptom for many years. Other specific tests are directed by the history and physical examination (Table 9.8). For example, for a child with developmental delay and FTT, a blood lead test, metabolic

TABLE 9.7 Clinical Clues to Differentiate Predominant Organic Disease from Predominant Organic Disease Not Present

Predominant Organic Disease Not Present	Predominant Organic Disease Present
Spoon or bottle refusal	Accepts spoon or bottle first
Presence of anticipatory gagging and "pocketing" of food in mouth	Absent
Picky about texture or type of food	Accepts a variety of foods
Presence of abnormal feeding practice (nocturnal feeding, force feeding, prolonged meals)	Absent
Onset after a trigger or traumatic event (e.g., choking episodes, prolonged nasogastric feeding)	Usually absent
Vivacious infant	Lethargic infant
Poor appetite	Interest in eating
Absence of organic symptoms	Diarrhea or abdominal distention

From Shashidar H, Toila V. Failure to thrive. In: Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*. 4th ed. Philadelphia: Elsevier; 2011:141.

screening tests, a karyotype or other genetic testing, imaging of the head, or human immunodeficiency virus screening may be necessary, whereas a child with apparent malabsorption is evaluated completely differently (such as for cystic fibrosis or celiac disease). If height growth is affected, a bone age can be useful to determine if an endocrine evaluation is necessary.

OVERALL APPROACH TO MANAGEMENT

The evaluation of a child with FTT should proceed in a stepwise manner (Fig. 9.5). Once the clinician has arrived at a working diagnosis, treatment can be instituted. It is important to develop a therapeutic alliance with family members. Parents whose children are not growing according to expectation may be feeling guilty or may have a sense of failure. A nonjudgmental approach, avoiding the assignment of blame, is important. Although the clinician can make suggestions, it is the family that must feel empowered to implement the plan.

Providing specific information that can be easily implemented in the family's home environment will be more successful than giving general advice. Suggestions that a parent feed more food to a child may be disregarded, particularly when the family members believe they are already doing their best. Pressuring parents may increase caregiver guilt, frustration, and anxiety if the child does not grow as expected.

Even with the strong suspicion of a biomedical cause, it is reasonable to give specific advice on enhancing calorie intake while further evaluation and treatment is ongoing. If the condition is chronic, the child may need long-term nutritional supplementation. If the condition is acute and treatable, the child needs extra calories for catch-up growth.

Steps to Improve Calorie Intake

Mealtime Behavior

A pleasant, safe setting should be created for mealtime. An infant seat is appropriate for the first several months. Once a child can sustain a sitting position, a high chair is advantageous. The high chair allows the child to feel safe from falling, frees up his or her hands for feeding, and keeps the child confined in one place to focus on the meal. A bib prevents the need for frequent changes of clothing. For an older child, a booster seat is appropriate along with child-sized utensils. Parents who feed an infant or toddler while holding the child in their laps find that the meal is a struggle; this also prevents the child from developing the skills needed for self-feeding.

To promote the important social aspect of mealtime, family members should be seated and eating with all children whenever possible. Use of a small, child-sized table and chair prevents the child from observing and learning from siblings and adults during family meals. Toddlers and older infants are usually interested in the food served to other family members, and this encourages experimentation with new foods. There should be conversation during the meal, but the child's food intake should not be the focus of the conversation.

Distractions should be minimized during meals. The television and other electronic media should be off. There should not be other commotion in the kitchen. However, for the infant, a small washable toy on the tray or table may help keep attention on the meal.

Parents should understand that experimenting with food is part of the natural curiosity of older infants and toddlers. If the parent is constantly wiping the child and berating him or her for getting messy, the child cannot learn that eating can be a fun experience. If a parent has particular difficulty with messiness, the examiner can suggest spreading newspaper or a plastic sheet under the high chair. Another simple technique is the "two-spoon method" of feeding the child. The parent should provide a spoon to the child to dip into the food, and the parent has the second spoon, which provides most of the feeding.

Once the child has communicated that the meal is finished, the parent can offer one or two more bites but then should accept that the child is no longer hungry, and the meal should be ended. The duration of the meal for a toddler is typically not more than 15 or 20 minutes. Food should not be brought out until the next regular meal or snack.

Beverages

Exclusive breast-feeding is the preferred nutritional source for infants from birth to 6 months. Formula-fed infants should be held during a feeding until they are able to sit on their own and hold the bottle. Bottles should never be propped. After 1 year of age, cow's milk should be consumed. Although 1-2% milk is acceptable, whole milk is preferred for underweight toddlers. The volume of formula or whole cow's milk consumed should be about 24 ounces per day. If a child is drinking an excessive amount of formula, review the preparation procedures to ensure that the proper dilution is used.

All children naturally enjoy sweet foods. However, if they are introduced early or used instead of more nutritionally complete foods, children may develop a preference for sweets, especially juices. In particular, toddlers who are allowed to have bottles with sweetened juices throughout the day eat little at mealtime, resulting in undernutrition. In addition, because of limited absorption of dietary sugars, particularly in juices with high fructose-to-glucose ratios (such as apple and pear juice), children with excessive juice intake may suffer from bloating, excessive flatulence, abdominal pain, and chronic diarrhea because of undigestible carbohydrate malabsorption. Juice should not be introduced until after children are 6 months of age. When introduced, only 100% fruit juice should be offered in a cup. Intake should be limited to 4-6 ounces per day for children aged 1-6 years and to 8-12 ounces per day for older children and adolescents.

Various methods are available to enhance the calorie density of infant dietary beverages for nutritional supplementation. Formulas can be made with less water. Polycose and vegetable oils can be added. Pumped/expressed breast milk can be enhanced with breast milk fortifier (premature infants) or powdered formula (full-term infants).

TABLE 9.8 Some Causes of Failure to Thrive and Screening Tests

Cause	Screening Tests
Environmental and Psychosocial*	
Inadequate caloric intake	History; observation in hospital
Emotional deprivation and disruptions	History; observation in hospital
Rumination; chronic diarrhea, gastroesophageal reflux	History; observation in hospital
Anorexia nervosa and bulimia	History; examination
Secondary to impact of organic disease	History and observation
Organic	
Central nervous system abnormalities, infection	Neurodevelopmental assessment; brain MRI
Gastrointestinal system Malabsorption, cystic fibrosis, inflammatory bowel disease, parasites, aganglionic megacolon; liver disease; food intolerance; celiac disease; gastroesophageal reflux, eosinophilic esophagitis	Examination of stools: stool fat, sweat test, stool ova and parasites; tissue transglutaminase antibodies; liver function tests; barium swallow, erythrocyte sedimentation rate, food challenge, esophageal and intestinal biopsy
Partial cleft palate	Physical examination; observation of feeding
Chronic heart failure	Physical examination; chest x-ray; echocardiography
Endocrine disorders	Growth chart; thyroid function tests; bone age, cortisol level GH testing
Pulmonary disease Bronchopulmonary dysplasia; bronchiectasis; cystic fibrosis	Physical examination; chest roentgenography; tuberculin test, pulmonary function tests, sweat test
Renal disease Anomalies; infection; renal failure; renal tubular disorder	Urinalysis; blood urea nitrogen; ultrasonography; urinary amino acid screen; urine pH
Chromosomal disorders or syndromes Turner syndrome Skeletal dysplasias	Chromosomal analysis; identification of peculiar facies or multisystem defects, skeletal radiographs
Other metabolic, syndromic, or inborn errors	Urine and blood amino and organic acids, mitochondrial DNA, specific gene probes
Chronic infection Tuberculosis, mycotic, congenital, AIDS	Tuberculin test; appropriate laboratory identification of infectious agent, PCR
Chronic inflammation	
Juvenile idiopathic arthritis, SLE	Physical examination; erythrocyte sedimentation rate; CBC, ANA
Immunodeficiency disease DiGeorge syndrome; severe combined immunodeficiency syndrome AIDS or AIDS-related complex	History of rash and diarrhea; thymus size; tonsil size; skin tests; CBC, cell markers, FISH for DiGeorge syndrome HIV test
Malignancies (kidney, hematologic, adrenal, brain)	Imaging (CT, ultrasonography) of abdomen, chest; brain CT or MRI, bone marrow scan
Congenital syndromes caused by alcohol, Dilantin, other drugs, infection	Physical examination; history, TORCH evaluation

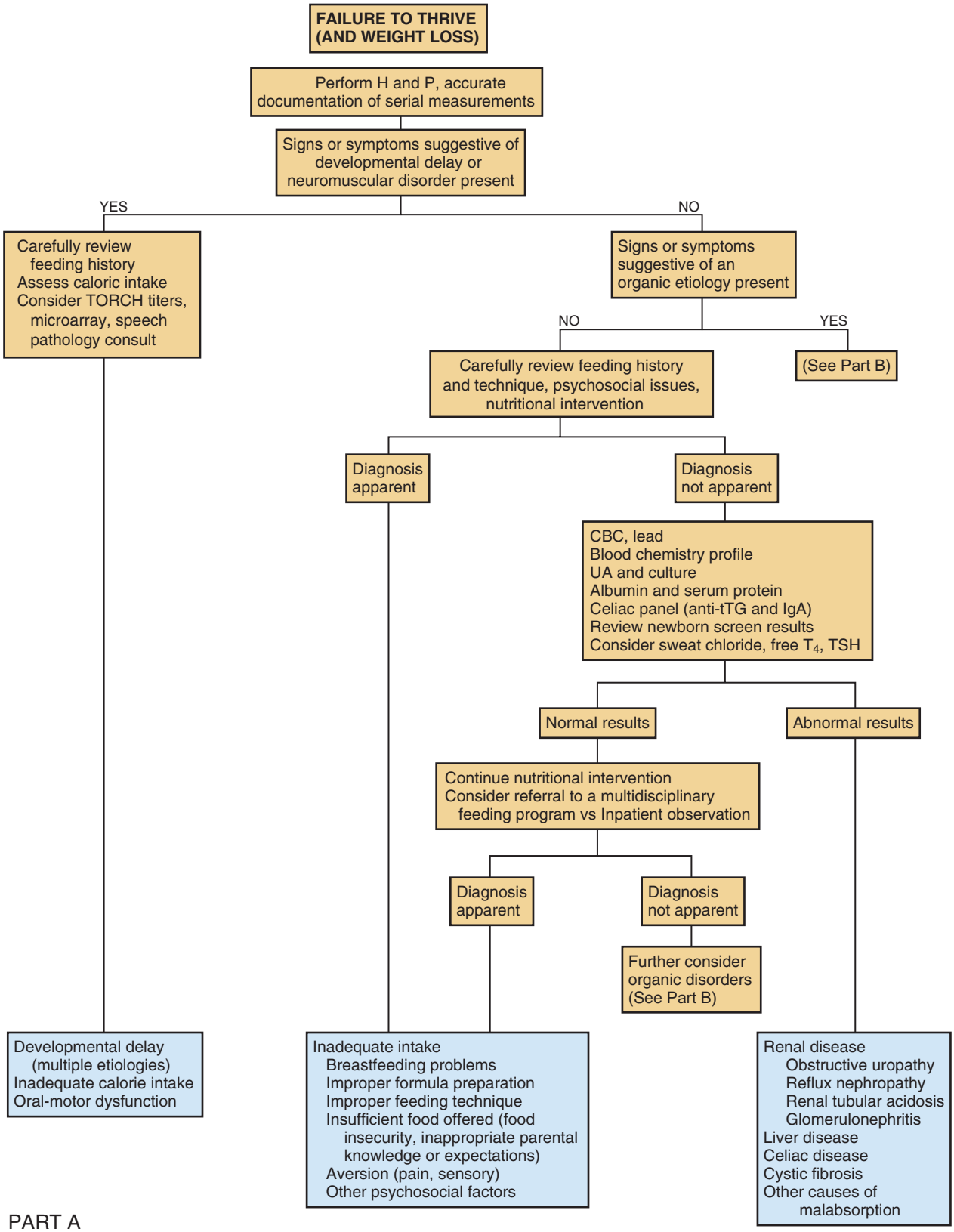
*Nonorganic may also be combined with organic.
AIDS, acquired immunodeficiency syndrome; ANA, antinuclear antibodies; CBC, complete blood cell count; CT, computed tomography; FISH, fluorescent in situ hybridization; GH, growth hormone; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; SLE, systemic lupus erythematosus; TORCH, toxoplasmosis, other, rubella, cytomegalovirus, herpes simplex.
Modified from Barbero GJ. Failure to thrive. In: Behrman RE, ed. *Nelson Textbook of Pediatrics*. 14th ed. Philadelphia: WB Saunders; 1992:215.

Food Selection

Including older children in food shopping and preparation will increase interest in eating. At mealtime, older toddlers and preschool-aged children may be permitted some flexibility in food selection from two or three choices. Providing choices allows the child to assume some control over the feeding. Each choice must be nutritionally sound and acceptable to the parent. Parents should not become bound by social constraints when it comes to foods served at certain meals.

Infants and young toddlers may have preferences for certain food textures, temperatures, and presentations. These preferences are often short-lived. Normal children may become "picky" eaters in the second and third years of life. New foods should routinely be introduced but not forced on the child. With repetition and modeling, children will try new foods. For some children, food preferences may be strong and cyclic. For example, a child may go through a cycle in which he or she requests peanut butter and jelly sandwiches for nearly every meal. If a variety of fruits or vegetables are given along with the sandwich, this may be a reasonable compromise.

Although it is the caregiver's responsibility to provide appropriate food, it is the child's responsibility to decide on the quantity of food to be eaten. "Force feeding" will convince the child that mealtime is



PART A

FIGURE 9.5 Flow Chart for the Stepwise Evaluation of a Child with Failure to Thrive (and Weight Loss). anti-tTG, anti–tissue transglutaminase; CBC, complete blood count; ENT, ear, nose, and throat; GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease; H, history; HIV, human immunodeficiency virus; ICP, intracranial pressure; IgA, immunoglobulin A; IgE, immunoglobulin E; O&P, ova and parasites; P, physical examination; PPD, purified protein derivative; T4, throxine; TORCH, toxolasmosis, other, rubella, cytomegalovirus, and herpes simplex; TSH, thyroid-stimulating hormone; UA, urinalysis; UGI, upper gastrointestinal series. (From Pomeranz AJ, Sabnis S, Busey SL, et al, eds. *Pediatric Decision-Making Strategies*. 2nd ed. Philadelphia: Elsevier; 2016.)

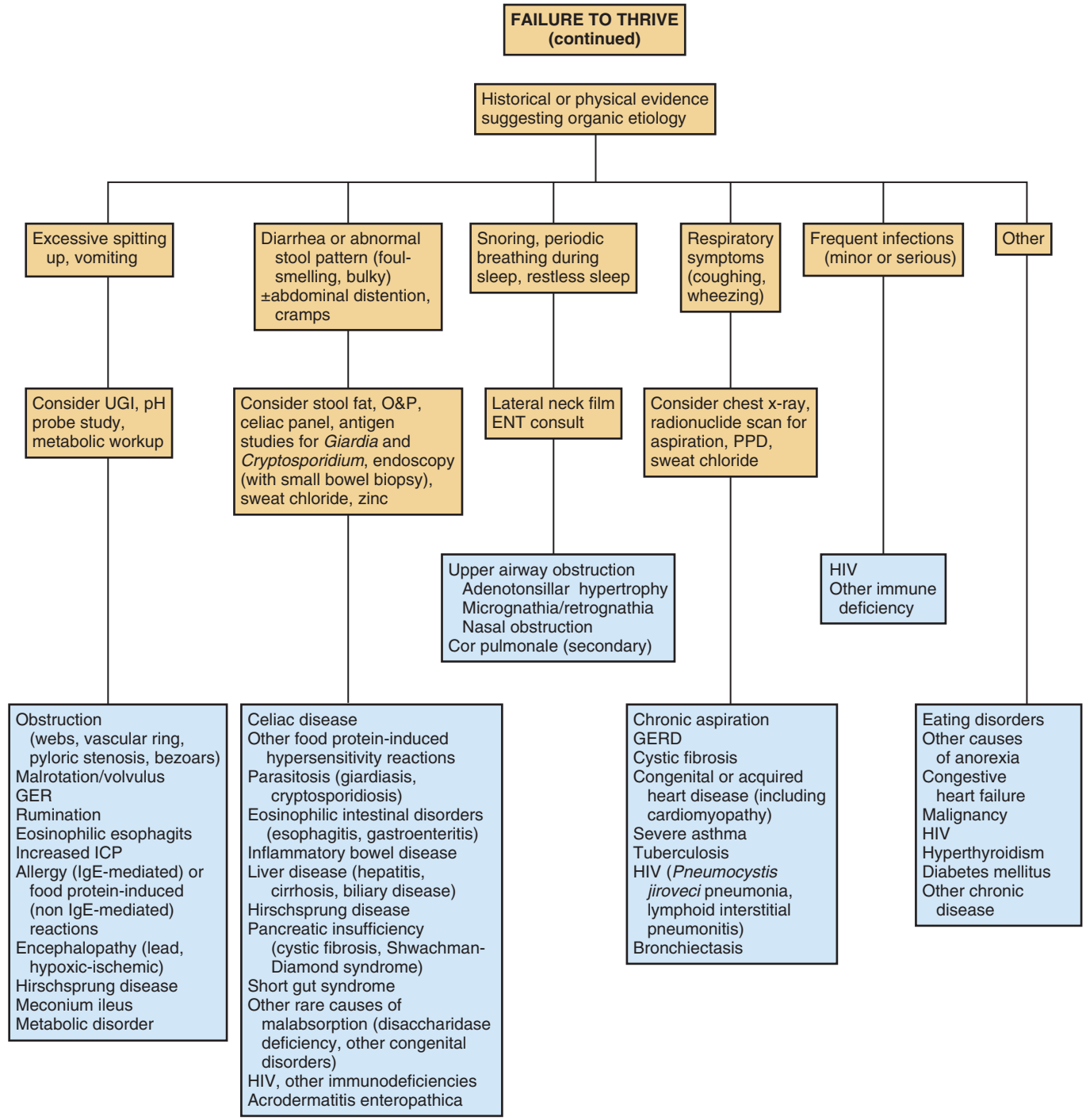


FIGURE 9.5, cont'd

something to be feared. Parents must learn to read a child's cues for hunger and satiety.

Daily Routines and Snacks

Once children are receiving solid foods, they should be on a regular schedule of meals that are served at predictable times during the day. This may mean three meals and two or three snacks per day for infants and toddlers. The practice of "grazing"—having food available to the child throughout the day—should not be allowed. Frequent snacking allows the child to be satiated, preventing interest in standard meals. This may lead to poor nutritional intake. Planned snacks afford the opportunity to supplement the child's diet with high-quality foods with good nutritional content. For toddlers and preschool-aged children, beverages should be introduced only after a good portion of the meal has been eaten.

Calculating Caloric Need

In order to calculate the minimal daily caloric requirements needed for catch-up growth, the examiner should determine the weight age (age at which current weight would be at 50%) and recommended

TABLE 9.9 Normal Calorie Requirements and Weight Gain by Age

	Calorie Requirement (kcal/kg/day)	Weight Gain* (g/day)
Premature	150	20-40
Full-term to 3 months	100-120	25-39
3-6 months		14-20
6- 9 months	90-100	9-13
9-12 months		7-10
Toddler	75-85	6-9

*Based on WHO growth charts (5% and 95%).

calories for weight age (Table 9.9). The ideal weight for current height (50% weight for current height) should also be determined. Calories needed for catch-up growth are calculated as:

$$\frac{(\text{kcal/kg for weight age}) \times (\text{ideal weight for height in kilograms})}{\text{actual weight in kilograms}}$$

For most children, calories needed for catch-up growth can be easily calculated as:

$$\frac{(120\ \text{kcal/kg}) \times (\text{ideal weight for height in kilograms})}{\text{actual weight in kilograms}}$$

Most infants will achieve catch-up growth on 160-180 kcal/kg/day. Some infants may need considerably more, up to 1.5-2 times the daily requirements for catch-up. Caloric intake can be estimated from the diet history.

NUTRITIONAL SUPPLEMENTATION FOR THE OLDER INFANT AND CHILD

Several products are available for nutritional supplementation. The complete liquid formulations are excellent products; very similar nutritional value can be found in packaged instant-breakfast drinks when mixed with whole milk, at much lower cost. These nutrient-dense beverages should supplement the child's diet, not supplant other foods.

Many food products (powdered milk, margarine, cheese, wheat germ, peanut butter) can be added to acceptable foods in order to increase calories. It is easier to increase caloric density than increase the amount of food eaten. Attention should be paid to maximizing protein intake needed for growth.

If a child does not seem to be taking an adequate variety of foods, a supplement of multivitamins with minerals may be indicated. Particularly during periods of rapid catch-up growth, additional vitamins and minerals can be beneficial. Iron and zinc deficiencies may impede normal growth (see Table 9.5). Supplementation of zinc and other trace minerals has been shown to enhance catch-up growth in malnourished children. A trial of an appetite stimulant, such as cyproheptadine, can be effective in some children.

Referral Resources and Other Options

Multidisciplinary Team

Children with FTT have complex medical and psychosocial issues. As a result, a biomedical model of care may be insufficient for managing the child and family. A multidisciplinary approach may be beneficial in complicated cases by relieving the medical provider of the responsibilities of investigating the home situation, reviewing the family's finances and resources, and observation of mealtime.

The team might include a physician, social worker, psychologist, nutritionist, nurse, child life specialist, and home visitor. Each team member evaluates the patient and family according to his or her discipline. The team then discusses the case and develops a plan for ongoing management. Children treated by teams have been found to have better outcomes than do children receiving routine care.

The psychological evaluation may identify children with developmental delays, and can assess family stressors and help identify strengths and weaknesses in the family. In some families, the child may be the indicator that there is an underlying disturbance, such as depression or marital stress. The psychologist can also offer support and reassurance as the family goes through a difficult period caused by potential long-term nutritional rehabilitation of the child. In addition, the psychologist can help the caregiver understand that improving the feeding situation takes a great effort on the part of the parent as well as the child and that new strategies are required for successful weight gain.

The nutritionist's expertise is essential for a thorough evaluation and follow-up plan. When taking a complete nutritional history, the nutritionist can analyze the nutritional and caloric values of the foods eaten. Alternative meal plans can then be developed to maximize calories and nutritional content.

A social worker's contribution to the team is an assessment of the child's environment and factors that may be contributing to the child's poor growth. Areas for investigation include social supports, housing conditions (crowding, space for food storage, proper refrigeration), and financial hardships. Families may need assistance with arranging work leave, rearranging work schedules, transportation, or respite care. Families can be directed to community-support services that focus both on social/emotional and material/financial issues. Participation in the WIC program ameliorates food insecurity. If child maltreatment is suspected, the social worker assists with communication with the appropriate social service agency.

When feasible, home observation provides a wealth of information to the clinician about the environment in which the child resides and eats meals. Does the child have an appropriate place in which to eat? Is there a supply of appropriate foods in the home? What are the other environmental factors that may be impeding the child's growth? Studies of home interventions have had mixed success, but young children with highest risks have improved developmental outcomes with home intervention.

Recording or Direct Observation

Observation or recording of a meal provides an opportunity to assess the child's willingness and ability to participate in the meal, the parenting style, and the interaction between the child and parents. Parent feeding style can be classified as responsive/authoritative, controlling/authoritarian, indulgent/permissive, or neglectful/rejecting. Parent and child strengths should be pointed out to the parent. Problematic communication, both verbal and nonverbal, should be reviewed. Difficulties that are observed should be discussed and become the basis for further intervention.

Involvement of Social Service Agencies

Clinicians caring for children with FTT often find themselves working in conjunction with other agencies, including *social service agencies*. Children who are refused food or are abused in any way must be reported. It may, however, be difficult to determine what constitutes

neglectful care. Families that are disorganized and overwhelmed, have other pressing social issues, or refuse to follow recommendations, resulting in lack of sufficient progress in the child's growth, must be reported to the local agency. This may include parents with cognitive deficits or mental health problems. It is important for all agencies to work together and articulate a plan, so that the families involved do not receive conflicting instructions and messages.

Behavioral Strategies

In some situations, behavior-modification programs are used. These may include strategies to determine specific parameters in the feeding environment that will improve the child's intake. These may include colors, textures, tastes, etc. In more difficult cases, a strict behavior modification program may be used.

Non-Oral Enteral Feeding

For some children, maximizing oral intake may nonetheless provide insufficient calories for catch-up growth. The clinician may consider other forms of enteral feeding. This intervention is needed if, despite all other attempts to maximize oral feeding, the child's growth is falling further below the 5th percentile or if the child is showing signs of severe malnourishment (e.g., hypoalbuminemia, or low prealbumin levels).

Initially, nasogastric (NG) feeding can be used for night feedings. The child should be encouraged to eat orally during the day. If the need for the NG tube is extended for a longer duration (some authorities use 3 months), then a referral should be made for placement of a percutaneous gastrostomy tube (G-tube). This is used for supplemental nutrition for most children and is not a substitute for oral intake. Children receiving supplemental alimentation should be monitored very closely. Once the weight for height is near the 50th percentile, the supplement should be adjusted to prevent obesity. The G-tube is removed when the child can sustain an adequate growth rate eating orally.

It is very important that some oral stimulation continue even if the G-tube is the main source of nutrition. If children are denied the chance to develop competence in age-appropriate feeding behaviors, they are likely to develop food aversions. This makes reintroduction of oral intake extremely difficult.

CHILDREN WITH SPECIAL HEALTH CARE NEEDS

This category encompasses a variety of children: children with isolated dysphagia for whom eating represents more work than pleasure, children with sensory issues for whom food tastes and textures can be experienced as adverse, and children who are technology dependent and not able to self-regulate caloric intake.

During the medical assessment, if a child is found to have drooling, coughing, gagging, pocketing of food in the cheek, retention of food in the mouth, or oral aversion, consider oral motor problems. An assessment by a speech therapist or occupational therapist with specific training in oral motor therapy can help reveal specific problems that are amenable to therapy. A modified barium swallow may be recommended to assess the risk of aspiration. Some children with oral motor dysfunction develop oral aversion, as if it is not worth the effort to put anything in their mouths. Oral motor therapy or involvement in an intensive feeding program that addresses feeding therapy in a multidisciplinary fashion may be indicated for these children.

Children with autism often have sensory issues that cause feeding aversion. Again oral motor evaluation and therapy may be of help, but the therapy may need to focus on oral desensitization rather than motor skills. These children will sometimes accept only a very limited number of foods, or a single color, or texture. The clinician can ensure adequate micronutrient intake with vitamins and other supplements, but may need to disguise them in the accepted foods.

Technology-dependent children represent a very different challenge. Here, it is necessary to monitor growth regularly, and adjust caloric intake as necessary. Increased activity or work, due perhaps to improved motor skills, or decrease in respiratory support, can abruptly increase a child's caloric need and cause weight loss if caloric intake is not increased. In general, increases of 10% are well tolerated, and can be adequate to improve growth. This can be done by increasing volume or caloric density depending on the particular patient's clinical situation. Follow-up weight checks in 2-4 weeks can inform the clinician if the increase was adequate, or excessive, and additional adjustments can be made. Failure to gain weight appropriately even with additional calories should prompt further evaluation for increased utilization or improper home feeding.

CRITERIA FOR HOSPITALIZATION

Decisions about when to hospitalize an infant with FTT are inevitably influenced by practical considerations of the availability and quality of hospital services, cost, and distance from the family's home. The medical issues are whether hospitalization will facilitate further diagnostic steps and whether the affected child is malnourished enough to create a sense of urgency about nutritional rehabilitation. Loss of more than 30% of the average weight for length (to less than 70% of expected weight for length) constitutes severe malnutrition, which most physicians would be reluctant to treat on an outpatient basis unless there is no satisfactory alternative. In addition, hospitalization is indicated if there is a concern about **factitious disorder (Munchausen syndrome)** by proxy. In this situation, a parent may be purposefully manipulating the child in order to produce FTT or other symptoms.

Most children with FTT gain weight in the hospital within 1-2 weeks, but obtaining a weight gain in a short amount of time does not prove that the home environment was the problem. Alternatively, even a 1- to 2-week hospitalization in a child without an organic cause of the growth failure may not produce a sustainable weight gain. The foreign surroundings and lack of familiar faces might prevent the child from eating appropriately. Parents may not be able to remain with the child in the hospital if they have other small children to attend to at home.

Sufficient time must be anticipated in the hospital for substantial recovery; in severe cases, full recovery requires about 6 weeks. After initial stabilization and reassurance that the infant is doing well, the child can spend much of this recovery period in a less expensive, non-intensive supervised medical care facility that emphasizes nutritional support and psychosocial stimulation. Creative approaches to well-organized outpatient day programs or frequent home visiting by properly trained health care workers may provide an attractive alternative to hospitalization.

MONITORING

Long-term follow-up is required to ensure that initial weight gains are sustained. At the follow-up visits, the 24-hour diet recall is assessed, or a 3-day diet history is brought by the family. At all visits, the child's growth parameters must be plotted. Dividing weight gained by the number of days since the last measurement provides a mean growth rate. This can be compared with the normal growth rate in children by age group (see Table 9.9). A child in need of catch-up growth should exceed the expected growth rate for normal children. Periodically, the family can be observed or recorded during a feeding session to determine improvement from prior sessions.

LONG-TERM OUTCOMES

Children with early FTT may suffer long-term consequences in growth, cognitive development, and social functioning. Outcomes depend on cause, age at intervention, and associated risk factors and may not be as ominous as early studies suggested. Parental self- perceived competence and child adaptability have been associated with good outcomes.

Children with FTT who experience other social stressors are at higher risk for adverse outcomes. Poverty and associated family and environmental problems may exacerbate the negative effects of FTT. Children with FTT who experience neglect are more likely to have poor outcomes. However children who are diagnosed early and given appropriate treatment and family support services have better recovery than those who are treated later.

FTT may have long-term effects on growth. It may affect ultimate stature and possibly brain growth and development. Children in whom the FTT has an organic cause that can be successfully managed often do well. For those with undetermined causes or persistent FTT, outcome can be poor. Growth may continue to be delayed. Ultimate stature may be shorter than that predicted from mean parental heights (see Chapter 43). Similarly some children who were SGA at birth may remain small for their life span; nutritional enhancement will have minimal effect.

Of interest is that with long-term follow-up, some children with FTT have been observed to develop obesity. Starvation followed by aggressive nutrition rehabilitation may lead to the development of insulin resistance. The factors that lead some children to develop these consequences of overnutrition are not fully understood.

Poor developmental and cognitive outcomes have been found in many children with FTT. However, studies of these children have multiple confounding factors, and it is difficult to ascribe outcomes solely to the nutritional deficiencies. Some of the children who fare poorly may have had initial mild deficits that were undetected. Those who were symmetrically small for gestational age and those with microcephaly are particularly at risk for diminished cognitive potential. Children who are stunted in the first 2 years of life have poor long-term outcomes. Home intervention by child development specialists may lessen the impact of FTT on cognitive skills. Children should be referred for early intervention services as soon as deficits are detected. Better success will be achieved if intervention is started early.

Children with FTT may manifest behavioral problems, even after the nutritional issues appear to be resolved. If the behaviors are particularly difficult to manage, the services of a psychologist or behavior specialist are warranted.

SUMMARY AND RED FLAGS

FTT (or growth faltering) is a complex condition encompassing biomedical and psychosocial causes. In the United States, it is most often associated with various psychosocial attributes of the parents, family, or child. The keys to determining the cause are a thorough history and physical examination, including assessment of the growth pattern over time. Red flags include refusal to eat, poor response to feedings, an inappropriately small head size, and abnormal physical signs. Clinicians should be vigilant in identifying chronic disease as well as indicators of child abuse and neglect (see Table 9.4). Episodes of recurrent emesis, altered mental status, metabolic acidosis, and hypoglycemia should raise suspicions of an inborn error of metabolism. Microcephaly, seizures, developmental delay or developmental regression, and hypotonia or hypertonia should lead to suspicions of a chronic neurologic problem. Specialists should be consulted for suspected conditions or specific questions. Identifying and treating the medical and psychosocial causes while enhancing calorie intake can result in good outcomes.

REFERENCES

A bibliography is available at ExperConsult.com.

REFERENCES

Reviews

American Academy of Pediatrics Committee on Nutrition. Kleinman RE, Greer FR, eds. *Pediatric Nutrition*. 7th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2014.

American Academy of Pediatrics Committee on Nutrition. The use and misuse of fruit juice in pediatrics. *Pediatrics*. 2001;107:1210-1213.

Birch LL, Doub AE. Learning to eat: birth to age 2 y. *Am J Clin Nutr*. 2014;99:723S-728S.

Blissett J. Relationships between parenting style, feeding style and feeding practices and fruit and vegetable consumption in early childhood. *Appetite*. 2011;57:826-831.

Centers for Disease Control and Prevention. WHO Growth Standards Are Recommended for Use in the U.S. for Infants and Children 0 to 2 Years of Age. <http://www.cdc.gov/growthcharts/who_charts.html>.

Coleman-Jensen A, Rabbitt MP, Gregory C, et al. *Household Food Security in the United States in 2014*, ERR-194, U.S. Department of Agriculture, Economic Research Service, September 2015.

Gahagan S. The development of eating behavior—biology and context. *J Dev Behav Pediatr*. 2012;33:261-271.

Jaffe A. Failure to thrive: current clinical concepts. *Pediatr Rev*. 2011;32:100-107.

Kerzner B, Milano K, MacLean WC, et al. A practical approach to classifying and managing feeding difficulties. *Pediatrics*. 2015;135:344-353.

Meyers A, Joyce K, Coleman SM, et al. Children's HealthWatch. Health of children classified as underweight by CDC reference but normal by WHO standard. *Pediatrics*. 2013;131:e1780-e1787.

Schwartz ID. Failure to thrive: An old nemesis in the new millennium. *Pediatr Rev*. 2000;21:8.

Suskind DL. Nutritional deficiencies during normal growth. *Pediatr Clin North Am*. 2009;56:1035-1053.

Villar J, Altman D, Purwar M, et al. for the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). The objectives, design and implementation of the INTERGROWTH-21st Project. *BJOG*. 2013;120:9-26.

Wright C. Identification and management of failure to thrive: a community perspective. *Arch Dis Child*. 2000;82:5-9.

Treatment and Outcomes

Black MM1, Dubowitz H, Krishnakumar A, et al. Early intervention and recovery among children with failure to thrive: follow-up at age 8. *Pediatrics*. 2007;120:59-69.

Black MM, Cutts DB, Frank DA, et al. Children's Sentinel Nutritional Assessment Program Study Group. Special Supplemental Nutrition Program for Women, Infants, and Children participation and infants' growth and health: a multisite surveillance study. *Pediatrics*. 2004;114:169-176.

Boddy J, Skuse D, Andrews B. The developmental sequelae of nonorganic failure to thrive. *J Child Psychol Psychiatry*. 2000;41:1003-1014.

Hoddinott J1, Behrman JR, Maluccio JA, et al. Adult consequences of growth failure in early childhood. *Am J Clin Nutr*. 2013;98:1170-1178.

Ong KKL, Ahmed ML, Emmett PM, et al. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. *BMJ*. 2000;320:967-971.

Romano C, Hartman C, Privitera C, et al. Current topics in the diagnosis and management of the pediatric non organic feeding disorders (NOFEDS). *Clin Nutr*. 2015;18:195-200.

Ud Din Z, Emmett P, Steer C, et al. Growth outcomes of weight faltering in infancy in ALSPAC. *Pediatrics*. 2013;131:e843-e849.

10

Abdominal Pain

Adrian Miranda

Acute abdominal pain is usually a self-limiting, benign condition that is commonly caused by gastroenteritis, constipation, or a viral illness. The challenge is to identify children who require immediate evaluation for potentially life-threatening conditions. Chronic abdominal pain is also a common complaint in pediatric practices, as it comprises 2-4% of pediatric visits. At least 20% of children seek attention for chronic abdominal pain by the age of 15 years. Up to 28% of children complain of abdominal pain at least once per week and only 2% seek medical attention. The primary care physician, pediatrician, emergency physician, and surgeon must be able to distinguish serious and potentially life-threatening diseases from more benign problems (Table 10.1). Abdominal pain may be a single acute event (Tables 10.2 and 10.3), a recurring acute problem (as in abdominal migraine), or a chronic problem (Table 10.4). The differential diagnosis is lengthy, differs from that in adults, and varies by age group. Although some disorders occur throughout childhood (constipation, gastroenteritis, lower lobe pneumonia, urinary tract infections), others are more common in a specific age group (see Table 10.2).

PATHOPHYSIOLOGY OF ABDOMINAL PAIN

Abdominal pain results from stimulation of nociceptive receptors and afferent sympathetic stretch receptors. The pain is classified as visceral or parietal (somatic).

Visceral Pain

Visceral pain receptors are located on the serosa surface, in the mesentery, within intestinal muscle, and mucosa of hollow organs. Pain is initiated when receptors are stimulated by excessive contraction, stretching, tension or ischemia of the walls of hollow viscera, the capsule of a solid organ (liver, spleen, kidney), or of the mesentery. Increased contraction of the smooth muscle of hollow viscera may be caused by infection, toxins (bacterial or chemical agents), ulceration, inflammation, or ischemia. Increased hepatic capsule tension may be secondary to passive congestion (heart failure, pericarditis) or inflammation (hepatitis).

Afferent fibers involved in processing visceral pain are unmyelinated C-fibers that enter the spinal cord bilaterally, resulting in dull, poorly localized pain. Visceral pain is often of gradual onset, and although localization may be imprecise, some general rules may be helpful (Fig. 10.1).

Parietal Pain

Parietal pain arises from direct noxious (usually inflammation) stimulation of the contiguous parietal peritoneum (e.g., right lower quadrant at the McBurney point, appendicitis) or the diaphragm (splenic rupture, subdiaphragmatic abscess). Parietal pain is transmitted through A-delta fibers to specific dorsal root ganglia and thus is usually sharp, and more intense. It can usually be exacerbated by movement or cough, is accompanied by tenderness over the site of irritation, and lateralizes to one of four quadrants. Because of the relative localization of the noxious stimulation to the underlying peritoneum and the more anatomically specific and unilateral innervation (peripheral-nonautonomic nerves) of the peritoneum, it is usually easier to identify the precise anatomic location that is producing parietal pain (Fig. 10.2).

ACUTE ABDOMINAL PAIN

The clinician evaluating the child with abdominal pain of acute onset must decide quickly whether the child has a "surgical abdomen" (a serious medical problem necessitating treatment and admission to the hospital) or a process that can be managed on an outpatient basis. Even though surgical diagnoses are fewer than 10% of all causes of abdominal pain in children, they can be life-threatening if untreated. Approximately 55% of children evaluated for acute abdominal pain have a specific medical diagnosis; in another 45%, the cause is never defined.

◆ History

Obtaining an accurate history is critical for making an accurate diagnosis but is dependent both on the ability and willingness of the child to communicate and on the skill of the parent or guardian as an observer. The person providing an infant's care is the best source of information about the current illness; the examining physician should try to elicit as much information from the child as possible. Some children give a good account of their illness when they are simply asked to describe it; most children must be asked open-ended, non-leading questions. To determine the presence of anorexia, the physician must ask questions about food intake, the time the food was eaten, and how that behavior compares to the child's normal intake. The answers are often quite different from the responses to the more general questions "Are you hungry?" and "Have you eaten today?"

During the history taking, the child should remain in the parent's arms, at play, or comfortably seated beside the parent, as appropriate for the child's age. While the history is obtained, there is no particular reason that the child should be undressed. The clinician must resist the urge to speed things up by examining the child while taking the history. On occasion, when seeing a seriously ill child, the physician may need to abbreviate the diagnostic process, but taking short cuts may lead to inaccurate conclusions.

Essential Components of the History

Time of onset of pain. Pain of fewer than 6 hours' duration is accompanied by nonspecific findings, and observation is often needed to determine the nature of the illness. Pain lasting from 6-48 hours is more apt to have a cause that warrants medical intervention, although delays in presentation and diagnosis in children are not unusual. Timing of the progression of symptoms must be detailed.

(See *Nelson Textbook of Pediatrics*, p. 1764.)

TABLE 10.1 Distinguishing Features of Abdominal Pain in Children

Disease	Onset	Location	Referral	Quality	Comments
Functional: irritable bowel syndrome	Recurrent	Periumbilical	None	Dull, crampy, intermittent, duration 2 hr	Caused by unknown physiologic factors; diarrhea/constipation are symptoms
Gastroenteritis	Acute or gradual	Periumbilical, rectal-tenesmus	None	Crampy, dull, intermittent	Emesis, fever, watery diarrhea or dysentery (mucus and blood)
Esophageal reflux	Recurrent, after meals, bedtime	Substernal	Chest	Burning	Sour taste in mouth, Sandifer syndrome
Duodenal ulcer	Recurrent, before meals, at night	Epigastric	Back	Severe burning, gnawing	Relieved by food, milk, antacids; family history
Pancreatitis	Acute	Epigastric/hypogastric	Back	Constant, sharp, boring	Nausea, emesis, marked tenderness
Intestinal obstruction	Acute or gradual	Periumbilical–lower abdomen	Back	Alternating cramping (colic) and painless periods	Distention, obstipation, bilious emesis, increased bowel sounds
Appendicitis	Acute or gradual (1-2 days)	Initially periumbilical or epigastric; later localized to the right lower quadrant	Back or pelvis if retrocecal	Sharp, steady	Nausea, emesis, local tenderness with/without fever; patient is motionless
Meckel diverticulitis (mimics appendicitis)	Recurrent or constant	Generalized diffuse with perforation: periumbilical–lower abdomen	None	Sharp	Hematochezia: painless unless intussusception, diverticulitis, or perforation
Inflammatory bowel disease	Recurrent	Depends on site of involvement		Dull cramping, tenesmus	Fever, weight loss, with/without hematochezia
Intussusception	Acute	Periumbilical–lower abdomen	None	Cramping, with painless periods	Guarded position with knees pulled up, "currant jelly" stools
Lactose intolerance	Recurrent with milk products	Lower abdomen	None	Cramping	Distention, gaseousness, diarrhea
Urolithiasis	Acute, sudden	Back	Groin	Severe colicky pain	Hematuria; calcification on KUB x-ray study, CT scan
Pyelonephritis	Acute, sudden	Back	None	Dull to sharp	Fever, costochondral tenderness, dysuria, pyuria, urinary frequency
Cholecystitis/ cholelithiasis	Acute	Right upper quadrant	Right shoulder, scapula	Severe colicky pain	Hemolysis with/without jaundice

CT, computed tomography; KUB, kidney, ureter, and bladder.
Data from Andreoli TE, Carpenter CJ, Plum F, et al. *Cecil Essential of Medicine*. Philadelphia: WB Saunders; 1994:326; Behrman R, Kliegman R. *Nelson Essentials of Pediatrics*. 2nd ed. Philadelphia: WB Saunders; 1994:396.

Location of pain. The location of the pain at its onset and any change in location are very important (Table 10.5; see also Table 10.1). Most intraperitoneal visceral pain is a response to the stimulation of stretch fibers in the bowel wall and is mediated through the spinal nerves. This pain is sensed as a deep, aching periumbilical pain. Pain caused by inflammation of the parietal peritoneum (acute appendicitis) is localized to the area of the inflamed organ or is diffuse if the inflammation is extensive and involves more of the peritoneal cavity. Pain resulting from obstruction of an organ is localized to the area of that organ and radiates to the commonly innervated region (e.g., stones in the ureter cause intense flank pain with radiation into the groin). Pain that is migratory or fleeting in location is rarely suggestive of a problem requiring operative intervention.

Character of pain. The character of the pain is often difficult for the child to describe. Some older children may be able to differentiate cramping, aching, and burning sensations, but most children do not do this well. Children can relate whether the pain comes and goes or is continuous and unrelenting. The character of the pain is usually unknown in the toddler and infant, although the parent can determine whether the discomfort is constant, cramping, or intermittent. If the child intermittently draws the legs up in a flexed position and cries, the clinician can assume that intermittent pain is present.

Child's activity level. The effect of the pain on the child's activities is an important indicator of the severity of the underlying disease. If the pain is sufficiently severe to awaken the child from a sound sleep, it is of much more significance than pain that occurs only at school and never on weekends. If a child has had to avoid a favorite activity, the pain is more apt to have a defined organic cause. This applies only to children with acute abdominal pain because children with chronic functional abdominal pain may wake up from sleep and may miss favorite activities due to pain and disability. Asking whether motion worsens the pain helps differentiate peritoneal irritation or musculoskeletal diseases from more nonspecific problems. The child with acute appendicitis lies motionless, whereas the child with a renal stone, gallstone, gastroenteritis, or pancreatitis may toss and turn and writhe in discomfort. Localized, superficial, tender trigger points in the

TABLE 10.2 Causes of Acute Abdominal Pain by Age Group

Neonate
Necrotizing enterocolitis*
Obstruction*
Malrotation with volvulus*
Idiopathic or drug (indomethacin, steroid)–induced intestinal perforation

Infant (<2 yr)
Intussusception*
Incarcerated hernia*
Urinary tract infection*
Gastroenteritis*†
Intestinal obstruction
Malrotation with volvulus
Trauma (e.g., abuse)
Pneumonitis (lower lobe)
Hirschsprung disease
Aerophagia
Spontaneous bacterial peritonitis
Gastroesophageal reflux

Child (2-11 yr)
Appendicitis*
Gastroenteritis*†
Trauma*
Henoch-Schönlein purpura
Hemolytic uremic syndrome
Hepatitis
Peptic ulcer disease
Sickle cell anemia: vasoocclusive crisis
Pancreatitis
Pneumonia (lower lobe)
Abdominal tumors
Pyelonephritis/cystitis
Testicular torsion
Torsed cryptorchid testis
Incarcerated hernia
Typhlitis
Pharyngitis/tonsillitis
Meckel diverticulitis
Superior mesenteric artery syndrome
Mesenteric adenitis
Spontaneous bacterial peritonitis
DKA
Streptococcal pharyngitis
Idiopathic*

Adolescent (12-19 yr)
Appendicitis*
Pelvic inflammatory disease*
Trauma*
Tubo-ovarian abscess
Fitz-Hugh–Curtis syndrome
Labor (pregnancy)
Hepatitis
Pancreatitis (any cause)
Ectopic pregnancy
Crohn disease
Ovarian cyst/mittelschmerz*
Sickle cell crisis
Peptic ulcer disease
Omental torsion
Psoas abscess or hemorrhage
Mesenteric adenitis
Urinary tract infection
Muscle strain (exercise, coughing)
DKA
Testicular torsion
Idiopathic*

*Most commonly seen problem.
†Gastroenteritis indicates intestinal infection with viral, bacterial, protozoal, or parasitic agents. Giardiasis and cryptosporidiosis are particularly common and may produce acute or chronic pain.
DKA, diabetic ketoacidosis.

abdominal wall may suggest abdominal wall (muscle, cutaneous) pain. The localized pain results from entrapment of cutaneous terminal branches of intercostal nerves (7th-12th) penetrating the rectus abdominis muscle and can easily be missed without the proper history or exam.

Gastrointestinal symptoms. The presence or absence of gastrointestinal symptoms may differentiate intestinal problems (acute appendicitis, gastroenteritis, acute cholecystitis) from those arising from other intraabdominal organs (urinary tract infection, ovarian disease, abdominal wall pain).

Anorexia and nausea are difficult symptoms for a small child to describe. Often, if simply asked whether he or she is hungry, a child will respond in the affirmative. Questions about recent food intake, normal eating habits, the last normal meal, and the current desirability of a favorite food often provide more accurate information about the

TABLE 10.3 Sudden Acute Excruciating Abdominal Pain (Within Minutes)

Intestinal Perforation
Peptic ulcer disease
Appendicitis
Diverticula

Luminal Occlusion
Urolithiasis
Cholelithiasis
Strangulated hernia

Vascular Occlusion
Midgut volvulus
Emboli
Endocarditis
Strangulated hernia
Ovarian torsion
Testicular torsion

Intraabdominal Hemorrhage
Ectopic pregnancy
Ruptured aortic aneurysm
Ruptured spleen

presence or absence of anorexia and nausea than do direct questions about appetite or nausea.

Vomiting associated with acute pain is usually related to intestinal disease, such as ileus, gastroenteritis, or acute problems of the gastrointestinal tract that warrant surgery. However, vomiting may occur as a response to severe non-intestinal pain such as in testicular torsion; this vomiting is usually not recurring and is not a prominent feature. Vomiting may be a sign of increased intracranial pressure, which may or may not be accompanied by associated headache or vital sign changes (bradycardia, hypertension, irregular respirations), a bulging fontanel, an altered level of consciousness, or neurologic findings (3rd or 6th cranial nerve palsies). Care should be taken to determine whether the pain occurs before or after the onset of the vomiting. With acute surgical lesions (those caused by intestinal obstruction, acute appendicitis, acute cholecystitis), the pain usually occurs before or during the vomiting. If the vomiting occurred before the onset of pain, the clinician should suspect gastroenteritis or another nonspecific problem. The appearance of the vomited material is also important. Feculent or dark-green material suggests intestinal obstruction. Dark brown or frankly bloody material indicates gastritis, prolapse gastropathy, or peptic ulcer disease as the source of pain.

Diarrhea occurs commonly in intestinal diseases of viral, parasitic, or bacterial origin. The stool volume is large, and defecation is usually preceded by cramping pain that is alleviated by the passage of the diarrheal stool. Diarrhea may also occur in the presence of acute appendicitis or other pelvic infections (such as those resulting from pelvic inflammatory disease, tubo-ovarian abscess); in these cases, diarrhea is caused by inflammation and irritation of an area of colon adjacent to an inflammatory mass. The diarrhea in this instance is of small volume and is frequent. It is important to obtain an estimate of the volume and consistency of stool. Diarrhea may also occur in lesions that cause partial obstruction of the bowel, such as strictures, adhesions, and Hirschsprung disease. In this situation, the patient also has some degree of abdominal distention. **Constipation** alone can cause acute abdominal pain and may also indicate other gastrointestinal dysfunction. Some constipated children present with a picture very similar to that seen in acute appendicitis but have a large amount of stool filling the entire colon. It is therefore important to obtain a good history of not only bowel movement frequency but also consistency as well (see Chapter 16). The history and exam is sufficient to make the diagnosis of constipation, and imaging is usually not necessary. Once the diagnosis is made, appropriate treatment should start with a proper clean-out followed by maintenance therapy. The clinician should not be fooled by the symptom of tenesmus, where the patient has a feeling of constantly needing to pass stools despite having an

TABLE 10.4 Causes of Chronic and Recurrent Abdominal Pain by Age Group*

Infant (<2 yr)	Child (2-11 yr)	Adolescent (12-19 yr)
Colic†	Constipation†	Irritable bowel syndrome†
Inguinal hernia	Functional pain†	Psychogenic factors†
Malabsorption‡	Giardiasis†	Dysmenorrhea†
Milk allergy	Peptic ulcer disease	Mittelschmerz†
Hirschsprung disease	Toxins (lead)	Peptic ulcer disease
Cystic fibrosis	Pancreatitis	Gallbladder disease
Rotational defects	Parasites	Pelvic inflammatory disease
Malformations	Tumors/masses	Ovarian cysts
Esophagitis	Diskitis/osteomyelitis	Diabetes mellitus
	Abdominal migraine	Inflammatory bowel disease
	Diabetes mellitus	Malignancy
	Volvulus	Giardiasis
	Intraabdominal abscess§	Serositis (e.g., SLE, familial Mediterranean fever)
	Choledochal cyst	Intraabdominal abscess§
		Hereditary angioedema

*See also Table 10.6.
†Most common diagnoses.
‡Includes lactose and sorbitol (and other fruit-juice polyalcohols) intolerance.
§Hepatic, pancreatic, subphrenic, psoas, perinephric, renal, pelvic.
SLE, systemic lupus erythematosus.

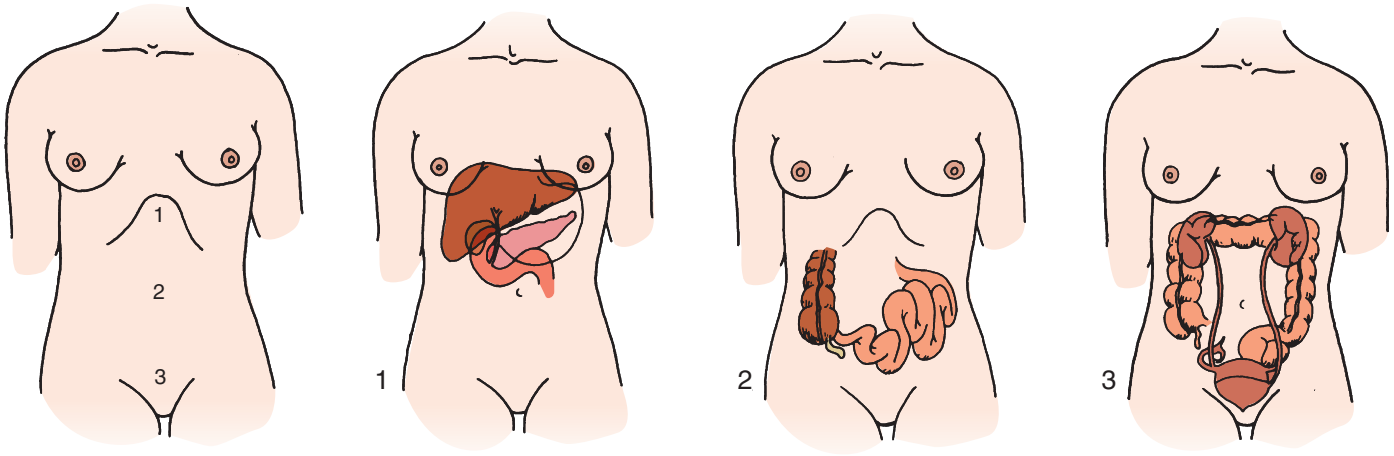
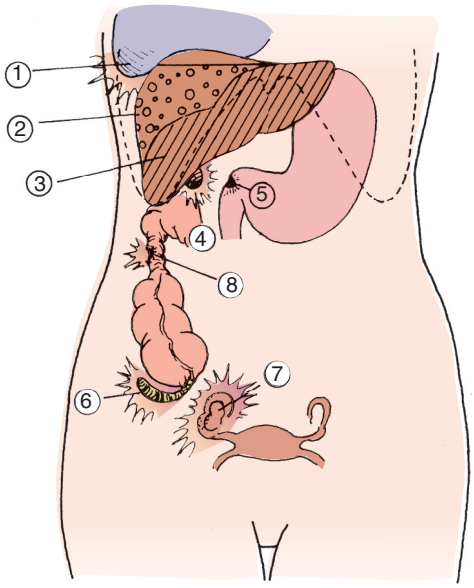
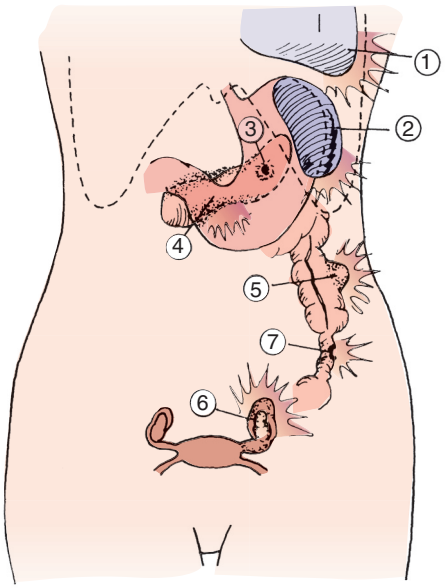


FIGURE 10.1 "Visceral" abdominal pain: deep, dull, diffuse. The three general localizations of midline "visceral" abdominal pain are epigastric *(1)*, periumbilical *(2)*, and hypogastric *(3)*. *1,* Epigastric pain usually suggests disease of the thorax, stomach, duodenum, pancreas, liver, or gallbladder. *2,* Periumbilical pain usually implies disease of the small intestine, cecum, or both. *3,* Hypogastric pain usually implicates the large intestine, pelvic organs, or urinary system. (From Reilly BM. Abdominal pain. In: *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991:702.)



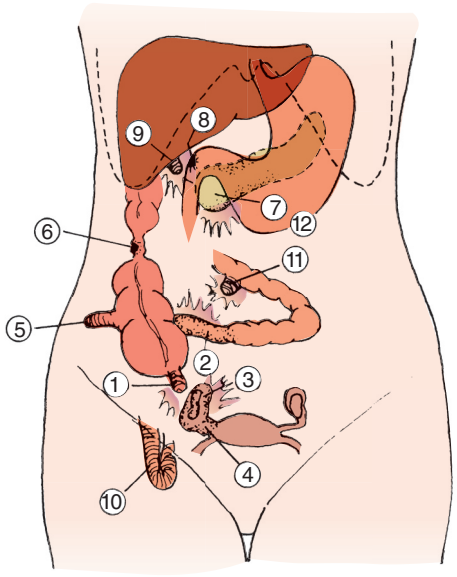
1. Pleurisy
2. Subdiaphragmatic abscess
3. (Peri) hepatitis
4. Cholecystitis
5. Perforated duodenal ulcer
6. Appendicitis
7. Ectopic pregnancy, tuboovarian hemorrhage, abscess, or rupture
8. Perforated colon (cancer or diverticulum)

A



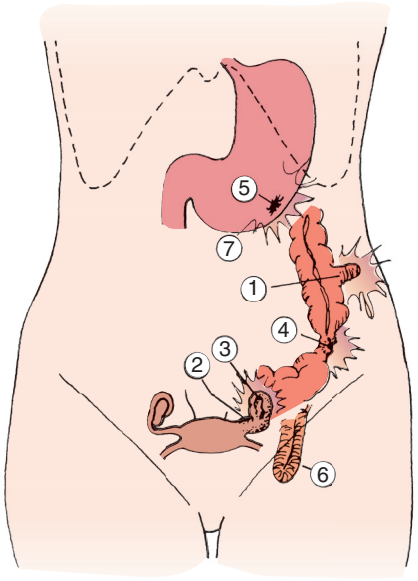
1. Pleurisy
2. Splenic rupture or infarct
3. Pancreatitis
4. Diverticulitis
5. Ectopic pregnancy, tuboovarian hemorrhage, abscess, or rupture
6. Appendicitis
7. Perforated colon (carcinoma)

B



1. Appendicitis
2. Acute Crohn's disease
3. Ectopic pregnancy, tuboovarian abscess, or ovarian torsion/ hemorrhage
4. Pelvic inflammatory disease
5. Cecal diverticulitis
6. Colon cancer (perforation)
7. Acute pancreatitis and/or pseudocyst
8. Perforated duodenal ulcer
9. Acute cholecystits
10. incarcerated inguinal hernia
11. Meckel's diverticulitis
12. Leaking aortic aneurysm

C



1. Sigmoid diverticulitis
2. Pelvic inflammatory disease
3. Ectopic pregnancy, tuboovarian abscess, or ovarian torsion/hemorrhage
4. Perforated sigmoid carcinoma
5. Perforated gastric ulcer
6. incarcerated inguinal hernia
7. Leaking aortic aneurysm

D

FIGURE 10.2 Common and uncommon conditions that may cause "parietal" pain and localized peritonitis in the various quadrants of the abdomen. *A,* Right-upper quadrant. *B,* Left-upper quadrant. *C,* Right-lower quadrant. *D,* Left-lower quadrant. (From Reilly BM. Abdominal pain. In: *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991:703.)

TABLE 10.5 Localization of Abdominal Pain: Referred or Radiated

REFERRED	
Extraabdominal Lesion Pain Referred to Abdomen	**Intraabdominal Extraperitoneal Origin**
Thorax	Pancreas
Spine	Kidney
Hips	Ureters
Pelvis	Great vessels
	Pelvic organs
	Retroperitoneal space

RADIATED
Origin Is Primary Site with Simultaneously Perceived Pain in a Secondary Site
Cholecystitis radiates to subscapular area
Splenic injury radiates to shoulder
Ureteral colic (stones) radiates to testis, upper leg or groin
Pancreatitis radiates to back

empty colon. Tenesmus can be seen in the setting of proctocolitis or inflammatory bowel disease and is often misinterpreted by the patient as constipation.

Associated symptoms. The presence of headache, sore throat, and other generalized aches and pains moves the examiner away from a diagnosis of an acute problem warranting surgery and strongly suggests a viral flu-like illness. Asking the child to point to the area of worst pain sometimes results in the child pointing to the head or throat. The examiner must be careful to remember the whole child and not to focus on the abdomen just because that is the area of the presenting complaint. Many systemic diseases directly or indirectly produce abdominal pain and must be considered in the differential diagnosis (Table 10.6).

Family history and personal medical history. Viral gastroenteritis, other viral syndromes, and food poisoning may affect the patient's family or schoolmates; it is important to ask about other family members, classmates, or playmates who have recently had similar symptoms. Certain systemic and inherited diseases, such as sickle cell anemia, diabetes mellitus, celiac disease, spherocytosis, familial Mediterranean fever, and porphyria, are associated with episodes of abdominal pain. A strong family history of migraine headaches in a child with several previous episodes of intense abdominal pain that have resolved, who presents with a new "attack," suggests the possibility of abdominal migraine. The family must be asked about familial diseases and any previous episodes of pain in the child. Previous intraabdominal operations may result in adhesions that can cause pain, intestinal obstruction, or both. A history of previous intraabdominal surgeries suggests the possibility of bowel obstruction. Some specific medical illnesses result in identifiable or predictable causes of abdominal pain (Table 10.7).

◆ Physical Examination

The physical examination begins when the clinician enters the room and observes the child's activity and demeanor while obtaining the history. Does the child appear ill? Is the patient lethargic, rolling about in discomfort, alert but lying very still, or bouncing all over the room? Each of these activities conveys a message. The listless, lethargic child may be in shock, dehydrated, and very ill. The child who is crying out loudly and generally dominating the scene probably does not have a problem that warrants surgery and may have mild pain that is self-resolving. The child who seems only mildly ill but moves with great care, if at all, is assumed to have an inflammatory process until it is proven otherwise.

Physical examination techniques and findings are age dependent. Younger children may have difficulty cooperating because of fear or discomfort. Younger children may be more cooperative if kept on their parent's lap. Older children should be asked to get onto the examination table with as little assistance as possible. If the child does this easily, the probability of an acute intraabdominal inflammatory process is quite low. Outer bulky clothing should be removed to allow good exposure of the abdomen without the child having to feel vulnerable.

The examination must be performed in a relaxed, friendly manner with attention fully focused on the child. An accurate examination depends on the child's trust and cooperation. A conversation with the child about family, friends, pets, school, sports, music, or other specific interests of that child diverts attention (distraction) from the examination and increases cooperation. The examiner should never surprise the child and should never lie. The first surprise or untruth, such as the statement "This won't hurt," destroys any trust that has developed.

Low-grade fever (<38.3°C) is seen in early appendicitis but is also common in many other diseases. The absence of fever does not exclude the diagnosis of acute appendicitis or other problems necessitating surgical intervention. Tachycardia may reflect anxiety or may be caused by dehydration, shock, fever, or pain. Tachypnea suggests a metabolic acidosis (shock, diabetes mellitus, or toxic ingestion), an intrapulmonary process, sepsis, or fever. The vital signs must be viewed in context but may be the first clue to a serious illness.

Examination of the head, neck, chest, and extremities may precede the abdominal examination. In children too young to describe the location of the pain, a careful examination of the ears is important, but can be performed at the end of the examination. Streptococcal pharyngitis or mononucleosis is sometimes accompanied by severe abdominal pain. Affected children will present with fever, appear ill, and have tender cervical adenopathy and an obvious tonsillitis, pharyngitis, or both.

Decreased breath sounds and/or rales in a lower-lung lobe, especially on the right side, may indicate pneumonia. Children with lower lobe bacterial pneumonia present with severe abdominal pain, high fever, tachypnea, and, on occasion, vomiting. This presentation could mimic that of a child with peritonitis; however, the abdominal findings are not consistent with the diagnosis of an acute intraabdominal process, and examination of the lungs should demonstrate the pneumonia.

The abdominal examination should be performed systematically and with the child as comfortable as possible. Before the examiner actually touches the child's abdomen, he or she should observe it, looking for distention, inguinal masses, peristaltic waves, and scars from old injuries or surgical incisions. Inguinal and femoral hernias are often overlooked but a common cause of abdominal pain. Next, the child should be asked to indicate with one finger the point of greatest pain. The point may be a vague circle in the area of the umbilicus, but if the child specifies a defined spot, the examiner should avoid that area until the remainder of the abdomen has been palpated.

Gentleness is essential to successful palpation of the abdomen. The examiner must warm both hands and the stethoscope before touching the patient. The stethoscope is an excellent tool for palpation of the abdomen. Auscultation of the chest can simply be extended to the abdomen, with the examiner assuring the child that the stethoscope did not hurt on the chest. The initial examination of the abdomen with

TABLE 10.6 Systemic Causes of Acute Abdominal Pain

Metabolic, Hematologic
- Acute porphyria
- Familial Mediterranean fever
- Hereditary angioedema
- Sickle cell crisis
- Leukemia
- Acute hemolytic states
- Diabetic ketoacidosis
- Hemolytic uremic syndrome
- Addison disease
- Uremia
- Electrolyte disturbances
- Hyperparathyroidism-hypercalcemia (urolithiasis, pancreatitis)
- Hypertriglyceridemia (pancreatitis)
- Fabry disease

Musculoskeletal
- Arthritis/diskitis
- Osteomyelitis
- Thoracic nerve root dysfunction
- Trauma/child abuse
- Hernia
- Psoas abscess or hemorrhage

Neurologic
- Abdominal epilepsy
- Abdominal migraine
- Brain tumor
- Multiple sclerosis
- Radiculopathy
- Neuropathy
- Herpes zoster
- Dysautonomia (Riley-Day syndrome)

Drugs, Toxins
- Heavy metal poisoning
  - Lead
  - Arsenic
  - Mercury
- Mushroom ingestion
- Narcotic withdrawal
- Black widow spider bite

Infectious, Inflammatory
- Acute rheumatic fever
- Infectious mononucleosis
- Rocky Mountain spotted fever
- Measles
- Mumps
- Pneumonia (lower lobe)
- Pericarditis
- Pharyngitis
- Epididymitis/orchitis
- Henoch-Schönlein purpura
- Hemolytic uremic syndrome
- Systemic lupus erythematosus
- Endocarditis
- Anaphylaxis

Other
- Pneumothorax
- Pulmonary embolism
- Functional
- Aerophagia

the stethoscope should be just for listening, with no pressure exerted, so that no discomfort results.

Bowel sounds are usually nonspecific in most children with abdominal pain; however, in certain processes, they are helpful. High-pitched tinkling sounds or rushes are usually associated with an obstructive process. Bowel sounds in gastroenteritis are ordinarily very active and loud but may be normal. Acute appendicitis is accompanied by normal sounds in the early stages, but bowel sounds disappear with diffuse peritonitis.

Watching the child's reaction to the auscultation may be a valuable clue to areas of true tenderness. As the examiner continues to listen over the entire anterior abdomen, the pressure on the head of the stethoscope increases until the examiner is, in fact, palpating with the stethoscope. This often is a much more reliable method of eliciting true tenderness and guarding than is the palpating hand.

Palpation is begun as far away from the area of pain identified by the child as possible. The examiner's hand should be softly placed flat (in parallel) on the child's abdomen. Directing fingers into the abdomen (perpendicular) as a method of palpation is unnecessary and often frightening. The clinician should watch the child's face, not the abdomen, during the palpation. Some children are extremely stoic, and only the slightest grimace betrays the discomfort they are experiencing. Attention is paid during palpation to the presence of masses. The examiner should focus on finding the location of pain and the presence or absence of guarding or rebound tenderness. **Guarding** refers to the voluntary or involuntary (often referred to as rigidity) contraction of the abdominal musculature. Fear of pain, rather than actual pain elicited by palpation, is the most common cause for voluntary guarding while involuntary guarding results from reflexive spasms of the abdominal musculature in the setting of peritoneal irritation. A **rigid** or **board-like** abdomen is the result of involuntary guarding and cannot be overcome by distraction. Voluntary guarding usually starts before the palpation starts and can be overcome by asking the child to take deep breaths, flexing the knees and hips, or by using other distractions appropriate to the child's age and temperament. When encountering tenderness, the examiner should palpate only deeply enough to elicit the complaint of pain and some guarding. There is no need to bring on unnecessary pain by deep palpation.

Rebound pain is an indicator of peritoneal irritation and is elicited during examination of the anterior abdominal wall. It occurs when an

TABLE 10.7 Current or Past Aspects of Medical History That May Suggest Cause of Abdominal Pain

Historical Factor	Cause of Pain
Cystic fibrosis	Pancreatitis, diabetes mellitus, meconium ileus equivalent, appendicitis, intussusception, biliary or urinary stones
Sickle cell anemia	Vasoocclusive crisis, cholelithiasis, hepatitis, hemolytic crisis, renal infarction, splenic sequestration
Diabetes mellitus	Pancreatitis, gastric neuropathy
Cirrhosis, nephrotic syndrome	Primary bacterial peritonitis
SLE, other autoimmune disorders	Vasculitis, pancreatitis, serositis, infarction
Corticosteroids	Gastric ulceration, pancreatitis
NSAID	Ileal perforation, gastric ulceration, renal-papillary necrosis
HIV	Gastroenteritis, hepatitis, pancreatitis, esophagitis, lymphoma
Mononucleosis	Hepatitis, splenic rupture
Henoch-Schönlein purpura	Mucosal hemorrhage, intussusception
Hemolytic uremic syndrome	Colitis
Upper respiratory tract infection	Pneumonia, mesenteric adenitis
Pneumonia	Mesenteric adenitis
Prior surgery	Abscess, adhesions, obstruction, stricture, pancreatitis, ectopic pregnancy
Inborn errors of metabolism, hypertriglyceridemia, hypercalcemia	Pancreatitis
Drugs (valproic acid)	Pancreatitis

HIV, human immunodeficiency virus; NSAID, nonsteroidal antiinflammatory drug; SLE, systemic lupus erythematosus.

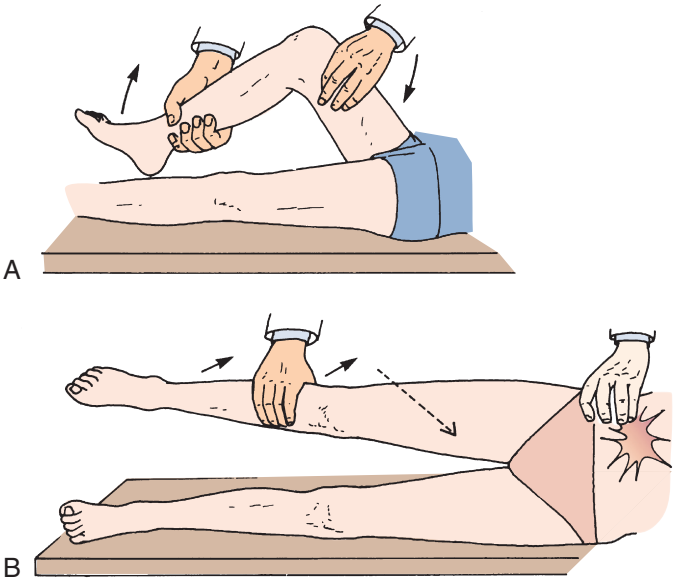


FIGURE 10.3 *A,* The obturator sign. Pain occurs when the hip is flexed and rotated. Internal rotation is most likely to cause pain as a result of pelvic or retroperitoneal disease or both. *B,* The psoas sign. The test may be performed passively or actively. The hip is passively extended, thus stretching the psoas muscle *(solid arrow)*. The hip is actively flexed usually against resistance, thus tensing the psoas muscle *(dotted arrow)*. (From Reilly BM. Abdominal pain. In: *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991:714.)

inflamed focus within the abdomen is compressed and the pressure is then quickly released, resulting in sudden and sometimes severe pain. The standard method to elicit rebound is to palpate deeply, then suddenly remove the palpating hand. *Although this sign aids in the determination of the presence of an intraperitoneal inflammatory process, it is not necessary to cause extra discomfort or stress, particularly in younger children; it is not recommended.* Peritoneal irritation can also be detected by maneuvers such as asking the child to jump, cough, or tapping the feet while observing for facial signs of discomfort.

Other areas of inflammation can be detected by maneuvers that move muscles adjacent to the inflammation. A positive **Carnett test** occurs when pain is unchanged or increased when the supine patient tenses the abdominal wall by lifting the head and shoulders off the examining table. Carnett sign is a sensitive tool to discriminate *abdominal wall* pain from visceral pain. The psoas sign occurs when elevation and extension of the leg against the pressure of the examiner's hand causes pain. An inflammatory mass, such as an inflamed appendix, a psoas abscess, or a perinephric abscess, in contact with the psoas muscle is the cause of this pain. Likewise, the **obturator sign** is pain with flexion of the thigh at right angles to the trunk and external rotation of the same leg while the patient is in the supine position. This sign results from contact of an inflammatory mass with the obturator muscle (Fig. 10.3).

The flanks and back must be inspected and palpated. Percussion at the costovertebral angle elicits pain in the presence of renal or perinephric inflammation. Vertebral body and disk disease may be detected by palpitation of the spine. The perineum and genitalia must be inspected and palpated as necessary. External examination of the genitalia in prepubertal girls is adequate. If a more thorough examination or an intravaginal examination is needed in prepubertal girls, it should generally be performed with the patient under anesthesia. In postpubertal girls, a pelvic examination may be valuable, regardless of the patient's sexual activity history.

The need for a **rectal examination** is controversial. If a diagnosis is already obvious, the rectal examination may be deferred. If an imaging study or colonoscopy is planned, a rectal examination may be unnecessary. If constipation is suspected as the cause for pain, rectal examination should be performed but should be the last part of the physical examination and should be performed only once. The child should be relaxed and should be given an honest explanation of the procedure. The examiner should use plenty of lubricant and should perform the rectal examination very gently. If the child strongly resists, it is pointless to perform a forceful examination. This is when the rectal examination may truly be deferred. Lateralizing pain, masses, and the presence and character of stool in the rectum are assessed. The stool should always be tested for blood except in children with gastrostomy or nasogastric tubes since it will invariably be positive and can be misleading.

Clues to an organic and at times more serious cause of abdominal pain are noted in Table 10.8. Furthermore, peritoneal signs, which suggest a "surgical abdomen," most often caused by peritonitis are noted in Table 10.9. In addition, the presence of shock suggests other serious diseases (see Table 10.9).

TABLE 10.8 Red Flags and Clues to an Organic Cause of Abdominal Pain

Age <4 years old
Localized pain in nonperiumbilical site
Referred pain
Pain awakes child from sleep
Sudden onset of excruciating pain
Crescendo nature of pain
Sudden worsening of pain
Fever (high fever >39.4°C suggests pneumonia, pyelonephritis, dysentery, cholangitis, more than perforation or abscess)
Jaundice
Distention*
Dysuria
Emesis (especially bilious)
Anorexia
Weight loss
Positive family history (metabolic disorders, peptic ulcer disease)†
Change in urine or stool color (blood, acholic) or frequency
Vaginal discharge
Sexual activity
Delayed sexual development (chronic pain)
Anemia
Elevated erythrocyte sedimentation rate
Specific physical findings (hepatomegaly, absent bowel sounds, adnexal tenderness, involuntary guarding, focal or diffuse tenderness, positive rectal examination results, perianal disease, joint swelling)

*Consider 5 Fs: fat, feces, flatus (aerophagia, obstruction), fluid (ascites, hydronephrosis, cysts), fetus (pregnancy or fetal-like abnormal growth [e.g., tumors]).
†Family history is also positive for dysfunctional pain syndromes (constipation, irritable bowel, dysmenorrhea, and lactase deficiency).

TABLE 10.9 Peritoneal Signs of a "Surgical Abdomen"

Severe pain
Patient's eyes anxiously open during examiner's palpation
Patient is motionless
Absent bowel sounds
Extreme tenderness to palpation
Voluntary guarding with gentle palpation
Involuntary guarding: board-like rigidity
Rebound tenderness (do not intentionally elicit)
Pain with movement or cough
If Shock Is Present, Consider:
Severe pancreatitis
Trauma: intraabdominal hemorrhage
Ruptured spleen (trauma, mononucleosis)
Spontaneous bacterial peritonitis
Secondary peritonitis (appendicitis, intussusception, perforated ulcer)
Urosepsis
Associated severe gastrointestinal bleeding
Rupture of fallopian tube from ectopic pregnancy
Pulmonary embolism
Aortic dissection
Volvulus
Child abuse
Addisonian crisis (adrenal insufficiency)

◆ Laboratory Evaluation

After a careful history is obtained and thorough physical examination is performed, the diagnosis or a short list of possible diagnoses should be apparent. Laboratory data are supportive in confirming or ruling out suspected disease.

Complete Blood Cell Count

The hemoglobin and hematocrit levels can reveal anemia caused by acute or chronic blood loss (as with ulcers, inflammatory bowel disease, Meckel diverticula) or the anemia of chronic disease (as with systemic lupus erythematosus, inflammatory bowel disease). The white blood cell count indicates the possibility of infection or blood dyscrasias. In uncomplicated acute appendicitis, the white blood cell count ranges from normal values to as high as 16,000. A very high white blood cell count (>18,000/mm^3) indicates intestinal gangrene, perforation, peritonitis, or abscess formation, but this count may also be high in acute bacterial gastroenteritis, streptococcal diseases, pyelonephritis, pelvic inflammatory disease, hemolytic uremic syndrome, and pneumonia.

The differential cell count may also be helpful. In studies of children with acute appendicitis, 95% had neutrophilia, but only half had leukocytosis in the first 24 hours. If the child's history and physical examination findings are highly suggestive of appendicitis, a normal or mildly elevated white blood cell count should not dissuade the clinician from that diagnosis. However, a striking lymphocytosis may suggest gastroenteritis or a systemic illness. Overreliance on the complete blood count alone can cause delay in reaching the correct diagnosis.

Urinalysis

The urinalysis is an important and useful laboratory test in the evaluation of abdominal pain. The presence of ketones and a high specific gravity suggest poor food intake and dehydration. Large amounts of glucose and ketones in the urine indicate diabetic ketoacidosis. A pregnancy test should be performed on postpubertal girls, regardless of sexual activity history. The presence of both white cells and bacteria indicates a urinary tract infection; either finding alone may not be sufficient for that diagnosis. White blood cells may be present in the urine from irritation caused by an inflammatory mass adjacent to the bladder or ureter; hematuria may be seen with nephrolithiasis.

Other Laboratory Tests

Other laboratory tests, such as measurement of serum electrolytes, amylase, lipase; liver function studies including gamma-glutamyl transpeptidase (GGT); and inflammatory markers (C-reactive protein or sedimentation rate), should be ordered on the basis of the differential diagnosis after a thorough history and physical examination are completed.

◆ Imaging Evaluation

Multitudes of imaging studies are available; none should be obtained until the patient has been examined.

Plain Radiography

Plain radiographs, especially kidney-ureter-bladder (KUB) films, with or without upright lateral views of the chest and abdomen, are routinely obtained in most emergency departments as part of the evaluation of acute abdominal pain. The chest film helps assess the presence of a lower lobe pneumonia, which often causes severe abdominal pain, especially in small children. However, early in the disease, the physical examination may be more helpful. Often, if the KUB-abdominal radiographic study includes the lower lobes, the chest radiographic study can be deferred and performed only if the KUB demonstrates lung abnormalities.

Only approximately 10% of abdominal radiographic studies are positive when they are obtained as part of the routine work-up for abdominal pain. Of those that are limited to patients with serious illness, 46% of the results are positive. Plain abdominal radiographs may be helpful to confirm the presence of intestinal obstruction, pneumatosis intestinalis, renal or biliary tract calculi, calcified fecaliths, or intestinal perforation (pneumoperitoneum–free air). These studies detect bowel distention (air-fluid levels on upright views), calcification, free air, and large masses but are not helpful in detecting most other diseases. If free air or intestinal obstruction is suspected, the abdominal films must include a flat and upright or decubitus view of the abdomen to demonstrate the air-fluid interface.

In **acute appendicitis**, a calcified appendicolith (appendiceal fecalith) may be seen (Fig. 10.4). This finding automatically makes the diagnosis of appendiceal dysfunction and confirms the need for appendectomy. The absence of an appendicolith on KUB does not rule out appendicitis. More often, the noncalcified appendicolith may obstruct the appendix; ultrasonographic or computed tomographic (CT) imaging is necessary to visualize this lesion. If an inflammatory mass lies near the iliopsoas muscle, mild lumbar scoliosis may be present as a result of spasm of the muscle.

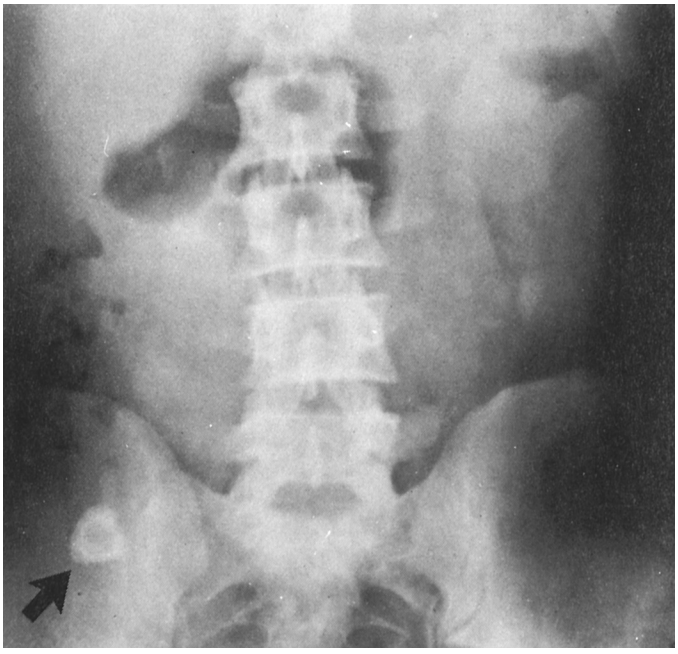


FIGURE 10.4 The patient described the gradual onset of anorexia, nausea, and vague periumbilical abdominal pain. Twenty-four hours later, the pain was much more severe in the right-lower quadrant, where localized peritoneal signs were apparent. The radiographic film of the abdomen reveals a huge calcified density in the right-lower quadrant; it proved to be an appendiceal fecalith at surgery. (From Reilly BM. Abdominal pain. In: *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia, WB Saunders, 1991:16.)

Radiographic studies are not always necessary. If the diagnosis is already obvious, specific therapy is indicated. In some situations, other types of imaging studies are more useful, and plain radiographs are not prerequisite.

Ultrasonography

Ultrasonographic examination is ideal for children. It is usually painless, readily available, emits no radiation, requires no intravenous contrast material, and can be performed without sedation. Unfortunately, it is operator dependent and can be difficult to perform in the setting of extreme pain or lack of cooperation. Lower-abdominal **gynecologic pain** in females, especially in adolescent females, can be confused with appendicitis. Pelvic ultrasonography demonstrates pathologic processes of the ovaries and fallopian tubes, the size of the uterus, and the presence of free fluid in the pelvis. An enlarged, inflamed appendix can also be visualized (Fig. 10.5). Any female with abdominal pain in whom the diagnosis is not obvious should undergo an ultrasonographic examination.

Gallstones, a dilated thick-walled gallbladder, or a dilated common bile duct can be visualized by ultrasonography; all 3 support the diagnosis of biliary disease. Edema and enlargement of the pancreas are seen in acute pancreatitis. Ultrasonography also details the character of abdominal masses, differentiating cystic from solid masses, and can be helpful in demonstrating free fluid or abscesses. The anatomy of the urinary tract is well defined by ultrasonography; nephromegaly may be seen with pyelonephritis. The choice of ultrasonography versus CT is dependent on the expertise of the regional imaging center. Abdominal ultrasonography is an excellent screening method for detecting intussusception and midgut volvulus. If an ileus or intestinal obstruction is present, interpretation of the ultrasonographic examination becomes difficult because of the multiple air-filled loops of intestine.

Contrast Studies

In some situations, certain bowel lesions are best delineated with a contrast medium placed in the bowel, either in an upper gastrointestinal series or by enema. If a colonic obstruction is suspected, such as in **Hirschsprung disease**, the appropriate contrast material is a barium enema. However, the sensitivity and specificity of contrast enema for detection of Hirschsprung disease is approximately 70% and 83%, respectively. If the suspicion is high for the disease, the patient should be referred for further evaluation with either suction rectal biopsy or anorectal manometry. If the presence of gastrointestinal perforation is possible, regardless of the etiology, a water-soluble agent should be used instead of barium.

Malrotation of the midgut with a volvulus in infants and older children is often seen on ultrasonography but can be diagnosed by an upper gastrointestinal study. In the infant who presents with an acute abdomen and bilious vomiting and in the older child who manifests chronic abdominal pain and intermittent vomiting, the oral barium contrast study is highly reliable to rule out causes of obstruction such as intestinal malrotation with midgut volvulus or other causes for anatomic obstruction (duodenal web, annular pancreas, superior mesenteric artery syndrome).

Intussusception is both diagnosed and treated by means of barium enema; however, initial diagnosis is possible with ultrasonography. The sudden onset of severe, diffuse pain, along with the suggestion of a soft, nontender mass in the right upper quadrant of the abdomen in a previously well young child constitute the classical picture of intussusception. Evidence of blood in the stool is usually a late finding and should not be expected early in the disease process. The plain films may be

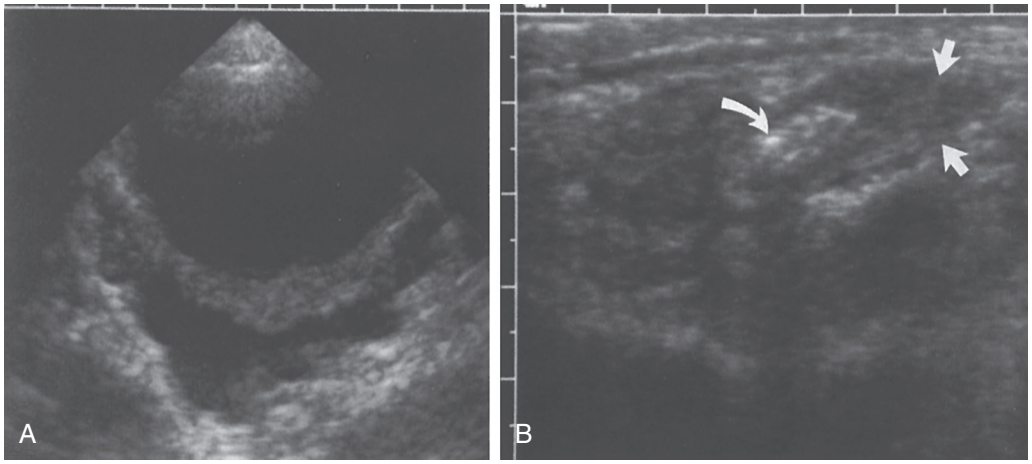


FIGURE 10.5 A transverse scan of the pelvis shows free fluid pooling behind the bladder *(A)*. The longitudinal scan of the right lower quadrant *(B)* shows a shadowing appendicolith *(curved arrow)* in a thick-walled appendix, typical of appendicitis. *Straight arrows* outline the appendiceal tip, which looks ready to perforate. Free fluid in the pelvis always increases the suspicion of appendicitis. (From Teele R, Share J. Appendicitis and other causes of intraabdominal inflammation. In: *Ultrasonography of Infants and Children*. Philadelphia: WB Saunders; 1991:349.)

nonspecific, may show evidence of intestinal obstruction, or may show a mass in the right upper quadrant. A high index of suspicion is all that is needed to justify the barium enema study; some centers now use air rather than barium. Sedation with morphine is helpful for comforting the child and for performing a useful study. The weight of the barium column often completely reduces the intussusception, eliminating the need for surgical intervention. Brisk reflux of contrast into the terminal ileum signifies a complete reduction. This study should always be performed in consultation with a surgeon and with the child prepared to go to the operating room in case of failure of reduction or perforation of the colon. Successful hydrostatic reduction of the intussusception is accomplished in 50-75% of cases. Contraindications for reduction enemas include perforation and signs of peritonitis. It should be kept in mind that patients beyond the usual age range (3 months-6 years) for intussusception often have an anatomic lead point (polyp, Meckel diverticulum, lymphoma); successful hydrostatic reduction may not be possible in these situations. In the presence of pneumoperitoneum, peritonitis, or unsuccessful hydrostatic reduction, surgical intervention is indicated. Recurrences occur in 5% of patients treated with reduction enemas.

A mass from appendicitis that is pressing against the cecum or thickening of the cecal wall may be seen on the barium enema study, but ultrasonography and CT scanning with oral contrast media are much more reliable.

Computed Tomography

While ultrasound is an important diagnostic tool in the evaluation of acute abdominal pain in children, abdominal CT scan may also be valuable. Clinicians are reluctant to perform a CT scan due to the risk of radiation, especially in young children who are particularly sensitive to the adverse effects of radiation exposure. CT is very useful in the initial evaluation of abdominal trauma and in the determination of the extent of abdominal masses. Intravenous and gastrointestinal contrast must be used in CT of the abdomen to obtain the most information, especially if inflammatory bowel disease is suspected. CT is usually not helpful in the evaluation of chronic abdominal pain in children, and while it may be useful to evaluate a chronic, undefined inflammatory process, MRI has superior accuracy over CT with no radiation risk. Unfortunately, MRI is not always easily accessible on emergency basis and the examination can be time consuming.

◆ Management

The immediate concern in management is the differentiation of serious surgical and medical problems from the more common but less serious causes of acute abdominal pain. A guide to the treatment of the child with acute-onset abdominal pain is noted in Fig. 10.6. A mild, nonspecific illness may be treated on an outpatient basis, with follow-up by telephone or in the office. However, the child with abdominal pain who appears ill without a specific diagnosis may warrant evaluation by a pediatric surgeon. If the diagnosis is still not apparent, the child should be admitted for active observation, which includes no oral food or liquid, appropriate intravenous fluids, hourly vital signs, and frequent examinations. If the abdominal examination is difficult because of poor cooperation, or severe pain, analgesia is appropriate. In the case of appendicitis, morphine therapy does not reduce the diagnostic accuracy by an experienced clinician. Analgesics may permit an adequate abdominal examination but do not eliminate the tenderness caused by an inflammatory process. The examination should be repeated every 2-3 hours. About 10% of children admitted for observation go on to show obvious signs of a process warranting surgery in the first few hours. In approximately 50% of the observed children, a specific nonsurgical diagnosis becomes apparent.

SPECIFIC CAUSES OF ACUTE ABDOMINAL PAIN

Appendicitis

Appendicitis is an acute inflammation of the appendix that may be initiated by luminal obstruction by a fecalith, lymphoid hyperplasia (secondary to viral infections), inflammation, or, in rare cases, parasites (pinworm, *Ascaris* species). Obstruction with ongoing distal secretion of mucus causes distention of the appendix, increased luminal pressure, and subsequent arterial obstruction and ischemia. Mucosal ulceration, fibropurulent serosal exudates, and bacterial infection lead to gangrene from vascular obstruction with subsequent perforation. On occasion, the greater omentum may seal over a ruptured

(See *Nelson Textbook of Pediatrics,* p. 1887.)

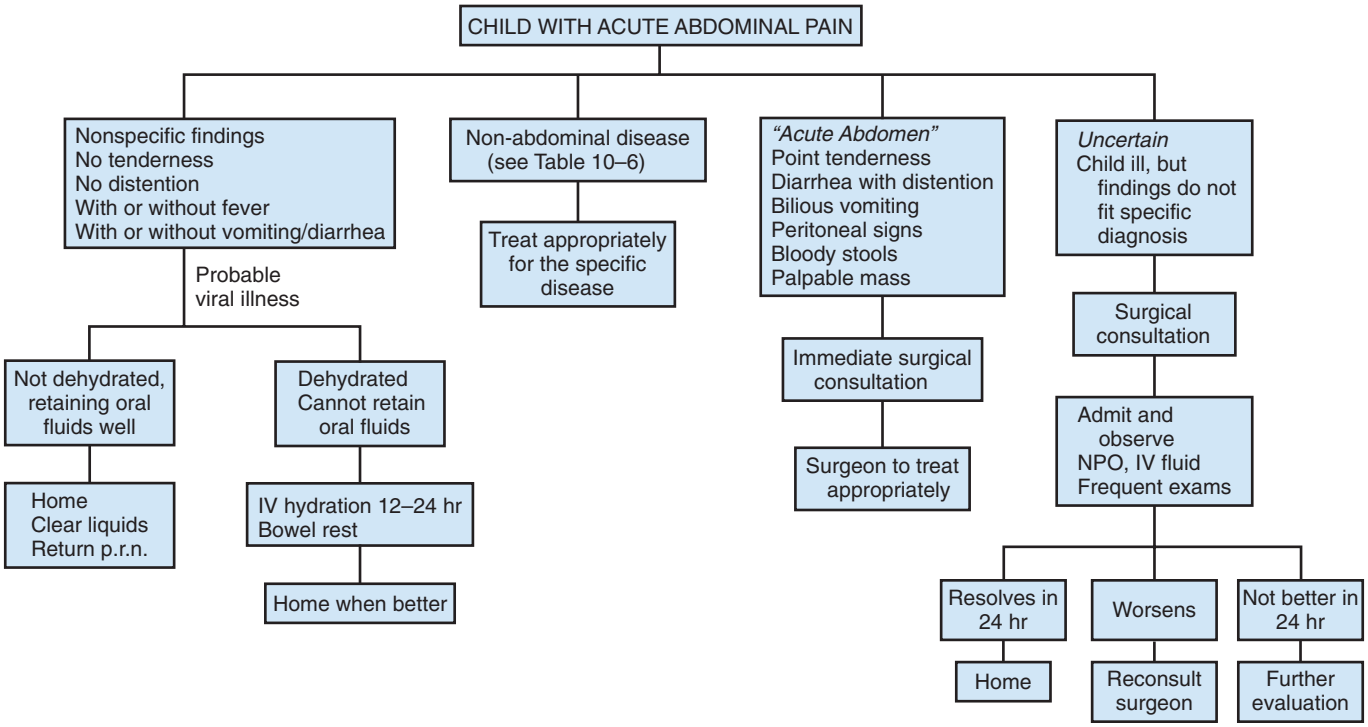


FIGURE 10.6 Algorithm for evaluating acute abdominal pain. IV, intravenous; NPO, nil per os (no oral intake); p.r.n., as needed.

appendix, producing a right lower quadrant mass and periappendiceal abscess.

Appendicitis may be simple (focal inflammation, no serosal exudate), suppurative (obstructed, inflamed, edematous, increased local peritoneal fluid with omental and mesenteric containment, or walled off), gangrenous (similar to suppurative, plus gray-green or red-black areas of gangrene, with or without microperforations, and purulent peritoneal fluid), ruptured (gross perforation, usually on antimesenteric side; peritonitis present), or abscessed (development of pus from rupture into right ileal fossa, lateral to cecum or retrocecal, subcecal, or pelvic). The bacteriologic components of appendicitis include normal intestinal flora, such as enterococci, *Escherichia coli*, *Pseudomonas* species, *Klebsiella* species, and anaerobic bacteria, such as *Clostridium* and *Bacteroides* species.

Appendicitis affects approximately 60,000 children each year in the United States; it primarily affects adolescents and young adults but may develop at any age, even in neonates. The disease is particularly severe in very young children, often because of a delay in diagnosis with subsequent perforation. Appendicitis in young children is difficult to diagnose because of atypical manifestations and the clinician's inability to obtain an accurate history. The thinness of the appendix and the paucity of the omentum in younger children may result in rapid, unimpeded spread of intraabdominal infection after rupture.

Diagnosis

An accurate and early diagnosis is critical for avoiding perforation and peritonitis and for excluding other causes of abdominal pain. Appendicitis usually manifests initially with a gradual onset of periumbilical (occasionally epigastric) pain, which may begin as a dull ache but becomes constant (or, less often, colicky) and of mild to moderate intensity. This is then followed by anorexia, nausea, and sometimes emesis. Emesis preceding the pain is more typical of gastroenteritis. On occasion, an inflamed appendix irritates the colon, producing diarrhea. Furthermore, the appendix may irritate the bladder, causing urinary frequency and dysuria. Pain may transiently stop, but as local peritonitis develops, the pain will continue but shift to the right lower quadrant. The shifting of pain from the periumbilical area to the right lower quadrant area may take 12-36 hours but usually occurs in 2-8 hours and may not yet be evident in an acute onset of less than 4-6 hours. McBurney point corresponds to the location of the base of the appendix and is found by placing the little finger of one hand in the umbilicus and the thumb on the anterior superior ileal spine. The index finger, if extended perpendicularly to the abdominal wall, identifies McBurney point. Unfortunately, the appendix is not always in its classic position; thus, appendicitis may produce pain in the pelvis, in the retrocecal area (back or flank pain, psoas muscle spasm with limp), or elsewhere (Fig. 10.7). With these locations, the psoas or obturator sign may be positive (see Fig. 10.3).

Patients with unperforated appendicitis may present with a low-grade fever (<38.5°C) and display very characteristic behaviors. They can be anxious while watching where examiners place his/her hands, be motionless, walk slowly, get on the examining table with difficulty, or exhibit a nondistended but tender abdomen with voluntary guarding, reduced bowel sounds, and point tenderness in any area overlying the appendix. Rectal examination may reveal right-sided or diffuse tenderness and a mass.

Perforation or extensive gangrene should be suspected in the presence of progression for more than 36-48 hours; high fever; diffuse abdominal pain and tenderness; a rigid, board-like abdomen; leukocytosis; a right lower quadrant mass; and other signs of generalized peritonitis (see Table 10.9).

Laboratory and Radiographic Testing

Ultrasonography has been of benefit in the diagnosis of appendicitis and in excluding other important disease processes (Table 10.10). Helpful ultrasonographic features suggestive of appendicitis include a

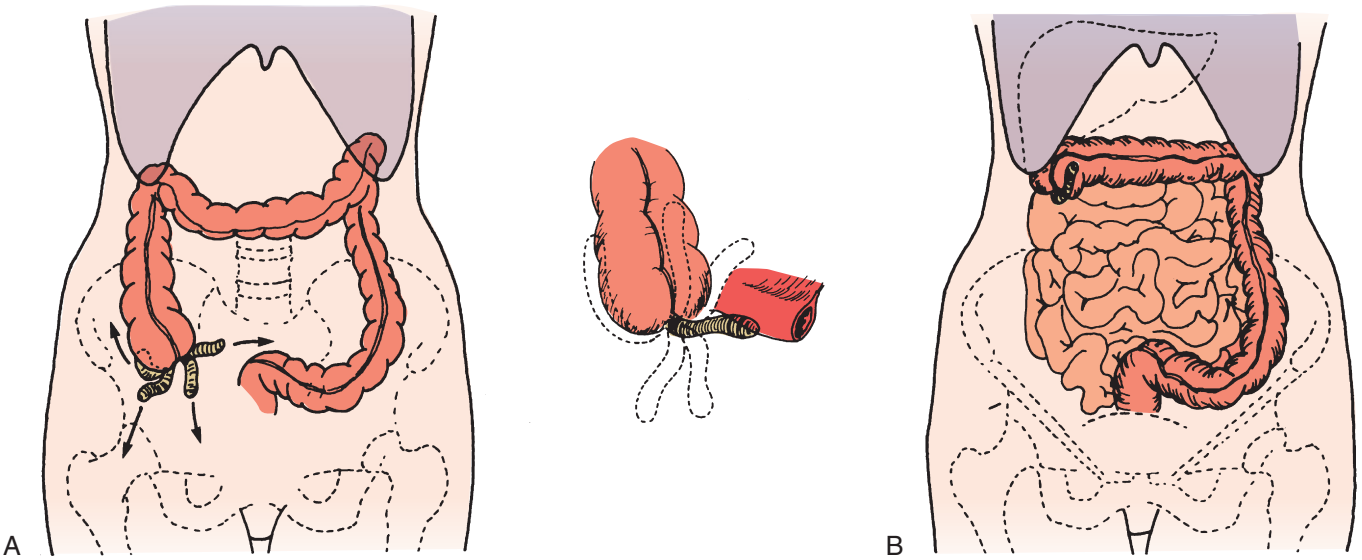


FIGURE 10.7 The appendix. *A,* The appendix may be located anteriorly, medially, or retrocecally or in the pelvis. *B,* The location of the appendix depends on the location of the cecum. Because the bowel may be quite mobile in some patients, the appendix may be located in many different sites in the abdomen. In this figure, the appendix is in the right upper quadrant. (From Reilly BM. Abdominal pain. In: *Practical Strategies in Outpatient Medicine.* 2nd ed. Philadelphia: WB Saunders; 1991:728.)

TABLE 10.10 Final Diagnoses in Cases of Clinically Suspected Appendicitis

Appendicitis	Perforated peptic ulcer
Gastroenteritis	Urinary tract infection
Pelvic inflammatory disease	Meckel diverticulitis
Ovarian cyst: torsion	Pancreatitis
Ectopic pregnancy	Primary peritonitis
Mesenteric adenitis	Cholecystitis

noncompressible appendix, an inability to visualize the appendix when ruptured, the presence of periappendiceal fluid, or the presence of an appendicolith (Figs. 10.8 and 10.9). Ultrasonography helps define other disease processes, such as mesenteric adenitis (Fig. 10.10) and gynecologic processes. These conditions must be considered in all female patients. Ectopic pregnancy is a particularly serious condition that must not be missed (Fig. 10.11). Gastroenteritis is one of the more common conditions to be considered in the differential diagnosis (Table 10.11).

Treatment

Appendicitis is treated by surgical appendectomy and ligation of the stump by open or laparoscopic methods. If an abscess is present in the right lower quadrant and the patient demonstrates few signs of toxicity, elective nonurgent appendectomy may be delayed to permit preoperative rehydration and broad-spectrum antibiotic therapy. If the appendix is not perforated, some centers treat with only broad-spectrum antibiotics. In operative appendicitis, parenteral antibiotics are given before surgery and are continued postoperatively only in the presence of frank contamination, such as gangrenous or perforated appendicitis. The duration of antibiotic therapy is determined by the presence of infectious complications. If the appendix appears normal, other intraabdominal sources of pain should be sought during the surgery.

Complications of appendicitis are uncommon but include sepsis, intraabdominal abscess formation, wound infections, hepatic abscesses, ileus, and peritoneal adhesion formation. There is subsequent risk for intestinal obstruction and tubal infertility in females.

Pancreatitis

Pancreatitis is an acute inflammatory condition of the pancreas and is often a result of obstruction of the pancreatic duct. Release and activation of pancreatic digestive enzymes subsequently result in extensive destruction (autodigestion) and necrosis of pancreatic and, if severe, adjacent tissue. Proteolysis, fat necrosis, and hemorrhage are noted in severe or fatal cases of pancreatitis, which is often complicated by multiorgan dysfunction syndrome (e.g., hypotension, acute respiratory distress syndrome, acute kidney injury, cardiogenic shock). Pancreatitis is less common in children than in adults, in whom the cause is often alcohol ingestion or gallstones. The etiologic factors in childhood encompass a broad differential diagnosis and often include passage of biliary stones, drugs (valproate), multisystem diseases (hemolytic uremic syndrome, cystic fibrosis), trauma (including child abuse), biliary or pancreatic anatomic anomalies, infections, and metabolic conditions (hypercalcemia, hypertriglyceridemia) (Table 10.12).

Manifestations

Manifestations of acute pancreatitis include intense epigastric abdominal pain that may be described as steady, boring, constant, achelike, knifelike, and exacerbated by recumbency, that radiates to the back, upper abdominal quadrants, or the scapula. Emesis is common, often protracted, and occasionally bilious. Fever is usually low to moderate grade; high fever (>39°C) suggests the presence of a primary infectious process with or without secondary pancreatitis or bacterial superinfection and pancreatic abscess formation. The patient often assumes a hunched-over or knee-chest lateral fetal posture and may manifest epigastric tenderness; bowel sounds may be reduced or absent. Signs of peritonitis suggest more extensive necrosis, as do signs of spreading hemorrhage, such as blue-green discoloration of the flanks (Grey Turner sign) or of the periumbilical region (Cullen sign). Intravascular

(See *Nelson Textbook of Pediatrics,* p. 1913.)

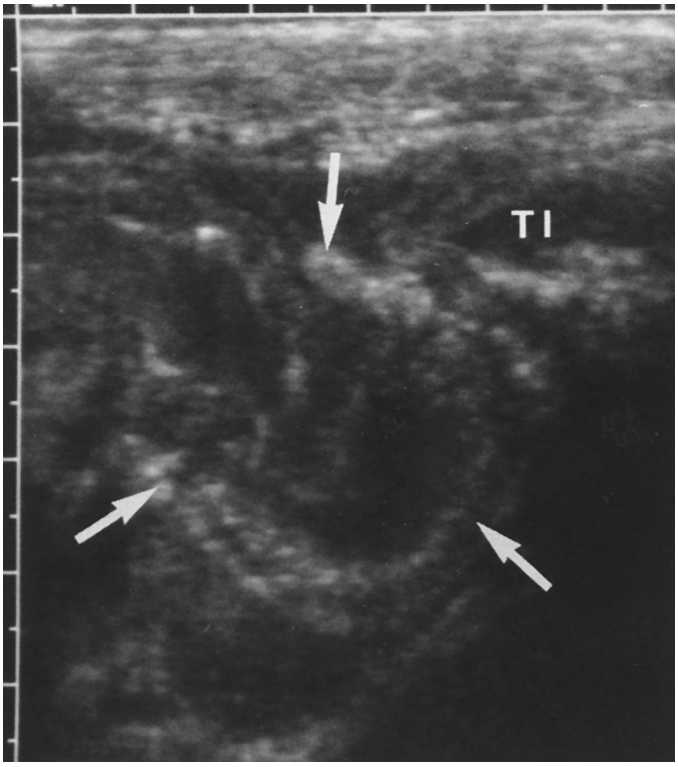


FIGURE 10.8 An ultrasound scan of the right lower quadrant in a 6-year-old girl, demonstrating a thick-walled cecum *(arrows)* outlined by echogenic fluid. No appendix was found in spite of careful ultrasonographic searching. During surgery, the patient was found to have a perforated appendix and early periappendiceal abscess. TI, terminal ileum. (From Teele R, Share J. Appendicitis and other causes of intraabdominal inflammation. In: *Ultrasonography of Infants and Children*. Philadelphia: WB Saunders; 1991.)

fluid depletion, cardiogenic shock, hemorrhagic shock, hypocalcemic tetany, or systemic inflammatory response syndrome with multiorgan system failure may ensue. Pain may last for 3-10 days.

The diagnosis is confirmed by an elevated serum amylase and/or lipase level (lipase levels may be elevated initially with normal amylase values). The differential diagnosis of hyperamylasemia is seen in Table 10.13. Ultrasonography and CT scan are helpful in identifying the acutely inflamed pancreas (Fig. 10.12), the degree of necrosis, and the later development of a pancreatic pseudocyst (Fig. 10.13).

Adverse prognostic factors in severe acute pancreatitis include the presence of leukocytosis (white blood count >16,000/mm^3), hyperglycemia (glucose level >200 mg/dL), a high lactic dehydrogenase level (>350 U/L), and a high aspartate aminotransferase level (>250 U/L) on admission and a decrease in hematocrit value (>10%), an increase in blood urea nitrogen level (>5 mg/dL), a low calcium level (<8 mg/dL), hypoxia (Pao_2 <60 mm Hg), acidosis (base deficit >4 mmol/L), or severe dehydration by 48 hours of hospitalization. The degree of pancreatic necrosis may be determined from the failure of CT scans to depict intravenous contrast parenchymal enhancement; severe pancreatitis is associated with more than 50% necrosis of the gland.

Complications

Complications of pancreatitis include local tissue necrosis with or without superinfection (pancreatic abscess), fistulization (to colon), left-sided pleural effusion, gastrointestinal hemorrhage (ulceration, vascular rupture, splenic rupture), shock, coagulopathy, acute kidney injury, myocardial depression, acute respiratory distress syndrome, hyperglycemia, hypocalcemia, subcutaneous nodules (fat necrosis), hypoalbuminemia, mental changes, and retinopathy.

Management

The management of acute pancreatitis consists of supportive care, such as nasogastric tube decompression for patients with an ileus or severe emesis, administration of intravenous fluids, administration of

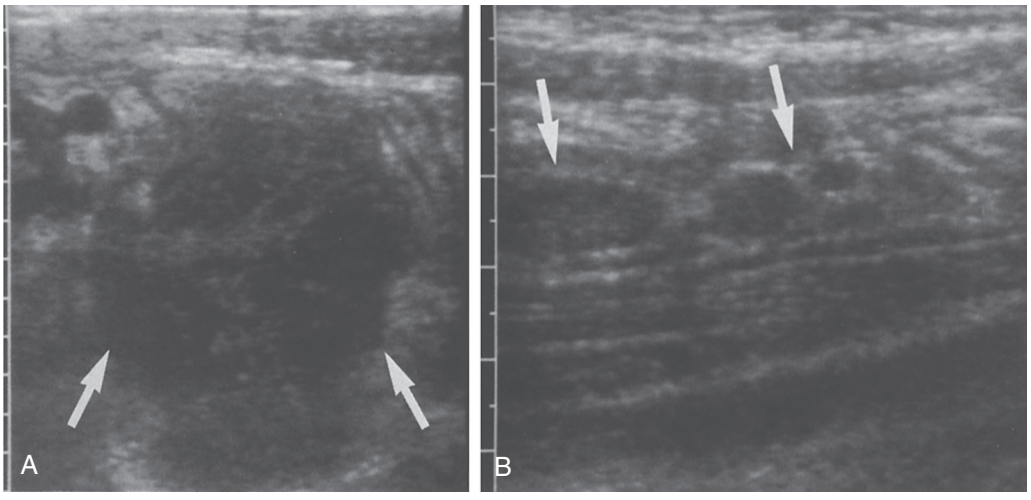


FIGURE 10.9 An 11-year-old girl presented with fever, diarrhea, and vomiting. Ten days before admission to the hospital, she was seen by a physician because of abdominal pain. She had been partially treated with antibiotics for a presumed "strep throat" in the interim. When she presented to the hospital, she again had pain in the right lower quadrant, especially when the ultrasound transducer was pressed over the area. *A,* The right-lower quadrant abscess *(arrows)* was quickly identified. The appendix could not be visualized. *B,* In scans along the psoas, multiple lymph nodes *(arrows)* were apparent. The child's appendix had ruptured 1 week before admission, but her symptoms had been masked by the antibiotics that she had been given. (From Teele R, Share J. Appendicitis and other causes of intraabdominal inflammation. In: *Ultrasonography of Infants and Children*. Philadelphia: WB Saunders; 1991:348.)

narcotics for pain, and therapy for accompanying complications (e.g., shock, adult respiratory distress syndrome, and acute kidney injury). Endoscopic sphincterotomy by endoscopic retrograde cholangiopancreatography (ERCP) is of benefit if gallstones are present, although ERCP has risks that include the induction of pancreatitis.

Enteral alimentation should be initiated as soon as possible, even with a partial ileus, as early feeds are *not associated* with increased pain, longer hospital course, or elevation in serum lipase. Alimentation may be by oral, nasogastric, or nasojejunal routes.

Additional therapies include prophylactic antibiotics in acute necrotizing pancreatitis. Infected necrotic tissue must be removed surgically; large persistent pseudocysts are managed by CT-guided drainage or surgical drainage.

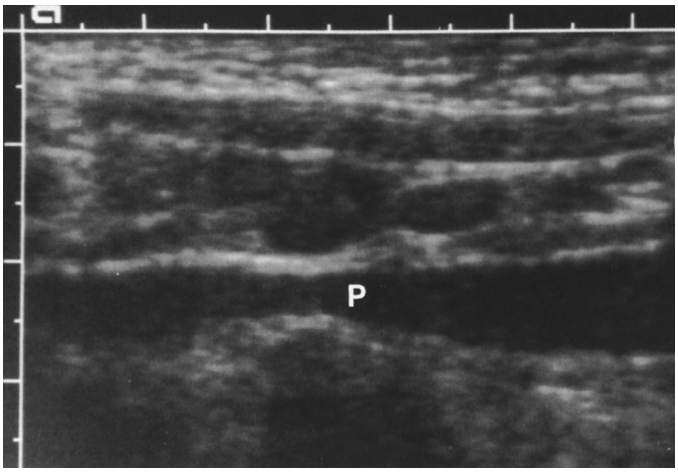


FIGURE 10.10 This longitudinal scan of the right lower quadrant shows lymph nodes arranged in a line along the psoas muscle *(P)*. These are nodes enlarged from mesenteric adenitis. The patient did not have appendicitis. (From Teele R, Share J. Appendicitis and other causes of intraabdominal inflammation. In: *Ultrasonography of Infants and Children*. Philadelphia: WB Saunders; 1991.)

Cholelithiasis

Gallstones are uncommon in children, but they complicate chronic diseases, such as hemolytic anemia (sickle cell anemia, spherocytosis), cholestatic jaundice in which total parenteral nutrition is given, and other cholestatic diseases. Gallstones may result from prematurity or drug intake (furosemide, ceftriaxone), or they may be idiopathic. Biliary obstruction (stone in cystic or common bile duct) often results in jaundice; sudden onset of severe, sharp right upper quadrant pain; localized deep tenderness in the right upper quadrant (superficial tenderness suggests an associated cholecystitis); and emesis. The pain is episodic and colicky, but often constant, superimposed with waves of more intense pain, and may radiate to the angle of the ipsilateral scapula, back, or other areas of the abdomen or chest. Patients frequently move about to find a comfortable position. There may be associated diaphoresis, pallor, tachycardia, weakness, nausea, and lightheadedness. A round or pear-shaped, tender mass may be palpated in the right upper quadrant of the abdomen if the gallbladder is distended. The pain may be diurnal, with increased intensity at night. Many patients with single or multiple gallstones without obstruction are asymptomatic.

Acute cholecystitis is caused by inflammation of the gallbladder wall as a result of duct obstruction (i.e., calculus) or nonobstructing (i.e., acalculous) conditions and is manifested by fever, mild jaundice, severe abdominal pain, emesis, nausea, and leukocytosis. Pain may be similar to that in cholelithiasis and radiates to the right scapula,

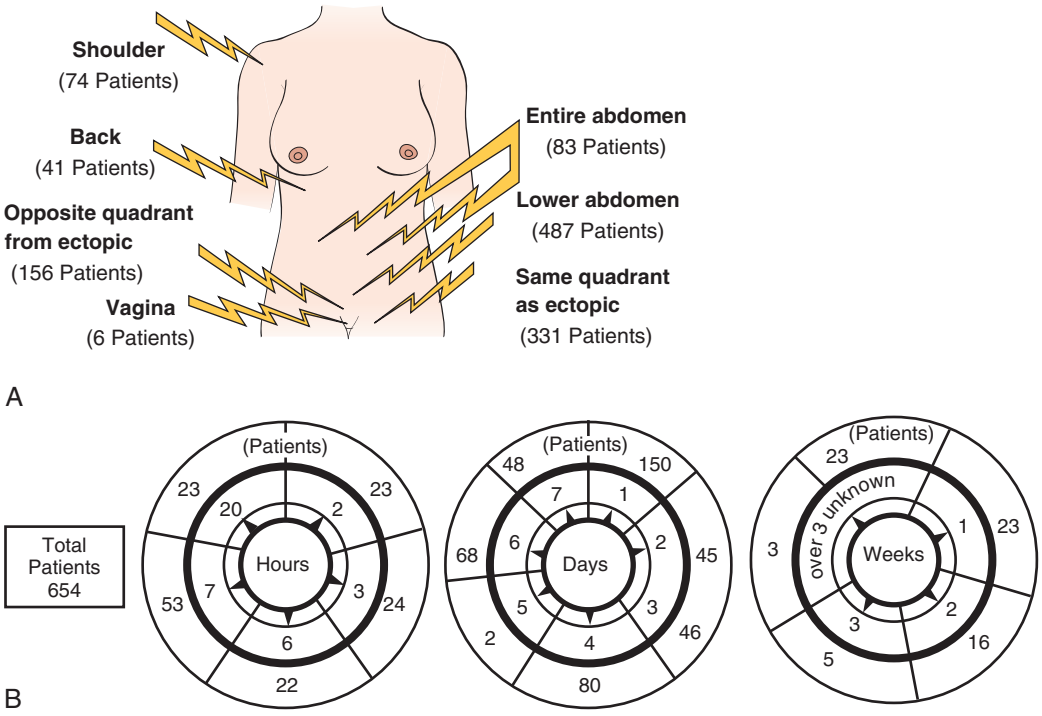


FIGURE 10.11 Ectopic pregnancy. *A,* Anatomic location of pain in 654 patients with ectopic pregnancy. *B,* Duration of abdominal pain before the diagnosis of ectopic pregnancy was confirmed among 654 patients. (Modified from Breen JL. A 21-year survey of 654 ectopic pregnancies. *Am J Obstet Gynecol.* 1970;106:1004-1019.)

(See *Nelson Textbook of Pediatrics,* p. 1971.)

TABLE 10.11 Comparison of Gastroenteritis and Appendicitis

	Gastroenteritis	Appendicitis
Pain	Diffuse, cramps, intermittent	Periumbilical shifting to RLQ; constant Exacerbated by movement, coughing
Vomiting	With or before pain	Follows pain
Diarrhea	Frequent, large volume	Can occur; small volume (from irritation of bowel); may be watery, too
Fever	Variable	Low grade, goes up with gangrene or perforation
Course	Intermittently improves	Worsens with time
Systemic symptoms	Variable: headache, malaise, myalgia, arthralgia, sore throat	Rare
Physical examination	General: fussy, restless, frequent motion Abdomen: soft, mild, diffuse tenderness, hyperactive bowel sounds	Quiet, discomfort with movement Abdomen: RLQ tenderness, guarding peritoneal signs, with/without rectal tenderness/mass, absent bowel sounds
Laboratory values	WBC count: variable, may be quite high Urine: nonspecific	WBC count: mild elevation, early left shift; becomes high only with gangrene or perforation Urine: may have WBCs and/or RBCs if bladder irritated, ketosis if vomiting is prolonged
Imaging studies	Abdominal films: nonspecific ileus Ultrasonography: not indicated	Abdominal films: often nonspecific, with/without fecalith, with/without loss of psoas definition, with/without scoliosis caused by inflammation in RLQ Ultrasonography: enlarged appendix, peritoneal fluid, RLQ abscess, absent appendix, fecalith

RBC, red blood cell; RLQ, right lower quadrant; WBC, white blood cell.

shoulder, or chest. The Murphy sign is demonstrated by palpating an acutely inflamed gallbladder, which causes the patient to halt respiration and feel the pain. Fever of greater than 39.5°C suggests perforation or gallbladder gangrene, whereas a high direct bilirubin level (>4 mg/dL) suggests a common duct stone. Pain may last for 5-10 days. Passage of stones or microlithiasis (sludge) may also produce acute pancreatitis. Intolerance to fatty foods is, unfortunately, a nonspecific observation.

Diagnosis

The diagnosis is confirmed by ultrasonography that demonstrates acalculous or calculus-induced cholecystitis or acute duct obstruction by a stone (Fig. 10.14).

Treatment

Some treatment of obstructing stones may include endoscopic, open, or laparoscopic cholecystectomy. Some patients may go directly to surgery. However, medical management may include ursodeoxycholic acid for stone dissolution. Meperidine is used for pain relief, and broad-spectrum antibiotics are indicated for cholecystitis or cholangitis.

Peptic Ulcer Disease

Peptic ulceration is becoming recognized in children with increasing frequency. Risk factors for peptic ulcer disease include gastritis, a positive family history of ulcer disease, presence of *Helicobacter pylori*, treatment with nonsteroidal antiinflammatory agents and corticosteroids, cigarette smoking, and severe injury (burns, head injury, shock). Manifestations include pain, gastrointestinal bleeding (melena, hematemesis, anemia), emesis, and, in rare cases, perforation. Nocturnal pain, pain relieved by food, and a family history of peptic ulcer disease are often present in older affected children. The pain is often chronic, recurrent, and located in the epigastrium; tenderness may be localized to the epigastric region, but this is an inconsistent finding.

Acute perforation is uncommon in children but is characterized by sudden worsening of pain or a new abrupt onset of excruciating epigastric pain. There is associated pallor, faintness, weakness, syncope, diaphoresis, and a rigid abdomen. Corticosteroids may mask some of the signs of perforation.

CHRONIC ABDOMINAL PAIN

Recurrent abdominal pain (RAP) in children remains one of the most challenging common conditions treated by pediatricians. Intermittent severe, episodic pain can be frightening to both families and care providers because it may be an indication of serious disease. It has been reported to occur in 10-15% of children between the ages of 4 and 16 years. In only a small minority of patients with RAP, the symptoms can be explained by discernable organic disease. However, the term *RAP* is a descriptive term and should not be used as a diagnosis. RAP may be caused by several different conditions that include, but are not limited to, celiac disease, inflammatory bowel disease, peptic ulcer, biliary tract disease, pancreatitis, or functional pain. Pain pathways can initially be influenced by the presence of pathology such as inflammation or tissue damage that often persists despite the absence of identifiable pathology.

The term **functional abdominal pain** refers to pain that has no anatomic, histologic, or "organic" etiology. This type of pain is the hallmark of functional gastrointestinal disorders (FGIDs) that include irritable bowel syndrome (IBS), functional dyspepsia (FD), functional abdominal pain (FAP), and abdominal migraine (AM). A common feature among patients with functional gastrointestinal disorders is the heightened sensitivity to experimental pain, also known as visceral hyperalgesia. A unifying theory of all functional gastrointestinal disorders is the alteration of the brain-gut axis that can present with clusters of symptoms related to abnormal signals arising from the gastrointestinal tract or abnormal processing of signals in the central nervous

TABLE 10.12 Causes of Acute Pancreatitis in Children

Drugs and Toxins
Alcohol
Acetaminophen
Azathioprine
L-Asparaginase
Cimetidine
Corticosteroids
Didanosine
Estrogens
Furosemide
Gila monster bite
6-Mercaptopurine
Methyldopa
Organophosphates
Pentamidine
Scorpion bites
Spider bites
Sulfonamides
Tetracycline
Thiazides
Valproic acid

Hereditary Pancreatitis
SPINK1
CFTR
Cationic trypsinogen

Infections
Coxsackie B virus
Epstein-Barr virus
Hepatitis A, B
HIV
Influenza A
Leptospirosis
Measles
Mumps
Mycoplasma
Rubella
Reye syndrome

Obstructive
Ascariasis
Biliary sludge
Biliary tract malformation
Cholelithiasis
Crohn disease
Duplication cyst
Pancreatic pseudocyst
Pancreas divisum
Postoperative
Sphincter of Oddi dysfunction
Tumor

Systemic Disease
α_1-Antitrypsin deficiency
Cystic fibrosis
Diabetes mellitus
Henoch-Schönlein purpura
Hemochromatosis
Hemolytic uremic syndrome
Hyperlipidemia types I, IV, and V
Hyperparathyroidism
Hypothermia
Kawasaki syndrome
Systemic lupus erythematosus
Malnutrition
Organic acidemias
Periarteritis nodosa
Peptic ulcer
Postpancreatic transplantation
Refeeding after malnutrition
Reye syndrome
Uremia

Traumatic
Blunt injury
Child abuse
Post-ERCP
Surgical trauma
Total body cast

CFTR, cystic fibrosis transmembrane conductance receptor; ERCP, endoscopic retrograde cholangiopancreatography; HIV, human immunodeficiency virus; SPINK1, serine protease inhibitor Kazal type 1.
Modified from Behrman RE, ed. *Nelson Textbook of Pediatrics*. 14th ed. Philadelphia: WB Saunders; 1992:999.

system. Without proper explanation of the term *functional*, most families would not understand the condition since the term is very vague and nondescriptive. Symptoms are physiologic and modifiable by sociocultural and psychologic influences. Functional pain can be triggered or influenced by gastrointestinal infections, food, allergies, as well as stress or physical and sexual abuse. These experiences may have a long-lasting impact on a child and make him or her more susceptible to the development of FGIDs by affecting motility, altered intestinal permeability, or visceral hyperalgesia, which conversely impact the development of altered or maladaptive coping skills later in life. The *functional* nature of this pain does not mean that the pain is imaginary or that it may not interfere with the child's daily activities. Patients with functional abdominal pain experience real pain and should not be considered to be faking it or not experiencing it at all. Psychosocial factors, along with altered gut physiology, ultimately play an important role in the development of several pain-associated FGIDs, including

TABLE 10.13 Differential Diagnosis of Hyperamylasemia

Pancreatic Pathology
Acute or chronic pancreatitis
Complications of pancreatitis (pseudocyst, ascites, abscess)
Factitious pancreatitis
Complication of ERCP

Salivary Gland Pathology
Parotitis (mumps, *Staphylococcus aureus*, CMV, HIV, EBV)
Sialadenitis (calculus, radiation)
Eating disorders (anorexia nervosa, bulimia)

Intraabdominal Pathology
Biliary tract disease (cholelithiasis)
Peptic ulcer perforation
Peritonitis
Intestinal obstruction
Appendicitis

Systemic Diseases
Metabolic acidosis (diabetes mellitus, shock)
Renal insufficiency, transplantation
Burns
Anorexia-bulimia
Pregnancy
Drugs (morphine)
Head injury
Cardiopulmonary bypass

CMV, cytomegalovirus; EBV, Epstein-Barr virus; ERCP, endoscopic retrograde cholangiopancreatography; HIV, human immunodeficiency virus.
Modified from Kliegman RM, Stanton BF, St. Geme JW, Schor NF, eds. *Nelson Textbook of Pediatrics.* 20th ed. Philadelphia: Elsevier; 2016: Table 351-2, p. 1915.

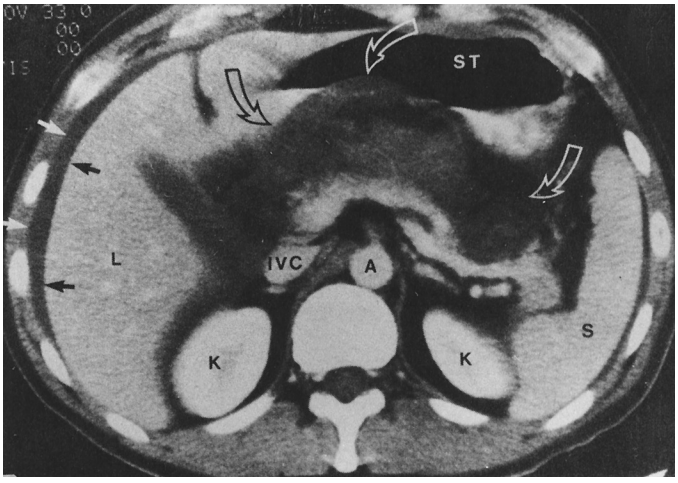


FIGURE 10.12 Acute pancreatitis. Computed tomographic (CT) scan through the body of the pancreas demonstrates a halo of decreased attenuation around the pancreas that represents a peripancreatic zone of edema and fluid *(curved arrows)*. Note the pancreatic ascites, most obvious lateral to the liver *(small arrows)*. If intravenous contrast were administered before the CT scan, the inflamed pancreas would appear more dense (whiter). A, aorta; IVC, inferior vena cava; K, kidney; L, liver; PV, portal vein; S, spleen; ST, stomach. (From Freeny P, Lawson T. In: Putman CE, Ravin CE, eds. *Textbook of Diagnostic Imaging*. Philadelphia: WB Saunders; 1988.)

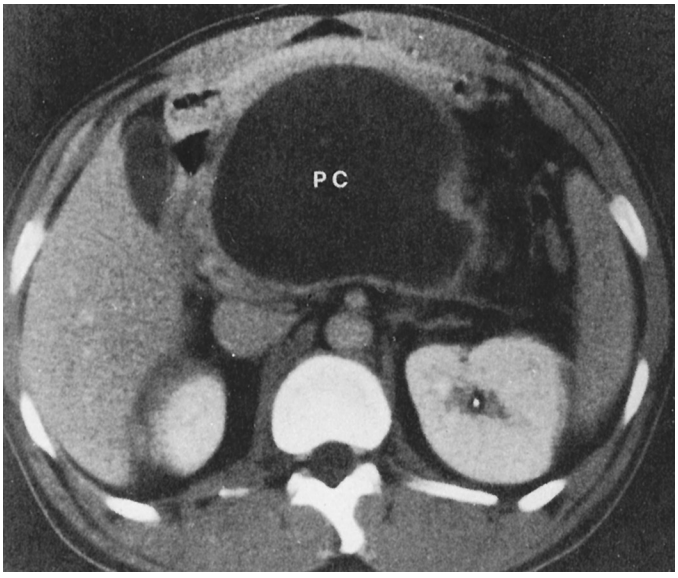


FIGURE 10.13 Pseudocyst. Follow-up computed tomographic scan (same patient as in Fig. 10.12) 5 months after the episode of acute pancreatitis demonstrates a large pseudocyst (PC). This large pseudocyst will probably not resolve spontaneously and may need drainage. (From Freeny P, Lawson T. In: Putman CE, Ravin CE, eds. *Textbook of Diagnostic Imaging*. Philadelphia: WB Saunders; 1988.)

functional abdominal pain, irritable bowel syndrome, functional dyspepsia, and abdominal migraine. The diagnostic Rome criteria for each of these disorders permit clinicians to make a clinical diagnosis with limited diagnostic testing. Applying the criteria in the clinical setting allows the care provider to validate the reality of the symptoms and develop an appropriate physician-patient relationship aimed at improving symptoms and functioning. All too often, the clinician repeatedly performs unnecessary diagnostic tests to rule out pathology. This often leads to dismissal of the patient's concerns or prevents an effective collaboration in the patient's care that promotes a vicious cycle of symptom anxiety and health-seeking behavior. Applying the Rome criteria along with a proper history and physical examination that includes "red flags" is most of the time sufficient to make a clinical diagnosis of a FGID and to initiate proper treatment.

MAKING A DIAGNOSIS OF FUNCTIONAL ABDOMINAL PAIN

The history should be detailed and, in most instances, obtained separately from the parents and the child. A private conversation with each often provides better insight into all factors affecting the child. In addition to covering the historical information already detailed, the clinician should pay attention to factors in the child's environment, family, school, and social interactions that may be sources of undue stress. Care providers often have difficulty making a positive diagnosis of a functional gastrointestinal disorder, particularly since there are no biologic markers. The diagnostic evaluation of a child with abdominal pain begins with a history to distinguish chronic from acute pain and addressing red flags. The revised **Rome III criteria** for childhood functional abdominal pain are met if the duration of pain exceeds 2 months

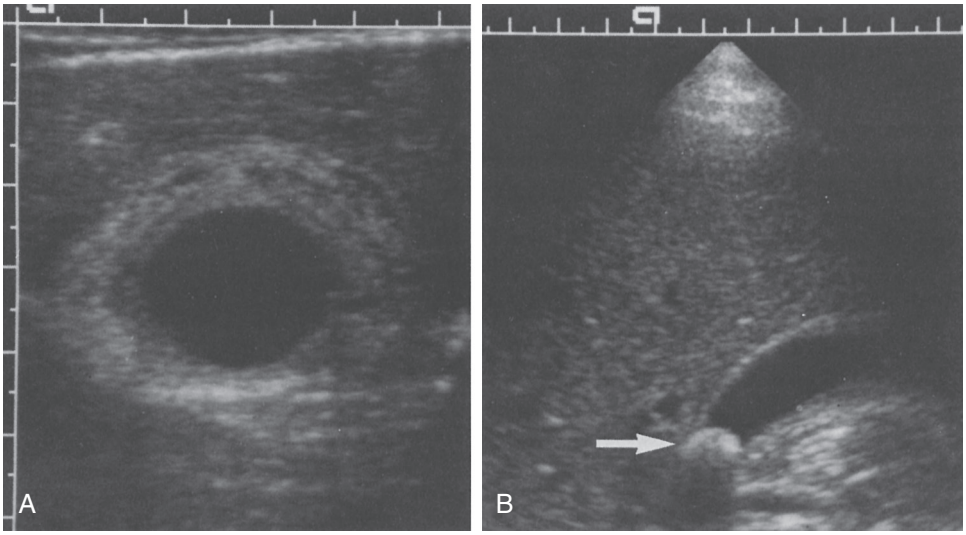


FIGURE 10.14 Transverse scan with linear array transducer shows pericholic edema in a teenaged boy, who presented with severe pain in the right upper quadrant from acute cholecystitis *(A)*. A longitudinal scan of the right upper quadrant *(B)* shows a stone *(arrow)* that was thought to be impacted in the neck of the gallbladder because it did not change at all with position. The patient had severe pain with palpation over the gallbladder. (From Teele R, Share J. The liver. In: *Ultrasonography of Infants and Children*. Philadelphia: WB Saunders; 1991.)

(episodic or continuous). Children with pain-associated FGIDs may be subclassified into one of four clinical diagnostic categories that include (1) **functional dyspepsia** (abdominal pain associated with symptoms centered in the upper abdomen), (2) **irritable bowel syndrome** (abdominal pain associated with altered bowel pattern), (3) **functional abdominal pain** (isolated paroxysmal abdominal pain), or (4) **abdominal migraine** (paroxysmal intense pain that can be associated with either pallor, headache, photophobia, nausea, or vomiting). The diagnosis of abdominal migraine is sometimes easier to make since symptoms are episodic and occur abruptly after periods of normal well-being. It is not uncommon to get a history of the child waking up in the middle of the night with pain and vomiting and then having complete resolution of symptoms after 1-2 days. The frequent occurrence or change in location of pain or alternating bowel habits in the same patient, however, is not uncommon. Clinicians do not always feel comfortable simply relying on Rome criteria or are unaware that they exist. Functional pain should be considered when abdominal pain persists a month beyond the usual course of an acute illness (i.e., gastroenteritis). Children often present with intermittent, periumbilical pain that usually waxes and wanes and can often experience other comorbid symptoms, including headaches, joint pain, dizziness, pallor, and diaphoresis. Nausea occurs in as many as 50% of children with pain-associated FGIDs and is a major factor contributing to significant disability.

Severity and Location of Pain

Functional pain can vary in intensity ranging from mild intermittent pain to severe intense pain that disrupts a child's life, family, and school attendance. Excluding organic causes of chronic abdominal pain remains a challenge for pediatricians, particularly given the heterogeneity of FGID symptoms. Although the location of pain does not always help differentiate between functional and organic causes, periumbilical pain has been shown to be most likely associated with functional pain. Substernal pain should raise the suspicion for an esophageal cause, such as erosive esophagitis from gastroesophageal reflux. Chronic abdominal pain in the presence of dysphagia or history of food impaction should prompt a referral to the specialist to rule out **eosinophilic esophagitis**. Epigastric pain can be caused from pathology in the esophagus, stomach, duodenum, and pancreas or from functional dyspepsia. Pain originating from hepatobiliary structures, including the gallbladder, liver, and head of the pancreas usually is primarily in the right upper quadrant. Certain conditions must be considered in patients who present with chronic pain in the right lower quadrant and these include chronic appendicitis, abdominal wall pain, or Crohn disease. Identifying certain characteristics or "red flags" that can assist the clinician in detecting organic disease in patients with chronic abdominal pain would be important, since it could limit unnecessary diagnostic testing in those with FGID and potentially prevent a delay in the diagnosis a specific organic disease.

◆ Approach to Treatment

Although clinically challenging, with the correct approach, managing the child with functional pain can be very rewarding for both the patient and physician. The first goal is to identify physical and psychologic stress factors that may have an important role in onset, severity, exacerbations, or maintenance of pain. Equally important is to reverse environmental factors that serve as reinforcers of the pain behavior. Parents and the school must work together to support the child. Regular school attendance is extremely important and should be encouraged even in the presence of pain. It is oftentimes helpful for the care provider to communicate directly to school officials to explain the nature of the problem. At home, less attention should be directed toward the symptoms. In the clinic, defining the problem and establishing an effective physician-patient relationship is an important part of therapy. Attention should focus on improvement of daily symptoms and quality of life, as well as the child's return to normal activities. Once the evaluation, including the history, physical examination, and appropriate screening laboratory tests, has been completed, and findings are normal, a search for nonorganic sources of pain should not be continued. Instead, the appropriate treatment should be initiated.

The child with functional pain may improve once the child and the family understand the nature of the pain and a proper explanation is given by the provider. Knowing that there is no serious organic disease and that the sensations are not imaginary is usually welcome information to the family. However, the conversation about functional abdominal pain should be brought up during the first visit and should not be discussed only after doing extensive testing. The family should understand that testing is only to confirm the absence of other disorders and confirm the possibility of functional pain.

There is a spectrum of functional pain in terms of severity. Some patients have minimal severity and frequency of pain while others have daily, unremitting pain that results in school absences, functional disability, and diminished quality of life. The total number of days missed from school is a good indicator of disability and should always be asked during the visit. For those with mild symptoms not interfering with daily activities, simple treatment strategies such as stool softeners for constipation often provide sufficient relief, such that the child can resume a more normal life. Similarly, dietary manipulation with lactose or fructose avoidance is often an important first step in the child with mild, chronic abdominal pain. **Carbohydrate malabsorption** or intolerance from lactose, sorbitol, or high-fructose corn syrup (fruit juices and sodas) may produce pain that responds to dietary elimination of the offending sugar. These simple strategies should not be tried on the child with significant disability and school absences, mainly because they are unlikely to work and time would be lost in trying to get the child back to functioning. The clinician should refrain from talking to patients and family using negative comments such as "you will have to learn to live with this pain." This leads to considerable gloom and hopelessness and will make the condition much more difficult to treat. Sometimes, despite diligent evaluation by the most skilled and patient clinician, symptoms can persist. There are no U.S. Food and Drug Administration–approved drugs for the treatment of chronic abdominal pain in children and little evidence of efficacy for most commonly used medications. It is important to consider that the clinician must spend time educating the family regarding the suspected mechanisms and how and why pharmacotherapy may or may not work. In the more severe, disabled patients, patient education should be considered part of a therapeutic program that includes physical reconditioning, exercise, sleep restoration and in many cases, thought reprocessing. Psychologic therapies such as cognitive behavioral therapy, hypnosis, relaxation, meditation, or biofeedback have been shown to be as effective, and sometimes better than pharmacologic therapy. Families should always be educated on the potential modification, of the "pain behavior" and potential benefits of lifestyle modifications.

A therapeutic trial with medications should be discussed with the family and should have a well-defined duration and goals. Also, the dose should be adequate to achieve the desired effect. If history and physical examination suggest dyspepsia or epigastric pain without red flags, a trial of acid suppression is very appropriate as an initial step. Similarly, if the history and physical examination suggest constipation as the cause for pain, then the proper therapy with osmotic laxatives or cathartics should be initiated. Pharmacologic therapy, including anticonvulsant or antidepressant agents, has not consistently proven to be effective in children with functional abdominal pain. Such therapy has sometimes been effective in young adults but is not recommended for younger children under 8 years of age. Amitriptyline has been used in small doses and anecdotally has been successful in alleviating functional abdominal pain. It is widely used for chronic pain conditions including migraine headaches, fibromyalgia, neuropathic pain and is considered to be effective at much lower doses than those used for depression.

Cyproheptadine is an antagonist of serotonin, histamine H_1, and muscarinic receptors. It has been used to treat allergic rhinitis, migraine headaches, and anecdotally as an appetite stimulant in children. Antispasmodics such as hyoscyamine or dicyclomine can produce significant anticholinergic side effects including dry mouth, dizziness, and blurred vision. Most antispasmodics should be used as adjuvant therapy for the treatment of chronic abdominal pain and only for episodic pain and not as daily treatment.

Small intestinal bacterial overgrowth may be a cause of chronic abdominal pain. Rifaximin has low systemic absorbance and localized effect on intestinal flora and is approved for diarrhea-predominant IBS in adults. In adolescents with functional pain, bloating, and/or diarrhea, empirical treatment with this antibiotic may be considered. Although short-term treatment appears to be well tolerated in adults, multiple treatments with rifaximin may be needed, which increases the concern for antimicrobial resistance.

The dearth of successful treatment options for chronic abdominal pain often results in patients opting for alternative methods. There appears to be a growing desire among patients and families for a more "natural" approach to therapy. It has been suggested that approximately 35% of adult patients with functional bowel disorders use complementary or alternative medicine despite the perceived lack of efficacy by some clinicians.

If the symptoms are mild and not severe enough to interfere with a child's school or daily activities, using alternative therapies for which there are some scientific evidence of benefit may be a good starting point. These include peppermint oil, melatonin, and STW5 (Iberogast). Concentrated peppermint oil is increasingly being used in the treatment of abdominal pain in children. The menthol component of peppermint oil acts as a calcium channel blocker that causes relaxation of intestinal smooth muscle. Peppermint oil, administered in pH-dependent, enteric-coated capsules has been shown to reduce abdominal pain severity over placebo in both adults and children. Melatonin is likely to be effective in less severe patients with functional pain with minimal co-morbidities and has the added benefit of having a low side effect profile. Iberogast is a mixture of nine herbal plant extracts that is being used as an alternative approach for the treatment of functional dyspepsia and IBS. The exact mechanism of this herbal preparation is not known but several trials have suggested that it is effective in alleviating symptoms of FD and IBS. The combination consists of liquid extracts from chamomile flowers, bitter candytuft, angelica root, caraway fruits, milk thistle, lemon balm leaves, greater celandine, licorice root, and peppermint leaves.

RED FLAGS

Red flags or "alarm signals" are critical to investigate in the history and physical exam of abdominal pain. The presence of red flags raises the suspicion of an underlying organic disorder and includes pain localized away from the umbilicus, pain related to menstrual cycle, back pain, multisystem complaints, anorexia, weight loss, evidence of GI bleeding (anemia, hematemesis, melena, hematochezia, rectal bleeding, occult bleeding), profuse diarrhea, extraintestinal symptoms (fever, rash, recurrent aphthous ulcers), and a positive family history of inflammatory bowel disease, celiac disease, or peptic ulcers. Anemia, hematochezia, and weight loss in children with chronic abdominal

pain are predictive of inflammatory bowel disease. Physical findings of linear growth deceleration, localized fullness or mass effect, hepatomegaly, splenomegaly, back or costovertebral angle tenderness, perianal skin tags or fistulas, soiling, or occult blood in stools should be taken seriously and should prevent the diagnosis of a FGID until further work-up is completed. Biochemical analysis that raises suspicion for organic disorders include iron deficiency anemia, high sedimentation rate or C-reactive protein, hypoalbuminemia, and abnormal liver or kidney function tests, or elevated amylase and lipase. A high stool calprotectin level suggests an inflammatory process and should be obtained in the presence of diarrhea. In cases in which recurrent vomiting is a significant part of the history, an upper GI series should be obtained to rule out gastric outlet disorder, malrotation, or partial small bowel obstruction. An abdominal ultrasound should also be considered in order to investigate the possibility of gallstones, pseudocyst, ureteropelvic junction obstruction, or a retroperitoneal mass. Contrast CT scans in the evaluation of chronic functional pain is seldom helpful and should not be ordered unless a specific cause is being investigated.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Agency for Healthcare Research and Quality. Diagnosis of right lower quadrant pain and suspected acute appendicitis – Executive Summary. Comparative Effectiveness Review, No. 157, Dec 2015. <www.effectivehealthcare.ahrq.gov/ehc/products/528/2159/appendicitis-executive-151214.pdf>.

Apley J. *The Child with Abdominal Pains*. 2nd ed. Oxford: Blackwell Scientific; 1975.

Harberg FJ. The acute abdomen in childhood. *Pediatr Ann*. 1989;18:169-178.

Hatch EI. The acute abdomen in children. *Pediatr Clin North Am*. 1985;32:1151-1164.

John SD. Imaging of acute abdominal emergencies in infants and children. *Curr Probl Pediatr*. 2001;31:315-358.

Acute Abdominal Pain

Alford BA, McIlhenny J. The child with acute abdominal pain and vomiting. *Radiol Clin North Am*. 1992;30:441-453.

Barr RG, Levine MD, Watkins JB. Recurrent abdominal pain of childhood due to lactose intolerance. *N Engl J Med*. 1979;300:1449-1451.

Bonadio WA. Clinical features of abdominal painful crisis in sickle cell anemia. *J Pediatr Surg*. 1990;25:301-302.

Buchert GS. Abdominal pain in children: An emergency practitioner's guide. *Emerg Med Clin North Am*. 1989;7:497-517.

Byrne WJ, Arnold WC, Stannard MW, et al. Ureteropelvic junction obstruction presenting with recurrent abdominal pain: Diagnosis by ultrasound. *Pediatrics*. 1985;76:934-937.

Daneman A, Navarro O. Intussusception. *Pediatr Radiol*. 2003;33:79-85.

Grey DWR, Dixon MD, Collin J. The closed eye sign: An aid to diagnosing non-specific abdominal pain. *BMJ*. 1988;297:836-837.

Helms M, Vastrup P, Gerner-Smidt P, et al. Short and long term mortality associated with foodborne bacterial gastrointestinal infections: Registry based study. *BMJ*. 2003;326:357-360.

Henrikson S, Blane CE, Koujok K, et al. The effect of screening sonography on the positive rate of enemas for intussusception. *Pediatr Radiol*. 2003;33:190-193.

Jeddy TA, Vowles RH, Southam JA. "Cough sign": A reliable test in the diagnosis of intraabdominal inflammation. *Br J Surg*. 1994;81:279-281.

Katz JA, Wagner ML, Gresik MV, et al. Typhlitis: An 18-year experience and postmortem review. *Cancer*. 1990;65:1041-1047.

Kim MK, Strait RT, Sato TT, et al. A randomized clinical trial of analgesia in children with acute abdominal pain. *Acad Emerg Med*. 2002;9:281-287.

Leahy AL, Fogarty EE, Fitzgerald RJ, et al. Discitis as a cause of abdominal pain in children. *Surgery*. 1984;95:412-414.

Lebenthal E, Rossi TM, Nord KS, et al. Recurrent abdominal pain and lactose absorption in children. *Pediatrics*. 1981;67:828-832.

Moustaki M, Zeis PM, Katsikari M, et al. Mesenteric lymphadenopathy as a cause of abdominal pain in children with lobar or segmental pneumonia. *Pediatr Pulmonol*. 2003;35:269-273.

Murphy TV, Gargiullo PM, Massoudi MS, et al. Intussusception among infants given an oral rotavirus vaccine. *N Engl J Med*. 2001;344:564-572.

Soltero MJ, Bill AH. The natural history of Meckel's diverticulum and its relation to incidental removal. *Am J Surg*. 1976;132:168-173.

Thomas SH, Silen W. Effect on diagnostic efficiency of analgesia for undifferentiated abdominal pain. *Br J Surg*. 2003;90:5-9.

Towne BH, Mahour GH, Woolley MM, et al. Ovarian cysts and tumors in infancy and childhood. *J Pediatr Surg*. 1975;10:311-320.

Peptic Ulcer Disease

Chiang B-L, Chang M-H, Lin M-I, et al. Chronic duodenal ulcer in children: Clinical observation and response to treatment. *J Pediatr Gastroenterol Nutr*. 1989;8:161-165.

Colin-Jones DG. Acid suppression: How much is needed? Adjust it to suit the condition. *BMJ*. 1990;301:564-565.

Drumm B, Rhoads JM, Stringer DA, et al. Peptic ulcer disease in children: Etiology, clinical findings, and clinical course. *Pediatrics*. 1988;82:410-414.

Gormally S, Drumm B. *Helicobacter pylori* and gastrointestinal symptoms. *Arch Dis Child*. 1994;70:165-166.

Hosking SW, Ling TKW, Chung SCS, et al. Duodenal ulcer healing by eradication of *Helicobacter pylori* without anti-acid treatment: Randomised controlled trial. *Lancet*. 1994;343:508-510.

Huang JQ, Sridhar S, Hunt RH. Role of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: A meta-analysis. *Lancet*. 2002;359:14-22.

Murphy MS, Eastham EJ, Jimenez M, et al. Duodenal ulceration: Review of 110 cases. *Arch Dis Child*. 1987;62:554-558.

Suerbaum S, Michetti P. *Helicobacter pylori* infection. *N Engl J Med*. 2002;347:1175-1186.

Appendicitis

Benjamin IS, Patel AG. Managing acute appendicitis. *BMJ*. 2002;325:505-506.

Doraiswamy NV. Leukocyte counts in the diagnosis and prognosis of acute appendicitis in children. *Br J Surg*. 1979;66:782-784.

Flum DR, Morris A, Koepsell T, et al. Has misdiagnosis of appendicitis decreased over time? *JAMA*. 2001;286:1748-1754.

Jones DJ. Appendicitis. *BMJ*. 1992;305:44-48.

Knight PJ, Vassy LE. Specific diseases mimicking appendicitis in childhood. *Arch Surg*. 1981;116:744-746.

Lee SL, Walsch AJ, Ho HS. Computed tomography and ultrasonography do not improve and may delay the diagnosis and treatment of acute appendicitis. *Arch Surg*. 2001;136:556-562.

Murch SH. Diarrhoea, diagnostic delay, and appendicitis. *Lancet*. 2000;356:787.

Neilson IR, Laberge J-M, Nguyen C. Appendicitis in children: Current therapeutic recommendations. *J Pediatr Surg*. 1990;25:1113-1116.

Oestreich AE, Adelstein EH. Appendicitis as the presenting complaint in cystic fibrosis. *J Pediatr Surg*. 1982;17:191-194.

Paulson EK, Kalady MF, Pappas TN. Suspected appendicitis. *N Engl J Med*. 2003;348:236-242.

Tate JJT, Dawson JW, Chung SCS, et al. Laparoscopic versus open appendectomy: Prospective randomized trial. *Lancet*. 1993;342:633-637.

Pancreatitis

Beckingham IJ, Bornman PC. Acute pancreatitis. *BMJ*. 2001;322:595-598.

Bornman PC, Beckingham IJ. Chronic pancreatitis. *BMJ*. 2001;322:660-663.

Fernandez-del Castillo C, Rattner DW, Warsha AL. Acute pancreatitis. *Lancet*. 1993;342:475-479.

Kahler SG, Sherwood WG, Woolf D, et al. Pancreatitis in patients with organic acidemias. *J Pediatr*. 1994;124:239-243.

Lee SP, Nicholls JF, Park HZ. Biliary sludge as a cause of acute pancreatitis. *N Engl J Med*. 1992;326:589-593.

Mitchell RMS, Byrne MF, Baillie J. Pancreatitis. *Lancet*. 2003;361:1447-1455.

Munoz-Bongrand N, Panis Y, Soyer P, et al. Serial computed tomography is rarely necessary in patients with acute pancreatitis: A prospective study in 102 patients. *J Am Coll Surg*. 2001;193:146-152.

Rabeneck L, Feinstein AR, Horwitz RI, et al. A new clinical prognostic staging system for acute pancreatitis. *Am J Med*. 1993;95:61-70.

Steinberg W, Tenner S. Acute pancreatitis. *N Engl J Med*. 1994;330:1198-1210.

Weizman Z, Durie PR. Acute pancreatitis in childhood. *Pediatrics*. 1988;113:24-29.

Williamson RCN. Endoscopic sphincterotomy in the early treatment of acute pancreatitis. *N Engl J Med*. 1993;328:279-280.

Yazdani K, Lippmann M, Gala I. Fatal pancreatitis associated with valproic acid. *Medicine (Baltimore)*. 2002;81:305-310.

Hepatobiliary Tract Disease

Cuschieri A. Management of patients with gallstones and ductal calculi. *Lancet*. 2002;360:739-740.

De Caluwe D, Akl U, Corbally M. Cholecystectomy versus cholecystolithotomy for cholelithiasis in childhood: Long-term outcome. *J Pediatr Surg*. 2001;36:1518-1521.

Debray D, Pariente D, Gauthier F, et al. Cholelithiasis in infancy: A study of 40 cases. *J Pediatr*. 1993;122:385-391.

Indar AA, Beckingham IJ. Acute cholecystitis. *BMJ*. 2002;325:639-644.

Johnston DE, Kaplan MM. Pathogenesis and treatment of gallstones. *N Engl J Med*. 1993;328:412-421.

Kim SH. Choledochal cyst: Survey by the surgical section of the American Academy of Pediatrics. *J Pediatr Surg*. 1981;16:402-407.
Krige JEJ, Beckingham IJ. Liver abscesses and hydatid disease. *BMJ*. 2001;322:537-540.
Reif S, Sloven DG, Lebenthal E. Gallstones in children. *Am J Dis Child*. 1991;145:105-108.

Chronic Abdominal Pain

Barr RG. Changing our understanding of infant colic. *Arch Pediatr Adolesc Med*. 2002;156:1172-1174.
Castile RG, Telander RL, Cooney DR, et al. Crohn's disease in children: Assessment of the progression of disease, growth and prognosis. *J Pediatr Surg*. 1980;15:462-469.
Garrison MM, Christakis DA. Infant colic. *Pediatr Case Rev*. 2001;1:19-24.
Horwitz BJ, Fisher RS. The irritable bowel syndrome. *N Engl J Med*. 2001;344:1846-1850.
Levine MD, Rappaport LA. Recurrent abdominal pain in school children: The loneliness of the long distance physician. *Pediatr Clin North Am*. 1984;31:969-991.
Liebman WM. Recurrent abdominal pain in children: A retrospective survey of 119 patients. *Clin Pediatr (Phila)*. 1978;17:149-153.
Mamula P, Telega GW, Markowitz JE, et al. Inflammatory bowel disease in children 5 years of age and younger. *Am J Gastroenterol*. 2002;97:2005-2010.
Murphy MS. Management of recurrent abdominal pain. *Arch Dis Child*. 1993;69:409-415.
Silverberg M. Chronic abdominal pain in adolescents. *Pediatr Ann*. 1991;20:179-185.
Talley NJ, Spiller R. Irritable bowel syndrome: A little understood organic bowel disease? *Lancet*. 2002;360:555-564.
Thiessen PN. Recurrent abdominal pain. *Pediatr Rev*. 2002;23:39-46.
Wade S, Kilgour T. Infant colic. *BMJ*. 2001;323:437-440.

11

Diarrhea

Bhaskar Gurram

Diarrhea is defined as a stool volume of greater than 10 g/kg/day in infants and toddlers and greater than 200 g/day in older children. Functionally, diarrhea should be considered if a patient is passing 3 or more unusually loose stools in a 24-hour period or is passing stools more frequently than usual, with a consistency looser than what is considered normal for that individual. Diarrhea is classified broadly by the duration of symptoms. **Acute diarrhea** is usually a self-limited illness that lasts for 2 weeks or less. **Chronic diarrhea** persists for more than 2 weeks. The etiologies of acute and chronic diarrhea differ by age (Table 11.1).

Diarrhea is further classified by pathophysiology, which typically involves 1 or more of the following mechanisms: (1) **osmotic diarrhea**, characterized by the presence of an increased intraluminal osmotic load leading to passive diffusion of fluid into the gastrointestinal lumen; (2) **secretory diarrhea**, characterized by increased secretion of fluid into the gastrointestinal lumen beyond the capacity to be reabsorbed; and (3) altered gastrointestinal tract motility. Differentiating osmotic from secretory diarrhea allows for a more directed diagnostic evaluation (Table 11.2). **Osmotic diarrhea** may be related to the malabsorption of carbohydrate, fat, or protein or to the presence of nonabsorbable substances in the gastrointestinal lumen. The characteristics of the stool may provide information that allows for the identification of the malabsorbed substance, particularly for isolated carbohydrate and fat malabsorption (Table 11.3). **Secretory diarrhea** is characterized by an excess of crypt cell fluid and electrolyte secretion that exceeds the absorptive capabilities of the villi and is classified by the presence or absence of normal villi. **Inflammatory diarrhea** of both infectious and noninfectious etiologies usually involves both osmotic and secretory components. Finally, surgical bowel resection may decrease the surface area available for the resorption of both fluid and solutes, leading to both a secretory and osmotic diarrhea. The causes of diarrhea based on pathophysiology are presented in Table 11.4.

ACUTE DIARRHEA

◆ History

Acute diarrhea in children is most often infectious (Table 11.5), although it may be secondary to noninfectious inflammatory processes, toxins, or medications. The etiology of acute diarrhea is suggested by both the history and characteristics of the stool. Fever or blood in the stool suggests an infectious cause. Watery diarrhea is typical of viral gastroenteritis, as well as some bacterial and parasitic infections. **Dysentery**, characterized by severe diarrhea and the presence of blood and mucus in the stool, suggests bacterial colitis. Vomiting and diarrhea developing within hours of ingesting food suggests exposure to preformed toxins in the food, rather than the acquisition of an enteric pathogen from the food, which is characterized by a predominantly diarrheal illness developing within days of exposure (Fig. 11.1). A recent history of travel suggests **traveler's diarrhea**, more than 80% of which is caused by bacterial species that are endemic to the area of travel, to which the patient has not been previously exposed. Recent travel may also suggest parasitic or helminthic infection. Exposure to health care settings suggests **nosocomial diarrhea**. Patients with a history of immunodeficiency or malnourishment may be more likely to have an infection with atypical or opportunistic organisms or to have a more protracted and severe course. Hematuria or oliguria may suggest **hemolytic uremic syndrome** as a complication of infection with *Escherichia coli* 0157:H7 or *Shigella*.

◆ Physical Examination

Physical examination should focus on assessing the level of hydration and the need for fluid resuscitation (Table 11.6). The general examination may reveal nonenteric infections that could present with diarrhea, such as otitis media, pneumonia, or sepsis. Abdominal tenderness or masses suggest appendicitis, intussusception, or less commonly, toxic megacolon. Generalized toxicity or shock may occur with hemolytic uremic syndrome or with sepsis, such as from invasive *Salmonella* or staphylococcal toxic shock syndrome.

Viral Diarrhea

Rotavirus infection. Rotavirus is the leading cause of severe diarrhea in infants and young children. The introduction of an effective vaccine has decreased the incidence, with most infections occurring in unvaccinated children under 3 years of age. Transmission is by the fecal-oral route and the incubation period ranges from 1 to 3 days. Patients typically present with the acute onset of fever and vomiting followed 1-2 days later by watery diarrhea. Symptoms generally persist for 3-8 days. In moderate to severe cases, dehydration, electrolyte abnormalities, and acidosis may occur. In immunocompromised children, persistent infection and chronic diarrhea can develop, with persistently positive diagnostic assays. Chronic infection is to be differentiated from postinfectious malabsorption seen in some immunocompetent children, in whom the small intestinal mucosa may require 3-8 weeks to recover its absorptive ability. Diagnosis is confirmed by nucleic acid amplification assays, enzyme immunoassay (EIA), immunochromatography, or latex agglutination assay for group A rotavirus antigen detection in the stool.

Norovirus infection. Norovirus is a single-stranded RNA virus of the *Calciviridae* family and is the leading cause of epidemic outbreaks of acute gastroenteritis, as well as the most common cause of foodborne illness and foodborne disease outbreaks in the United States. Young children have the highest incidence of infection. Transmission is via the fecal-oral route or through contaminated food or water. Norovirus gastroenteritis typically presents with the abrupt onset of vomiting accompanied by watery diarrhea, abdominal cramps, nausea,

TABLE 11.1 Differential Diagnosis of Acute and Chronic Diarrhea by Age

Infants	Children	Adolescents
Acute		
Common	Infectious gastroenteritis	Infectious gastroenteritis
Infectious gastroenteritis	Food poisoning	Food poisoning
Systemic infection	Antibiotic-associated diarrhea	Antibiotic-associated diarrhea
Medication-induced (e.g., antibiotics, laxatives)	Food poisoning	Hyperthyroidism
Food protein–induced enterocolitis syndrome (FPIES)	Systemic infection	
Food poisoning		
Overfeeding		
Rare		
Hirschsprung-associated enterocolitis		
Neonatal opioid withdrawal		
Chronic		
Disorders of Absorption and Transport of Nutrients and Electrolytes	***Disorders of Absorption and Transport of Nutrients and Electrolytes***	***Disorders of Absorption and Transport of Nutrients and Electrolytes***
Primary lactase deficiency	Lactose intolerance	Lactose intolerance
Secondary (e.g., postinfectious) lactase deficiency	Secondary (e.g., postinfectious) lactase deficiency	Laxative abuse
Congenital sucrose-isomaltase deficiency	Congenital sucrose-isomaltase deficiency	***Disorders of Intestinal Motility***
Congenital chloride diarrhea	Primary bile acid diarrhea	Irritable bowel syndrome
Congenital sodium diarrhea	Familial diarrhea syndrome	Pesudoobstruction and bacterial overgrowth
Acrodermatitis enteropathica	***Disorders of Intestinal Motility***	***Infectious Etiologies***
Glucose-galactose malabsorption	Toddler's diarrhea	Giardiasis
Fanconi-Bickel syndrome	Irritable bowel syndrome	Cryptosporidium
Lysininuric protein intolerance	***Infectious Etiologies***	***Neuro-Enteroendocrine Diarrhea***
Chylomicron retention disease	Giardiasis	Primary adrenal insufficiency
Abetalipoproteinemia	Cryptosporidium	***Defects in Intestinal Immune-Related Homeostasis***
Enterokinase deficiency	***Defects in Enterocyte Structure***	Inflammatory bowel disease
Maltase-glucoamylase deficiency	Trichohepatoenteric syndrome (syndromic diarrhea)	Celiac disease
Primary bile acid diarrhea	***Neuro-Enteroendocrine Diarrhea***	Eosinophilic gastroenteritis and colitis
Familial diarrhea syndrome	Proprotein convertase 1/3 deficiency	***Pancreatic Insufficiency***
Diarrhea-associated *DGAT1* mutation	X-linked lissencephaly	Chronic pancreatitis
Defects in Enterocyte Structure	Secretory tumors (e.g., neuroblastoma, VIPoma)	
Congenital tufting enteropathy	***Defects in Intestinal Immune-Related Homeostasis***	
Microvillus inclusion disease	Celiac disease	
Trichohepatoenteric syndrome (syndromic diarrhea)	Inflammatory bowel disease	
Neuro-Enteroendocrine Diarrhea	Eosinophilic gastroenteritis and colitis	
Enteric anendocrinosis	Early-onset enteropathy with colitis	
Mitchell-Riley syndrome	XIAP deficiency	
Proprotein convertase 1/3 deficiency	Autoimmune enteropathy	
X-linked lissencephaly	***Pancreatic Insufficiency***	
Secretory tumors (e.g., neuroblastoma)	Cystic fibrosis	
Defects in Intestinal Immune-Related Homeostasis	Chronic pancreatitis	
Cow's milk or soy-milk protein colitis		
Eosinophilic gastroenteritis and colitis		
Early-onset enteropathy with colitis		
IPEX syndrome		
IPEX-like disorders		
XIAP deficiency		
Autoimmune enteropathy		
Other primary immune deficiency disorders (e.g., SCID)		
Pancreatic Insufficiency		
Cystic fibrosis		
Shwachman-Diamond syndrome		
Johansson-Blizzard syndrome		
Pearson syndrome		

DGAT1, Diacylglycerol O-acyltransferase 1; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; SCID, severe combined immunodeficiency; VIP, vasoactive intestinal peptide; XIAP, X-linked inhibitor of apoptosis.

and vomiting. Systemic manifestations, including myalgia, fatigue, and headache may accompany gastrointestinal symptoms. Diagnosis is confirmed by nucleic acid amplification assays that detect viral RNA from the stool.

Bacterial Diarrhea

Most bacterial diarrheal illnesses are foodborne and affect infants and young children more frequently than adults. Bacterial infections of the intestine cause diarrhea via direct invasion of the intestinal mucosa, followed by intraepithelial cell multiplication or invasion of the lamina propria. Cellular invasion may be followed by the production of cytotoxin, which disrupts cell function, and/or the production of enterotoxin, which alters cellular electrolyte and water balance. Bacterial adherence to the mucosal surface may result in flattening of the microvilli and disruption of normal cell functioning. Symptomatic differentiation from viral causes of diarrhea may be difficult, and sequelae of infections are varied (Table 11.7).

Salmonella *infection.* Nontyphoidal *Salmonella* organisms are estimated to cause 1 million annual gastrointestinal infections in the United States. The attack rate is highest in infancy; the incidence of symptomatic infections is lower in patients older than 6 years. *Salmonella* infection may cause an asymptomatic intestinal carrier state (rare in children), enterocolitis with diarrhea, or bacteremia without gastrointestinal manifestations but with subsequent local infections, such as meningitis or osteomyelitis. *Salmonella* infection is usually spread through contaminated water supplies or food (e.g., meat, chicken, eggs, raw milk, and fresh produce). Most infections in the United States are sporadic rather than epidemic. Although an infected food handler may contaminate food sources, farm animals or pets are often the vector. Cats, turtles, lizards, snakes, and iguanas may also harbor *Salmonella* organisms. Outbreaks may occur among institutionalized children; outbreaks in daycare centers are rare.

After a 12- to 72-hour incubation period, gastroenteritis develops and is characterized by the sudden onset of diarrhea, abdominal cramps and tenderness, and fever. The diarrhea is watery, with stools containing polymorphonuclear leukocytes and, on occasion, blood. The peripheral blood white blood cell count is usually normal. Symptoms slowly resolve within 3-5 days, although excretion of the organism may persist for several weeks. The organism is readily isolated from culture of the stool or a rectal swab, or may be identified via multiplex polymerase chain reaction (PCR) assays that detect multiple bacterial, viral, and parasitic enteric pathogens.

Shigella *infection.* Most *Shigella* infections in the United States occur in young children 1-4 years of age, with a peak seasonal incidence in late summer and early autumn. It may also be the most common bacterial cause of diarrhea outbreaks in daycare settings. The organism is transmitted via the fecal-oral route, most often by the hands. During a 12- to 72-hour incubation period, patients may develop a nonspecific prodrome characterized by fever, chills, nausea, and vomiting. A predominantly rectosigmoid colitis develops and results in abdominal cramps and watery diarrhea. In more severe infections (**bacillary dysentery**), blood and mucus are passed in small, very frequent stools. High fever in young infants may induce febrile seizures, and some patients may develop hemolytic uremic syndrome. Bacterial culture of the stool or a rectal swab, or the use of multiplex PCR assays, allows for differentiating this organism from other pathogens. If positive, antibiotic treatment is usually indicated.

Campylobacter *infection.* Many animal species, including poultry, farm animals, and household pets, serve as reservoirs for *Campylobacter jejuni*. Transmission occurs through ingestion of contaminated food, especially undercooked food, and through person-to-person spread via the fecal-oral route. The disease is common in infants and adolescents, and both daycare and college outbreaks have been reported. Asymptomatic carriage is uncommon. *Campylobacter* infection causes disease that may range from mild diarrhea to frank dysentery. The organism causes diffuse, invasive enteritis that involves the ileum and colon. Fever, cramping, abdominal pain, and bloody diarrhea are characteristic and may mimic symptoms of acute appendicitis or inflammatory bowel disease. Fever and diarrhea usually resolve after 5-7 days; prolonged illness or relapse occasionally occurs. *Campylobacter* infection is also known to cause meningitis, abscesses, pancreatitis, and pneumonia. Guillain-Barré syndrome has been reported after *Campylobacter* infection. Identification is via stool or rectal swab bacterial culture, or via multiplex PCR assay. If positive, antibiotic treatment is indicated.

Yersinia *infection.* Infection with either *Yersinia enterocolitica* or *Y. pseudotuberculosis* may cause various clinical syndromes, including gastroenteritis, mesenteric adenitis, pseudoappendicitis, and postinfectious reactive arthritis. The organism is present in animals and may be spread to humans by consumption of undercooked meat (especially pork), unpasteurized milk, and other contaminated foods. Person-to-person spread also occurs. Young children are particularly susceptible to disease, and the frequency of infections increases during the summer months.

The organisms may be identified via multiplex PCR assay or may be cultured from rectal swab or stool specimens, but selective media are required, and the organism may not be identified via culture for several weeks. The microbiology laboratory should be notified if

TABLE 11.2 Differentiating Osmotic from Secretory Diarrhea

	Osmotic	Secretory
Stool volume	Small (<200 mL/24 hr)	Large (>200 mL/24 hr)
Response to fasting	Diarrhea improves	Diarrhea continues
Stool sodium	<70	>70
Stool osmotic gap*	>50	<50
Stool pH	<5	>6

*Stool osmotic gap = 290 – 2 (stool Na^+ + stool K^+)

TABLE 11.3 Distinguishing Isolated Carbohydrate from Isolated Fat Malabsorption

	Isolated Carbohydrate Malabsorption	Isolated Fat Malabsorption
Stool character	Loose and watery, non–foul-smelling	Bulky large stool, foul-smelling, oil droplets visible
Perianal rash/skin erosion	Present	Present
Signs of fat-soluble vitamin deficiency	Variable	Present
Stool pH	Acidic (usually <6)	Alkaline
Stool reducing/non-reducing substances	Present	Absent

TABLE 11.4 Differential Diagnosis of Diarrhea by Pathophysiology

Osmotic Diarrhea

1. Carbohydrate malabsorption
   - Lactose intolerance
   - Osmotic laxatives (lactulose, polyethylene glycol 3350)
   - Antacids (magnesium hydroxide)
   - Ingestion of excessive amounts of non-absorbable sugar or sugar alcohols (sorbitol in chewing gum, diet candy, sucralose)
   - Dietary ingestion of excessive fructose (high-fructose corn syrup, ingestion of high-fructose–containing fruits in excessive amounts)
   - Disaccharidase deficiency (sucrose-isomaltase deficiency, glucose-galactose malabsorption, maltase-glucoamylase deficiency, congenital lactase deficiency)
   - Gastrocolic fistula, jejuno-ileal bypass, short-bowel syndrome
2. Fat malabsorption
   - Pancreatic insufficiency
   - Defective handling of bile acids (e.g., primary bile acid malabsorption, cholestasis)
   - Defective mucosal lipid handling (e.g., intestinal lymphangiectasia, abetalipoproteinemia, chylomicron retention disease)
3. Protein malabsorption
   - Primary enterokinase deficiency
   - Hartnup disease

Secretory Diarrhea

- Normal villous architecture
  - Chloride-losing diarrhea (Cl^- – HCO_3^- exchanger defect)
  - Sodium-losing diarrhea (Na^+ – H^+ exchanger defect)
  - Familial diarrhea syndrome (gain-of-function mutation of guanylate cyclase 2C)
  - Neurogenin-3 mutation
- Villous atrophy
  - Microvillous inclusion disease
  - Tufting enteropathy
  - Acrodermatitis enteropathica
  - Trichohepatoenteric syndrome (phenotypic or syndromic diarrhea)
  - Congenital disorders of glycosylation defects

Autoimmune polyglandular syndrome type 1
Neuroendocrine tumors

Inflammatory (Combination of Secretory and Osmotic)

1. Infectious
2. Celiac disease
3. Inflammatory bowel disease
4. Autoimmune enteropathy and infantile-onset inflammatory bowel disease
   - Interleukin-10 and interleukin-10 receptor defects
   - Hyperimmunoglobulin D from mevalonate kinase deficiency presenting as severe neonatal colitis
   - IPEX/IPEX-like syndrome
5. Postinfectious enteropathies
6. Eosinophilic gastroenteritis
7. Idiopathic

Decreased Surface Area for Absorption

1. Short-bowel syndrome

IPEX, Immune dysregulation, polyendocrinopathy, enteropathy, X-linked.

TABLE 11.5 Causes of Acute Gastroenteritis in Children

Viruses

- Noroviruses and other *Calciviridae*
- Rotavirus
- Astrovirus
- Enteric adenovirus
- Picornaviruses

Bacteria

- Non-typhoidal *Salmonella* species
- *Campylobacter jejuni*
- *Shigella*
- *Yersinia enterocolitica*
- Enteropathogenic *Escherichia coli*
- Shiga toxin-producing *Escherichia coli*
- *Salmonella typhi* and *Salmonella paratyphi*
- *Vibrio cholarae*
- *Aeromonas* species

Protozoa

- *Cryptosporidium*
- *Giardia lamblia*
- *Entamoeba histolytica*

Helminths

- *Strongyloides stercoralis*

Yersinia infection is suspected. Antibiotics are not effective in alleviating symptoms of *Yersinia* enteritis or in shortening the period of bacterial excretion. Patients with extraintestinal infection should receive therapy.

Escherichia coli *infection*. Although *E. coli* comprise the predominant normal flora in the colon, some strains are pathogenic. Diarrhea caused by *E. coli* can be watery, inflammatory, or bloody, depending on the strain involved. These diarrheogenic *E. coli* strains are classified into 5 major groups on the basis of serogrouping or pathogenic mechanisms: (1) enteropathogenic *E. coli* (EPEC), an important cause of diarrhea in infants; (2) enterotoxigenic *E. coli* (ETEC), a cause of diarrhea in infants and a cause of traveler's diarrhea; (3) enteroinvasive *E. coli*, a cause of watery ETEC-like illness or, less commonly, a dysentery-like illness; (4) enterohemorrhagic *E. coli*, a cause of hemorrhagic colitis and hemolytic uremic syndrome (HUS); and (5) enteroaggregative *E. coli*, a cause of persistent diarrhea.

Enteric infections with *E. coli* are acquired via the fecal-oral route. Enterohemorrhagic strains are the only diarrhea-producing *E. coli* strains common in the United States and have been associated with foodborne epidemic outbreaks transmitted in some cases by undercooked meat.

EPEC is a well-established cause of infantile diarrhea, especially in developing countries. Asymptomatic carriage is common. At least 2 separate mechanisms are responsible for diarrhea: adherence to intestinal epithelial cells leading to villous injury and mucosal inflammation, and production of a toxin similar to that of *Shigella* organisms. Chronic infection resulting in failure to thrive may also occur.

ETEC is the major cause of traveler's diarrhea; occasional nosocomial outbreaks have also occurred in hospitalized infants. At least 3 different types of *E. coli* enterotoxins (heat-labile, heat-stable toxin A, and heat-stable toxin B) have been identified. Definitive diagnosis requires enterotoxin identification, and this method is not widely available.

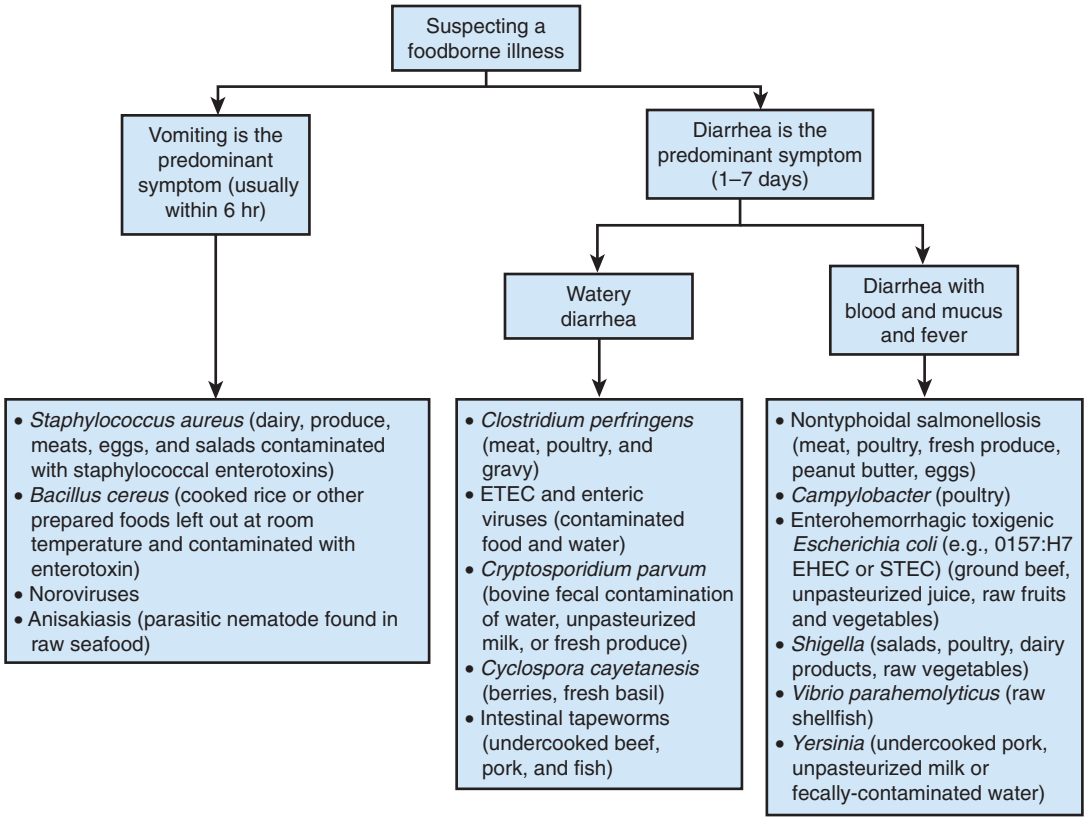


FIGURE 11.1 Differentiating causes of foodborne illness. EHEC, enterohemorrhagic *E. coli*; ETEC, enterotoxigenic *E. coli*; STEC, Shiga toxin–producing *E. coli*.

TABLE 11.6 Assessment of Degree of Dehydration

Signs and Symptoms General Appearance	Mild	Moderate	Severe
Infants/young children	Thirsty; alert; restless	Thirsty; restless or listless	Drowsy or lethargic; limp, cold, sweaty, cyanotic
Older children	Thirsty; alert; restless	Thirsty; alert (usually)	Usually conscious (but at reduced level), apprehensive; cold, sweaty, cyanotic extremities; wrinkled skin on fingers/toes; muscle cramps
Tachycardia	Absent	Present	Present
Palpable pulses	Present	Present (weak)	Decreased
Blood pressure	Normal	Orthostatic hypotension	Hypotension
Cutaneous perfusion	Normal	Normal	Reduced/mottled
Skin turgor	Normal	Slight reduction	Reduced
Fontanel	Normal	Slightly depressed	Sunken
Mucous membranes	Moist	Dry	Very dry
Tears	Present	Present/absent	Absent
Respirations	Normal	Deep, may be rapid	Deep and rapid
Urine output	Normal	Oliguria	Anuria/severe oliguria

From Lewy JE. Nephrology: Fluids and electrolytes. (Modified from World Health Organization Guide.) In: Behrman RE, Kliegman RM, eds. *Nelson Essentials of Pediatrics*. 2nd ed. Philadelphia: WB Saunders; 1994:582.

TABLE 11.7 Complications of Bacterial Enteric Infections

Complication	Important Bacterial Agents	Clinical Considerations
Dehydration	*Vibrio cholerae*, any bacterial enteropathogen	Complication of all forms of acute watery diarrhea; should prompt aggressive fluid and electrolyte replacement
Bacteremia	*Salmonella, Campylobacter fetus*	Organisms that deeply penetrate the intestinal mucosa are prone to cause bacteremia; certain high-risk conditions predispose to systemic *Salmonella* infection
Hemolytic uremic syndrome	Shiga toxin–producing *Escherichia coli, Campylobacter jejuni*	Shiga toxin is absorbed, causing injury to endothelial cells of the glomerular capillaries with intravascular coagulation
Guillain-Barré syndrome	*Campylobacter, Salmonella, Shigella flexneri, Yersinia*	Most cases occur as a result of molecular mimicry, with antibodies directed to *Campylobacter* lipooligosaccharides and peripheral nerve gangliosides; probability of development of Guillain-Barré syndrome within 2 mo after *Campylobacter* infection estimated at <2/10,000 cases
Reactive arthritis and iritis	Inflammatory bacterial pathogens (e.g., *Campylobacter*) are most important, but most bacterial pathogens can produce the syndrome	Occurs in 2.1/100,000 cases of *Campylobacter* infection and 1.4/100,000 cases of *Salmonella* infection; affected persons may be HLA-B27–positive or HLA-B27–negative
Postinfectious irritable bowel syndrome	*Vibrio cholerae*, any bacterial enteropathogen	Enteric bacterial infection with intestinal inflammation in a susceptible host leads to altered intestinal findings and postinfectious irritable bowel syndrome; duration is ≥5 yr

Enterohemorrhagic *E. coli* produces a **Shiga-like cytotoxin** and causes diarrhea, hemorrhagic colitis, and, in about 20% of infected persons, **hemolytic uremic syndrome (HUS)**. Both epidemic and sporadic cases have been recognized. Infection is more common in the summer and fall. A particular serotype, *E. coli* 0157:H7, has been linked to the development of HUS in young children. The most common manifestations of enterohemorrhagic *E. coli* infection begin with severe abdominal cramps and watery diarrhea, followed by grossly bloody stools and emesis. Fever is uncommon. Fecal leukocytes are absent or few. Other manifestations include asymptomatic infection and watery diarrhea without progression to hemorrhagic colitis. *E. coli* 0157:H7 is cleared from the stool in 5-12 days. If HUS develops, symptoms become noticeable in the week after the onset of diarrhea and consist of renal failure, microangiopathic hemolytic anemia, thrombocytopenia, and diarrhea. There is no role for antimicrobial therapy in enterohemorrhagic *E. coli* disease. Antibiotics neither shorten the duration of disease nor prevent progression to HUS; they may predispose to HUS.

Clostridium difficile *infection.* *Clostridium difficile* causes acute and chronic diarrhea in children when the normal colonic flora is disrupted. **Pseudomembranous colitis** is the most severe form of this infection, occurring as a result of a severe inflammatory response to the *C. difficile* toxins. Transmission occurs through person-to-person contact and through environmental contamination via the spores formed by *C. difficile*, which retain viability for up to 1 week on dry surfaces.

The prevalence of carrier status for *C. difficile* in healthy, asymptomatic outpatients is as high as 50% in healthy infants, but is usually less than 5% in patients over 5 years of age. *C. difficile* and its toxin have been identified in the feces of healthy infants in concentrations similar to those found in adults with pseudomembranous colitis. The apparent resistance of infants to *C. difficile* and its toxin is related to the developmental absence of the toxin-binding site in the immature intestine. Asymptomatic carriage rates in hospitalized patients may be as high as 20%. Infection is highly associated with recent antibiotic exposure, particularly to broad-spectrum antibiotics, which disrupt the endogenous colonic flora that inhibits the growth of *C. difficile*. Other risk factors for *C. difficile* diarrhea include inflammatory bowel disease, gastrointestinal surgery or procedures, and immunocompromised status.

C. difficile infection should be considered in patients in whom diarrhea develops during or within several weeks of antibiotic therapy. Illness associated with this organism varies from a mild, self-limited, nonbloody diarrhea to severe hemorrhagic colitis, protein-losing enteropathy, toxic megacolon, colonic or cecal perforation, peritonitis, sepsis, shock, and death. In rare cases, manifestations of *C. difficile* infection include fever or abdominal pain without diarrhea.

The colitis is caused by potent toxins produced by the organism: **toxin A**, a lethal enterotoxin that causes hemorrhage and fluid secretion in the intestines; and **toxin B**, a cytotoxin detectable by its cytopathic effects in tissue culture. Both toxins play a role in disease production, although toxin A may be more important.

C. difficile infection is currently diagnosed either by enzyme immunoassay for *toxins* in stool or by nucleic acid amplification tests that identify the microbial *toxin* genes in unformed stool. Sigmoidoscopy or colonoscopy reveals pseudomembranes in 30-50% of cases, typically in association with more severe disease. Treatment is indicated for severe disease.

Aeromonas *infection.* *Aeromonas* species are gram-negative bacilli that are found in a variety of freshwater sources and that are capable of causing a wide array of disease, including a mild, self-limited diarrheal illness in children. Occasionally, *Aeromonas* may cause dysentery or a protracted diarrheal illness. The most common manifestation is a watery, nonbloody, nonmucoid diarrhea seen during the late spring, summer, and early fall. More severe infections may resemble ulcerative colitis, with chronic bloody diarrhea and abdominal pain.

Plesiomonas *infection.* *Plesiomonas shigelloides* is a *Vibrio*-like organism found in soil and water that is sometimes implicated in childhood diarrhea. It has been linked to consumption of raw shellfish or contaminated water, exposure to reptiles and tropical fish, and travel to Mexico and Asia. After an incubation period of 1-2 days, patients typically develop watery diarrhea and vomiting, although some may develop dysentery. Diagnosis is via stool culture. Symptoms may last up to 2 weeks, although the disease is typically self-limited in immunocompetent individuals.

Parasitic Diarrhea

Giardiasis. *Giardia intestinalis* is a flagellated protozoan that can cause diarrhea, malabsorption, abdominal pain, and weight loss. It spreads through contaminated food and water, as well as through person-to-person contact via the fecal-oral route. The latter mode of transmission is responsible for outbreaks of diarrhea in daycare centers and residential facilities. Infection is often asymptomatic. Symptomatic illness usually develops 1-3 weeks after exposure and may mimic acute gastroenteritis with low grade or no fever, nausea, vomiting, and watery diarrhea. In some patients, a chronic illness develops, characterized by intermittent, foul-smelling diarrhea, abdominal bloating, nausea, abdominal pain, and weight loss. Up to 40% of patients may develop secondary lactase deficiency following infection. Diagnosis is via EIA or direct fluorescent antibody (DFA) tests, which offer superior sensitivity and specificity compared to microscopy. If microscopy is performed, three separate samples of fresh stool should be examined for cysts or trophozoites, because excretion of the organism is only intermittent. Treatment is typically indicated in the presence of symptoms, to prevent institutional outbreaks, or to prevent spread to immunocompromised individuals.

Entamoeba histolytica *infection.* *Entamoeba histolytica* is acquired in warm climates via the ingestion of cysts in fecally contaminated food or water. Infected individuals are often asymptomatic. Amebic dysentery may occur, but hepatic abscess and other remote infections are uncommon. Because cysts are shed in the stool on an intermittent basis, examination of several fecal specimens may be required for identification. Stool antigen detection assays allow for differentiation between *E. histolytica* and the more prevalent though less pathogenic *E. dispar*, which may also be detected on microscopy. Treatment is indicated to prevent the development of extraintestinal manifestations or spread to other individuals.

Cryptosporidium *infection.* This intracellular protozoan causes watery diarrhea in both immunocompetent and immunocompromised hosts and is an important cause of severe diarrhea in individuals infected with the human immunodeficiency virus. *Cryptosporidium* has also been recognized as an occasional cause of self-limited diarrhea in travelers, as well as in children in daycare centers and persons in residential institutions. The mechanisms by which these organisms cause diarrhea are unknown. Nucleic acid amplification assays and EIA tests are available for diagnosis. Identification via microscopy requires specialized staining techniques that should be requested if *Cryptosporidium* infestation is suspected.

Other Causes of Acute Diarrhea

Parenteral secondary diarrhea. Acute diarrhea that accompanies infections outside of the gastrointestinal tract is termed **parenteral diarrhea**. Upper respiratory tract and urinary tract infections may be associated with increased bowel movement frequency or stool water. The mechanism is unclear but may involve alterations in bowel motility, changes in diet, or the effects of antibiotic treatment.

Medications. Various nonlaxative prescription and over-the-counter medications may cause acute diarrhea (Table 11.8). The most commonly implicated agents are antibiotics, acting through mechanisms other than *C. difficile*.

Food poisoning (Table 11.9; see Fig. 11.1). **Staphylococcal food poisoning** results from ingestion of preformed enterotoxin, produced in contaminated food that has incubated at or above room temperature for a suitable period. Staphylococcal food poisoning is suggested by the sudden onset of vomiting that is followed by explosive diarrhea, usually within 4-6 hours after ingestion of the contaminated food. The illness is self-limited and usually resolves within 12-24 hours. The diagnosis is based on the typical historical presentation. Treatment is supportive; antibiotics are not indicated.

TABLE 11.8 Medications and Substances Associated with Diarrhea in Children

Agent	Mechanism
Stimulant laxatives (e.g., senna, bisacodyl)	Increased intestinal secretion (phenolphthalein, bisacodyl)
Antacids	Osmotic effect (Mg^{2+})
Prokinetic agents	Increased peristalsis (metoclopramide, bethanechol, cisapride)
Measles-mumps-rubella vaccine	Unknown
Thyroid hormone	Increased peristalsis
Chemotherapeutics	Intestinal mucosal injury
Heavy metals	Toxic effect
Organophosphates	Cholinergic effects
Diuretics	Unknown
Digitalis	Unknown
Colchicine	Unknown
Indomethacin	Prostaglandin synthesis inhibition
Theophylline	Increased peristalsis

Bacillus cereus, a gram-positive sporulating organism found in soil, is usually associated with contamination of refried rice or vegetables. Two food poisoning syndromes can occur. A short incubation period disease (1-6 hours) results from ingestion of preformed toxin and is characterized by nausea, vomiting, and diarrhea, similar to staphylococcal food poisoning. A long incubation period disease (8-16 hours) is caused by in vivo production of an enterotoxin and is characterized by abdominal pain, tenesmus, and profuse watery diarrhea. Vomiting is usually absent. Both syndromes resolve spontaneously within 24 hours and are managed with supportive care.

Clostridium perfringens food poisoning has been associated with ingestion of contaminated beef and poultry. The disease results from the production and release of an enterotoxin into the lower bowel 8-24 hours after ingestion of the vegetative form of the organism. Onset is sudden, with abdominal pain and watery diarrhea. Fever and vomiting are absent. Treatment is supportive.

CHRONIC DIARRHEA

The etiology of chronic diarrhea is dependent on the age of the patient (see Table 11.1) and is additionally influenced by socioeconomic factors and the clinical setting. In developing countries, chronic diarrhea is frequently caused by acute infections, as malnutrition tends to prolong the course of infectious enterocolitis. The most common etiologies of chronic diarrhea in developed countries are functional intestinal disorders, nutrient malabsorption (cystic fibrosis), celiac disease, and inflammatory bowel diseases, but persistent infections of the intestinal tract may also occur.

◆ History

The history should establish the age of onset, as well as the frequency and nature of the stools, including the presence of blood, nighttime stooling, urgency, weight loss, and any associated systemic symptoms. History should also ascertain any recent travel, other sick contacts, or swimming in freshwater sources. A history of recurrent infections, use of intravenous drugs, or other signs, symptoms, or risk factors for

TABLE 11.9 Foodborne Gastrointestinal Illnesses

Cause	Incubation Period	Clinical Clues	Common Vehicle	Diagnosis
Monosodium glutamate	Minutes to 2 hr	Burning in abdomen, chest, extremities, and neck; lightheadedness; chest pain	Found in some Asian cuisines	Large amount of monosodium glutamate in implicated food
Heavy metals (copper, zinc, cadmium, tin)	Minutes to 2 hr	Metallic taste, diarrhea, prominent vomiting, no fever	Carbonated or acidic beverages in metal containers	Chemical study of implicated beverage
Mushroom poisoning*	Minutes to 2 hr	Altered mental status with visual disturbance (encephalopathy)	Noncommercially obtained mushrooms	Identify mushroom and/or toxic chemical (e.g., muscarine, psilocybin)
Fish/Shellfish-Related Toxins*				
Scombrotoxin poisoning	Minutes to 2 hr	Histamine reaction: flushing, headache, dizziness, burning of throat and mouth	*Scombridae* fish (includes tuna, mackerel, and bonito species), mahi-mahi	Identify fish and/or chemical toxin (ciguatoxin, tetrodotoxin, histamine, etc.)
Paralytic shellfish poisoning	Minutes to 2 hr	Paresthesia, dizziness, sometimes paralysis	Mussels, clams, oysters, scallops contaminated with toxins, typically from dinoflagellate algae species	
Tetrodotoxin poisoning	Minutes to 2 hr	Paresthesia	Various pufferfish and angelfish species. The toxin is produced by symbiotic or infecting bacteria in the fish species	
Ciguatoxin poisoning	2-24 hr	Itching, arthralgias, metallic taste, Paresthesias, cramps, visual disturbances, "Loose" painful teeth	Barracuda, red snapper, grouper, amberjack	
Norovirus	24-48 hr	Epidemic watery diarrhea	Contaminated ice machines, shellfish, ready-to-eat foods	Nucleic acid amplification assays
Staphylococcal enterotoxins	2-8 hr	Prominent vomiting, no fever, duration less than 24 hr	Ham, poultry, pastries (cream-filled), mixed salads, egg salad	Identification of preformed toxin or isolation of 10^5 colony-forming-units of organism from food
Bacillus cereus				
Emetic form: short incubation	2-8 hr	Prominent vomiting, no fever, duration less than 48 hr	Fried rice, macaroni-and-cheese, vegetables, other ready-to-eat foods left at room temperature. Symptoms and rapidity of onset are due to presence of preformed toxin	Identification of preformed toxin or isolation of 10^5 colony-forming-units of organism from food
Diarrheal form: longer incubation	8-14 hr	Abdominal cramps, severe diarrhea, no fever, duration less than 48 hr	Fried rice, macaroni-and-cheese, vegetables, other ready-to-eat foods left at room temperature. Symptoms are due to in vivo toxin production	Identification of preformed toxin or isolation of 10^5 colony-forming-units of organism from food or stool
Clostridium perfringens	8-14 hr	Abdominal cramps, severe diarrhea, no fever, duration less than 48 hr	Meat, poultry, gravy	Identification of preformed toxin or isolation of 10^5 colony-forming-units of organism from food or stool
Enterotoxigenic *Escherichia coli* (ETEC)	12 hr to several days	Abdominal cramps, watery diarrhea may be prolonged up to 7 days	Incomplete data (rarely reported)	Identification of enterotoxin or isolation of organism from stool
Invasive *Escherichia coli*	12 hr to days	Prolonged febrile diarrhea and/or dysentery	Incomplete data (rarely reported)	Isolation of organism from stool
Vibrio cholerae	12 hr to days	Abdominal cramps, watery diarrhea (rice-water stools). May be prolonged up to 1 wk	Contaminated food and water (very rare in United states)	Isolation of organism from food or stool
Vibrio parahemolyticus	12 hr to days	Prolonged febrile diarrhea and/or dysentery	Seafood	Stool culture (or food culture)

Continued

TABLE 11.9 Foodborne Gastrointestinal Illnesses—cont'd

Cause	Incubation Period	Clinical Clues	Common Vehicle	Diagnosis
Shigella species	12 hr to days	Prolonged febrile diarrhea and/or dysentery	Fish, mixed salads	Stool culture (or food culture)
Campylobacter species	12 hr to days	Prolonged febrile diarrhea and/or dysentery	Unpasteurized milk, poultry or meat	Stool culture (or food culture)
Clostridium botulinum	12 hr to days	Diarrhea, constipation Guillain-Barré syndrome	Home-canned foods, fish, honey	Botulinum toxin in food, stool, and serum
Yersinia enterocolitica	Uncertain	Prolonged diarrhea and/or dysentery	Milk, pig intestine	Stool culture

*Potentially dangerous; observation in hospital often required.
Modified from Reilly BM. *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991:888.

immunodeficiency should be documented. Family history should be probed for the presence of gastrointestinal disorders or immunodeficiency.

◆ Physical Examination

Hydration status should be assessed. Growth parameters should be obtained and charted on appropriate age-matched growth charts. The physical examination should assess for signs of malnutrition, vitamin and micronutrient deficiency, and dermatologic manifestations of systemic diseases. Jaundice may suggest hemolysis or hepatic dysfunction. Signs of fat-soluble vitamin deficiency include bone deformities in vitamin D deficiency, dry scaly skin and Bitot spots in vitamin A deficiency, hyporeflexia or gait abnormalities in vitamin E deficiency, and bruises or bleeding in vitamin K deficiency. Joint examination may reveal arthritis associated with inflammatory bowel disease. Abdominal examination may reveal evidence suggestive of neuroendocrine tumors, and perianal examination may reveal evidence of inflammatory bowel disease (fistula, skin tags).

◆ Diagnostic Evaluation

The clinician should attempt to focus the diagnostic evaluation on only those conditions suggested by the history and physical examination. Invasive diagnostic procedures should be limited to those patients whose presentation contains red flags for serious disease (Table 11.10). Laboratory investigation should begin with microbiologic studies for bacteria and parasites in the stool. Acute infection with bacteria, such as *Yersinia*, *E. coli*, and *Salmonella* may develop into a chronic illness and can be detected by routine stool cultures and multiplex PCR assays. *C. difficile* testing should be performed, especially in the presence of risk factors. Antigen detection and PCR-based assays for *Giardia* and *Cryptosporidium* are more sensitive and specific than routine microscopy-based examinations and are indicated if these infections are suspected.

Except in the setting of neonatal-onset diarrhea, stool electrolytes and osmolality are of limited use. The differentiation of osmotic and secretory diarrhea is typically made by a trial of fasting and determining if there is improvement in the stool output: osmotic diarrhea improves or resolves upon fasting, whereas secretory diarrhea does not. **Stool-reducing substances** are positive in the setting of osmotic diarrhea secondary to carbohydrate malabsorption. In patients with osmotic diarrhea and negative reducing substances, it is essential to determine whether steatorrhea is present. If qualitative assays for fecal fat are negative, a more precise indication of steatorrhea may be obtained by quantifying fecal fat and calculating the coefficient of fat absorption, which requires a 72-hour collection of stool. Low fecal elastase suggests pancreatic insufficiency. Elevated levels of **stool alpha-1-antitrypsin (A1AT)** are suggestive of protein-losing enteropathy (PLE). Elevated **fecal calprotectin** or **fecal lactoferrin** are indicative of intestinal inflammation. The presence of fecal leukocytes or occult blood may indicate mucosal inflammation as well, though neither is sufficiently sensitive nor specific.

TABLE 11.10 Red Flags in the Evaluation of Diarrhea

Presence of blood in stools
Persistent right upper or right lower quadrant abdominal pain
Involuntary weight loss or growth failure
Delayed puberty
Presence of associated symptoms, such as unexplained fever, suggesting inflammatory arthritides or other systemic diseases
Nocturnal fecal urgency or diarrhea
Perirectal/perianal disease
Persistent dysphagia

Blood tests should include a complete blood count to evaluate for anemia and thrombocytosis, which may suggest blood loss and inflammation, respectively. In the presence of anemia, red blood cell indices may reveal a microcytosis potentially indicative of iron deficiency or a macrocytosis suggestive of vitamin B_{12} or folate deficiency. A normocytic anemia may be seen in chronic inflammatory diseases. White blood cell count and differential and quantification of immunoglobulins A, G, and M screen for immune disorders. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) support inflammation but are nonspecific. Low albumin could be indicative of a chronic inflammatory process or PLE. Elevated anti-tissue transglutaminase immunoglobulin A (IgA) antibody is sensitive and specific for celiac disease, but a low total serum IgA level may result in a false-negative test. Levels of the fat-soluble vitamins A, 25-OH vitamin D, vitamin E, and vitamin K (reflected by prothrombin time) may be measured if fat malabsorption is suspected.

The algorithmic approach to evaluating chronic diarrhea is depicted in Fig. 11.2*A* and *B* and is enumerated in Table 11.11.

Disorders of Carbohydrate Malabsorption

The brush border epithelium of the small bowel contains enzymes necessary for carbohydrate digestion. These enzymes hydrolyze disaccharides and oligosaccharides into monosaccharides that are then absorbed by transporters on the luminal surface of enterocytes.

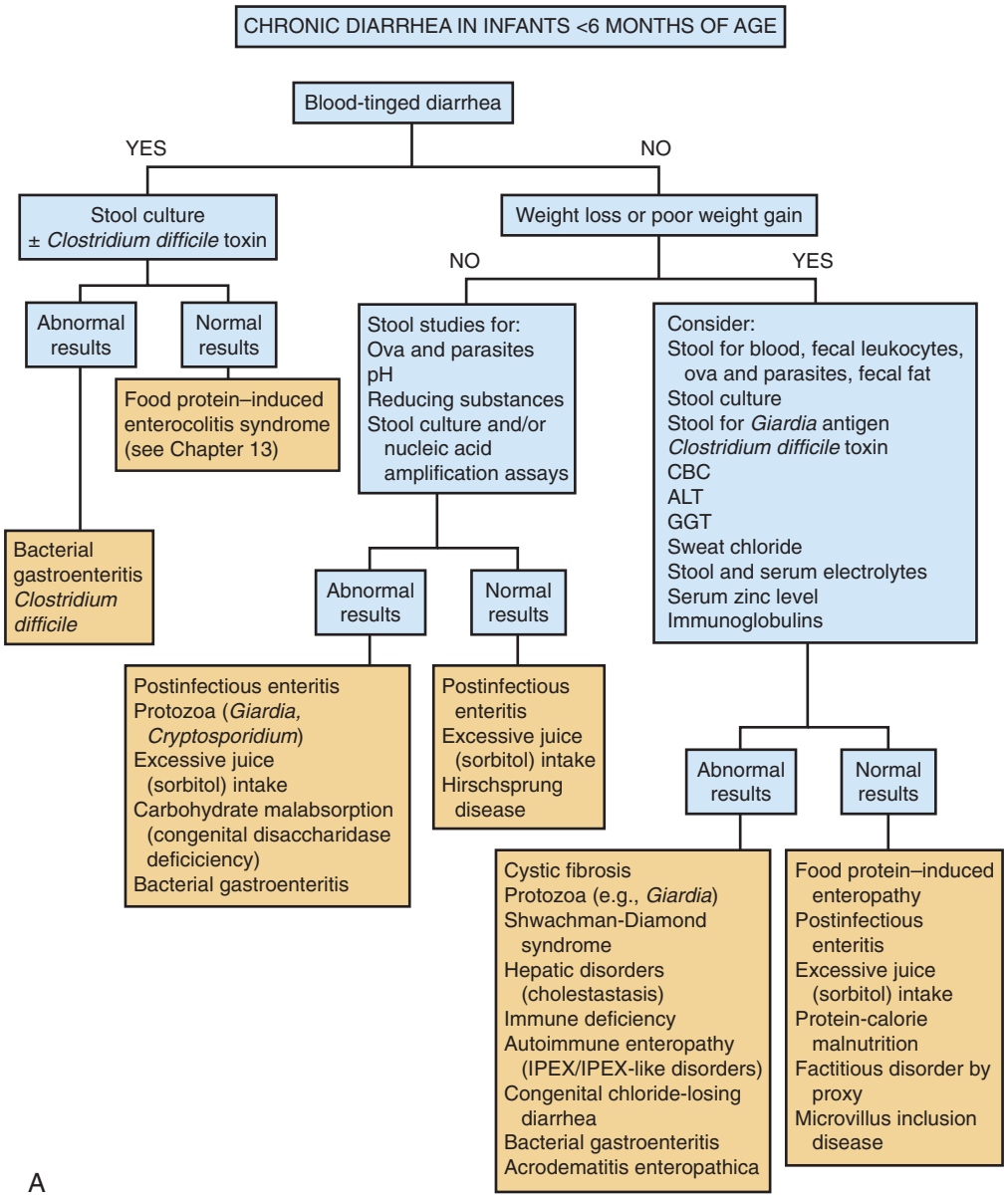
Carbohydrate malabsorption is secondary to either deficiency of a particular enzyme (e.g., congenital sucrase-isomaltase deficiency) or an abnormality in a transport protein involved with the absorption of monosaccharides (e.g., glucose-galactose malabsorption). The onset of various carbohydrate malabsorption syndromes can vary based on the timing of the introduction of particular carbohydrates (Table 11.12).

Patients with carbohydrate malabsorption disorders present with severe watery diarrhea, which results from osmotic action exerted by the malabsorbed carbohydrate in the intestinal lumen. Colonic bacteria ferment the malabsorbed sugars, which generates a mixture of gases (e.g., hydrogen, methane, and carbon dioxide) and short-chain fatty acids. These gases form the basis of carbohydrate-specific breath hydrogen testing, which is often used in diagnosis. The stools become acidified to a pH of less than 7, which can lead to diaper dermatitis.

Disaccharidase Deficiency

Congenital sucrase-isomaltase deficiency (CSID). CSID is an inherited deficiency of the ability to hydrolyze sucrose, maltose, and starch. Exposure to these products leads to osmotic diarrhea, pain, bloating, abdominal distention, and at times, chronic malnutrition and failure to thrive. The sucrase-isomaltase gene is located on chromosome 3 (3q25.2-q26.2) and more than 25 mutations in the gene have been identified. These mutations result in a variety of defects in the structure and function of the enzyme, including isolated deficiencies in sucrase activity or isomaltase activity. This genetic heterogeneity results in phenotypic variability ranging from completely absent to low-residual sucrase activity, and from completely absent to normal isomaltase activity. Because sucrase-isomaltase is responsible for up to 80% of the maltase activity in the brush border, maltase activity is significantly reduced in almost all cases.

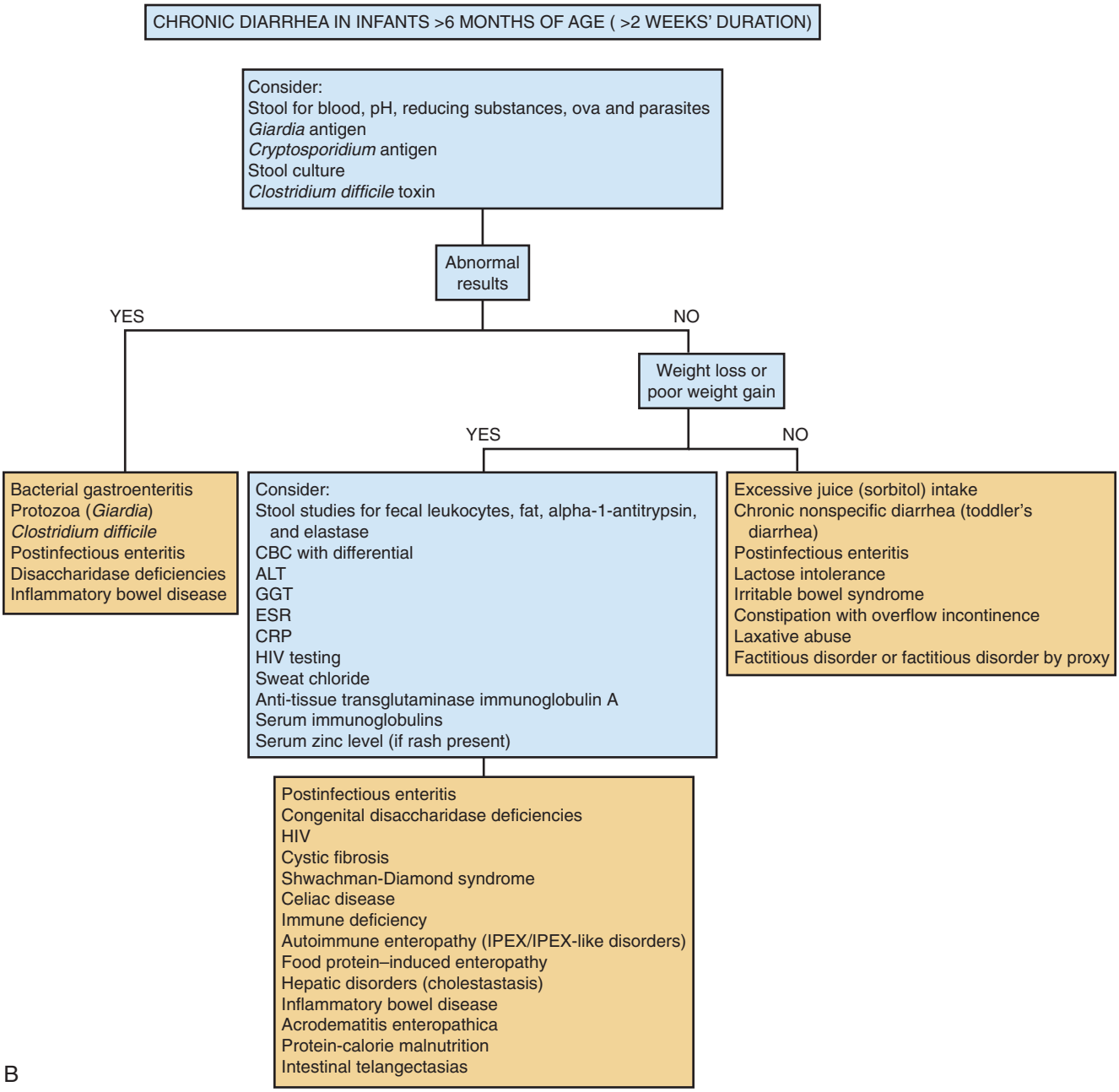
The exact prevalence of CSID is unclear, although rates are as high as 10% in the Greenland Inuit population, 7% in Canadians of native ancestry, and about 3% in Alaskans of native ancestry. Estimates of the prevalence of CSID in other North American and European populations generally range from 1 in 500 to 1 in 2000 among non-Hispanic



A

FIGURE 11.2 *A,* The algorithmic approach to chronic diarrhea in infants <6 months of age. ALT, alanine aminotransferase; CBC, complete blood count; GGT, gamma-glutamyl transferase; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked.

Continued



B

FIGURE 11.2, cont'd *B,* The algorithmic approach to chronic diarrhea in children >6 months of age. ALT, alanine aminotransferase; CBC, complete blood count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GGT, gamma-glutamyl transferase; HIV, human immunodeficiency virus; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked. (Modified from Pomeranz AJ, Sabnis S, Busey SL, Kliegman RM, eds. *Pediatric Decision-Making Strategies.* 2 ed. Philadelphia: Elsevier; 2016:87-89.)

whites, with a lower prevalence in African Americans and whites of Hispanic descent.

The classic presentation of CSID is severe watery diarrhea, failure to thrive, irritability, and diaper dermatitis in a 9- to 18-month-old infant who has been exposed to sucrose and starch in the form of fruit juices, fruit purees, and starch-laden foods such as crackers and cookies (see Table 11.4). Intrinsic factors that contribute to the severity of presentation during infancy include the shorter length of the colon and a decreased capacity for colonic reabsorption of fluid and electrolytes, more rapid small intestinal transit, a high carbohydrate diet, and lower levels of amylase prior to 2 years of age. Some patients with milder sucrase deficiency may improve with age as their colonic bacteria develop an increased capacity to ferment residual sucrose and the intestinal tract develops an increased capacity for reabsorption. Patients may be misdiagnosed as having food allergies or irritable bowel syndrome, or may remain undiagnosed. Symptoms may abate with the restriction of carbohydrate in the diet or with the use of enteral sucrase enzyme supplements.

Diagnosis typically requires endoscopy for histologic examination of small bowel morphology and measurement of disaccharidase levels on biopsy specimens. Diagnosis requires the following:

1. Normal small bowel morphology
2. Absent or markedly reduced sucrase activity
3. Isomaltase activity varying from absent to full activity

TABLE 11.11 Diagnostic Studies in the Evaluation of Chronic Diarrhea

Initial Studies

Stool examination for blood, leukocytes, reducing substances, and *Clostridium difficile* toxin; stool examination for ova and parasites and cultures for infectious bacterial pathogens

Complete blood count

Serum electrolytes, blood urea nitrogen, creatinine, calcium, phosphorus, albumin, total protein

Urinalysis and culture

Stool electrolytes

Second-Phase Studies

Sweat chloride test

Breath analysis

D-Xylose test

Serum carotene, folate, vitamin B_{12}, and iron levels

Fecal alpha-1-antitrypsin level

Fecal fat studies or coefficient of fat absorption studies

Fatty test meal, Lundh test meal

Third-Phase Studies

Fat-soluble vitamin levels: A, 25-hydroxy D, and E

Contrast radiographic studies: upper gastrointestinal series or barium enema

Small intestinal biopsy for histology and mucosal enzyme determination

Bentiromide excretion test

Specialized Studies

Schilling test

Serum/urine bile acid determination

Endoscopic retrograde pancreatography

Provocative pancreatic secretion testing

From Wyllie R, Hyams JS, eds. *Pediatric Gastrointestinal Disease*. 2nd ed. Philadelphia: WB Saunders; 1999:283.

TABLE 11.12 Typical Age of Presentation of Carbohydrate Malabsorption Syndromes

Carbohydrate Malabsorption Syndrome	Age of Symptom Onset
Congenital glucose-galactose malabsorption Congenital lactase deficiency	Neonatal period
Sucrase-isomaltase deficiency Glucoamylase deficiency	Weaning age
Primary lactase deficiency	Uncommon before 2 or 3 yr of age Around 5 yr of age in Asians, Hispanics, and African American populations Over 5 yr of age, more typically in adolescence in Caucasians of European decent

4. Reduced maltase activity
5. Normal lactase activity, or in the setting of reduced lactase, a sucrase:lactase ratio of <1.0.

Other less invasive methods of diagnosis include sucrose breath hydrogen quantification and differential urinary disaccharide assessment; however, both of these modalities are associated with high false-positive and false-negative rates. Furthermore, differential urinary disaccharide testing requires a 10-hour urine collection specimen, which is often impractical in infants and younger children.

Maltase-glucoamylase deficiency. Maltase-glucoamylase is a brush border hydrolase that serves as an alternate pathway for starch digestion that complements sucrase-isomaltase activity. Congenital maltase-glucoamylase deficiency is rare, with only several cases described in the literature. Genetically, maltase-glucoamylase shares approximately 59% of its sequence with sucrase-isomaltase, and the enzyme has two catalytic sites that are identical to those of sucrase-isomaltase. Symptoms are similar to those seen in CSID. Diagnosis requires the demonstration of reduced glucoamylase activity in the setting of normal small bowel histology and normal pancreatic amylase activity.

Congenital glucose-galactose malabsorption (CGGM). Congenital glucose-galactose malabsorption results from defective sodium-coupled transport of glucose and galactose into enterocytes. It is a rare autosomal recessive disorder that results from mutations in the sodium-glucose cotransporter gene *SGLT1* located on chromosome 22q12.3. CGGM presents as a neonatal-onset profuse, watery diarrhea that ceases immediately following the elimination of glucose and galactose sources from the diet. Symptoms recur if the patient is fed formula containing either of these carbohydrates, including polymers such as sucrose and lactose. The disorder may lead to dehydration and electrolyte abnormalities, both of which can become life-threatening, and patients may be hypoglycemic. Stool-reducing substances are positive secondary to the presence of glucose in the stools. Intestinal morphology is normal. The diagnosis can be further established by an abnormal glucose breath hydrogen test and *SGLT1* sequencing, although neither is required to confirm the diagnosis.

Congenital lactase deficiency. A rare autosomal recessive disorder leading to very low or complete absence of brush border lactase-phlorizin hydrolase activity, **congenital lactase deficiency** usually presents with diarrhea starting soon after the introduction of breast milk or any lactose-containing formula. Most infants manifest within the first 10 days of life. Unless the disorder is recognized and treated quickly, the condition is life-threatening secondary to dehydration and electrolyte abnormalities. Small bowel biopsies reveal normal histology although low or completely absent lactase concentrations. A presumptive diagnosis can be made if osmotic diarrhea in a neonate resolves by introducing lactose-free formula.

Primary lactase deficiency (lactose intolerance). Approximately 65% of the world's population has primary lactase deficiency, although prevalence varies by ethnicity. While primary lactase deficiency is nearly universal in Asian and Native American populations and is as high as 80% in Hispanic, African American, and Ashkenazi Jewish populations, as few as 2% of individuals of northern European ancestry are affected. Age of onset varies by ethnicity as well. Approximately 20% of Hispanic, Asian, and African American children younger than 5 years of age are affected, whereas white children typically do not develop symptoms of lactose intolerance until after 5 years of age. Children with clinical signs of lactose intolerance at an earlier age than would be typical for their ethnicity may warrant an evaluation for an alternate cause.

Symptoms typically develop insidiously over the course of many years, with most affected individuals experiencing onset of symptoms

in late adolescence or adulthood. Within 30 minutes to 2 hours of ingesting lactose, patients develop abdominal cramping and distention, foul-smelling flatulence, nausea, and diarrhea. While the severity of symptoms is directly correlated with the quantity of ingested lactose, each individual exhibits a unique dose threshold beyond which he or she becomes symptomatic.

Diagnosis is suggested historically. When lactose intolerance is suspected, a trial of a lactose-free diet can assist in confirming the diagnosis. Patients must be sure to eliminate all sources of lactose, including some that may be hidden (Table 11.13). Generally, a 2-week trial of a strict lactose-free diet producing resolution of symptoms, followed by a subsequent reintroduction of dairy foods resulting in recurrence of symptoms is diagnostic. In subtler cases, hydrogen breath testing is the least invasive and most helpful test to diagnose lactose malabsorption.

Secondary lactase deficiency. Secondary lactase deficiency develops when an inflammatory process, such as a viral infection, damages the brush border epithelium and leads to the loss of the lactase-containing epithelial cells from the tips of the villi. The immature epithelial cells that replace these are often lactase deficient, leading to lactose malabsorption. Secondary lactase deficiency in most children with acute gastroenteritis is rarely clinically significant. *Most affected children can safely continue breast milk or standard lactose-containing formula without any significant effects, although infants under 3 months of age may develop clinically significant symptoms.* Giardiasis, cryptosporidiosis, and other parasites that infect the proximal small intestine often lead to lactose malabsorption from direct injury to the epithelial cells by the parasite. Secondary lactase deficiency with clinical signs of lactose intolerance can be seen in celiac disease, Crohn disease, and immune-related and other enteropathies and should be considered if children with these diagnoses have symptoms of lactose intolerance.

TABLE 11.13 Hidden Sources of Lactose

- Bread and other baked goods
- Waffles, pancakes, biscuits, cookies, and the mixes to make them
- Processed breakfast foods such as doughnuts, frozen waffles and pancakes, toaster pastries, and sweet rolls
- Processed breakfast cereals
- Instant potatoes, soups, and breakfast drinks
- Potato chips, corn chips, and other processed snacks
- Processed meats such as bacon, sausage, hot dogs, and lunch meats
- Margarine
- Salad dressings
- Liquid and powdered milk-based meal replacements
- Protein powders and bars
- Candies
- Nondairy liquid and powdered coffee creamers
- Nondairy whipped toppings
- Certain medications

If a food label includes any of the following words, the product contains lactose:

- Milk
- Lactose
- Whey
- Curds
- Milk by-products
- Dry milk solids
- Nonfat dry milk powder

From *National Digestive Diseases Information Clearinghouse*. Lactose intolerance. <http://digestive.niddk.nih.gov/ddiseases/pubs/lactoseintolerance>; 2015.

Diagnostic evaluation should be directed toward these entities when secondary lactase deficiency is suspected and an infectious etiology is not found.

Severe malnutrition can also produce secondary lactose intolerance via small bowel atrophy. Most infants and children with malabsorption attributable to malnutrition are able to continue to tolerate dietary carbohydrates, including lactose. However, the World Health Organization recommends avoidance of lactose in children with persistent postinfectious diarrhea lasting more than 14 days, if they fail a dietary trial of milk or yogurt. Treatment of secondary lactase deficiency and lactose malabsorption attributable to an underlying condition generally does not require elimination of lactose from the diet but, rather, treatment of the underlying condition.

Table 11.14 lists additional important causes of chronic neonatal or infantile diarrhea.

CHRONIC NONSPECIFIC DIARRHEA

Chronic nonspecific diarrhea, also known as **functional** or **toddler's diarrhea**, typically affects children between 1 and 3 years of age and is characterized by the passage of several watery and unformed stools each day. Stools are typically relatively well formed in the morning but become looser as the day progresses. The stools often appear to contain undigested vegetable matter but lack blood, mucus, or excessive fat. Children with functional diarrhea, if offered an unrestricted and age-appropriate diet, gain weight normally. However, in an attempt to treat the diarrhea, many children are placed on restrictive diets that may lack dairy, fats, and occasionally starches; such restrictions lead to failure to thrive. Rome-III diagnostic criteria specify that all of the following must be present:

1. Daily painless, recurrent passage of 3 or more large, unformed stools
2. Symptoms that last more than 4 weeks
3. Onset of symptoms that begins between 6 and 36 months of age
4. Passage of stools that occurs during waking hours
5. There is no failure-to-thrive if caloric intake is adequate

Chronic nonspecific diarrhea is thought to be a variant of irritable bowel syndrome (IBS), and a family history of IBS is common. The pathophysiology may involve abnormal intestinal motility with decreased mouth-to-anus transit time. Excessive fruit juice intake may also contribute to the diarrhea by overwhelming the carbohydrate absorptive capacity of the gut. Chronic nonspecific diarrhea is a benign and self-limited condition that usually resolves without intervention by 3-4 years of age. Parents should be reassured and encouraged to place the child on a regular, unrestricted diet to provide adequate calories. The diarrhea often improves with removal of prior dietary restrictions and by limiting fruit juice intake. Some patients may improve with increasing the fat content of the diet (e.g., switching from low fat milk to whole milk), which can slow gastrointestinal transit time.

Small Intestinal Bacterial Overgrowth (SIBO)

The normal small intestine is colonized with relatively few bacteria, typically less than 10^4 organisms/mL. Various conditions such as short bowel syndrome, malnutrition, pseudo-obstruction, bowel strictures, and achlorhydria from medications such as proton pump inhibitors may result in overgrowth of aerobic and anaerobic bacteria in the small bowel. Symptoms of abdominal pain, bloating, abdominal distention, and diarrhea arise as bile acids are deconjugated and fatty acids are hydroxylated by bacteria, leading to an osmotic diarrhea. The diagnosis can be made by breath hydrogen testing showing early and late rise in breath hydrogen after ingestion of lactulose. Quantitative jejunal aspirate cultures showing greater than 10^5 organisms/mL

TABLE 11.14 Disorders Leading to Early-Onset Chronic Diarrhea

Disorder	Pathophysiology and Known Genetic Associations	Characteristic Signs and Symptoms	Diagnostic Evaluation
Disorders of Absorption and Transport of Nutrients and Electrolytes			
Congenital chloride diarrhea	AR, *SLC26A3* Alterations in the intestinal Cl^-/HCO_3^- exchanger	Profuse secretory diarrhea Acidic stools Hypochloremic, hypokalemic metabolic alkalosis Fecal chloride concentration >90 mmol/L	Clinical features Molecular genetic testing
Congenital sodium diarrhea	AR, *SPINT2* Impaired jejunal Na^+/H^+ exchange due to the reduced activity of serine peptidase inhibitor, Kunitz type 2	Profuse watery secretory diarrhea High fecal sodium losses Alkaline stools Hyponatremic, hypokalemic metabolic acidosis	Clinical features Molecular genetic testing
Acrodermatitis enteropathica	AR, *SLC39A4* Impaired duodenal and jejunal zinc transport	Presents around the time of weaning from breast milk (0-9 mo of age in formula-fed infants) Very severe perioral and perianal rash Improvement in rash within 3 wk of oral zinc supplementation	Clinical features Molecular genetic testing
Lysininuric protein intolerance	AR, *SLC7A7* Impaired amino acid transport due to altered light chain of the solute carrier family 7, member 7	Presents around the time of weaning Recurrent vomiting with episodes of diarrhea Episodes of stupor and coma after a protein-rich meal Poor feeding Aversion to protein-rich food Failure to thrive Enlargement of the liver and spleen Muscular hypotonia	Clinical features Elevated ammonia after a protein-rich meal Abnormal urine and serum amino acid profile Molecular genetic testing
Chylomicron retention disease	AR, *SAR1B* Impaired chylomicron transport within enterocytes owing to the altered activity of a small GTPase	Vomiting, osmotic diarrhea, and failure to thrive	Low cholesterol levels and normal triglycerides Low fat-soluble vitamins, in particular vitamin E Endoscopy: lipid accumulation in enterocytes
Abetalipoproteinemia	AR, *MTTP* Impaired microsomal triglyceride transfer protein activity, lower synthesis of VLDL and reduced absorption of lipids	Presents in the first few months of life with FTT, diarrhea, and steatorrhea Fat-soluble vitamin deficiency Hypotonia, abnormal gait Retinitis pigmentosa	Low cholesterol, low triglycerides, absent apolipoprotein B Acanthosis of red blood cells
Primary bile acid diarrhea	AR, *SLC10A2* Reduced enterohepatic reabsorption of bile acids by solute carrier family 10, member 2	Presents in the first few months of life with secretory diarrhea and failure to thrive Diarrhea worse with fatty foods	SeHCAT test with a selenium-labeled bile acid. Retention <10% after 7 days is diagnostic Stool bile acid measurement
Familial diarrhea syndrome	AD, *GUCY2C* Increased activity of guanylate cyclase 2C enhances levels of cGMP, hyperactivating intestinal cystic fibrosis transmembrane conductance regulator	Early-onset chronic secretory diarrhea, abdominal distention and bloating Subset of patients with inflammatory bowel disease and irritable bowel syndrome	Molecular genetic testing
Diarrhea-associated *DGAT1* mutation	AR, *DGAT1* Impaired activity of diacylglycerol O-acyltransferase	Infantile-onset chronic diarrhea and protein-losing enteropathy	Molecular genetic testing
Defects in Enterocyte Structure			
Congenital tufting enteropathy	AR: *EPCAM* (defective activity of epithelial cell adhesion molecule causes altered cell–cell adhesion) AR: *SPINT2* (impaired activity of serine peptidase inhibitor, Kunitz type 2, which is involved in epithelial regeneration)	Presents in the first few months of life with chronic watery diarrhea and impaired growth Some patients have superficial punctate keratitis and choanal atresia	Endoscopy: blunted villi and characteristic focal epithelial "tufts" composed of closely packed enterocytes with rounding of the apical plasma membrane that results in a teardrop configuration of the affected epithelial cell Molecular genetic testing

Continued

TABLE 11.14 Disorders Leading to Early-Onset Chronic Diarrhea—cont'd

Disorder	Pathophysiology and Known Genetic Associations	Characteristic Signs and Symptoms	Diagnostic Evaluation
Microvillus inclusion disease	AR: *MYO5B* (reduced activity of myosin 5B causes abnormal recycling of endosomes) AR: *STX3* (impaired activity of syntaxin 3, which is involved in membrane fusion of apical vesicles)	Neonatal-onset chronic unremitting diarrhea Some develop cholestatic liver disease that worsens after intestinal transplantation	On higher magnification, the surface enterocytes are focally piled-up and disorganized, with extensive vacuolization of the apical cytoplasm and loss of brush border definition On periodic acid–Schiff (PAS) staining of the apical brush border is poorly defined and there is PAS-positive staining of the apical cytoplasm of enterocytes Molecular genetic testing
Trichohepatoenteric syndrome (syndromic diarrhea)	AR: *TTC37* (impaired synthesis or localization of brush border transporters due to the reduced activity of tetratricopeptide repeat domain 37) AR: *SKIV2L* (unknown mechanism due to the impaired activity of SKI2W helicase)	Chronic infantile diarrhea, facial dysmorphism, and hair abnormalities. Other associated symptoms: IUGR, immunodeficiency, skin abnormalities, liver disease, congenital cardiac defects, and platelet anomalies	Moderate to severe villus atrophy with inconstant infiltration of mononuclear cells Molecular genetic testing
Neuro-Enteroendocrine Diarrhea			
Enteric anendocrinosis	AR, *NEUROG3* Altered neurogenin-3, which regulates the development of gut epithelial cells into endocrine cells	Severe secretory diarrhea in infancy Insulin-dependent diabetes mellitus in childhood	Molecular genetic testing
Mitchell-Riley syndrome	AR, *RFX6* Reduced activity of regulatory factor X6 involved in pancreatic morphogenesis and development	Malabsorptive diarrhea Duodenal atresia and biliary abnormalities Neonatal diabetes mellitus	Molecular genetic testing
X-linked lissencephaly and mental retardation	X-linked, *ARX* Impaired activity of aristaless related homeobox transcriptional factor, which regulates enteroendocrine cell development	Mental retardation, seizures, lissencephaly, abnormal genitalia Occasionally congenital diarrhea	Molecular genetic testing
Defects in Intestinal Immune-Related Homeostasis			
Eosinophilic gastroenteritis and colitis	Various causes, including food allergies (cow's milk protein), medications, infections (e.g., *Helicobacter pylori*), immune dysregulation disorders, and idiopathic	Diarrhea, blood in stools, low albumin, anemia	Endoscopic mucosal biopsies showing more than normal eosinophilic infiltration
Early-onset enteropathy with colitis	AR, mutations of IL-10 or its receptors, IL10RA and IL10RB. Altered IL-10 or its receptor subunits involved in the control of intestinal microbial stimulations	Enterocolitis with ulcerative lesions in the perianal area and in the intestinal mucosa. Most present during the first 6 mo of life Folliculitis	Lack of STAT3 phosphorylation in response to IL-10 Molecular genetic testing
IPEX syndrome	X-linked, *FOXP3* mutation Impaired activity of forkhead box P3 involved in the development of $CD4^+CD25^+$ regulatory T cells	Severe neonatal-onset inflammatory diarrhea Eczematous skin rash Endocrinopathy (infantile diabetes mellitus) Peripheral eosinophilia and increased serum IgE Autoimmune hemolytic anemia Autoimmune thrombocytopenia and neutropenia	Flow cytometry might show decreased peripheral FOXP3+ regulatory T cells Molecular genetic testing

TABLE 11.14 Disorders Leading to Early-Onset Chronic Diarrhea—cont'd

Disorder	Pathophysiology and Known Genetic Associations	Characteristic Signs and Symptoms	Diagnostic Evaluation
IPEX-like disorders	AR: *Il2RA* (impaired synthesis of α chain of IL-2 receptor on regulatory T cells) AR: *STAT5B* (impaired activity of *STAT5B* involved in IL-2 signaling in regulatory T cells) AD: *STAT1* (enhanced or reduced activity of *STAT1* causes the reprogramming of regulatory T cells into Th1-like cells) AR: *ITCH* (altered activity of itchy E3 ubiquitin protein ligase implicated in the development of regulatory T cells) AR: *LRBA* (impaired activity of lipopolysaccharide-responsive beige-like anchor protein stimulates apoptosis of regulatory T cells)	Presentation similar to IPEX	Molecular genetic testing
Pancreatic Insufficiency			
Cystic fibrosis	AR, Mutations involving CFTR. More than 1300 mutations have been described. Most common is ΔF508 mutation	Meconium ileus in neonate Megacolon Chronic diarrhea from pancreatic insufficiency starting from 1 mo of age Failure to thrive Conjugated hyperbilirubinemia	Low stool elastase High sweat chloride (>60 mEq/L) Newborn screening Molecular genetic testing
Shwachman-Diamond syndrome	AR *SBDS* gene in over 90%	Chronic diarrhea from pancreatic insufficiency Bone marrow failure Skeletal changes Pancreatic lipomatosis on diagnostic imaging (ultrasound or computed tomography)	Clinical features Molecular genetic testing
Johanson-Blizzard syndrome	AR *UBRI* gene	Chronic diarrhea from pancreatic insufficiency Dysmorphic features: aplastic alae nasi, extension of the hairline to the forehead with upswept frontal hair, low-set ears, large anterior fontanel, micrognathia, thin lips, microcephaly, aplasia cutis (patchy distribution of hair with areas of alopecia), dental anomalies, poor growth, and anorectal anomalies (mainly imperforate anus)	Clinical features Molecular genetic testing
Pearson syndrome	Sporadic: caused by de novo single, large deletions of mtDNA, which can range from 1000 to 10,000 nucleotides	Chronic diarrhea from pancreatic insufficiency Sideroblastic anemia, variable neutropenia, thrombocytopenia, and vacuolization of bone marrow precursors Lactic acidosis and liver failure	Clinical features Molecular genetic testing

AD, autosomal dominant; AR, autosomal recessive; cGMP, cyclic guanosine monophosphate; IUGR, intrauterine growth restriction; IgE, immunoglobulin E; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; SeHCAT, selenium homocholic acid taurine; STAT3, signal transducer and activator of transcription 3; IL, interleukin; mtDNA, mitochondrial DNA; VLDL, very low density lipoprotein.

are suggestive of SIBO, although established cutoff ranges and specificity are imperfect.

Irritable Bowel Syndrome (IBS)

Irritable bowel syndrome is characterized by recurrent abdominal pain and altered bowel habits that typically presents in adolescence. Symptoms include abnormal stool frequency (either 4 or more stools per day, or 2 or fewer stools per week), abnormal stool form (either loose and watery or lumpy and hard), abnormal passage of stool (e.g., straining, urgency, feeling of incomplete evacuation), the passage of mucus, and bloating or distention. Diagnosis requires that patients have a normal physical examination and growth curve and meet both of the following criteria at least once per week for at least 2 months before diagnosis:

1. Abdominal discomfort (an uncomfortable sensation not described as pain) or pain associated with 2 or more of the following at least 25% of the time:
    a. Improvement with defecation
    b. Onset associated with a change in frequency of stool
    c. Onset associated with a change in form (appearance) of stool

2. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms

The etiology and pathogenesis of irritable bowel syndrome are not well understood. Visceral hypersensitivity has been well documented in children with IBS. Genetic predisposition, early stressful events, and ineffective coping mechanisms are compounding factors. Additional mechanisms may include infection, inflammation, intestinal trauma, allergy, and disordered gut motility.

Celiac Disease

Celiac disease is an immune-mediated systemic disorder elicited by exposure to gluten and related proteins in genetically susceptible individuals. Clinical presentations vary, although the hallmarks of celiac disease include enteropathy and the presence of disease-specific antibodies. Prevalence is as high as 1% in Western nations, with most affected individuals presenting in childhood. A genetic predisposition is suggested by familial aggregation and the high concordance in monozygotic twins, which approaches 100%. A strong association with human leukocyte antigen (HLA)-DQ2.5, and to a lesser degree HLA-DQ8, has been identified. A family or personal history of autoimmune disease and certain genetic conditions confers a higher risk (Table 11.15).

The pathogenesis of celiac disease first involves exposure to **gliadin**, a protein component of **wheat gluten,** or structurally related storage proteins (**prolamines**) found in rye and barley. Altered processing by intraluminal enzymes, changes in intestinal permeability, and activation of the innate immune response precede the development of an adaptive immune response that results in systemic autoimmunity and an inflammatory enteropathy characterized by **villous atrophy,** elongated crypts, and intraepithelial lymphocytosis.

Celiac disease symptoms are protean and reflect its systemic nature. The age of onset is variable and a high degree of suspicion is needed. Manifestations include recurrent abdominal pain, nausea and vomiting, iron deficiency with or without anemia, short stature, aphthous stomatitis, chronic fatigue, arthritis, raised aminotransferase levels, and reduced bone mineral density. Rare manifestations include ataxia, **dermatitis herpetiformis**, which is a blistering rash with pathognomonic cutaneous IgA deposits, and **celiac crisis**, which is a rare life-threatening syndrome mostly observed in children, that is characterized by severe diarrhea, hypoproteinemia, and metabolic and electrolyte imbalances. The classic presentation of a toddler with chronic diarrhea, abdominal distention, and failure to thrive is uncommon. Most patients are identified via serologic screening in the context of a strong family history or other risk factors.

Serological tests are the cornerstone of screening for celiac disease in patients with risk factors or a suggestive history (Table 11.16). Establishing the diagnosis is dependent on the levels of disease-specific antibodies detected. Total serum IgA should be obtained to exclude IgA deficiency. If total serum IgA is normal and anti-tissue transglutaminase IgA antibodies are negative, celiac disease is unlikely. Patients with positive anti-tissue transglutaminase IgA antibodies that are less than 10 times the upper limit of normal should undergo upper endoscopy with multiple biopsies. If biopsies demonstrate total or partial villous atrophy, elongated crypts, and increased intraepithelial lymphocytes (>25 lymphocytes/100 enterocytes), the diagnosis is confirmed. Patients with positive anti-tissue transglutaminase IgA antibodies that are greater than or equal to 10 times the upper limit of normal should have anti-endomysial IgA antibodies and HLA testing performed. If the patient is positive for anti-endomysial IgA antibodies and is positive for DQ2 or DQ8 HLA testing, the diagnosis is confirmed; if either or both are negative, the patient should undergo biopsy.

Patients with celiac disease experience relief in their symptoms when placed on a strict gluten-free diet. Complications associated with untreated celiac disease include osteoporosis, impaired splenic function, neurologic disorders, infertility or recurrent abortion, ulcerative jejunoileitis, and cancer. Enteropathy-associated T-cell lymphoma and adenocarcinoma of the jejunum are rare complications of celiac disease. **Refractory celiac disease** is diagnosed when there are persistent or recurrent malabsorptive symptoms and signs of villous atrophy on biopsy despite strict adherence to a gluten-free diet for more than 12 months. Refractory celiac disease can be classified as **type 1** (characterized by the presence of normal intraepithelial lymphocytes), or **type 2** (characterized by abnormal intraepithelial lymphocytes; clonal intraepithelial lymphocytes lacking surface markers CD3, CD8, and T-cell receptors; or both). Type 2 refractory celiac disease is associated with a higher risk of ulcerative jejunoileitis and lymphoma.

TABLE 11.15 Conditions Whose Presence Confers a Higher Risk of Celiac Disease

Condition	Incidence of Celiac Disease (%)
First-degree relative with celiac disease	2-20
Type 1 diabetes mellitus	3-12
Juvenile idiopathic arthritis	1.5-2.5
Down syndrome	0.3-5.5
Turner syndrome	6.5
Williams syndrome	9.5
IgA nephropathy	4
IgA deficiency	3
Autoimmune thyroid disease	3
Autoimmune liver disease	13.5

TABLE 11.16 Serologic Tests for Celiac Disease

Test	Sensitivity (Percent)	Specificity (Percent)	Comments
Anti-tissue transglutaminase IgA	>95 (73-100)	>95 (77-100)	Recommended screening test
Anti-tissue transglutaminase IgG	Widely variable (12.6-99.3)	Widely variable (86.3-100)	Useful in patients with IgA deficiency
Anti-endomysial antibody IgA	>90.0 (82.6-100)	98.2 (94.7-100)	Useful in patients with an uncertain diagnosis. Expensive.
Anti-deamidated gliadin peptide IgG	>90.0 (80.1-98.6)	>90.0 (86.0-96.9)	Useful in patients with IgA deficiency and young children

IgA, immunoglobulin A; IgG, immunoglobulin G.

Inflammatory Bowel Disease (IBD)

Inflammatory bowel disease is divided broadly into **ulcerative colitis** and **Crohn disease**, idiopathic systemic chronic inflammatory diseases whose primary symptoms are related to relapsing gastrointestinal tract inflammation. Common signs and symptoms include diarrhea, abdominal pain, blood in the stools, and nutritional compromise. Ulcerative colitis consists of mucosal inflammation restricted to the colon, while Crohn disease consists of **transmural inflammation** that affects all layers of the intestinal wall and may involve any portion of the gastrointestinal tract from the mouth to the anus. Ulcerative colitis involves the colon in a continuous fashion, typically starting in the rectum and extending proximally to variable degrees. Crohn disease is characterized by **skip lesions**, in which there are areas of normal-appearing mucosa interspersed with inflammatory lesions.

The prevalence of ulcerative colitis is as high as 246 per 100,000 persons, and the prevalence of Crohn disease is as high as 199 per 100,000 persons. Approximately 25% of all IBD is diagnosed in children and adolescents, although presentation prior to 6 years of age is rare.

Clinical presentation. Up to 80% of children with Crohn disease will present with diarrhea. Stool may contain microscopic blood, although may not be grossly bloody, especially in the absence of significant left-sided colonic disease. Diarrhea is more common in colonic disease and may be absent altogether in cases of isolated small bowel inflammation. In ulcerative colitis, diarrhea is a more consistent presenting feature, often insidious in its development but eventually progressing to hematochezia. Nocturnal diarrhea with urgency may be a sign of left-sided colonic inflammation in both entities. Gastrointestinal and extraintestinal manifestations otherwise vary between Crohn disease and ulcerative colitis (Table 11.17). Extraintestinal manifestations are present in up to 23% of children at diagnosis, with a higher frequency in those over 6 years of age.

Physical examination should establish nutritional status and include an assessment of growth parameters, including the review of previous growth charts. Pubertal status should also be recorded. Oral cavity examination should look for aphthous ulcers that are present in approximately 10% of IBD patients (more commonly in Crohn disease). An eye examination should look for **episcleritis**, painful inflammation of the outer layer of the sclera, and patients with known IBD should be followed by an ophthalmologist to assess for **uveitis** and **keratopathy**. A detailed abdominal examination should document abdominal distention, mass, tenderness and hyper- or hypoactive bowel sounds. Particular attention should be paid to assessing the perianal region for any abscesses or fistulas. Skin examination should look for **erythema nodosum**, painful raised red lesions about 1-3 cm in diameter typically found on the shins; **pyoderma gangrenosum**, a severe ulcerating rash; and psoriatic lesions. Two clinical features suggest a diagnosis of Crohn disease over ulcerative colitis: the presence of perianal disease and the presence of structuring and fistulizing disease of the bowel. No other systemic or extraintestinal manifestations reliably suggest one diagnosis over the other (Table 11.18).

Diagnosis. IBD is a clinical diagnosis that integrates history and physical findings with objective data from imaging studies, laboratory evaluation, and endoscopic findings including histopathology. Diagnosis should neither be confirmed nor excluded on any one variable or result: up to 54% of patients with mild ulcerative colitis and 21% of patients with mild Crohn disease have normal hemoglobin, albumin, CRP, and ESR levels at the time of initial diagnosis. Important mimics of IBD include irritable bowel syndrome, Behçet disease, infectious enterocolitis (particularly enterovirus and *Yersinia*),

TABLE 11.17 Clinical Manifestations of Inflammatory Bowel Disease

Manifestation	Comments
Gastrointestinal	
Diarrhea with or without blood	Isolated small bowel Crohn disease may not manifest with diarrhea or grossly bloody stools
Abdominal pain	
Hematochezia	More common in ulcerative colitis
Anorexia, weight loss, and fatigue	More common in Crohn disease
Growth failure and pubertal delay	More common in Crohn disease
Abdominal mass	Only in Crohn disease
Fever and night sweats	More common in Crohn disease
Vomiting and nausea	Seen in both but severe would suggest intestinal obstructive process from Crohn disease
Extraintestinal	
Iritis and uveitis	More common in Crohn disease
Aphthous ulceration	More common in Crohn disease
Erythema nodosum	More common in Crohn disease
Pyoderma gangrenosum	More common in ulcerative colitis
Musculoskeletal • Axial arthropathy and ankylosing spondylitis • Polyarticular arthritis • Pauciarticular arthritis • Osteoporosis	
Liver • Primary sclerosing cholangitis • Autoimmune hepatitis and overlap syndrome • Cholelithiasis	
Autoimmune pancreatitis	
Cardiovascular • Myocarditis • Pericarditis	
Pulmonary Crohn disease	Commonly involves large airways, but parenchymal disease, such as organizing pneumonia, interstitial disease, and necrobiotic nodules, has been described
Renal • Nephritis • Amyloidosis • Urolithiasis (especially oxalate stones)	More common in Crohn disease compared to ulcerative colitis
Hematologic • Iron-deficiency anemia, anemia of chronic disease, vitamin B_{12} deficiency or folate deficiency • Immune thrombocytopenia • Deep vein thrombosis	

TABLE 11.18 Comparison of Crohn Disease and Ulcerative Colitis

Feature	Crohn Disease	Ulcerative Colitis
Malaise, fever, weight loss	Common	Common
Rectal bleeding	Sometimes	Usual
Abdominal mass	Common	Rare
Abdominal pain	Common	Common
Perianal disease	Common	Rare
Ileal involvement	Common	None (backwash ileitis)
Strictures	Common	Unusual
Fistula	Common	Very rare
Skip lesions	Common	Not present
Transmural Involvement	Usual	Not present
Crypt abscesses	Variable	Usual
Intestinal granulomas	Common	Rarely present
Risk of cancer*	Increased	Greatly increased
Erythema nodosum	Common	Less common
Mouth ulceration	Common	Rare
Osteopenia at onset	Yes	No
Autoimmune hepatitis	Rare	Yes
Sclerosing cholangitis	Rare	Yes

*Colonic cancer, cholangiocarcinoma, lymphoma in Crohn disease.
From Bishop WP, Ebach DR. Intestinal tract. In: Marcdante KJ, Kliegman RK, eds. *Nelson Essentials of Pediatrics.* 7th Edition. Philadelphia: Saunders; 2015:437-444.

TABLE 11.19 Differential Diagnoses of Presenting Symptoms of Crohn Disease

Primary Presenting Symptom	Differential Diagnosis
Right lower quadrant abdominal pain, with or without mass	Appendicitis, infection (e.g., *Campylobacter, Yersinia* species, tuberculosis or atypical mycobacteria), lymphoma, intussusception, mesenteric adenitis, Meckel diverticulitis, ovarian cyst or ovarian torsion, ectopic pregnancy
Chronic periumbilical or epigastric abdominal pain	Irritable bowel syndrome, constipation, lactose intolerance, peptic ulcer disease, functional dyspepsia
Rectal bleeding, no diarrhea	Fissure, polyp, Meckel diverticulum, solitary rectal ulcer syndrome
Bloody diarrhea	Infection, allergic colitis, hemolytic uremic syndrome, Henoch-Schönlein purpura, ischemic bowel, radiation colitis
Watery diarrhea	Irritable bowel syndrome, lactose intolerance, giardiasis, *Cryptosporidium* infection, sorbitol, laxatives
Perirectal disease	Fissure, hemorrhoid (rare), streptococcal infection, condyloma (rare)
Growth delay	Endocrinopathy
Anorexia, weight loss	Celiac disease, other systemic illnesses, anorexia nervosa
Arthritis	Collagen vascular disease, infection
Liver abnormalities	Chronic hepatitis
Oral ulcers	Celiac disease

and tuberculosis (Tables 11.19 and 11.20). As such, every patient with a history and examination suggestive of IBD should have stool studies for infectious organisms and special request should be made for *Yersinia* culture if multiplex PCR assays that include *Yersinia* testing are not available. Patients presenting with suggestive symptoms prior to 6 years of age may require an evaluation for an underlying immune dysregulation disorder as an additional mimic of IBD (Table 11.21). Stool biomarkers such as calprotectin and lactoferrin should be utilized to exclude non-inflammatory causes before considering endoscopic procedures. The suggested diagnostic evaluation of suspected inflammatory bowel disease is presented in Table 11.22.

TABLE 11.20 Infectious Agents Mimicking Inflammatory Bowel Disease

Agent	Manifestations	Diagnosis	Comments
Bacteria			
Campylobacter jejuni	Acute diarrhea, fever, fecal blood and leukocytes	Culture or nucleic acid amplification assay	Common in adolescents, may relapse
Yersinia enterocolitica	Acute diarrhea that can become chronic, right lower quadrant pain, mesenteric adenitis–pseudoappendicitis, fecal blood and leukocytes Extraintestinal manifestations may mimic Crohn disease	Culture or nucleic acid amplification assay	Common in adolescents as fever of unknown origin, weight loss, abdominal pain
Clostridium difficile	Onset during or following a course of antibiotics, watery → bloody diarrhea, pseudomembrane on sigmoidoscopy	Cytotoxin assay or nucleic acid amplification assay	May be nosocomial Toxic megacolon possible
Escherichia coli O157:H7	Colitis, fecal blood, abdominal pain	Culture and typing or nucleic acid amplification assay	Hemolytic uremic syndrome possible
Salmonella	Watery → bloody diarrhea, foodborne, fecal leukocytes, fever, pain, cramps	Culture or nucleic acid amplification assay	Usually acute
Shigella	Watery → bloody diarrhea, fecal leukocytes, fever, pain, cramps	Culture or nucleic acid amplification assay	Dysentery symptoms
Edwardsiella tarda	Bloody diarrhea, cramps	Culture	Ulceration on endoscopy
Aeromonas hydrophila	Cramps, diarrhea, fecal blood	Culture	May be chronic May be acquired from contaminated drinking water or swimming in contaminated pools or freshwater sources
Plesiomonas shigelloides	Diarrhea, cramps	Culture	Shellfish source
Tuberculosis	Rarely bovine, now *Mycobacterium tuberculosis* Ileocecal area, fistula formation	Culture, purified protein derivative, biopsy, interferon gamma release assay	Can mimic Crohn disease
Parasites			
Entamoeba histolytica	Acute bloody diarrhea and liver abscess, colic	Trophozoite in stool, colonic mucosal flask ulceration, serologic tests	Travel to endemic area
Giardia lamblia	Foul-smelling, watery diarrhea, cramps, flatulence, weight loss; no colonic involvement	"Owl"-like trophozoite and cysts in stool; rarely duodenal intubation	May be chronic
Opportunistic Organisms in the Setting of Immune Deficiency			
Cryptosporidium	Chronic diarrhea, weight loss	Stool microscopy	Mucosal findings not like inflammatory bowel disease
Isospora belli	Chronic diarrhea, weight loss	Stool microscopy	Tropical location
Cytomegalovirus	Colonic ulceration, pain, bloody diarrhea	Culture, biopsy	More common when on immunosuppressive medications

From Grossman AB, Baldassano RN. Chronic ulcerative colitis. In: Kliegman RM, Stanton BF, St. Geme JW III, Schor NF, eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:1823.

TABLE 11.21 Chronic Inflammatory-Like Intestinal Disorders Including Monogenetic Diseases

Infection (See Table 11.20)

Idiopathic Pathogen-Negative AIDS Enteropathy

Immune–Inflammatory

Severe combined immunodeficiency
Agammaglobulinemia
Chronic granulomatous disease
Wiskott-Aldrich syndrome
Common variable immunodeficiency
Acquired immunodeficiency
Dietary protein enterocolitis
Polyglandular autoimmune syndrome type 1
Behçet disease
Lymphoid nodular hyperplasia
Eosinophilic gastroenteritis
Omenn syndrome
Graft-versus-host disease
IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome
Interleukin-10 signaling defects
Autoimmune enteropathy*
Microscopic colitis
Hyperimmunoglobulin M syndrom
Hyperimmunoglobulin E syndrome
Mevalonate kinase deficiency
Familial Mediterranean fever
Phospholipase Cγ2 defects
Familial hemophagocytic lymphohistiocytosis type 5
X-linked lymphoproliferative syndromes types 1, 2
Congenital neutropenias
Leukocyte adhesion deficiency 1

Vascular–Ischemic Disorders

Systemic vasculitis (systemic lupus erythematosus, dermatomyositis)
Henoch-Schönlein purpura
Hemolytic uremic syndrome
Granulomatosis with angiitis

Other

Glycogen storage disease type 1b
Dystrophic epidermolysis bullosa
X-linked ectodermal dysplasia and immunodeficiency
Dyskeratosis congenita
ADAM-17 deficiency
Prestenotic colitis
Diversion colitis
Radiation colitis
Neonatal necrotizing enterocolitis
Typhlitis
Sarcoidosis
Hirschsprung colitis
Intestinal lymphoma
Laxative abuse
Endometriosis
Hermansky-Pudlak syndrome
Trichohepatoenteric syndrome
PTEN hamartoma syndrome

*May be the same as IPEX.

From Grossman AB, Baldassano RN. Chronic ulcerative colitis. In: Kliegman RM, Stanton BF, St. Geme JW III, Schor NF, eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:18, Table 336-5.

TABLE 11.22 Suggested Evaluation in Suspected Inflammatory Bowel Disease

Test	Common Abnormalities/Comments
Complete blood count with differential	Anemia, especially iron deficiency
Comprehensive metabolic panel	Hypoalbuminemia, elevated liver enzymes, low alkaline phosphatase (likely secondary to associated zinc deficiency)
Erythrocyte sedimentation rate	Elevated in CD > UC
C-reactive protein	Elevated in CD > UC
Stool cultures with *Yersinia*; ova and parasites	Always rule out infectious causes as the likely reason for symptoms
Clostridium difficile toxin assay or polymerase chain reaction assay	Could be an isolated reason for symptoms or could be a superimposed illness
Fecal occult blood	Positive in vast majority of patients. No need for this test if patient has grossly bloody stools
Fecal calprotectin (or lactoferrin)	To distinguish inflammatory bowel disease from irritable bowel syndrome (IBS) prior to considering invasive procedures such as enodoscopy
Esophagogastroduodenoscopy and ileocolonoscopy	After ruling out other causes of patient's symptoms
Imaging studies • MRI and MR-enterography (MRE) • CT abdomen • Abdominal ultrasound	Consider for evaluation of patients presenting with fistulizing or structuring disease. Also used for evaluation of small bowel after endoscopic procedures
Wireless capsule endoscope	Consider for evaluation of small bowel in very young children in whom MRE is difficult or in situations where conventional endoscope and imaging tools have been nondiagnostic

CD, Crohn disease; CT, computed tomography; MRI, magnetic resonance imaging; UC, ulcerative colitis.

SUMMARY AND RED FLAGS

Acute diarrhea is a common childhood illness. For most children, the etiologic agent is of no therapeutic significance. Exceptions are giardiasis, pseudomembranous colitis, dysentery suggestive of *Shigella* infection, amebiasis, or *Campylobacter* infection, all of which necessitate specific treatment. Oftentimes of greater importance are the secondary complications associated with fluid and electrolyte losses and the reduced oral fluid intake, which may result in shock and its systemic complications.

Red flags for acute diarrhea are the manifestations of dehydration (see Table 11.6). Young age (<6 months) is associated with a greater risk of dehydration, as are 10 or more stools a day and frequent emesis and fever.

Chronic diarrhea may be benign or may signify a more serious illness associated with malabsorption, inflammation, or congenital defects. Red flags include onset of diarrhea in the neonatal period, weight loss, growth stunting, anorexia, fever, fatty stools, blood in stools, extraintestinal manifestations associated with intestinal disease, history of travel to countries with poor sanitation and water supply, and specific nutritional deficiencies associated with malabsorption.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Corinaldesi R, Stanghellini V, Barbara G, et al. Clinical approach to diarrhea. *Intern Emerg Med*. 2012;7:255-262.

Das JK, Salam RA, Bhutta ZA. Global burden of childhood diarrhea and interventions. *Curr Opin Infect Dis*. 2014;27:451-458.

Granado-Villar D, Cunill-De Sautu B, Granados A. Acute gastroenteritis. *Pediatr Rev*. 2012;33:487-494, quiz 495.

Whyte LA, Jenkins HR. Pathophysiology of diarrhoea. *Paediatr Int Child Health*. 2012;22:443-447.

Acute Gastroenteritis

Belliot G, Lopman BA, Ambert-Balay K, et al. The burden of norovirus gastroenteritis: an important foodborne and healthcare-related infection. *Clin Microbiol Infect*. 2014;20:724-730.

Camilleri M, Murray JA. Diarrhea and constipation. In: Kasper D, Fauci A, Hauser S, et al., eds. *Harrison's Principles of Internal Medicine*. 19th ed. New York: McGraw-Hill; 2015.

Committee on Infectious Diseases, American Academy of Pediatrics. Prevention of rotavirus disease: updated guidelines for use of rotavirus vaccine. *Pediatrics*. 2009;123:1412-1420.

Committee on Infectious Diseases. *Clostridium difficile* infection in infants and children. *Pediatrics*. 2013;131:196-200.

Cortes JE, Curns AT, Tate JE, et al. Rotavirus vaccine and health care utilization for diarrhea in U.S. children. *N Engl J Med*. 2011;365:1108-1117.

Cortese MM, Parashar UD, Centers for Disease Control and Prevention (CDC). Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2009;58:1-25.

Crim SM, Griffin PM, Tauxe R, et al. Preliminary incidence and trends of infection with pathogens transmitted commonly through food - Foodborne Diseases Active Surveillance Network, 10 U.S. sites, 2006-2014. *MMWR Morb Mortal Wkly Rep*. 2015;64:495-499.

Croxen MA, Law RJ, Scholz R, et al. Recent advances in understanding enteric pathogenic *Escherichia coli*. *Clin Microbiol Rev*. 2013;26:822-880.

DuPont HL. Clinical practice. Bacterial diarrhea. *N Engl J Med*. 2009;361:1560-1569.

DuPont HL. The search for effective treatment of *Clostridium difficile* infection. *N Engl J Med*. 2011;364:473-475.

Guo B, Harstall C, Louie T, et al. Systematic review: faecal transplantation for the treatment of *Clostridium difficile*-associated disease. *Aliment Pharmacol Ther*. 2012;35:865-875.

Krones E, Hogenauer C. Diarrhea in the immunocompromised patient. *Gastroenterol Clin North Am*. 2012;41:677-701.

Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med*. 2011;364:422-431.

Man SM. The clinical importance of emerging *Campylobacter* species. *Nat Rev Gastroenterol Hepatol*. 2011;8:669-685.

Nash TE. Unraveling how *Giardia* infections cause disease. *J Clin Invest*. 2013;123:2346-2347.

Rudolph JA, Cohen MB. New causes and treatments for infectious diarrhea in children. *Curr Gastroenterol Rep*. 1999;1:238-244.

Steffen R, Hill DR, DuPont HL. Traveler's diarrhea. *JAMA*. 2015;313:71.

Chronic Diarrhea

Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med*. 2009;361:2066-2078.

Baumgart DC, Sandborn WJ. Crohn's disease. *Lancet*. 2012;380:1590-1605.

Binder HJ. Causes of chronic diarrhea. *N Engl J Med*. 2006;355:236-239.

Branski D. Disorders of malabsorption. In: Kliegman RM, Stanton BF, St. Geme JW III, et al., eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:1831-1850.

Bröer S. Lysinuric protein intolerance: One gene, many problems. *Am J Physiol Cell Physiol*. 2007;293:C540-C541.

Canani RB, Castaldo G, Bacchetta R, et al. Congenital diarrhoeal disorders: advances in this evolving web of inherited enteropathies. *Nat Rev Gastroenterol Hepatol*. 2015;12:293-302.

Chumpitazi BP, Robayo-Torres CC, Opekun AR, et al. Congenital sucrase-isomaltase deficiency. *J Pediatr Gastroenterol Nutr*. 2012;55:S36.

Danese S, Fiocchi C. Ulcerative colitis. *N Engl J Med*. 2011;365:1713-1725.

Fasano A, Catassi C. Celiac disease. *N Engl J Med*. 2012;367:2419-2426.

Fiskerstrand T, Arshad N, Haukanes BI, et al. Familial diarrhea syndrome caused by an activating GUCY2C mutation. *N Engl J Med*. 2012;366:1586-1595.

Ghaferi AA, Chojnacki KA, Long WD, et al. Pancreatic VIPomas: Subject review and one institutional experience. *J Gastrointest Surg*. 2007;12:382-393.

Gråfors JM, Casswall TH. Exclusive enteral nutrition in the treatment of children with Crohn's disease in Sweden: a questionnaire survey. *Acta Paediatr*. 2011;100:1018-1022.

Henderson P, Anderson NH, Wilson DC. The diagnostic accuracy of fecal calprotectin during the investigation of suspected pediatric inflammatory bowel disease: A systematic review and meta-analysis. *Am J Gastroenterol*. 2014;109:637-645.

Heyman MB, for the Committee on Nutrition. Lactose intolerance in infants, children, and adolescents. *Pediatrics*. 2006;118:1279-1286.

Husby S, Koletzko S, Korponay-Szabó IR, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Guidelines for the Diagnosis of Coeliac Disease. *J Pediatr Gastroenterol Nutr*. 2012;54:136-160.

Hyman PE, Milla PJ, Benninga MA, et al. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology*. 2006;130:1519-1526.

Levine A, Griffiths A, Markowitz J, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: The Paris classification. *Inflamm Bowel Dis*. 2010;17:1314-1321.

Levine A, Koletzko S, Turner D, et al. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr*. 2014;58:795-806.

Mouzaki M, Vresk L, Gonska T. Clinical challenges and images in GI. *Gastroenterology*. 2014;146:912-1138.

Saadah OI, Alghamdi SA, Sindi HH, et al. Congenital glucose-galactose malabsorption: a descriptive study of clinical characteristics and outcome from Western Saudi Arabia. *Arab Journal of Gastroenterology*. 2014;15:21-23.

Sherman PM, Mitchell DJ, Cutz E. Neonatal enteropathies: defining the causes of protracted diarrhea of infancy. *J Pediatr Gastroenterol Nutr*. 2004;38:16-26.

Tack GJ, Verbeek WHM, Schreurs MWJ, et al. The spectrum of celiac disease: epidemiology, clinical aspects and treatment. *Nat Rev Gastroenterol Hepatol*. 2010;7:204-213.

Terrin G, Tomaiuolo R, Passariello A, et al. Congenital diarrheal disorders: an updated diagnostic approach. *Int J Mol Sci*. 2012;13:4168-4185.

Treem WR. Clinical aspects and treatment of congenital sucrase-isomaltase deficiency. *J Pediatr Gastroenterol Nutr*. 2012;55(suppl 2):S7-S13.

Van Assche G, Dignass A, Reinisch W, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: Special situations. *J Crohns Colitis*. 2010;4:63-101.

Wang DZ. Neurotoxins from marine dinoflagellates: a brief review. *Mar Drugs*. 2008;6(2):349-371.

Wang J, Cortina G, Wu SV, et al. Mutant neurogenin-3 in congenital malabsorptive diarrhea. *N Engl J Med*. 2006;355:270-280.

Zella GC, Israel EJ. Chronic diarrhea in children. *Pediatr Rev*. 2012;33:207-218.

Zhang Y, Li Y. Inflammatory bowel disease: pathogenesis. *World J Gastroenterol*. 2014;20:91-99.

12

Vomiting and Regurgitation

Richard J. Noel

DEFINITIONS

Vomiting encompasses all retrograde ejection of gastrointestinal (or esophageal) contents from the mouth. Vomiting is subdivided according to its forcefulness; thus, effortless or nearly effortless regurgitation is distinguished from true vomiting, which is propelled both by forceful abdominal wall contractions and by retrograde intestinal peristalsis (Table 12.1).

True vomiting is often accompanied by nausea and retching. **Nausea** is an unpleasant, vaguely epigastric or abdominal sensation accompanied by a variety of autonomic changes: decreases in gastric tone, contractions, secretion, and mucosal blood flow; increases in salivation, sweating, pupil diameter, and heart rate; and changes in respiratory rhythm. During nausea, retrograde peristalsis from the small intestine to the gastric antrum or generalized simultaneous contractions of antrum and duodenum may produce duodenogastric reflux.

Retching is defined as strong, involuntary efforts to vomit, which may be seen as preparatory maneuvers to vomiting. These efforts consist of spasmodic contractions of the diaphragm and abdominal wall at the same time that the lower esophageal sphincter relaxes. This sphincter is also pulled cephalad by contraction of the longitudinal muscles of the upper esophagus and may herniate through the diaphragmatic hiatus, preventing the increased intraabdominal pressure from augmenting the sphincter pressure. During retching, gastric material is moved into the esophagus by the combination of increased abdominal pressure and decreased intrathoracic pressure, but this material may be returned to the stomach by secondary (non-swallow) esophageal peristalsis.

Vomiting (emesis) differs from retching in that material is expelled from the mouth. This is fostered by relaxation of the diaphragm and reversal of intrathoracic pressure from negative to positive. The upper esophageal sphincter also relaxes, perhaps in response to the increase of intraluminal pressure in the esophagus.

Regurgitation is considered a form of gastroesophageal reflux and, as such, is caused predominantly by lower esophageal sphincter dysfunction. Although apparently effortless, it may be propelled by contraction of abdominal wall musculature; this propulsion perhaps distinguishes regurgitant from nonregurgitant reflux, which remains in the esophagus.

Rumination is similar to regurgitation in its effortless appearance and its probable propulsion by somatic muscle contraction. However, ruminated material is usually reswallowed rather than ejected from the mouth, and psychological or behavioral problems are considered the cause.

NEUROANATOMY OF VOMITING

The stereotypical motor response of vomiting is mediated by efferent fibers in the vagal, phrenic, and spinal nerves. Input to these nerves rises from the brainstem "vomiting center." The final common pathway for this centrally programmed complex reflex is through medullary interneurons in the solitary tract nucleus and a variety of sites in the nearby reticular formation. These interneurons receive input from the cortex, vagus, vestibular system, and area postrema. The area postrema, the "chemoreceptive trigger zone," is located on the dorsal surface of the floor of the fourth ventricle, outside the blood–brain barrier, and has been identified as a crucial source for neural input that causes vomiting, particularly as a response to circulating drugs and toxins. Brain tumors, other central nervous system disease, and emotional stress, in contrast, cause vomiting via cortical afferent nerves, whereas intraabdominal disease, such as luminal obstruction or distention, causes vomiting via vagal afferent nerves. Vomiting may be classified by the origin of the afferent nerves (Table 12.2). When vomiting is a result of intraabdominal disease, it is useful to define whether obstruction, dysmotility, inflammation, or ischemia is the mechanism. Vomiting may also be acute, chronic, or cyclic (Tables 12.3 and 12.4).

DATA TO GUIDE THE DIAGNOSIS

◆ History

Demographics

The child's age is a major determinant of the diagnostic possibilities (Table 12.5). Affected neonates present with congenital disorders and, in particular, structural abnormalities of the gastrointestinal tract or severe metabolic diseases. Sepsis is also an important neonatal consideration. Older infants with vomiting may have less severe structural or metabolic disorders, or they may have common acquired disorders such as gastroenteritis, mild systemic infections, gastroesophageal reflux, or allergies. Some metabolic disorders first manifest in older infants when dietary changes expose them to provocative foods for the first time; gastroenteritis and other infections are important considerations in these relatively immunocompromised younger patients.

Toddlers frequently experience gastroenteritis, because they are repeatedly exposed to organisms to which they have no immunity; this age group also presents with acquired obstructive gastrointestinal disorders, such as intussusception or volvulus or with vomiting caused by ingested poisons. Throughout childhood and adolescence, a wide variety of acquired disorders become symptomatic, and some subtle congenital malformations may also first become evident at these older ages. Metabolic disorders continue to be an important but infrequent cause of recurrent vomiting throughout childhood. In adolescents, pregnancy, drug ingestion, chronic marijuana use, and eating disorders are added to the diagnostic considerations.

Characteristics of Vomiting

The contents (Table 12.6) and forcefulness (see Table 12.1) of the vomitus narrow the diagnostic possibilities. Hematemesis and bilious

(See *Nelson Textbook of Pediatrics,* p. 867.)

TABLE 12.1 Force of Vomiting

Force	Cause	Example
None	Esophageal emptying	Achalasia; some reflux
Minimal	Regurgitation	Regurgitant reflux; rumination
Moderate	Vomiting	Most vomiting diseases
Severe	Projectile vomiting with retching	Obstructions; metabolic; poisons

vomiting, in particular, are approached in a manner very different from that of vomiting without these characteristics, and they represent more serious underlying disorders.

Associated symptoms. Vomiting must be characterized as acute, chronic, or recurrent. Temporal associations of chronic or recurrent vomiting are important (Table 12.7). Associated symptoms must be described (Tables 12.8 and 12.9); they are crucial, for example, in distinguishing life-threatening intracranial and metabolic disorders (Table 12.10). Abdominal pain is a central symptom that, if present, narrows the diagnosis. Vomiting associated with neurologic symptoms requires very careful evaluation. Post-tussive emesis is not usually confused with vomiting of other causes; it should direct diagnostic attention to the cause of the cough itself. Regurgitation in an infant with apnea may signal reflux-associated apnea, although many infants with reflux-associated apnea have minimal regurgitation. Additionally, infant regurgitation is so common that it is quite nonspecific.

Medical, family, and social history. Previous surgery, hospitalizations, and medications may provide important clues. A family history of fetal or neonatal deaths suggests a genetic or metabolic cause; similar illness in the family members or other contacts may suggest infections or common toxic exposures. Psychosocial stressors may be found in adolescents with bulimia, peptic ulcer disease, chronic marijuana use, or intentional self-poisonings.

◆ Physical Examination

Although vomiting is a "gastrointestinal" symptom, it can be a manifestation of disease in multiple systems of the body (see Tables 12.8, 12.9). Vital signs identify fever, which is important in narrowing the differential diagnosis. Tachypnea may signify acidosis, which is seen with vomiting from metabolic causes or poisoning or with vomiting associated with marked diarrhea and dehydration or shock. Examination of the fundi is often inappropriately neglected. The absence of venous pulsations or sharp optic disk margins may be the only evidence of a brain tumor or other intracranial lesion causing vomiting. When in doubt, a formal ophthalmologic examination is warranted.

Abdominal Examination

Simple observation of operative scars may suggest the possibility of obstruction from intestinal adhesions, and visible distention may represent ascites caused by liver disease or intraluminal distention caused by intestinal obstruction or ileus. The order of the examination is important because auscultation performed after stimulation of intestinal motility by palpation may artifactually change the auscultatory findings. An important distinction in the vomiting child is whether bowel sounds are increased, as in gastroenteritis or in bowel obstructions, or absent, as in ileus caused by peritonitis or in pseudoobstruction. Increased bowel sounds resulting from luminal obstruction are often characterized by intermittent "rushes" of high-pitched sounds that are coordinated with episodes of colicky pain.

Abdominal pain and tenderness associated with vomiting often represent disorders necessitating further imaging and/or surgery.

TABLE 12.2 Differential Diagnosis of Vomiting by Anatomic Locus of Stimulus

I. Stimulation of Supramedullary Receptors
- A. Psychogenic vomiting
- B. Increased intracranial pressure (subdural effusion or hematoma, cerebral edema or tumor, hydrocephalus, meningoencephalitis, Reye syndrome)
- C. Vascular (migraine, severe hypertension)
- D. Seizures
- E. Vestibular disease, "motion sickness"

II. Stimulation of Chemoreceptive Trigger Zone
- A. Drugs: opiates, ipecac, digoxin, anticonvulsants
- B. Toxins
- C. Metabolic products (acidemia, ketonemia, hyperammonemia, uremia, etc.):
  - Acidemia, ketonemia (diabetic ketoacidosis, lactic acidosis, phenylketonuria, renal tubular acidosis)
  - Aminoacidemia (tyrosinemia, hypervalinemia, hyperglycinemia, lysinuria, maple syrup urine disease)
  - Organic acidemia (methylmalonic acidemia, propionic acidemia, isovaleric acidemia)
  - Hyperammonemia (urea cycle defects, Reye syndrome)
  - Uremia (renal failure)
  - Other (hereditary fructose intolerance, galactosemia, fatty acid oxidation disorders, diabetes insipidus, adrenal insufficiency, hypercalcemia, hypervitaminosis A)

III. Stimulation of Peripheral Receptors and/or Obstruction of the Gastrointestinal Tract
- A. Pharyngeal: gag reflex (sinusitis secretions, post-tussive, self-induced, rumination)
- B. Esophageal:
  - Functional: reflux, achalasia, other esophageal dysmotility
  - Structural: stricture, ring, atresia, etc.
- C. Gastric:
  - Peptic ulcer disease (including Zollinger-Ellison syndrome), infection, dysmotility/gastroparesis
  - Obstruction (e.g., bezoar, pyloric stenosis, web, chronic granulomatous disease, eosinophilic gastroenteritis)
- D. Intestinal:
  - Infection, enteritis, enterotoxin, appendicitis
  - Dysmotility (e.g., metabolic or diabetic neuropathy; intestinal pseudoobstruction)
  - Nutrient intolerance (e.g., cow's milk, soy, gluten, eosinophilic enteropathy)
  - Obstruction (e.g., atresia, web, stenosis, adhesions, bands, volvulus, intussusception, superior mesenteric artery syndrome, duplication, meconium plug, meconium ileus, Hirschsprung disease, distal intestinal obstruction syndrome in cystic fibrosis)
- E. Hepatobiliary, pancreatic: hepatitis, cholecystitis, pancreatitis, cholelithiasis
- F. Cardiac: intestinal ischemia
- G. Renal: pyelonephritis, hydronephrosis, renal calculi, glomerulonephritis
- H. Respiratory: pneumonia, otitis, pharyngitis, sinusitis, common cold
- I. Miscellaneous: peritonitis, sepsis, pregnancy; improper feeding techniques

Modified from Orenstein SR. Dysphagia and vomiting. In: Wyllie R, Hyams JS, eds. *Pediatric Gastrointestinal Disease: Pathophysiology, Diagnosis, Management*. Philadelphia: WB Saunders; 1983:147.

TABLE 12.3 Differentiating Acute, Chronic, and Cyclic Patterns of Vomiting

Clinical Feature	Acute	Chronic Recurrent	Cyclic Recurrent
Epidemiology	Most common	Two-thirds of recurrent vomiting cohort	One-third of recurrent vomiting cohort
Acuity	Moderate-severe, ± dehydration	Not acutely ill or dehydrated	Severe, dehydrated
Vomiting intensity	Moderate to high	Low, 1-2 emeses/hr at the peak	High frequency, ~6 emeses/hr at peak
Recurrence rate	No	Frequent, >2 episodes per week	Infrequent, ≤2 episodes per week
Stereotypy	Unique—*if child has had 3 similar episodes, consider cyclic pattern*	No	Yes
Onset	Variable	Daytime	Early morning
Symptoms	Fever, diarrhea	Abdominal pain, diarrhea	Pallor, lethargy, nausea, abdominal pain
Household contacts affected	Usually	No	No
Family history of migraine headaches		14% positive	82% positive
Causes	Viral infections	Ratio of GI to extra-GI causes 7:1; upper GI tract mucosal injury most common (esophagitis, gastritis)	Ratio of extra-GI to GI causes 5:1; cyclic vomiting syndrome most common (also hydronephrosis, metabolic)

From Li BUK, Kovacic K. Vomiting and nausea. In: Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*. 5th ed. Philadelphia: Elsevier; 2016:87.

TABLE 12.4 Causes of Vomiting by Temporal Pattern

Category	Acute	Chronic	Cyclic
Infectious	Gastroenteritis* Otitis media* Streptococcal pharyngitis Acute sinusitis Hepatitis Pyelonephritis Meningitis	*Helicobacter pylori** Giardiasis Chronic sinusitis*	Chronic sinusitis*
Gastrointestinal	Inguinal hernia Intussusception Malrotation with volvulus Appendicitis Cholecystitis Pancreatitis Distal intestinal obstruction syndrome	Anatomic obstruction GERD ± esophagitis* Eosinophilic esophagitis* Gastritis* Peptic ulcer or duodenitis* Achalasia SMA syndrome Stricturing Crohn disease	Malrotation with volvulus
Genitourinary	Pyelonephritis UPJ obstruction	Pyelonephritis Pregnancy Uremia	Acute hydronephrosis secondary to UPJ obstruction
Endocrine, metabolic	Diabetic ketoacidosis	Adrenal hyperplasia	Diabetic ketoacidosis Addison disease MCAD deficiency Partial OTC deficiency MELAS syndrome Acute intermittent porphyria
Neurologic	Concussion Subdural hematoma Encephalitis Migraine	Arnold-Chiari malformation Subtentorial neoplasm	Abdominal migraine* Migraine headaches* Arnold-Chiari malformation Subtentorial neoplasm Metabolic encephalopathy
Other	Toxic ingestion Chronic marijuana use Food poisoning	Rumination Functional Bulimia Pregnancy	Cyclic vomiting syndrome* Factitious disorder by proxy (e.g., ipecac poisoning)

*Most common disorders.
GERD, gastroesophageal reflux disease; MCAD, medium-chain acyl-CoA dehydrogenase deficiency; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes; OTC, ornithine transcarbamylase deficiency; SMA, superior mesenteric artery; UPJ, ureteropelvic junction.
From Li BUK, Kovacic K. Vomiting and nausea. In: Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*. 5th ed. Philadelphia: Elsevier; 2016:88.

TABLE 12.5 Differential Diagnosis of Vomiting by Age

I. Newborn
- A. Congenital obstructive gastrointestinal malformations:
  Atresias or webs of esophagus or intestine
  Meconium ileus or plug; Hirschsprung disease
- B. Inborn errors of metabolism:
  Organic acidemias, amino acidemias, hyperammonemias (urea cycle), adrenogenital syndromes

II. Infant
- A. Acquired or milder obstructive lesions:
  Pyloric stenosis, malrotation and volvulus, intussusception
- B. Metabolic diseases, inborn errors of metabolism
- C. Nutrient intolerances
- D. Functional disorders:
  Gastroesophageal reflux
- E. Psychosocial disorders:
  Rumination, injury from child abuse

III. Child
Most causes in Table 12.8

IV. Adolescent
Most childhood causes, plus pregnancy, drugs (of abuse, suicide), eating disorders

Modified from Orenstein SR. Dysphagia and vomiting. In: Wyllie R, Hyams JS, eds. *Pediatric Gastrointestinal Disease: Pathophysiology, Diagnosis, Management*. Philadelphia: WB Saunders; 1993:147.

TABLE 12.6 Contents of Emesis

Material	Source	Examples
Undigested food	Esophageal	Stricture, achalasia
Digested food: curds	Gastroduodenal	Pyloric stenosis, bezoar
Bile: green/yellow	Postampullary	Small bowel obstruction
Blood: red/brown	Lesion above ligament of Treitz	See Tables 12.13 and 12.14
Feculent: malodorous	Bacterial overgrowth Colon obstruction Necrotic bowel	Stasis syndrome Gastrocolic fistula Ischemic injury, peritonitis
Acid: clear (voluminous)	Gastric outlet obstruction Increased gastric secretion	Pyloric stenosis Zollinger-Ellison syndrome
Mucus	Gastric, respiratory mucus	Sinusitis, eosinophilic esophagitis

TABLE 12.7 Temporal Associations of Chronic or Recurrent Vomiting

Temporal Associations	Diagnosis	Other Clues
Time of day: early morning	Increased intracranial pressure Sinusitis with postnasal mucus Pregnancy Uremia	Headache, papilledema Sinus tenderness Secondary amenorrhea
During or after meals		
Any meals	Peptic ulcer disease, reflux	Epigastric pain, heartburn
Specific foods		See Tables 12.10, 12.17, 12.18
Fructose	Hereditary fructose intolerance	
Galactose	Galactosemia	
High protein	Metabolic inborn error	Hyperammonemia, acidosis
Specific protein		
Cow, soy	Cow's or soy milk intolerance	
Gluten	Gluten-sensitive enteropathy (celiac)	Failure to thrive
Various (especially egg, wheat, fish, nut, chocolate, strawberry)	Miscellaneous allergic, eosinophilic gastroenteropathies	History of asthma, hives, ↑eosinophils, family history of allergies
After fasting		
Food vomited	Gastric stasis/obstruction	Distention, tympany
Food not vomited	Metabolic disease	See Tables 12.10, 12.17, 12.18
Other precipitants		
Cough	Post-tussive	Respiratory disease
Infections	Metabolic Recurrent gastroenteritis	See Tables 12.10, 12.17, 12.18
Vestibular stimulation	Motion sickness	Nystagmus Vertigo
Hyperhydration	Ureteropelvic junction obstruction ("beer drinker's kidney," Dietl crisis)	Spontaneous resolution with normal hydration
Menses	Dysmenorrhea-associated vomiting Acute intermittent porphyria Pelvic inflammatory disease	Relief with NSAIDs Nonperitonitis pain, distention, tachycardia, constipation Vaginal discharge
Medications, toxins	Medication side effect: pancreatitis, hepatitis Acute intermittent porphyria Steroid withdrawal: Addison disease Poisonings; NSAID stricture; laxative, etc. Ipecac abuse in anorexia nervosa	Opiate withdrawal
Episodic/cyclic	Abdominal migraine, abdominal epilepsy Pheochromocytoma Porphyria Familial dysautonomia Metabolic inborn error Familial Mediterranean fever Malrotation and intermittent volvulus Intermittent intussusception Self-induced Cyclic vomiting	

NSAIDs, nonsteroidal antiinflammatory drugs.

TABLE 12.8 Clues to the Diagnosis and Localization of the Cause of Emesis

Associated Symptoms	Diagnoses to Consider
Local abdominal pain	
Epigastric	Peptic ulcer disease, reflux, pancreatitis
Periumbilical	Nonspecific or small intestinal obstruction
Pelvic	Cystitis, pelvic inflammatory disease, ovarian torsion
Right upper quadrant	Hepatitis, pancreatitis, cholecystitis, biliary colic, duodenal hematoma/ulcer, right pyelonephritis, pneumonia, perihepatitis
Left upper quadrant	Peptic ulcer disease, pancreatitis, splenic enlargement or torsion, left pyelonephritis, pneumonia
Right lower quadrant	Appendicitis, right tuboovarian disease
Left lower quadrant	Left tuboovarian disease, sigmoid disease
Right flank	UPJ/renal obstruction or infection, biliary obstruction, adrenal hemorrhage
Left flank	UPJ/renal obstruction or infection, adrenal hemorrhage
Other pain	
Headache	Increased intracranial pressure Sinusitis with postnasal mucus Migraine
Chest pain, dysphagia	Esophagitis, achalasia Pneumonia
Joint pain	SLE, FMF, IBD
Diarrhea	Partial intestinal obstruction Infectious enteritis Poison, inborn error of metabolism
Constipation	Intestinal obstruction or dysmotility (pseudoobstruction) Hypercalcemia, hypokalemia, porphyria, lead poisoning
Jaundice	Hepatitis, cholecystitis Hepatobiliary obstruction Metabolic disease Urinary obstruction or infection, pyloric stenosis (neonate)
Neurologic	Metabolic, toxic (lead), central nervous system disease, porphyria, hepatic failure Encephalopathy Vertigo Visual changes Abnormal tone, seizure Full fontanel
Cardiac	
Valvular disease	Mesenteric arterial thrombosis (or embolism)
Hypotension	Mesenteric thrombosis, intestinal ischemia
Hypertension	Pheochromocytoma
Respiratory	Pneumonia, otitis, aspiration of vomitus
Urinary	Pyelonephritis, hydronephrosis, calculi, renal hypertension, cholestasis, porphyria
Gynecologic	
Menstrual irregularity	Pregnancy, ectopic pregnancy
Vaginal discharge	Pelvic inflammatory disease
Menses-associated	Porphyria, endometriosis, dysmenorrhea

FMF, familial Mediterranean fever; IBD, inflammatory bowel disease; SLE, systemic lupus erythematosus; UPJ, ureteropelvic junction.

Vague periumbilical pain is quite nonspecific, but the localized, very sharp pain signifying inflammation of the peritoneum requires immediate attention. Initial luminal obstruction may progress to later ileus as peritonitis intervenes. Localization of nonperiumbilical pain or tenderness helps a great deal in determining the diseased intraabdominal organ (see Tables 12.8 and 12.9).

Abdominal pain often represents luminal obstruction, ischemia, or perforation (surgical disease), but nonsurgical diseases must also be considered. These disorders include nonobstructive inflammatory diseases (infectious gastroenteritis, pancreatitis), metabolic crises (e.g., adrenal crisis), and poisonings (e.g., lead, narcotics, insecticides).

Rectal Examination

A rectal examination may be helpful in the vomiting child as the presence and consistency of rectal stool may be determined. Simple fecal impaction may theoretically contribute to vomiting in young children, whereas liquid stools may suggest gastroenteritis. Pelvic masses and tenderness identified rectally may represent appendicitis, ovarian torsion, or pelvic inflammatory disease. The stool should always be tested for blood and should be considered for testing for pH, reducing substances, fat, leukocytes, and infectious organisms, depending on the situation.

Laboratory Data

Well-appearing infants with typical regurgitant reflux usually require no laboratory evaluation, except probably an upper gastrointestinal study if they do not respond readily to conservative therapy (see later discussion). Similarly, a single, brief episode of mild vomiting with a clear etiology and no suggestion of dehydration or other complications may necessitate no laboratory studies. Most other children—those with severe acute vomiting or with chronic or recurrent vomiting—should have screening studies of blood or urine (Table 12.11). Blood and urine screening for several metabolic disorders are positive only during an actual vomiting episode; therefore, attempts to obtain specimens at these times may increase the diagnostic yield. Examples include measuring serum lactate, serum and urine carnitine (possible fatty acid oxidation defect), and urine δ-aminolevulinic acid and porphobilinogen (possible acute intermittent porphyria).

Radiographic and Procedure Data

If the history and physical examination suggest the possibility of abdominal disease, endoscopic evaluation or abdominal plain films (including a second image such as an upright film) are usually warranted (Table 12.12). Endoscopy is particularly useful in hematemesis, in suspected peptic ulcer disease, or when tissue is needed for histologic study (e.g., establishing a diagnosis of *Helicobacter pylori* gastritis or of eosinophilic gastroenteropathy). Radiographic testing is useful in most other situations. Further evaluation, such as contrast studies, ultrasonography, computed tomography (CT), or magnetic resonance imaging, is tailored to the suspected diagnoses. It should be noted that endoscopy may not be performed when barium contrast remains in the areas to be examined; therefore, if it is thought that contrast fluoroscopy studies need to be followed by endoscopy, imaging should be performed with water-soluble contrast. In rare cases, manometric evaluation is prompted by the suggestion of motor dysfunctions, such as achalasia and chronic intestinal pseudoobstruction.

◆ Differential Diagnosis

General Approach

Cardinal symptoms or signs accompanying the vomiting direct the differential diagnosis. Abdominal pain, which frequently accompanies vomiting, can suggest both the type of disorder (e.g., luminal

TABLE 12.9 Clinical Clues to Diagnosis

Associated Symptom or Sign	Diagnostic Consideration
Systemic Manifestations	
Acute illness, dehydration	Infection, ingestion, cyclic vomiting, possible surgical emergency
Chronic malnutrition	Malabsorption syndrome
Temporal Pattern	
Low-grade, daily	Chronic vomiting pattern, e.g., upper GI tract disease (e.g., gastroesophageal reflux, functional disorders)
Postprandial	Upper GI tract disease (e.g., gastritis), gastroparesis, rumination, biliary disorders
Relationship to diet	Fat, cholecystitis, pancreatitis; protein allergy; hereditary fructose intolerance
Early morning onset	Sinusitis, cyclic vomiting syndrome, increased intracranial pressure
High intensity	Cyclic vomiting syndrome, food poisoning
Stereotypical (well between episodes)	Cyclic vomiting syndrome
Rapid onset and subsidence	Cyclic vomiting syndrome
Character of Emesis	
Effortless	Gastroesophageal reflux, rumination
Projectile	Upper GI tract obstruction
Mucous	Allergy, chronic sinusitis
Bilious	Postampullary obstruction, cyclic vomiting syndrome
Bloody	Esophagitis, prolapse gastropathy, Mallory-Weiss injury, allergic gastroenteropathy, bleeding diathesis
Undigested food	Achalasia
Clear, large volume	Ménétrier disease, Zollinger-Ellison syndrome
Malodorous	*H. pylori* , giardiasis, sinusitis, small bowel bacterial overgrowth, colonic obstruction
Gastrointestinal Symptoms	
Nausea	Absence of nausea can suggest increased intracranial pressure
Abdominal pain	Substernal, esophagitis; epigastric, upper GI tract, pancreatic; right upper quadrant, cholelithiasis
Diarrhea	Gastroenteritis, bacterial colitis
Constipation	Hirschsprung disease, pseudoobstruction, hypercalcemia
Dysphagia	Eosinophilic esophagitis, achalasia, esophageal stricture
Visible peristalsis	Gastric outlet obstruction
Surgical scars	Surgical adhesions, surgical vagotomy
Succussion splash	Gastric outlet obstruction with gastric distention
Bowel sounds	Decreased: paralytic ileus; increased: mechanical obstruction
Severe abdominal tenderness with rebound	Perforated viscera and peritonitis
Abdominal mass	Pyloric stenosis, congenital malformations, Crohn, ovarian cyst, pregnancy, abdominal neoplasm
Neurologic Symptoms	
Headache	Allergy, chronic sinusitis, migraine, increased intracranial pressure
Postnasal drip, congestion	Allergy, chronic sinusitis
Vertigo	Migraine, inner ear disease
Seizures	Epilepsy
Abnormal muscle tone	Cerebral palsy, metabolic disorder, mitochondrial disorder
Abnormal funduscopic exam or bulging fontanel	Increased intracranial pressure, pseudotumor cerebri
Family History and Epidemiology	
Peptic ulcer disease	Peptic ulcer disease, *H. pylori* gastritis
Migraine headaches	Abdominal migraine, cyclic vomiting syndrome
Contaminated water	*Giardia*, *Cryptosporidium* , other parasites
Travel	Traveler's *(Escherichia coli)* diarrhea, giardiasis

H. pylori, Helicobacter pylori.

From Li BUK, Kovacic K. Vomiting and nausea. In: Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*. 5th ed. Philadelphia: Elsevier; 2016:91.

TABLE 12.10 When to Consider Metabolic Work-up*

Nutritional abnormalities	Failure to thrive, anorexia
Dietary provocations	Fructose, galactose, protein, fasting
Neurologic abnormalities	Lethargy, coma Tone ↑ or ↓, developmental delay Seizures
Liver abnormalities	Hepatosplenomegaly Jaundice
Respiratory abnormalities	Apnea Hyperpnea (caused by metabolic acidosis or hyperammonemia)
Odd odors (breath, urine, ear wax)	Cabbage: tyrosinemia Sweaty feet: isovaleric acidemia Musty: phenylketonuria, hepatic coma (fetor hepaticus) Fruity: ketones (many, nonspecific) Maple syrup; maple syrup urine disease Other: 3-methylcrotonyl-CoA carboxylase deficiency Multiple carboxylase deficiency Acyl-CoA dehydrogenase deficiency Putrid: sinusitis Alcohol: alcohol ingestion
Miscellaneous abnormalities	Eye abnormalities (cataracts) Hair abnormalities (fragile) Pigmentation of skin ("tan") and mucosa Adrenal calcifications Ambiguous genitalia Cardiomyopathy Family history of fetal or neonatal deaths; consanguinity
Screening study abnormalities	Metabolic acidosis Hypoglycemia (hyperketonuric or hypoketonuric) Hyperkalemia (with hyponatremia) Hyperammonemia Hypertransaminasemia Anemia, leukocytopenia, thrombocytopenia Urinary non–glucose-reducing substance Urinary Fanconi syndrome

*See also Tables 12.17 and 12.18.

obstruction, inflammation, ischemia, or peritonitis) and the organ involved (see Table 12.8). Hematemesis leads to the considerations indicated in Tables 12.13 and 12.14. Symptoms referable to nongastrointestinal organ systems direct attention to those systems. For example, accompanying neurologic symptoms may direct attention to central nervous system disorders, metabolic disease, poisonings, or psychobehavioral disease.

Gastrointestinal Obstruction

Esophageal Obstruction

Esophageal lesions produce welling up or drooling of oropharyngeal secretions or esophageal contents rather than actual vomiting; the material is, of course, undigested. Respiratory symptoms from aspiration may be prominent.

Esophageal atresia. Infants with esophageal atresia present at birth with a prenatal history of polyhydramnios and intolerance of initial feeding. The esophageal atresia is accompanied by a distal tracheoesophageal fistula in 85% of cases, by a proximal fistula in a small percentage, and by no fistula in the remainder (Fig. 12.1). Esophageal atresia is associated with other anomalies in 15-50% of patients; cardiac, anorectal, and genitourinary defects are most common. Ten percent of all esophageal atresia patients and 25% of those without a fistula have the VATER or VACTERL (vertebral, anorectal, cardiac, tracheoesophageal, renal, radial, limb) association. Others may have Fanconi anemia, where esophageal atresia may provide an early sign for making the diagnosis. As many as 33% of affected infants are premature. Diagnosis can usually be made by plain films after passage of an opaque rubber catheter, which coils in the upper pouch (Fig. 12.2). Treatment is surgical.

Esophageal stenosis. Children with esophageal stenoses present in later infancy and occasionally in adulthood. Stenoses are divided into tracheobronchial rings that often contain cartilage, fibromuscular stenoses, and membranous webs. Diagnosis is by contrast radiography and may require pressure injections of contrast material if the stenosis is not tight. Tracheobronchial rings generally necessitate surgery, membranous webs can be treated with endoscopic dilation, and muscular stenoses may respond to dilation or may necessitate surgery.

Esophageal strictures. Esophageal strictures are acquired lesions that may be caused by reflux esophagitis, but more commonly result from caustic ingestions (acid, alkali) or other causes (Fig. 12.3). The strictures are best demonstrated with contrast radiography; endoscopic biopsies may be important for diagnosis of the etiology. Gastroesophageal reflux disease (GERD) may be treated pharmacologically, but may also require a fundoplication; endoscopic dilation of the stricture is performed repeatedly with balloons or bougies until the strictured site remains patent.

Pyloric Stenosis

Pyloric stenosis manifests with nonbilious projectile vomiting beginning at 2-3 weeks of age and increasing during the next month or so, usually in a firstborn male child. The vomitus may contain some blood, and propulsive gastric waves can be seen on the abdominal wall. Dehydration, poor weight gain, metabolic alkalosis, and mild jaundice are sometimes evident. A palpable "olive" in the epigastrium (felt best during or after feeding) represents the hypertrophied pyloric muscle.

Gastric distention is seen on the plain film, and a contrast study shows the "string sign" of contrast passing through the narrowed pyloric channel. Ultrasound diagnosis is less invasive (Fig. 12.4). Eosinophilia, eosinophilic infiltration of endoscopic antral biopsy specimens, and an excellent response to treatment with a casein hydrolysate or elemental "hypoallergenic" formula are suggestive of an allergic or idiopathic eosinophilic gastroenteropathy and not pyloric stenosis. In older children, gastric outlet obstruction may result from ulceration, chronic granulomatous disease, foreign bodies, and bezoars. Bezoars may be caused by hair, vegetable matter, milk curds, or medications. Long-acting formulated oral medications may also become bezoars in the distal intestine and cause obstruction.

Intestinal Obstruction

Rushes of bowel sounds associated with cramping and colic often indicate intestinal obstruction. Vomiting is a cardinal sign of intestinal obstruction, being more prominent in high small bowel obstruction than in low small bowel or colon obstruction. With high obstructions, vomiting is not feculent, the onset is often acute, and crampy pain may occur at frequent intervals; abdominal distention is minimal. With low obstructions, in contrast, the vomiting may be feculent and less acute in onset, the interval between cramping is longer, and distention is

Text continued on p. 215

TABLE 12.11 Diagnostic Tests: Blood and Urine

Blood Test	Findings	Possible Significance
CBC		
Hct/Hb	↑	Dehydration: general vomiting
	↓	Hematemesis; metabolic; chronic malnutrition; hypersplenism; hemolysis (e.g., sickle cell)
WBC (PMNs, bands)	↑	Sepsis; inflammatory/ischemic lesions
	↓	Metabolic; sepsis; viral; hypersplenism; malnutrition
Eosinophils	↑	Allergic (eosinophilic gastroenteropathy), parasitic, Addison disease
Platelets	↑	Inflammatory (e.g., inflammatory bowel disease)
	↓	Hematemesis; metabolic; hypersplenism
Electrolytes		
Na	↓ (↓)	Adrenal insufficiency; general vomiting
	↑	Salt poisoning, dehydration
K	↓	General vomiting
	↑	Adrenal insufficiency; uremia; bleeding; digitalis; diuretics (e.g., spironolactone)
Cl	↓ (↓)	Adrenal insufficiency; general vomiting
	↑	Salt poisoning, hypernatremic dehydration
Bicarbonate	↑ (pH ↑)	General vomiting, pyloric stenosis
	↓ (pH ↓)	Metabolic; adrenal insufficiency; poison; renal tubular acidosis; severe diarrhea; shock
Glucose	↑	Metabolic: diabetic ketoacidosis
	↓	Metabolic, toxins
BUN	↑	Dehydration, hematemesis
Creatinine	↑	Dehydration, renal failure
Calcium	↑	Hypercalcemia
Blood gas	↓ pH, ↓ P_{CO_2}	Metabolic disease; adrenal insufficiency; poison; severe diarrhea; shock
ALT, AST	↑	Hepatitis; metabolic
GGT, ALP	↑	Biliary obstruction
Bilirubin	↑	Hepatitis; metabolic; hemolysis (e.g., sickle cell)
Conjugated	↑	Biliary obstruction
Amylase, lipase	↑	Pancreatitis
NH_4	↑	Metabolic, liver failure, *Proteus* urinary infection
Ketones	↑	Metabolic, fasting/starvation
Amino acids	↑	Metabolic
Organic acids	↑	Metabolic
IgE, RAST (especially foods)	↑	Allergic enteropathies
PT, PTT	↑	Hematemesis, coagulopathy, liver failure, poisoning
Toxicology	+	Drug; poison
Culture	+	Sepsis; ischemic/perforated bowel
Urine Test		
pH	↑	General vomiting
WBC	+	Urinary tract infection
Protein, casts	+	Renal disease
Blood	+	Urinary tract infection or bleeding
Bilirubin	+	Liver disease, hemolysis
Electrolytes		
Na	↓	General vomiting
K	↑	General vomiting
Cl	↓	General vomiting
Bicarbonate	↑	General vomiting
Ketones	+	Metabolic, fasting/starvation
Reducing substance		
Glucose	+	Diabetic ketoacidosis
Nonglucose	+	Galactosemia
Fanconi syndrome	+	Metabolic
FeCl	+	Metabolic
Amino acids	↑	Metabolic
Organic acids	↑	Metabolic
Toxicology	+	Drug; poison
Culture	+	Urinary tract infection; sepsis

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count; Cl, chloride; FeCl, iron chloride; GGT, γ-glutamyltransferase; Hct/Hb, hematocrit/hemoglobin; IgE, immunoglobulin E; K, potassium; metabolic, inborn error of metabolism; Na, sodium; NH_4, ammonium; P_{CO_2}, partial pressure of carbon dioxide; PMNs, polymorphonuclear neutrophils; PT, prothrombin time; PTT, partial thromboplastin time; RAST, radioallergosorbent test; WBC, white blood cell count; +, present; ↑, increased; ↓, decreased; (↓), may or may not be decreased.

TABLE 12.12 Other Diagnostic Tests

Test	Findings	Possible Significance
Imaging		
Routine	Isolated/distended loops	Obstruction, ischemia
Plain abdomen	"Ladder" pattern	Small bowel obstruction
	"Inverted U" pattern	Distal colon obstruction
	Double bubble	Duodenal atresia
	Calcifications	Biliary, renal stones, appendicitis
	Free air	Intestinal perforation
	Free fluid	Ascites
	Foreign bodies	Foreign body
	Organomegaly, masses	Organomegaly, masses
Upright abdomen	Air-fluid levels	↑ Secretion: gastroenteritis Obstruction
Laterals, decubitus	Free air	Perforation
Chest film	Heart or lung disease; free air	Heart or lung disease; perforation
Barium		
Upper fluoroscopy	Malrotation; obstructions	Volvulus; obstructing lesions
Enteroclysis	Distal obstructions	Distal small bowel lesions
Lower fluoroscopy	Mass, obstruction, intussusception	Therapeutic: intussusception
Gastrografin		
Upper fluoroscopy		
Lower fluoroscopy		Therapeutic: meconium ileus, DIOS
Ultrasonography	Mass, cyst, abscess; pyloric stenosis; hepatobiliary, pancreatic, urinary, gynecologic lesions; blood flow in vessels	
CT/MRI abdomen	Mass, cyst, inflammatory lesions; hepatobiliary, pancreatic, urinary, gynecologic lesions	
MRI/CT head	CNS lesions	Neurogenic vomiting
Endoscopy		
Upper		
Diagnostic	Diagnosis: obstruction, hemorrhage, *Giardia* or *Helicobacter pylori* infection	Obstruction, hemorrhage
Therapeutic		Therapeutic: hematemesis
Lower		
Diagnostic	Diagnosis: distal obstruction, infection	Obstruction, infection
Therapeutic		Therapeutic: sigmoid volvulus
Manometry		
Esophagus	Failure of sphincter relaxation Dysmotility	Achalasia Pseudoobstruction
Small bowel	Dysmotility	Pseudoobstruction
Rectum/colon	Failure of sphincter relaxation Dysmotility	Hirschsprung disease Pseudoobstruction

CNS, central nervous system; CT, computed tomography; DIOS, distal intestinal obstruction syndrome: cystic fibrosis; MRI, magnetic resonance imaging.

TABLE 12.13 Hematemesis

Source of Blood	Lesion	Clues Regarding Source
Nasopharynx, respiratory	Epistaxis	Nosebleed history
	Hemoptysis	Cough, other respiratory symptoms
Esophageal	Varices	Copious blood; splenomegaly
	Esophagitis, Barrett ulcer	Heartburn
	Foreign body erosion	Foreign body history
	Aortoesophageal fistula	Copious blood; esophageal intubation
	Duplication	
Gastroduodenal	Mallory-Weiss tear	Emesis before hematemesis
	Peptic ulcer disease	History: smoking, alcohol, NSAIDs, pain, relation to meals
	Gastritis, ulcer	
	Duodenitis, ulcer	
	Stress ulcer	
	Dieulafoy ulcer	
	Vascular malformation	Recurrent (may have a negative endoscopy)
	Aortoenteric fistula	"Herald bleed," arterial graft or aneurysm
	Duplication	
	Pyloric stenosis, web	
	Hemobilia	Trauma, gallstones, pain, jaundice
Extrinsic		
Maternal	Intrapartum	Apt test
	Mastitis, cracked nipples	Maternal history, Apt test
Factitious	Psychologic	Affect, secondary gain
Nonblood	Red or brown food or medicine	Guaiac-negative

TABLE 12.14 Hematemesis: Causes Not to Miss and Red Flags

Finding	Etiology	Physical Examination and Laboratory Studies: Clues Regarding Source
Coagulopathy (PT ↑, PTT ↑)	Vitamin K deficiency	Newborn, antibiotics, fat malabsorption
	Genetic coagulopathies	Specific factor deficiencies
	Liver failure	Liver disease, factor VIII normal
	DIC	Sepsis, factor VIII ↓
	Drug Warfarin (Coumadin) Heparin	Drug history
Thrombocytopenia (platelets ↓)	Hypersplenism	Splenomegaly (Hct ↓, WBC↓)
	Chemotherapy	Chemotherapy history (Hct ↓, WBC ↓)
	DIC	Sepsis (PT ↑, PTT ↑)
Platelet dysfunction (bleeding time ↑)	Drug Salicylates/ NSAIDs Antibiotics	Drug history
Portal hypertension	Varices; gastritis	Splenomegaly Abdominal veins; angiomas Ascites Clubbing; palmar erythema

DIC, disseminated intravascular coagulation; Hct, hematocrit; NSAIDs, nonsteroidal antiinflammatory drugs; PT, prothrombin time; PTT, partial thromboplastin time; WBC, white blood cell count.

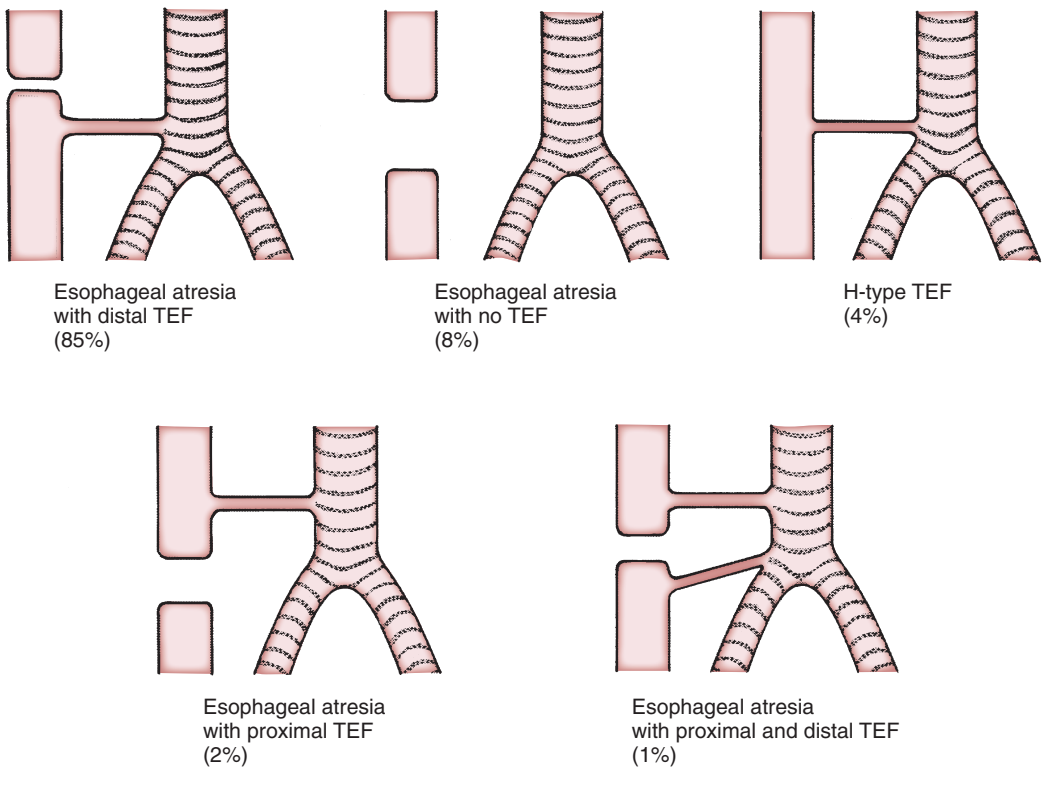


FIGURE 12.1 Various types of tracheoesophageal fistulas (TEF) with relative frequency (%).

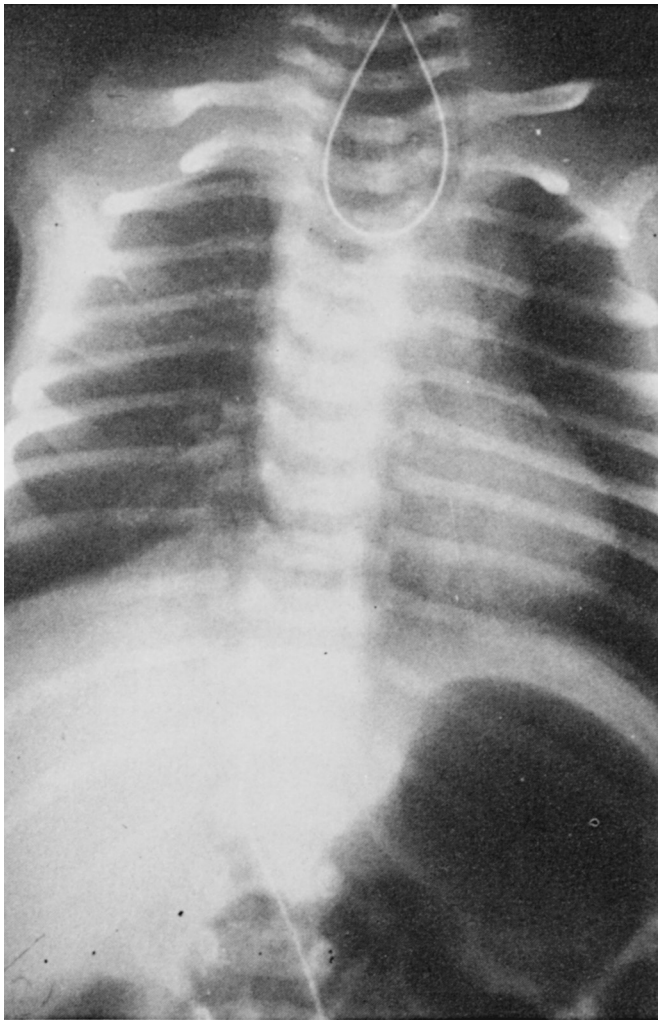


FIGURE 12.2 Tracheoesophageal fistula. Coiled radiopaque nasogastric tube in blind upper pouch.

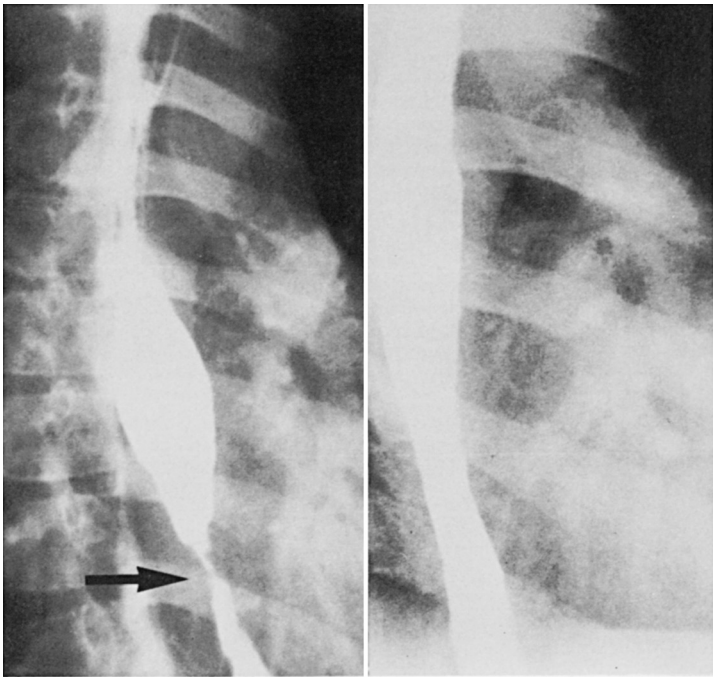


FIGURE 12.3 Esophageal stricture. Radiograph of a peptic esophageal stricture *(arrow)* before and after treatment with dilations.

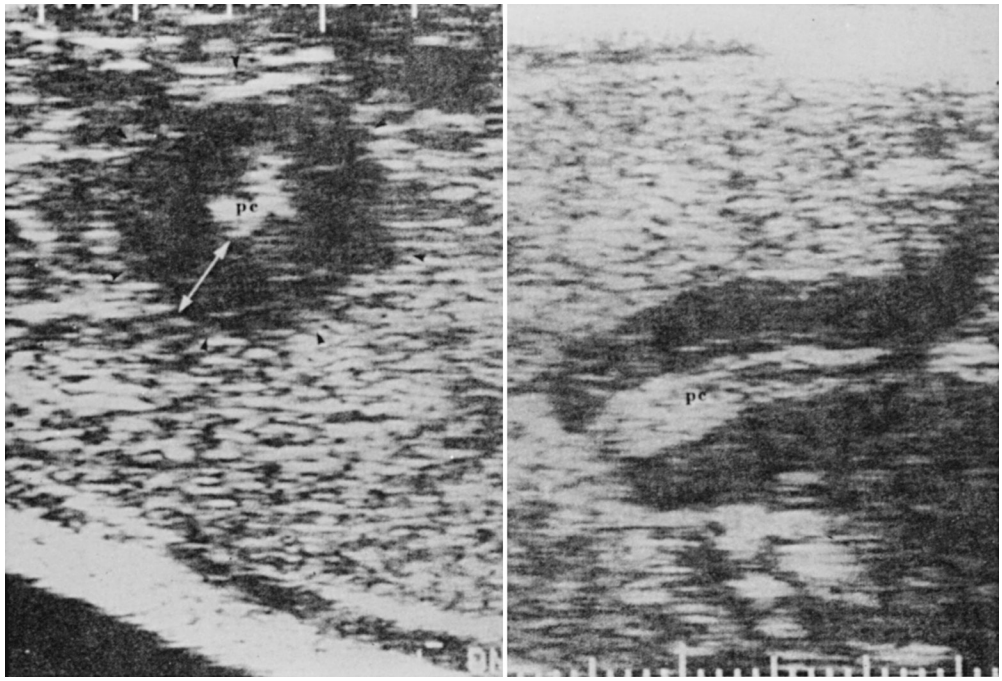


FIGURE 12.4 Pyloric stenosis. Cross-sectional *(left)* and transverse *(right)* sonograms of hypertrophic pyloric stenosis, showing increased thickness and length of pyloric muscle. pc, pyloric channel.

more notable. Identification of the site of obstruction is aided by the plain film and by other radiographic studies (see Table 12.12).

Obstructions may be categorized by type and site. Intraluminal lesions (e.g., tumors; intussusceptions; or extrinsic material such as feces, foreign bodies, bezoars, and gallstones) can be differentiated from bowel wall lesions (strictures, stenoses, atresias) and from extraluminal lesions (adhesions, congenital bands, tumors, volvulus). Radiographic studies are useful, beginning with the plain film and progressing to ultrasonography or CT. Fluoroscopy with contrast material such as barium or diatrizoate (Gastrografin, Hypaque, water-soluble contrast) is very helpful in identifying both the site and the type of obstruction, but the decision to introduce contrast into an intestine that may perforate or be operated on must be made with surgical and radiologic consultation. Often the decision to operate can be made without certain identification of the lesion, and contrast studies are unnecessary.

Infantile bilious vomiting is an important symptom of intestinal obstruction, which often signals a congenital gastrointestinal anomaly, particularly intestinal obstruction below the ampulla of Vater. Surgical consultation is needed early in these infants because they often require emergency therapy (Table 12.15).

Duodenal atresia, stenosis, and web; annular pancreas. The juxtaampullary duodenum is susceptible to a cluster of obstructing congenital anomalies. Infants with complete duodenal obstruction, most commonly atresia, present with bilious vomiting and a radiographic "double-bubble" sign (Fig. 12.5). Associated prematurity (and polyhydramnios) or anomalies, including renal, cardiac, and vertebral defects, occur in approximately 75% of infants; trisomy 21 is seen in about 50%. Double atresias, duplications, and malrotations are frequently seen. Infants with a partial duodenal obstruction caused by a stenosis or web may have such mild symptoms that they do not come to medical attention until regurgitation produces esophagitis or until a foreign body or bezoar is trapped at the obstruction. Treatment is surgery.

Duodenal hematoma. Blunt abdominal trauma (seatbelt injury, child abuse), or even endoscopic biopsies in the context of a coagulopathy, can produce an obstructing duodenal hematoma. Endoscopy in the setting of stem cell transplantation or other hematopoietic disease may place a patient at greater risk of such hematoma, requiring special consideration of the need for duodenal biopsies in these individuals. Therapy is symptomatic; jejunal feeding that bypasses the obstruction or parenteral nutrition may be required as the problem resolves.

Jejunal atresia, ileal atresia, and ileal stenosis. Patients with these congenital lesions present with bilious vomiting and more abdominal distention than those with duodenal lesions. The atresias are readily suspected and diagnosed in the neonatal period. Stenotic lesions may require radiography for diagnosis. Treatment is surgical.

Intestinal strictures. Strictures produce partial obstruction of the gastrointestinal tract and may be located from the esophagus to the anus. They may occur postsurgically (anastomotic), may follow necrotizing enterocolitis, may be caused by Crohn disease, or may result from ingestion of nonsteroidal antiinflammatory medications or high-dose pancreatic enzymes. Some patients may be treated with endoscopic dilatation, but many require surgical stricturoplasty (opening the bowel longitudinally and closing it transversely) or resection.

Adhesions. Obstructive symptoms in the child with a history of prior abdominal surgery may be caused by adhesive bands.

Duplications. These uncommon lesions may cause vomiting by extrinsic obstruction of the intestine or by intussusception. An abdominal mass may be palpable.

TABLE 12.15 Causes of Gastrointestinal Obstruction

Esophagus	
Congenital	Esophageal atresia (with or without fistula) Isolated esophageal stenosis Duplication Vascular ring
Acquired	Caustic agent esophageal stricture Peptic stricture Chagas disease Collagen vascular disease
Stomach	
Congenital	Antral webs
Acquired	Pyloric atresia* Bezoars/foreign body Pyloric stenosis Pyloric stricture (ulcer) Crohn disease Eosinophilic gastroenteropathy Prostaglandin-induced pyloric stenosis Chronic granulomatous disease
Small Intestine	
Congenital	Duodenal atresia Annular pancreas Malrotation/volvulus Malrotation/Ladd bands Ileal atresia, stenosis Duplications Meconium ileus Inguinal hernia Gastroschisis
Acquired	Postsurgical adhesions or strictures Crohn disease (stricture) Intussusception Duodenal hematoma (abuse, trauma) Meconium ileus equivalent
Colon	
Congenital	Meconium plug Hirschsprung disease Colonic atresia, stenosis Imperforate rectum/anus Rectal stenosis Malrotation/volvulus Small left colon syndrome (IDM)
Acquired	Ulcerative colitis (toxic megacolon)† Crohn disease (stricture) Chagas disease Stricture post-NEC

*Often associated with epidermolysis bullosa.
†Produces an ileus.
IDM, infant of diabetic mother; NEC, necrotiing enterocolitis.
From Behrman R, Kliegman R. *Nelson Essentials of Pediatrics*. 2nd ed. Philadelphia: WB Saunders; 1994:407.

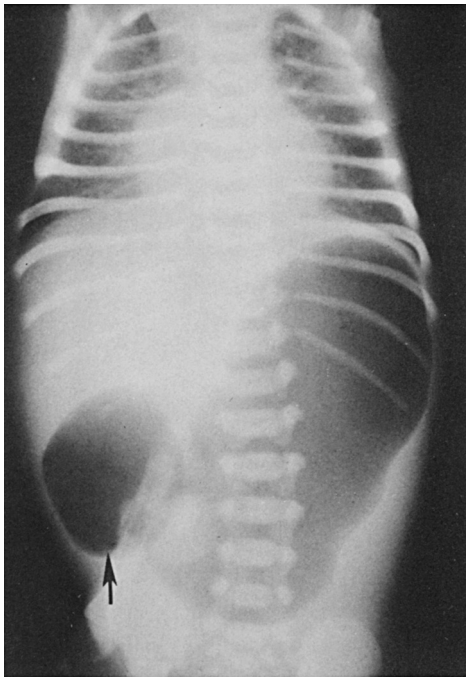


FIGURE 12.5 "Double-bubble" sign *(arrow)* in duodenal obstruction.

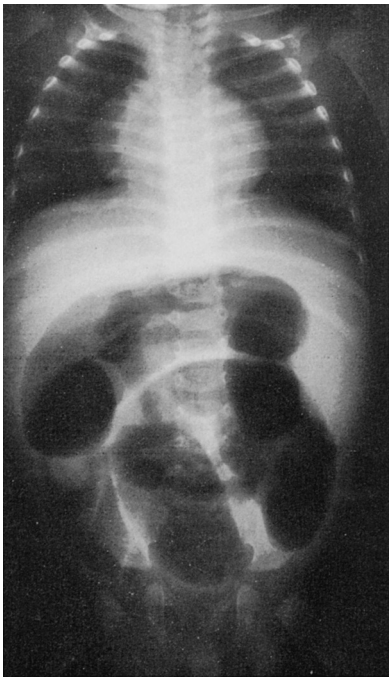


FIGURE 12.7 Intestinal obstruction.

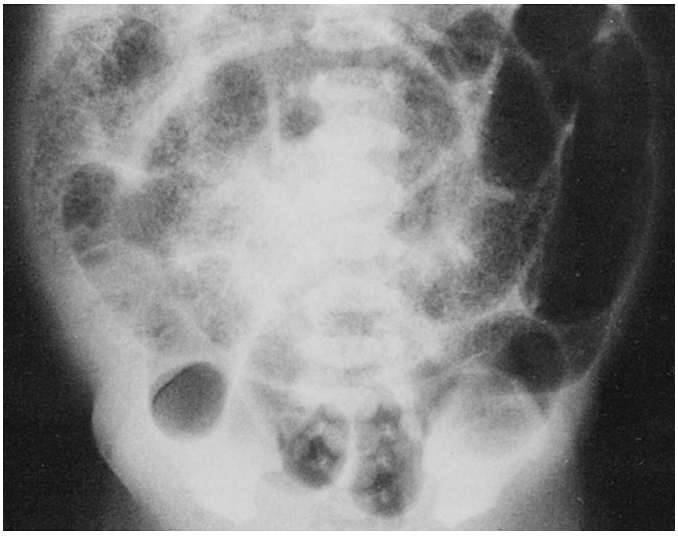


FIGURE 12.6 Meconium ileus.

Meconium ileus and distal intestinal obstruction syndrome (DIOS). Ten percent of infants with cystic fibrosis present in the newborn period with failure to pass meconium, caused by meconium ileus (Fig. 12.6). The inspissated meconium may be treated by diatrizoate (Gastrografin) enema, but some infants require surgery, particularly if they have a perforated viscus, which occurs prenatally in 10% and produces a calcified meconium peritonitis. Virtually all infants with meconium ileus have cystic fibrosis; the diagnosis should be confirmed by sweat test or DNA analysis. Older children with cystic fibrosis who stop defecating and have abdominal pain and occasionally vomiting are said to have distal intestinal obstruction syndrome (DIOS), formerly termed meconium ileus equivalent.

The sticky, poorly hydrated intestinal mucus plays a role. Initial treatment with intestinal lavage and enemas may be successful, but, if not, diatrizoate (Gastrografin) enemas (at times mixed with N-acetylcysteine) are nearly always successful. Surgery is rarely required. Close attention to fluid and electrolyte balance is vital in all infants and children treated with a hypertonic contrast medium such as diatrizoate (Gastrografin).

Incarcerated hernia. Whenever vomiting is accompanied by signs of obstruction, sites of potential herniation should be examined for incarceration of a loop of bowel (Fig. 12.7). Inguinal incarceration is most common, but other types of hernias are femoral, obturator, spigelian, umbilical (1 in 1500 incarcerate), epigastric, mesenteric, and postoperative incisional hernias.

Inguinal hernias are often reduced by gentle, firm, constant pressure that is directed through the scrotum toward the inguinal canal. Sedation and the Trendelenburg position may facilitate reduction.

Malrotation and volvulus. Volvulus is the twisting of a loop of bowel on the mesentery. Midgut volvulus occurs most often in the context of congenital intestinal malrotation, in which the small intestine is not normally fastened in place. This may only be clinically apparent on upper GI fluoroscopy when the duodenum and distal small bowel is seen to fill with contrast right of midline without crossing to the left upper quadrant (Fig. 12.8). More than half of patients found to have malrotation present symptomatically (the rest of such cases are discovered incidentally), and about half of the symptomatic patients present in the neonatal period with bilious vomiting caused by volvulus. Those presenting later often do not have bilious vomiting; the vomiting may be intermittent for years.

Volvulus is an extremely hazardous obstructing lesion. The luminal obstruction is closed at both ends, which leads to sepsis from rapidly proliferating and translocating bacteria. There is also vascular obstruction in which the root of the mesentery is twisted, which quickly produces ischemia of the small intestine. Even if volvulus is diagnosed and repaired promptly, massive intestinal resection may be necessary; this produces short bowel syndrome. Because volvulus may be intermittent, it may produce episodic or chronic intermittent vomiting or nonspecific abdominal pain before a lethal event. Upper intestinal contrast radiographs should be considered in the intermittently regurgitating infant, and surgery must be performed if a malrotation is

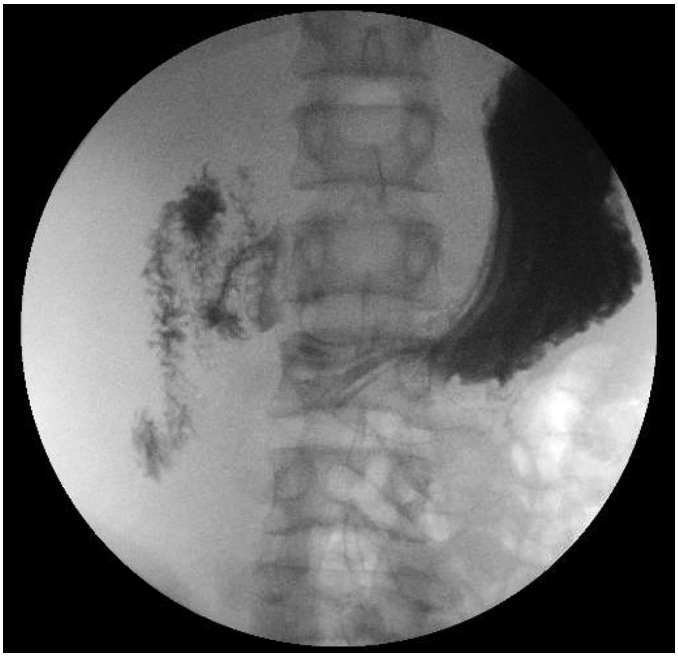


FIGURE 12.8 Contrast fluoroscopy (upper GI series) demonstrating malrotation. Note the small bowel fills with contrast all to the right of midline and does not cross over the left upper quadrant where the ligament of Trietz would be normally located.

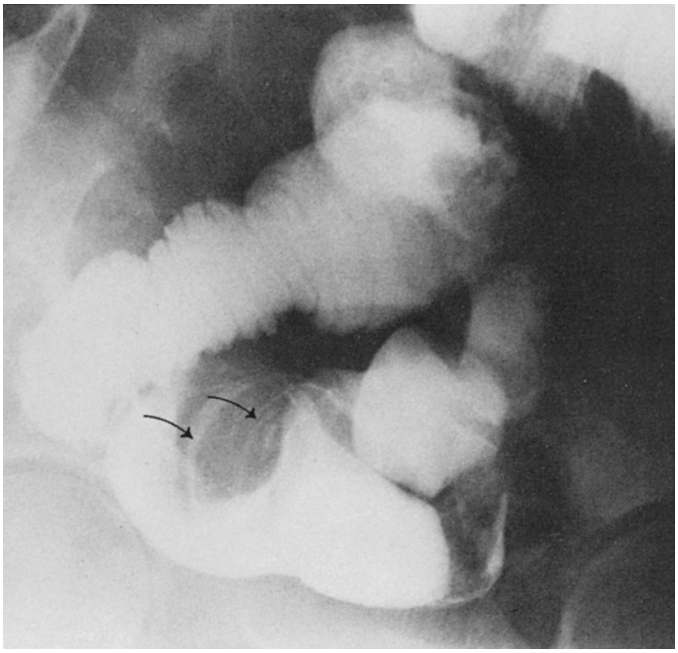


FIGURE 12.9 Enteroenteric intussusception *(arrows)*.

found (i.e., if the ligament of Treitz is not to the left of the spine), even if volvulus is not present at the time of the examination. In an infant in whom an ongoing volvulus is suspected, an abdominal flat plate may show a "double bubble with distal air" or a "volvulus/corkscrew" pattern. In the sick infant or child in whom volvulus seems likely, surgery without contrast studies may be preferred. Surgery deals both with the malrotation and with the often-accompanying, potentially obstructing Ladd bands.

Other types of volvulus not associated with malrotation include cecal, sigmoid, and transverse colonic volvulus. They are less common in children and less apt to produce short bowel syndrome, but they, too, may manifest with vomiting and result in death if untreated. Sigmoid volvulus is sometimes treated nonoperatively.

Meckel diverticulum. Meckel diverticula may cause obstructive vomiting by intussusception (Fig. 12.9) or by intestinal volvulus around a fibrous band. They may also cause vomiting by inflammatory changes, and they may bleed. This fibrous remnant of the omphalomesenteric duct is a small intestinal diverticulum. The "rule of 2s" identifies characteristic findings: These diverticula are present in 2% of the population; the male-female ratio is 2:1; the diverticula occur within 2 feet of the ileocecal valve and are 2 inches long; there are 2 major types of heterotopic mucosa (50% of patients have gastric mucosa, and a minority have pancreatic mucosa; in rare cases, colonic mucosa is present); the condition is confused with 2 diseases (appendicitis and peptic ulcer); and there are 2 complications (hemorrhage occasionally with perforation or intussusception).

Diagnosis of the ectopic gastric mucosa is by Meckel scan (technetium 99m pertechnetate); it has imperfect sensitivity, which may be improved by pentagastrin, glucagon, and cimetidine. Treatment is surgical.

Intussusception. The normal function of the intestine is to constrict above and relax below an intraluminal bolus. When such a bolus (a "lead point") is attached to the intestinal wall, the propulsive activity of the intestine produces telescoping of proximal intestine (intussusceptum) into distal intestine (intussuscipiens), causing both luminal obstruction, and mesenteric vascular compromise. Abdominal pain occurs in nearly all children with intussusception, whereas vomiting results in about 65%, and "currant-jelly stools" (from mucosal hemorrhage) occur in fewer than 20%. The pain is severe, crampy, and often contemporaneous with the vomiting. Between cramps, the child may be listless, may sleep, or may even play. Vomiting and bloody stools are more common in younger infants and in those with longer duration of symptoms. An abdominal mass is palpable in about 25% of patients.

The lead point of the intussusception is usually ileal, with the intussusception ileocecal or ileocolonic. It is probable that prominent ileal lymphoid nodules provide the lead point for most young children presenting with intussusception, 66% of whom are younger than 2 years, with a peak incidence late in the 1st year of life. Other lead points (Meckel diverticulum [see Fig. 12.9], appendix, duplication, polyp, lymphoma, hematoma from trauma or from Henoch-Schönlein purpura) or disorders (cystic fibrosis) must be considered in the very young or older child presenting with intussusception. Transient recurrent small bowel intussusception may also be a feature of celiac disease.

Visualization may be by ultrasonography if the diagnosis is uncertain but is more often by radiographic studies, inasmuch as radiologic reduction enemas are usually curative in infants.

Treatment is by hydrostatic reduction with barium; rectal insufflation of air has also been used but may be less able to document a lead point that necessitates surgical resection. Contraindications to reduction by hydrostatic enemas include the presence of symptoms for longer than 48-72 hours, peritonitis, and intestinal perforation. Approximately 10% of patients experience recurrences.

Superior mesenteric artery syndrome. Superior mesenteric artery (SMA) syndrome is caused by extrinsic compression of the duodenum, which is trapped between the SMA anteriorly and the aorta posteriorly as the SMA crosses over the duodenum in the root of the mesentery. The compression is usually just to the right of midline, where it produces a cutoff of the duodenum that is visible radiographically, often with proximal dilation. Synonyms include Wilkie syndrome, arteriomesenteric duodenal compression, and cast syndrome.

SMA syndrome may be suspected when bilious emesis and epigastric discomfort relieved by vomiting occur in the context of weight loss, lordosis, body casts, lengthy bed rest, or prior abdominal surgery, particularly when crampy pain is relieved by prone or knee-chest positions. Adolescents and young adults are most often affected.

Nutritional rehabilitation, either intravenously or by the enteral route, is important in SMA syndrome. The prone position may improve duodenal emptying. Surgery may be needed if there are chronic symptoms despite nutritional rehabilitation.

Constipation, meconium plug, and anal stenosis. These distal colonic problems produce obstipation primarily, but if they are severe and persistent, vomiting may result. Rectal examination provides the diagnosis. Enemas, laxatives, dietary changes, and behavioral modification are useful in treating constipation, whereas surgery is usually necessary to treat anal atresia or stenosis. Infants with meconium plug syndrome need clinical follow-up to monitor for the presence of coexistent Hirschsprung disease.

Gastrointestinal Dysmotility

Achalasia

Achalasia, like esophageal stenoses and strictures, produces effortless retrograde emptying of undigested food from the esophagus. Contrast radiography and esophageal manometry are needed for diagnosis. Nifedipine, sildenafil, and botulinum toxin have been reported to produce at least temporary clinical benefit in many patients, but ultimately balloon pneumatic dilation or surgical myotomy are required for sustained benefit.

Gastroesophageal Reflux

The apparently effortless *regurgitation* that represents gastroesophageal reflux in infants is of particular importance because (1) it is the most common cause of "vomiting" in infants; (2) physiologic reflux must be distinguished from reflux necessitating evaluation and therapy; and (3) the practitioner must be vigilant to avoid misdiagnosing other infantile vomiting diseases as reflux. Lethal malrotation with volvulus, partially obstructing duodenal web, and metabolic disorders are 3 examples of such misdiagnoses. Children with primary neurologic disease may be more likely to regurgitate and suffer from reflux disease; it must be remembered that many metabolic disorders manifest both as neurologic dysfunction and as regurgitation.

Reflux typically is a benign feature in healthy infants that improves and resolves in a predictable manner as a function of growth, development, acquiring upright positions, and introducing some solids in the diet. In these infants, regurgitation will be effortless and will not have associated failure to gain weight, feeding problems, or airway symptoms.

Infants with more problematic regurgitant reflux who come to medical attention should undergo upper gastrointestinal radiography to rule out the possibility of malrotation. Reflux may cause failure to gain weight (resulting from regurgitation of caloric feedings, odynophagia from esophagitis, or parental reluctance to feed a recurrently spitting infant), apnea, chronic respiratory disease, hoarseness or stridor, abdominal or chest pain, infantile irritability, or **Sandifer syndrome** (arching of the spine and turning of the neck). Regarding Sandifer syndrome, while the term is still utilized in the description of infants with reflux by some, one should recall that the original published description from 1964 described the sign in older children with profound neurologic impairment, and not in otherwise unremarkable healthy infants. Diagnostic evaluation should be tailored to the presentation: Regurgitation prompts barium contrast radiography with fluoroscopy; anorexia or infantile irritability prompts evaluation for esophagitis by endoscopy with esophageal biopsy, esophageal biopsy alone if feasible, or possibly pH study if no response to a 2-week trial of hypoallergenic formula and/or acid suppression is noted; apnea prompts pH or impedance study to be conducted with a sleep study (especially if the apnea is repetitive); hoarseness or stridor prompts laryngoscopy, endoscopy for esophageal histologic study, or possibly a trial of aggressive therapy that may include proton pump inhibitor (PPI) agents; heartburn prompts a 2- to 4-week trial of either histamine-blocking or PPI agents, followed by endoscopy if no response is seen or if symptoms resume as medication is tapered. In the setting of asthma, signs or symptoms of reflux should prompt evaluation by endoscopy with biopsies and pH/impedance testing. Coincident reflux disease or eosinophilic esophagitis require treatment; in settings where these are not found, empirical treatment of asthma with acid suppression is not effective and therefore not warranted.

Treatment of regurgitant reflux in infants is initiated with avoidance of seated or supine positioning (particularly postprandially) and with thickening of the feedings with 1 tablespoon of dry rice cereal per ounce of formula. In many infants, this reduces regurgitation remarkably. Problematic regurgitation persisting during this treatment, particularly if associated with poor weight gain or other signs of illness, necessitates upper gastrointestinal fluoroscopic evaluation and consideration of other causes for the vomiting, such as metabolic or allergic disease. A 2-week trial of a protein hydrolysate or elemental formula as empirical therapy for allergic vomiting (formula protein intolerance) may be helpful, particularly if there is a family history of allergy or if there is peripheral eosinophilia. If the diagnosis remains reflux, a prokinetic agent is frequently begun. Metoclopramide may be used; although its efficacy in reflux has never been proved, its therapeutic margin is narrow, and its side effect profile is concerning. An oral H_2-receptor antagonist or proton pump inhibitor is added if esophagitis is suspected or documented. In view of the current limitations and uncertainties surrounding prokinetic agents, however, many infants and children may be adequately managed with aggressive acid suppression alone.

Management is re-evaluated at least every 2 months for the need to increase doses, to discontinue medications, or to re-evaluate the diagnosis. Infants with reflux usually improve on this management, which can usually be discontinued between 8 and 18 months of age, as symptoms resolve. The rare infant who does not improve and develops nutritional, respiratory, or peptic complications from reflux is evaluated for surgical fundoplication (Fig. 12.10).

Gastric Stasis and Gastroparesis

Gastric stasis is suggested by the vomiting of food eaten hours earlier and by the presence of food in the stomach of a fasting patient undergoing an upper gastrointestinal series. If the contrast study excludes gastric outlet obstruction, gastroparesis is likely. Diabetic gastroparesis, in which autonomic neuropathy resulting from diabetes causes gastric atony, is the classic example of this disorder but is rare in childhood. Surgical vagotomy produces similar symptoms (typically in the setting of operated congenital heart disease). Other causes of generalized ileus or pseudoobstruction can involve the stomach primarily. Viral infections, perhaps including gastric cytomegalovirus, and drugs such as anticholinergics may also produce gastric stasis.

Gastric stasis may respond to the prokinetic agents, erythromycin or metoclopramide, particularly if the cause is neurogenic. These medications may have additive effects.

Ileus

Paralytic ileus, typified by the postoperative ileus that follows most abdominal surgery, is very common. As in intestinal obstruction,

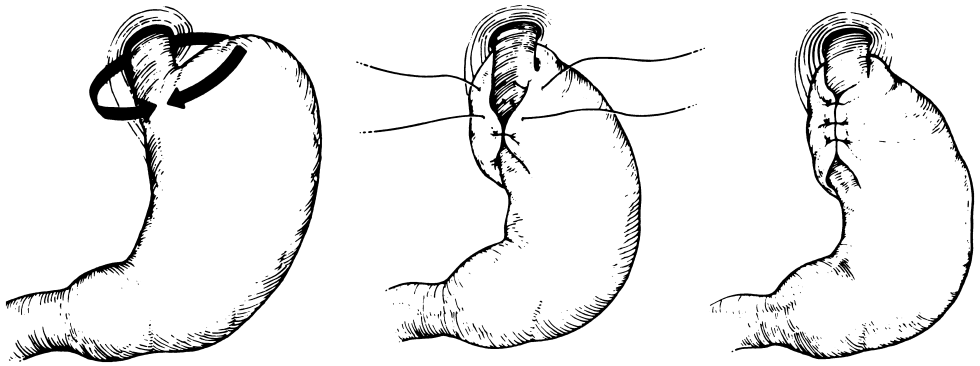


FIGURE 12.10 Diagrams of a Nissen fundoplication.

intestinal contents fail to progress, causing abdominal pain and vomiting. Typically, the bowel sounds are decreased or absent; there may be abdominal distention. Other causes of ileus include unrelieved intestinal obstruction, peritonitis, intestinal ischemia, and sepsis. Signs of ileus may follow signs of intestinal obstruction; in this context, ileus is an ominous sign. Other causes of paralytic ileus are drugs (phenothiazines, narcotics, laxative abuse, atropine), electrolyte disturbances (hypokalemia, hypercalcemia), endocrinopathies (hypothyroidism), or injuries (spinal fractures). Both chemotherapy and radiation therapy can produce reversible acute symptoms of vomiting, abdominal pain, and diarrhea within a few days to several weeks of the insult; intestinal motor disturbances are the suggested cause.

Treatment of ileus requires correction of any correctable provocative abnormalities and nasogastric tube decompression until normal peristalsis begins.

Pseudoobstruction

Intestinal pseudoobstruction represents intestinal dysmotility rather than obstruction. Pseudoobstruction is a chronic illness, sometimes with remissions and relapses, and is far rarer than acute ileus. Enteroclysis radiographic studies may be necessary to confirm the absence of partial obstruction. There is a family history in 20-30% of patients, and nearly 50% of children with the disorder are symptomatic in the 1st month of life, although diagnosis is often quite delayed. **Malrotation** may be found in up to 40% of patients with pseudoobstruction. The disorder may involve any part or the entire luminal gastrointestinal tract and occasionally (in up to 10% of patients) involves the urinary tract. A relatively quiet abdomen or prominent borborygmi may be present, and abdominal distention (in 70% of patients) is often associated with succussion splashes when the patient moves. Vomiting occurs in 50% of patients, and constipation may be prominent (in >50%). Weight loss is caused by both vomiting of nutrients and by bacterial overgrowth–induced malabsorption.

Several causes for pseudoobstruction have been identified; they are generally classified as either **neuropathic** or **myopathic**. Familial versus nonfamilial and primary versus secondary are 2 other classifications. Differentiation between neuropathic and myopathic types is best made by small intestinal manometry; esophageal manometry may contribute as well. Full-thickness intestinal biopsy is sometimes useful for distinguishing specific entities causing the disorder; special silver stains of the myenteric plexus are particularly helpful. The myopathic causes (in 10% of pediatric patients, a much lower proportion than that of adults) include collagen vascular causes of myositis or muscle fibrosis (progressive systemic sclerosis), various muscular dystrophies, megacystis-microcolon, and "familial visceral myopathies." The neuropathic causes (90%) include Hirschsprung disease, Chagas disease, diabetic and other autonomic neuropathies, autoimmune disorders producing inflammatory neurodegeneration, multiple endocrine neoplasia, and "familial visceral neuropathies." Both types of pseudoobstruction are difficult to manage; the myopathic form, representing dysfunction of the "end organ," is particularly difficult.

A 3rd category that is sometimes included in the myopathic type is fibrotic involvement of the muscularis propria. It may follow collagen vascular diseases, radiation therapy (>6 months after), or chemotherapy by months or years, causing either myopathic pseudoobstruction or obstruction resulting from inflammatory strictures.

Functional failure of intestinal propulsion can be treated with erythromycin or metoclopramide. These medications are more apt to be useful in neurogenic disorders than in myogenic ones. Because of their different sites of action, they may have additive effects. Patients with pseudoobstruction also benefit from antibiotic treatment of bacterial overgrowth syndrome, when present, or from nutritional rehabilitation with total parenteral nutrition. Collagen vascular or autoimmune causes of pseudoobstruction may respond to steroids. Cautious surgery is occasionally beneficial; some patients eventually require intestinal transplantation.

Gastrointestinal Inflammation

Esophagitis

Esophagitis may be associated with vomiting in the setting of eosinophilic esophagitis (EoE), where patients may also experience nausea and/or dysphagia. With regard to reflux disease, esophagitis is associated with vomiting, but it is usually not the primary cause.

Gastroenteritis

Gastroenteritis is a frequent cause of acute vomiting illness in childhood. The vomiting is often associated with diarrhea and sometimes with crampy abdominal pain or fever. Rotavirus, especially in infants, is notable for its prominent vomiting, which often precedes the diarrhea. "Food poisoning" also produces vomiting and diarrhea, often caused by bacterially derived toxin. The time course and symptoms suggest which organism is involved. Gastroenteritis, like regurgitant reflux, is common and often necessitates minimal diagnostic procedures and therapy; however, the examiner must constantly guard against making this diagnosis in a child who might have metabolic or surgical disease.

Treatment of acute gastroenteritis mandates attention to hydration. Oral rehydration is feasible in many children with gastroenteritis, but prominent vomiting may make intravenous rehydration necessary. A common error is to use clear liquids longer than 24 hours; this leaves nutritional needs unmet. Early refeeding in gastroenteritis is most successful when the food is low in fat and lactose and high in complex carbohydrates.

Peptic Ulcer Disease

The term *peptic ulcer disease* includes gastritis, gastric ulcer, duodenitis, and duodenal ulcer. In children, in contrast to adults, these disorders frequently cause vomiting. Defined causes for peptic ulcer disease include *H. pylori* infections, bile reflux gastritis, nonsteroidal anti-inflammatory agents, and rare gastrin-secreting tumors (Zollinger-Ellison syndrome). Stress ulcers occur in the context of sepsis, burns, surgery, head trauma, and severe acute illness.

The optimal diagnostic method is endoscopy, with evaluation for *H. pylori* or elevated gastrin in appropriate cases. Acid suppression is the preferred treatment. Discontinuation of tobacco smoke exposure is important. *H. pylori* infections are treated with evolving regimens of double or triple antibiotics plus acid suppression drugs; eradication rate is approximately 85% for most treatments. Zollinger-Ellison syndrome is optimally treated by tumor resection and evaluation for related endocrine tumors; PPI treatment is helpful if complete tumor resection is impossible.

Meckel Diverticulitis

In addition to presenting as gastrointestinal obstruction, via volvulus or intussusception, Meckel diverticula may become inflamed and mimic appendicitis.

Treatment is surgical, so preoperative distinction of Meckel diverticulitis from other causes of an acute abdomen is not crucial.

Mesenteric Adenitis

Mesenteric adenitis is often found on CT scans and refers to inflammation of lymph nodes in the mesentery. It is probably caused by viral (adenovirus, measles) or bacterial (*Yersinia enterocolitica*) infection, but the symptoms are similar enough to appendicitis that the diagnosis is usually not made before surgery. Ultrasonography can readily distinguish mesenteric adenitis from appendicitis.

Appendicitis

When vomiting occurs in appendicitis, it follows the periumbilical pain but may precede the localization of the pain to the McBurney point, two-thirds of the way between the umbilicus and the right anterior iliac spine. Before perforation, there is only occasional vomiting. After perforation, the fever may be higher; the child lies still with the right hip flexed, and vomiting may be more frequent and more feculent. In appendicitis, there is later vomiting, less diarrhea, fewer bowel sounds, and more rectal or rebound tenderness than in gastroenteritis. It is also associated with less diarrhea, less fever, and less leukocytosis than is bacterial enteritis, although *Yersinia*, in particular, has caused right lower quadrant pain mimicking appendicitis. Crohn disease is usually more chronic than is appendicitis but sometimes is diagnosed by surgeons at the time of appendectomy based on serosal changes to the bowel.

Inflammatory Bowel Disease

Crohn disease, in particular, may produce vomiting on occasion, particularly when obstructing intestinal strictures develop. Other extraintestinal manifestations of Crohn disease also, in rare cases, produce vomiting.

Allergic Enteropathy, Eosinophilic Gastroenteropathy, and Eosinophilic Esophagitis

Vomiting is a frequent response to ingestion of allergens and may be seen as early as the 1st weeks of life in infants with allergy to cow's milk or soy and in older children as potentially allergenic foods are introduced. There may be associated diarrhea and hematochezia and, in some children, urticaria or other systemic signs of allergy. A strong family history for allergic diathesis is very suggestive. Laboratory studies may show peripheral blood eosinophilia or an elevated serum immunoglobulin E level; positive radioallergosorbent test results to individual foods are helpful if present.

In infants, the simplest diagnostic test is a change to a protein hydrolysate or elemental formula for at least 2 weeks. If the vomiting (and other symptoms) resolve, it is generally not necessary to rechallenge for diagnosis, but empirical treatment can be continued for several months. Because infants usually outgrow these formula protein intolerances between 10 and 24 months of age, a normal diet can later be gradually introduced as tolerated. Older children with vomiting that represents eosinophilic gastroenteropathy or other immunoglobulin E–mediated food allergy are less likely to lose the allergy over time. Diagnosis otherwise is by upper intestinal endoscopy with biopsies, which demonstrate an increased number of mucosal and intraepithelial eosinophils and, possibly, varying degrees of villous injury. Eosinophilic esophagitis, which may occur independently of eosinophilic gastroenteropathy, should be kept in mind, particularly with patients manifesting dysphagia or reflux symptoms poorly responsive to standard therapy. At endoscopy, the esophageal mucosa displays a ringed or furrowed appearance with granularity (Fig. 12.11).

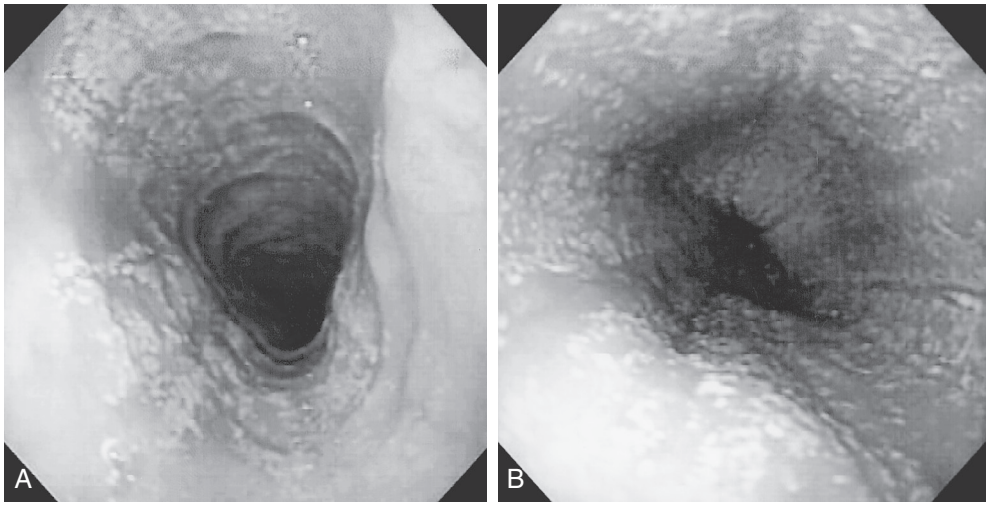


FIGURE 12.11 Endoscopic appearance of eosinophilic esophagitis, demonstrating concentric rings in proximal esophagus *(A)* and granularity with mucosal furrowing in distal esophagus *(B)*.

(See *Nelson Textbook of Pediatrics,* p. 1819.)

If sensitization to particular foods is identified through radioallergosorbent or skin testing, an elimination diet is employed; patients with prohibitive numbers of food allergies may require an amino acid–based diet. Steroids may be necessary for children with negative investigation findings for food allergy or for whom compliance with a restricted diet is problematic.

Gastrointestinal Ischemia and Vascular Insufficiency

Some of the causes of gastrointestinal ischemia can produce perforation, peritonitis, and death quite rapidly. Chronic low-grade gastrointestinal ischemia has also been described in high-level endurance athletes. A high degree of suspicion is useful because the signs are nonspecific.

Abdominal Migraine

In this periodic syndrome of abdominal symptoms, epigastric or periumbilical pain may accompany nausea and vomiting. Diarrhea, fever, chills, vertigo, irritability, and polyuria have also been reported. The symptoms are probably a result of muscular constriction of the mesenteric arteries, which causes ischemia. Some pathophysiologic overlap with cyclic vomiting syndrome also has been proposed. When these abdominal symptoms coexist with head pain, which occurs in 30-40% of patients with migrainous headaches, the diagnosis is simpler than when they occur in isolation, which happens in about 3% of patients who later experience typical migrainous headaches. Usually, isolated abdominal migrainous attacks occur suddenly, last an hour to days, and are consistent in character within the same individual. There is usually a family history of migraine, and patients are asymptomatic between attacks. A personal history of car (motion) sickness may be present. Abdominal migraine is closely associated with the cyclic vomiting syndrome (Table 12.16). Symptoms of abdominal migraine often respond to prophylactic propranolol, cyproheptadine, or amitriptyline.

Vasculitis

Inflammation of the mesenteric vessels is uncommon but may cause gastrointestinal complaints, including vomiting, abdominal pain, diarrhea, and gastrointestinal bleeding. Henoch-Schönlein purpura is the most common pediatric vasculitis; systemic lupus erythematosus, dermatomyositis, polyarteritis nodosa, and other hypersensitivity vasculitides are occasional causes. The most diagnostic sign of **Henoch-Schönlein purpura** is the palpable purpuric rash, typically found on the buttocks, posterior legs, and feet in 97% of patients. However, because the vomiting or hematemesis and the nonspecific abdominal pain (found in nearly 90%) may precede the rash, the diagnosis may initially be obscure. Repeated examination of the skin of a child with persistent vomiting and pain is therefore useful, particularly when the gastrointestinal symptoms are accompanied by polyarthritis, which occurs in 65% of such patients. Platelet function and coagulation studies are normal; hematuria is often present. Steroids may shorten the abdominal pain by 1 or 2 days, but they might also mask symptoms of accompanying intussusception or perforation.

TABLE 12.16 Diagnostic Criteria for Cyclic Vomiting Syndrome

- At least 5 episodes overall or a minimum of 3 episodes noted in a 6-mo period
- Recurrent episodes of vomiting and nausea lasting 1 hr to 10 days and occurring at least 1-wk apart
- Stereotypical pattern and symptoms in the individual patient
- Vomiting during episodes occurring at least 4 times per hr for at least 1 hr
- Returning to baseline health between episodes
- Not attributable to another disorder

From Li BUK, Kovacic K. Vomiting and nausea. In: Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*. 5th ed. Philadelphia: Elsevier; 2016:98.

Volvulus and Intussusception

Volvulus and intussusception have been discussed earlier, but, as noted, some of the symptoms and complications result from vascular obstruction and ischemia.

Mesenteric Ischemia

The mesenteric arteries may be occluded by emboli from a diseased heart or from thrombi formed locally. Nonocclusive ischemia may be caused by poor cardiac output, hypotension, dehydration, or endotoxemia. Mesenteric venous occlusion is very rare. Severe, crampy, diffuse abdominal pain may be accompanied by vomiting, diarrhea, or constipation. The crampy pain becomes continuous, and gangrene, peritonitis, sepsis, and shock supervene.

In a suggestive setting (e.g., heart disease), vomiting accompanied by diffuse severe abdominal pain should suggest the possible need for mesenteric and celiac angiography and emergency surgery. Acute arterial insufficiency may be preceded by chronic symptoms of "abdominal angina," which are episodes of several hours of crampy pain beginning about 20 minutes after meals. Such premonitory symptoms in suggestive settings should receive serious attention.

Gastrointestinal Perforation and Peritonitis

Gastrointestinal perforation is often the end stage of obstructing, inflammatory, or ischemic disorders. Perforation is heralded by sudden abdominal pain, with subsequent signs of peritonitis. Perforated peptic ulcer pain may track to the right lower quadrant and mimic appendicitis, but the onset is more sudden, and the child is sicker than with appendicitis. Shock, metabolic acidosis, sepsis, and disseminated intravascular coagulopathy may ensue. Vomiting is not prominent.

When luminal obstruction leads to perforation and peritonitis, the abdominal findings change in characteristic ways. Vague, crampy, periumbilical pain becomes sharp, continuous, and localized. Rushes of increased, high-pitched bowel sounds disappear, leaving the abdomen silent. The active, sometimes writhing child becomes still. Vomiting previously associated with cramping pain is no longer present. The physical examination discloses point tenderness, abdominal rigidity, involuntary guarding, and rebound tenderness.

Hepatobiliary Disorders

Hepatitis

The presence of acute viral hepatitis is usually suspected in patients who have jaundice, but up to 50% of patients with hepatitis A are anicteric, and even those in whom jaundice develops have a preicteric prodrome lasting up to a week. In children with acute hepatitis, therefore, the presenting symptom may be vomiting, another reason for including liver enzymes in the screening evaluation of the ill-appearing vomiting child. The vomiting is often accompanied by fatigue, fever, headache, rhinorrhea, sore throat, and cough.

The findings of serum antigens and antibodies to hepatitis viruses establish the diagnosis. Acute hepatitis with vomiting is treated symptomatically. Management also includes watching for the ominous findings of progressive encephalopathy, ascites, and coagulopathy.

Biliary Colic and Cholecystitis

Biliary obstruction produces vomiting and abdominal pain in children; the vomiting is usually less severe and occurs later than that in pancreatitis. Biliary colic is visceral pain resulting from transient obstruction of the cystic duct, usually by a stone. In occasional patients, biliary dyskinesia causes these symptoms. Biliary colic produces several hours of steady, vaguely localized pain, often in the right upper quadrant; most patients also have vomiting. Episodes of biliary colic commonly recur at unpredictable intervals, from weeks to years. Acute cholecystitis may ensue if the obstruction persists and leads to inflammation of the gallbladder. The pain may localize more clearly to the right upper quadrant and may radiate to the back or shoulder. There may be fever or mild jaundice. Serum alanine aminotransferase, aspartate aminotransferase, γ–glutamyl transpeptidase, alkaline phosphatase, and bilirubin levels may be elevated. In both biliary colic and acute cholecystitis, abdominal films and ultrasonography may disclose stones or gallbladder thickening. Common duct stones may produce concurrent elevations of liver enzymes and pancreatic enzymes. Recurrent biliary colic and cholecystitis are managed by cholecystectomy, which can be performed laparoscopically in many children. Endoscopic removal of common duct stones is also possible, although it does not prevent recurrence.

Pancreatitis

Pancreatitis is usually associated with epigastric abdominal pain, which may radiate to the back. Elevated serum amylase and lipase levels usually confirm the diagnosis.

Gynecologic and Urologic Disorders

Pyelonephritis

High fever, chills, nausea, vomiting, and, less often, diarrhea develop rapidly. There may be symptoms of cystitis with dysuria, frequency, urgency, and suprapubic pain. Costovertebral angle tenderness focuses the diagnosis on the urinary tract.

The urinalysis shows pyuria and bacteriuria, and the hemogram shows leukocytosis. Treatment is with antibiotics.

Ureteropelvic Junction Obstruction and Hydronephrosis

Ureteropelvic junction obstruction ("beer drinker's kidney," Dietl crisis) is caused by partial obstruction at the ureteropelvic junction and by the resulting hydronephrosis during fluid loading and diuresis. Congenital cases are usually diagnosed in the 1st year of life (usually on the basis of a renal hydronephrotic mass or urinary tract infection); 10-30% of affected older children present with flank or periumbilical pain, frequently accompanied by vomiting.

Typically, the symptoms commence in the evening after an increased fluid intake, although the hyperhydration history is often unclear. The child's pain and vomiting usually remit spontaneously in several hours, as dehydration gradually relieves the renal pelvic distention. Superimposed unilateral urinary tract infection may cause additional findings of fever, failure to thrive, and pyuria.

Ultrasonography at the time of an episode or after furosemide, or an intravenous pyelogram, provides the diagnosis; the treatment is surgical.

Renal Colic

Passage of a renal stone usually causes more pain than vomiting. Lateralized colicky pain, hematuria, and confirmatory radiologic studies assist the diagnosis.

Dysmenorrhea, Endometriosis, and Pelvic Inflammatory Disease

These gynecologic disorders manifest with lower abdominal pain but only occasionally manifest with vomiting. Association with menses or vaginal discharge aids the diagnosis. Motion of the cervix exacerbates the pain in pelvic inflammatory disease.

Ovarian Torsion

Torsion of a normal ovary occasionally occurs in girls of any age, probably caused by laxity of adnexal supports. Repeated attacks of crampy, lower abdominal pain culminates in a final acute episode with severe retching and vomiting, an enlarged ovarian mass, and eventual signs of peritonitis. Leukocytosis may be accompanied by fever. The location of the pain suggests the diagnosis, and the treatment is surgical.

Hyperemesis Gravidarum

Pregnant adolescents may have prolonged vomiting. In parallel to the experience with ruminating infants, esophagitis has been suggested to play a role in this disease.

Testicular Torsion

Testicular torsion is a vascular emergency. It is readily diagnosed by the site of pain; surgical treatment is required.

Respiratory Disorders

Sinusitis, Pharyngitis, and Otitis

Sinusitis may induce chronic, unexplained vomiting. The vomiting is more apt to occur in the morning and must be differentiated from serious intracranial processes. Sinus tenderness and sinus CT scans suggest the diagnosis, and a successful trial of antibiotic therapy confirms it. Less often, pharyngitis or otitis media may manifest acutely with nonspecific vomiting.

Pneumonia

Because pneumonia can also be caused by vomiting on the basis of aspiration, it is important to consider the direction of causality in children with pneumonia and vomiting. Aspiration of vomitus is particularly likely to occur in the context of obtundation or other neurologic dysfunction.

Central Nervous System Disorders

Increased Intracranial Pressure

Various causes of increased intracranial pressure (e.g., tumors) induce vomiting, typically described as projectile but without retching. This description may be an oversimplification, but the occurrence on awakening and before eating is important information.

A careful neurologic and funduscopic examination, attention to measurement of occipitofrontal head circumference, and relevant radiologic studies (CT or magnetic resonance scans) should help the examiner make the diagnosis.

Abdominal Epilepsy

The diagnosis of abdominal epilepsy is suggested by recurrent episodes of nausea or vomiting, usually accompanied by abdominal pain and by symptoms suggesting its central nervous system origin, such as headache, dizziness, confusion, or temporary blindness. Patients may sleep after an episode.

The diagnosis is aided by neurologic consultation, electroencephalography during an episode, and response to anticonvulsant therapy.

Vestibular Disorders, Motion Sickness

Motion sickness is a common experience in some situations. Vestibular disorders produce similar symptoms.

Because of the symptoms of nausea, nystagmus, vertigo, and dizziness, the diagnosis is usually obvious. Antihistamines and anticholinergics are particularly useful for motion sickness.

Ventriculoperitoneal Shunt Complications

Occlusion or infection of a shunt may produce vomiting on a neurologic basis, whereas the intraabdominal end of the shunt may provoke intestinal obstruction by volvulus, adhesions, or loculations. These possibilities must be kept in mind for the vomiting patient with a shunt.

Psychobehavioral Disorders

Psychogenic Vomiting

The syndrome of vomiting without organic cause illustrates the prominent influence that cortical and psychologic inputs may have in stimulating nausea and vomiting. Characteristic features of psychogenic vomiting include chronicity, association with stress and with meals, can be suppressed by distracting the patient, the patient's indifference toward the symptom itself, and relief by hospitalization. There may be no nausea or anorexia, and the vomiting may be self-induced.

Rumination

In the process of rumination, food is regurgitated, then mouthed or chewed and re-swallowed, apparently voluntarily and pleasurably. Adults and older children may regurgitate by contracting abdominal muscles; infants may put their fingers or fists deep in their mouths in an apparent attempt to stimulate regurgitation. Whereas such apparent self-stimulation probably has a psychogenic origin in many cases, some infants cease ruminating when esophagitis is treated, which suggests that in some cases what appears to be an attempt to stimulate the gag reflex may actually be a response to pain in the throat. Thus, diagnosis of and treatment for both psychogenic causes and esophagitis should be considered.

Two types of rumination, psychogenic and self-stimulating, have been described. The former tends to occur in normal infants with a disturbed parent-child relationship; the latter occurs in intellectually disabled individuals of any age and without regard to nurturing. Both positive reinforcement and negative reinforcement have been utilized in behavioral therapy.

Eating Disorders

Anorexia nervosa and bulimia are considered eating disorders primarily of psychogenic origin. However, symptoms of disordered upper gastrointestinal motility, including esophageal dysmotility, may manifest in a manner similar to these eating disorders, and patients with primary anorexia nervosa often manifest delayed gastric emptying, which may benefit from therapy with prokinetic agents.

Management

Psychiatric consultation and therapy are often needed for eating disorders, rumination, and psychogenic vomiting. Principles of behavior modification help to eliminate secondary gain from the vomiting. Nasogastric or nasojejunal feedings can be used to guarantee nutritional rehabilitation if voluntary oral nutrition is not readily reestablished; such tube feedings also provide the child with the incentive to return to oral nutrition. A prokinetic agent and H_2-receptor blocker therapy are often useful initially, both to treat esophagitis and to maximize forward movement of enteral nutrients through the gastrointestinal tract.

Metabolic Disorders

Metabolic diseases that cause vomiting are difficult to diagnose because they are both rare and diverse. Their diagnosis and treatment, however, are crucial because of the severe morbidity and death they can cause and their amenability to treatment. They are also important because of their relevance to genetic counseling, inasmuch as most metabolic disorders are hereditary, on an autosomal recessive basis. Situations that should prompt consideration of metabolic diseases are listed in Table 12.10.

The history and physical examination (Table 12.17) and screening studies (Table 12.18) that help distinguish among many of the specific metabolic disorders provide useful clues. Laboratory studies should be done while the child is symptomatic. Vomiting accompanied by hyperammonemia is a particular diagnostic problem, for which a schematic is presented in Fig. 12.12.

Poisonings and Drugs

Most ingested poisons, and some absorbed by inhalation, skin contact, or intravenous administration, induce vomiting, which can be seen as a physiologic protection against harmful substances. Symptoms and signs of some of the most common pediatric poisonings causing vomiting are indicated in Table 12.19. Acute known poisonings, either accidental or intentional, are a management problem rather than a diagnostic one and a Poison Control Center or other toxicology resources may be helpful.

Initial diagnostic evaluation can be directed by a careful search of the environment for poisonous items and by toxicology screens on blood, urine, vomitus, and stool; these materials should not be discarded. A few agents, such as lead, cause chronic poisoning, manifested by vomiting, among other symptoms. Because it may be particularly difficult to suspect and treat these poisonings, an index of suspicion of poisoning is important in the chronically vomiting child. Laboratory studies that are useful in addition to toxicology screenings are presented in Table 12.20.

Hematemesis

Endoscopic evaluation (and therapy) is often needed for children with hematemesis. Before such evaluation, however, it is important to know the most likely causes (see Table 12.13). The physician should also have determined that there is no underlying coagulopathy necessitating correction (see Table 12.14) and that hematemesis is a primary symptom, not a secondary one caused by a Mallory-Weiss tear.

Peptic ulcer disease, particularly duodenal ulcer, is the most common cause of hematemesis in children; in newborns, swallowed maternal blood (uterine, breast milk), esophagitis, gastritis, and duodenal ulcers are most common; in preschool children, gastric ulcers predominate; and in older children and adolescents, duodenal ulcers are most common. Esophagitis is occasionally severe enough to cause hematemesis, as is Barrett ulcer, a premalignant lesion superimposed on chronic esophagitis. Obstructive lesions such as pyloric stenosis and antral webs are occasionally associated with hematemesis.

Variceal bleeding is uncommon but serious. Gastric vascular malformations are rare and serious and may be difficult to diagnose. Duplications are lined by gastric mucosa in 30% of affected patients; if they are located above the ligament of Treitz, they may cause hematemesis. The metabolic and toxic (iron, salicylates, theophylline, corrosives, isopropyl alcohol, mushroom poisoning) causes of hematemesis should be kept in mind.

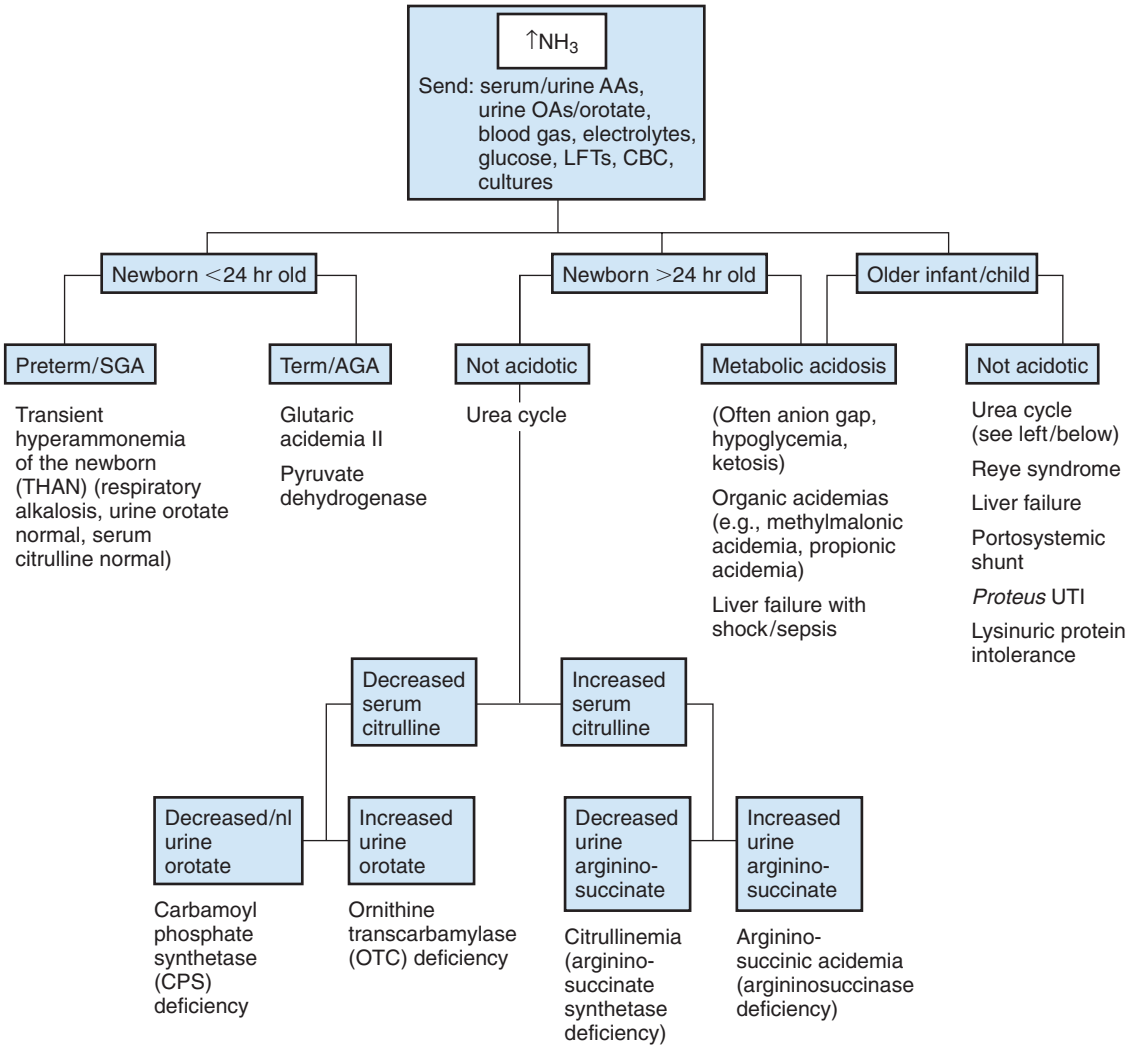


FIGURE 12.12 Flow diagram for evaluation of hyperammonemia in children. AAs, amino acids; AGA, appropriate for gestational age; CBC, complete blood count; LFTs, liver function tests; NH_3, ammonia; OAs, organic acids; SGA, small for gestational age; UTI, urinary tract infection.

Therapy of hematemesis includes, as needed, correction of any abnormalities of coagulation: hemostasis, stabilization of hemodynamic status, and direct attention to the bleeding site endoscopically (e.g., heater probe, injection therapy) or surgically. Reduction of gastric acid secretion pharmacologically is useful in virtually all cases of hematemesis and carries minimal risk.

Other Causes of Vomiting

Chemotherapy

Chemotherapy causes predictable vomiting, which is usually not a diagnostic but a management problem. It may be complicated by anticipatory vomiting. Ondansetron, high-dose metoclopramide (accompanied by diphenhydramine for prophylaxis of extrapyramidal side effects), dexamethasone, and the marijuana-related nabilone have all shown some effectiveness against chemotherapy-induced vomiting. Anxiolytics may also be beneficial as a component of combination antiemetic therapy.

Radiation Therapy

Like chemotherapy, radiation therapy may cause acute vomiting, apparently by stimulating giant retrograde peristaltic waves. Subacutely, diarrhea predominates as a complication of radiation therapy. Months to years later, vomiting may again be a result of radiation therapy, often caused by inflammatory ulcers and strictures. These lesions are difficult to treat without surgery.

Cyclic Vomiting

Cyclic vomiting syndrome (CVS) is a chronic, potentially disabling condition marked by a history of three or more bouts of intense, acute nausea and vomiting that may last hours or days, punctuated by entirely symptom-free intervals that last weeks to months (see Table 12.16). Work-up, which may ultimately include endoscopy and imaging studies of the gastrointestinal tract and brain, reveals no evidence of significant underlying primary disease. Typically, bouts begin in children 2-7 years old (range, 6 months to 18 years) and occur an average of 12 times yearly (range, 1-70). For a particular patient, episodes tend to begin at the same time of day (usually during the night or early morning hours) and have similar durations. An inciting event such as an infection or emotional excitement can be identified in 80% of episodes. Bouts are often accompanied by pallor, intolerance of noise or light, abdominal pain, or diarrhea. The pathophysiologic process of CVS remains speculative at this time but may

overlap with that of migrainous phenomena. One hypothesis purports that stress-initiated release of corticotropin-releasing hormone leads to cascading production of substances, such as adrenocorticotropic hormone, antidiuretic hormone, histamine, and catecholamines, which in turn mediate the syndrome's signs and symptoms. Some children may harbor subclinical defects in mitochondrial fatty acid oxidation metabolism or neuronal ion channel function that heighten their susceptibility to attacks when confronted by the increased cellular energy needs created by a physiologic or emotional stressor. Although CVS is now becoming better characterized, the physician should not be lulled into missing treatable, "look-alike" organic conditions. Reported cases of organic disease mislabeled "cyclic vomiting" have included intermittent intussusception or volvulus caused by enteric duplication, diverticulum, or malrotation; increased intracranial pressure in patients with shunts who have slit ventricles; and toxic or metabolic disease. Additional considerations in the differential diagnosis include brainstem glioma, obstructive uropathy, porphyria, and familial dysautonomia.

In CVS, the patient experiences nausea and pallor during the stereotypical and characteristic episodes but is symptom-free between episodes.

Medications potentially useful in CVS prophylaxis and in treatment of acute episodes are listed in Table 12.21.

Porphyria

Acute intermittent porphyria is an autosomal dominant disorder of episodic abdominal pain (85-95% of patients); 40-90% of patients have associated vomiting. The association of neurologic symptoms such as mental symptoms (50%), muscle weakness (50%), sensory loss (20%), and convulsions (15%); the onset after puberty; and the frequent association with menses or provocative drugs (phenobarbital) are suggestive. Elevated levels of porphobilinogen and δ-aminolevulinic acid in urine are suggestive, and decreased red blood cell porphobilinogen deaminase is diagnostic.

Familial Mediterranean Fever (Benign Paroxysmal Peritonitis, Periodic Peritonitis, Polyserositis)

Episodic attacks of abdominal pain with rapid development and resolution (within 48 hours) of peritoneal signs (fever, vomiting, absent bowel sounds) occurring in a child of Israeli or North African descent should suggest this autosomal recessive diagnosis. Synovitis, pleuritis, and an erysipelas-like skin lesion are also characteristic. The erythrocyte sedimentation rate is raised. Fifty percent of patients have their first attack between 1 and 10 years of age; 90%, by age 20. Amyloidosis, a possible etiologic role for C5a inhibitor deficiency, and probable response to colchicine has been described. Definitive genetic testing is now available for detection of the familial Mediterranean fever gene, which has been localized to the short arm of chromosome 16.

Familial Dysautonomia

Familial dysautonomia may manifest with episodic vomiting. It is an autosomal recessive disorder of the sensory and autonomic nervous systems affecting children of Ashkenazi Jewish descent. The gene for familial dysautonomia has been localized to the distal long arm of chromosome 9, allowing for both prenatal diagnosis and identification of carriers. Associated symptoms include disturbed swallowing, drooling, frequent pneumonias, absence of overflow tearing, erratic temperature control, skin blotching, postural hypotension, relative indifference to pain, corneal anesthesia, breath-holding spells, motor incoordination, spinal curvature, and growth retardation. Glossal fungiform papillae are also absent. The disease is diagnosed with the intradermal histamine test or the conjunctival methacholine (or pilocarpine) test. Management is complex and requires a multidisciplinary team.

Complications of Vomiting

The complications of vomiting are shown in Table 12.22. Their importance is twofold. First, these complications, particularly the metabolic, nutritional, esophagitis, and hemodynamic ones, must be treated. Second, there may be diagnostic implications. Hematemesis resulting from Mallory-Weiss tear should be distinguished from primary hematemesis caused by some other lesion. Metabolic acidosis or hyperkalemia should be recognized as atypical for vomiting illnesses and possible crucial signs of metabolic disease or severe intraabdominal disease.

Metabolic Complications

Dehydration results from the inability to ingest fluid effectively, because of anorexia or nausea, as well as from the loss of secretions in the emesis. Alkalosis resulting from loss of gastric hydrogen chloride in the vomitus is exacerbated by a shift of H^+ into cells because of potassium deficiency and by contraction of the extracellular fluid because of sodium deficiency. Potassium and sodium are lost in the vomitus and are also wasted by the kidneys when they accompany the renal excretion of bicarbonate caused by the alkalosis. In states of marked alkalosis, urine pH is 7 or 8, and urinary sodium and potassium levels are high, despite sodium and potassium depletion. Urine chloride, however, remains low, reflecting the nonrenal losses of sodium chloride and potassium chloride. If intravenous fluid therapy is required, it must be designed with an understanding of the sodium and potassium deficits. The usual metabolic alkalosis is adequately compensated by the patient's spontaneous hyperpnea and responds to fluid and electrolyte therapy.

Nutritional Complications

The nutritional deficits resulting from chronic vomiting and associated anorexia are obvious. Their correction must be included in the treatment plan for chronic vomiting. No more than a day or 2 of fluid therapy should take place without attention to nutritional needs. Frequent, small, high-carbohydrate feedings may minimize the stimulation to vomit, but continuous nasogastric feedings are sometimes needed for chronic vomiting. The presence of metabolic or allergic disease should be considered when the reintroduction of protein leads to relapse of symptoms.

Mallory-Weiss Tear

This linear mucosal laceration in the juxtaesophageal gastric mucosa usually occurs after prolonged forceful retching or vomiting, but it occasionally produces blood in the initial vomitus. Invisible radiographically, it is diagnosed endoscopically (if necessary). Mallory-Weiss tears usually necessitate no treatment, but transfusion is occasionally necessary. Intractable cases are quite rare and may be treated with vasopressin infusion, balloon tamponade, angiographic embolization, or surgery.

Peptic Esophagitis

Esophagitis, similar to that resulting from gastroesophageal reflux, may result from chronic vomiting from many causes. Diagnosed endoscopically or histologically, it should be treated. The treatment of esophagitis usually includes H_2-receptor antagonists or proton pump inhibitors; prokinetic agents may also be needed. The use of antacids should be tempered by knowledge of the acid-base status of the patient.

Text continued on p. 232

TABLE 12.17 Metabolic Disease: History and Physical Examination

	NEUROLOGIC			LIVER		GASTROINTESTINAL	RESPIRATORY			
	Lethargy, Coma	Hypo- or Hypertonicity	Seizure	Jaundice	Hepatomegaly	Diarrhea	Tachypnea	Apnea	Precipitants/ Aversions	Other
Galactosemia				+	+	+	(+)		Galactose	Eye: cataracts (use slit lamp)
Fructose-1-phosphate aldolase ↓: HFI	+		+	+	+	+	(+)		Fructose	Absent caries (older child)
Tyrosinemia	+			+	(+)	+				Odor: cabbage; Quebec native; ↑ AFP; hepatoma
Maple syrup urine disease	+	+	+				+	+	Protein; infections	Odor: maple syrup
Hypervalinemia*	+	+								
HHH syndrome*	+	+	+		(+)				Protein	Occasional bleeding tendency
Lysinuric protein intolerance	+	+			+/spl	+			Protein; fasting; infections	Hair fragile; Finnish native ↑; ferritin↑
Methylmalonic acidemia	+	+	(+)		(+)		+		Protein	Vitamin B_{12} responsive or not?
Propionic acidemia	+	+	(+)		(+)		+		Protein; infections	Osteoporosis
Isovaleric acidemia*	+	(+)	+			(+)	+		Protein; infections	Odor: sweaty feet
3-Methylcrotonyl-CoA carboxylase ↓*	(+)	+					+	+	Protein; infections	Odor: cat urine; biotin unresponsive
Multiple carboxylase ↓*	+	+	+				+	+		Odor: cat urine; biotin responsive; rash
Glutaric acidemia I	+	+			+		(+)		Infections	Fevers
Glutaric acidemia II	+	+	(+)		(+)		(+)		?Fasting	Odor: sweaty feet; heart; renal
Acyl-CoA dehydrogenase ↓: MCAD, etc.	+		(+)		(+)		(+)	(+)	Fasting; infections	
HMG-CoA lyase ↓*	+	+	(+)		(+)		+		Protein; fasting	
Wolman disease*				(+)	+/spl	+				Adrenal calcifications; foam cells

Farber disease*	(+)	(+)			(+)						Skin nodules; arthritis; hoarseness
Urea cycle (AL, AS, CPS, OTC)	+	+	+		+			+	+	Protein; infections	Respiratory alkalosis; trichorrhexis (AL)
Reye syndrome ?Miscellaneous fatty acid oxidation ↓	+	+	+	No	+						Prior virus (flu, varicella); salicylates
Diabetic ketoacidosis	+							+			Odor: ketones
Adrenal insufficiency	+						(+)				Pigment: skin, mucosa (80-98%); salt craving (20%)
Chronic, primary: Addison disease											
Acute: adrenal crisis										Sepsis; steroid DC	Shock; abdominal pain (34%); K ↑; Na ↓
Congenital adrenal hyperplasia	+										M or virilized F neonate; salt-losing
RTA, Fanconi syndrome								(+)			Acidosis and urine findings
Nephrogenic diabetes insipidus										Water deprivation	Polyuria; polydipsia; dehydration
Uremia	(+)		(+)		+/spl					Protein	Odor: uremic fetor; BUN ↑; BP ↑
Glucose-6-phosphatase ↓ (GSD I)			+		+			+		Fasting	Doll-like face; TG-xanthomas; epistaxis

*Fewer than 100 patients with each of these disorders have been reported. Incidences of the other 11 diseases listed before Reye syndrome are 1/20,000 to 1/200,000. GSD I is ~1/200,000; diabetes is acquired in ~1/400 children; adrenal insufficiency of all causes is relatively frequent; congenital adrenal hyperplasia with salt-losing 21-hydroxylase deficiency is ~1/5000.
AFP, alpha-fetoprotein; AL, arginosuccinic acid lyase deficiency; AS, arginosuccinic acid synthase deficiency; BP, blood pressure; BUN, blood urea nitrogen; CoA, coenzyme A; CPS, carbamyl phosphate synthase deficiency; DC, discontinuation; F, female; GSD, glycogen storage disease; HFI, hereditary fructose intolerance; HHH, hyperornithinemia-hyperammonemia-homocitrullinemia syndrome; HMG, 3-hydroxy-3-methylglutaric acidemia; K, potassium; M, male; MCAD, medium-chain; acyl-CoA dehydrogenase deficiency; Na, sodium; OTC, ornithine transcarbamylase deficiency; RTA, renal tubular acidosis; spl, splenomegaly; TG, triglycerides; +, common; (+), may occur; ↓, deficiency.

TABLE 12.18 Metabolic Disease: Laboratory Studies

	BLOOD								URINE†						
	pH ↓	*Glucose ↓*	*NH_3*↑*	*LFTs ↑*	*CBC (Hct↓*	*WBC↓*	*Plt↓)*	*Amino Acids*	*Ketones*	*Red. Subs.*	*FeCl+*	*Fanconi Syndrome†*	*Amino Acids*	*Organic Acids*	*Orotate*
Galactosemia	+	+		+	Lysis					+Non-glucose	?	+			
Fructose-1-phosphate aldolase ↓: HFI	+	+		+	+		+	+		+Non-glucose	?	+	+		
Tyrosinemia				+	+	(↑)	(↑)	+	Suc-ace	+phppa	+Green	+	+	+phppa	
Maple syrup urine disease	(+)	+						+	+		+Gray		+		
Hypervalinemia								+					+		
HHH syndrome			+					+					+	+	
Lysinuric protein intolerance			+	(+)	+	+	+	+					+	+	
Methylmalonic acidemia	+	+	+		+	+	+	(+)	+				(+)	+	
Propionic acidemia	+	+	+			+	+	+	+				+	+	
Isovaleric acidemia	+	No: ↑	+			+	+	+	+					+	
3-Methylcrotonyl-CoA carboxylase↓	+	+							+					+	
Multiple carboxylase ↓	+	+	+						+					+	
Glutaric acidemia type I	+	+	+	+					+				+	+	
Ethylmalonic-adipic aciduria, etc.	+	+	(+)	(+)					No				+	+	
Acyl-CoA dehydrogenase ↓: MCAD, etc.	+	+	(+)	(+)					No (↓)					+	
HMG-CoA lyase ↓	+	+	(+)	(+)					No					+	
Wolman disease				(+)	+	Vacuoles									

Farber disease														
Urea cycle defects		No	+			+						+	+	
Reye syndrome Miscellaneous fatty acid oxidation ↓	+	+	+	+		+						+		
Diabetic ketoacidosis	+	No: ↑					+	+ Glucose	+ Red					
Adrenal insufficiency														
Chronic, primary: Addison disease														
Acute: adrenal crisis														
Congenital adrenal hyperplasia														
Renal tubular acidosis; Fanconi syndrome	(+)							(Glucose)		+				
Nephrogenic diabetes insipidus														
Uremia														
Glycogen storage disease type I	+	+			(+)									

*See Fig. 12.12.

†Glucose, amino acids, phosphate, bicarbonate.

CBC, complete blood count; CoA, coenzyme A; FeCl, iron chloride; Hct, hematocrit; HFI, hereditary fructose intolerance; HHH, hyperornithinemia-hyperammonemia-homocitrullinemia syndrome; HMG, 3-hydroxy-3-methylglutaric acidemia; LFTs, liver function tests; MCAD, medium-chain acyl-CoA dehydrogenase deficiency; NH_3, ammonia; phppa, p-OH-phenylpyruvate; Plt, platelets; Red Subs, reducing substances; Suc-ace, succinylacetone; WBC, white blood cell; (+), may occur; +, common.

TABLE 12.19 Poisoning: History and Physical Examination

	VITAL SIGNS				NEUROLOGIC					PUPILS					
	P ↑↓	*R* ↑↓	*BP* ↑↓	*T* ↑↓	*Coma*	Ψ	*Paralysis*	*Ataxia*	*Sz*	↑	↓	*Nystagmus*	Skin	Odor	Other
Ipecac				•											ECG changes
Salicylates	•	•		•	•				•				Cyanotic	Acetone	Metabolic acidosis; tinnitus; uremia; bleeding
Acetaminophen													Jaundiced		III 24 hr → better × 48 hr → liver failure
Digitalis		•		•	•	•									CNS and arrhythmias; vision changes
Theophylline	•			•	•	•			•						Hematemesis/pain; arrhythmia
Fe (Iron)	•			•	•				•				Jaundiced		Hematemesis/pain → liver failure; pyloric stenosis
Pb (Lead)			•	•	•	•		•	•						Constipation; HA; abdominal pain; renal
Misc. (Sb, As, Cd, Cr, Hg, Zn)					•	•	•	•	•				Jaundiced	Garlic	Diarrhea; LFTs ↑; Hct ↓; nephritis; neuritis
Metal fume fever (oxides)				•											Muscle pain/HA; WBC ↑; respiratory distress
Opiates/narcotics		•	•	•	•	•			•		•		Cyanotic		Abdominal cramping
Opiate withdrawal		•		•					•	•					Irritable; BS ↑/pain; reflexes ↑ ; sweat; tear
Insecticides (miscellaneous)		•	•	•	•			•	•				Miscellaneous		Wheeze; salivation; sweat; tear
Especially organophosphates		•	•		•		•		•		•			Garlic	Diarrhea/abdominal pain; vision impaired
Corrosives															Pain; hematemesis; respiratory distress
Methanol		•		•	•					•		•	Cyanotic	Acetone	Blindness; metabolic acidosis
Ethanol	•	•			•	•		•	•		•		Pink	Alcohol	Vision impaired; hypoglycemia
Isopropyl alcohol			•		•									Acetone	Hematemesis/pain; oliguria
Ethylene glycol		•			•				•			•	Cyanotic		Anuria
"Food poisoning"															See Chapter 11
Fish poisoning							•		•						Some seasonally poisonous; paresthesia
Shellfish: summer ingestion									•						Respiratory paralysis; paresthesia
Plants (akee, hemlock)		•		•			•		•						Respiratory; renal; shock; liver
Mushroom poisoning		•			•	•			•	•	•		Jaundiced		Respiratory; hepatic failure; hematemesis
Venomous bites					•								Lesion		Bite history

As, arsenic; BP, blood pressure; BS, bowel sounds; Cd, cadmium; CNS, central nervous system; Cr, chromium; ECG, electrocardiographic; HA, headache; Hct, hematocrit; Hg, mercury; LFTs, liver function tests; P, pulse; R, respiration; Sb, antimony; Sz, seizure; T, temperature; WBC, white blood count; Zn, zinc; ψ, psychologic manifestations; •, present.

TABLE 12.20 Poisoning: Laboratory Studies and Treatment

	LABORATORY STUDIES										TREATMENT*			
	CBC	*Electrolytes*	*Ca, Mg, Phos*	*BUN, Creat*	Glucose	*LFTs, Coag*	*ABGs*	*UA*	Other	Level	*Lavage*	*Charcoal and 70% Sorbitol*	*Diuresis? Dialysis? Other?*	*Specific*
Ipecac								•	ECG		•	•		
Salicylates		•	•	•	•	•	•	•	FeCl Purple	•	•	•	•	Fluids, electrolytes HCO_3, vitamin K
Acetaminophen	•					•		•		•	•	•		*N*-acetylcysteine
Digitalis	•	•	•	•			•		ECG	•	• (Vagal hazard)	•		Digibind, antiarrhythmics
Theophylline		•	•				•		ECG	•	•	•	•	Antiarrhythmics, antiseizure
Fe (Iron)	•				•	•	•		KUB	•	•	No		Deferoxamine, fluids
Pb (Lead)	•		•					•	KUB Bones	• FEP				BAL-CaEDTA, fluids, succimer
Others (Sb, As, Cd, Cr, Hg, Zn, P)	•					•		•	KUB	•				
Metal fume fever (oxides)														
Opiates/narcotics														Narcan (0.01 mg/kg)
Opiate withdrawal														Methadone, paregoric, diazepam, phenobarbital
Organophosphate cholinesterase														Atropine
Corrosives	•								CXR		No	No		Antibiotics, endoscopy
Methanol		•					•			•		No	•	Ethanol
Ethanol					•	•			ECG	•	•	No	•	Glucose/bicarbonate
Isopropyl alcohol	•			•		•						No		
Ethylene glycol				•			•	•				?No	•	Ethanol, ?Ca gluconate
"Food poisoning"														
Fish poisoning											•			
Shellfish: summer ingestion														
Plants (akee, castor, hemlock)	•	•		•		•		•						
Mushroom poisoning				•		•		•			•	•		Atropine?, cimetidine
Venomous bites		•	•	•				•						Antiserum

*The utility of emesis/lavage varies with the poison, the amount ingested, and the duration since ingestion. If obtunded, lavage requires endotracheal tube airway protection. Avoid charcoal/sorbitol in recent bowel surgery or ileus.

ABGs, arterial blood gases; As, arsenic; BUN, blood urea nitrogen; BAL-CaEDTA, dimercaprol–calcium ethylenediaminetetraacetic acid; Ca, calcium, CBC, complete blood count; Cd, cadmium; Coag, coagulation studies; Cr, chromium; Creat, creatinine; CXR, chest radiography; ECG, electrocardiography; FeCl, iron chloride; FEP, free erythrocyte protoporphyrin; HCO_3, bicarbonate; Hg, mercury; KUB, kidney, ureter, and bladder; LFTs, liver function tests; Mg, magnesium; P, phosphorus; Phos, phosphate; Sb, antimony; UA, urinalysis; Zn, zinc; •, present.

Therapy

Therapy of vomiting starts with treatment of the cause, treatment of complications, and treatment of behavioral aspects that may perpetuate the vomiting. General supportive and more specific pharmacologic approaches to therapy are outlined in Table 12.21 and Table 12.23. The physician should be very careful about treating the vomiting symptom without diagnosing and treating its cause. In several situations, diagnostic procedures, such as diatrizoate (Gastrografin) enema for fecal obstructions in cystic fibrosis, barium enema for intussusception, and endoscopy with sclerotherapy for variceal hematemesis, are also therapeutic.

◆ Treatment of Behavioral Aspects

Treatment of psychobehavioral aspects of vomiting may also be important because of the cortical influences on emesis. Such treatment may include eliminating secondary gain for vomiting and reducing anxiety about the vomiting through a confident approach to the child.

Antiemetic Drugs

In situations of persistent vomiting, antiemetic drugs are useful to reduce the metabolic and nutritional consequences and perhaps to interrupt vicious circles in which psychogenic factors may also participate. Currently available antiemetic drugs include the prokinetic agents, metoclopramide, erythromycin, and domperidone, as well as the other medications listed in Table 12.21. These drugs function at many sites by:

- modifying central cortical input (anxiolytic agents)
- depressing the chemoreceptor trigger zone (metoclopromide, domperidone)
- reducing vestibular input
- enhancing the secretion or effects of acetylcholine from the motor neuron (cisapride, available in the United States on restricted-use protocol only)
- blocking serotonin receptors, which inhibit the function of the acetylcholine-secreting motor neuron (ondansetron)

TABLE 12.21 Pharmacologic Therapies for Vomiting Episodes

Disease/Condition	Therapy–Drug Class: Specific Agent/Trade Name (Dose)
Reflux	Dopamine antagonist: metoclopramide (Reglan) (0.1-0.2 mg/kg q.i.d. PO/IV) Peripheral dopamine antagonist: domperidone (Motilium) (0.2-0.6 mg/kg t.i.d.-q.i.d. PO)
Gastroparesis	Metoclopramide, domperidone; see above Motilin agonist: erythromycin (2-4 mg/kg t.i.d.-q.i.d. PO/IV)
Intestinal pseudoobstruction	Stimulation of intestinal migratory myoelectric complexes: octreotide (Sandostatin) (1 μg/kg b.i.d.-t.i.d. SC)
Chemotherapy	Metoclopramide; see above (0.5-1.0 mg/kg q.i.d. IV, with antihistamine prophylaxis of extrapyramidal side effects) Serotoninergic 5-HT_3 antagonist: ondansetron (Zofran) (0.15-0.3 mg/kg t.i.d IV/PO) Phenothiazines (extrapyramidal, hematologic side effects): prochlorperazine (Compazine) (~0.3 mg/kg b.i.d.-t.i.d. PO) chlorpromazine (Thorazine) (>6 mo of age: 0.5 mg/kg t.i.d.-q.i.d. PO/IV) Steroids: dexamethasone (Decadron) (0.1 mg/kg t.i.d. PO) Cannabinoids: nabilone (tetrahydrocannabinol) (0.05-0.1 mg/kg b.i.d.-t.i.d. PO)
Postoperative	Ondansetron, phenothiazines: see above
Motion sickness; vestibular disorders	Antihistamine: dimenhydrinate (Dramamine) (1 mg/kg t.i.d.-q.i.d. PO) Anticholinergic: scopolamine (Transderm Scoōp) (adults: 1 patch/3 days)
Adrenal crisis	Steroids: cortisol (2 mg/kg bolus IV followed by 0.2-0.4 mg/kg/hr IV [± 1 mg/kg IM])
Cyclic vomiting syndrome (CVS)*	Supportive: Analgesic: meperidine (Demerol) (1-2 mg/kg q4-6h IV/IM) Anxiolytic, sedative: lorazepam (Ativan) (0.05-0.1 mg/kg q6h IV) Antihistamine, sedative: diphenhydramine (Benadryl) (1.25 mg/kg q6h IV) Abortive: Serotoninergic 5-HT_3 antagonist: Ondansetron: see above Granisetron (Kytril) (10 μg/kg q4-6h IV) Nonsteroidal antiinflammatory agent (GI ulceration side effect): Ketorolac (Toradol) (0.5-1.0 mg/kg q6-8h IV) Serotoninergic 5-HT_{1D} agonist: sumatriptan (Imitrex) (>40 kg; 20 mg intranasally/25 mg PO, 1 time only) Prophylactic: (if >1 CVS bout/mo; taken daily) Antimigraine, β-adrenergic blocker: propranolol (Inderal) (0.5-2.0 mg/kg b.i.d. PO) Antimigraine, antihistamine: cyproheptadine (Periactin) (0.25-0.5 mg/kg/day ÷b.i.d.- t.i.d. PO) Antimigraine, tricyclic antidepressant: amitriptyline (Elavil) (0.33-0.5 mg/kg t.i.d. PO, and titrate to maximum of 3.0 mg/kg/day as needed; obtain baseline ECG at start of therapy, and consider monitoring drug levels) Antimigraine antiepileptic: phenobarbital (Luminal) (2-3 mg/kg q.h.s.) Erythromycin: see above Low-estrogen oral contraceptives: consider for catamenial CVS episodes

b.i.d., twice daily; ECG, electrocardiogram; GI, gastrointestinal; IM, intramuscularly; IV, intravenously, PO, orally; q4-6h, every 4-6 hours; q6h, every 6 hours; q6-8h, every 6-8 hours, q.h.s. each bedtime; SC, subcutaneously; t.i.d., three times daily; q.i.d., four times daily.
*Modified from Li BUK, Balint JP. Cyclic vomiting syndrome: Evolution in our understanding of a brain-gut disorder. *Adv Pediatr.* 2000;47:149.

TABLE 12.22 Complications of Vomiting

Complication	Pathophysiology	History, Physical Examination, and Laboratory Studies
Metabolic	Fluid loss in emesis	Dehydration
	HCl loss in emesis	Alkalosis*; hypochloremia
	Na, K loss in emesis	Hyponatremia; hypokalemia*
	Alkalosis → Na into cells	
	HCO_3 loss in urine	Urine pH 7-8
	Na and K loss in urine	Urine Na ↑, K ↑
	Hypochloremia → Cl conserved by kidneys	Urine Cl ↓
Nutritional	Emesis of calories and nutrients	Malnutrition; "failure to thrive"
	Anorexia for calories and nutrients	
Mallory-Weiss tear†	Retching → tear at lesser curve of gastroesophageal junction	Forceful emesis → hematemesis
Esophagitis	Chronic vomiting → esophageal acid exposure	Heartburn; Hemoccult + stool
Aspiration	Aspiration of vomitus, especially in context of obtundation	Pneumonia; neurologic dysfunction
Shock*	Severe fluid loss in emesis or in accompanying diarrhea	Dehydration (accompanying diarrhea can explain acidosis?)
	Severe blood loss in hematemesis	Blood volume depletion

*If patient is acidotic, hyperkalemic, or in shock, see Table 12.24.
†Occasionally produces blood in the initial vomitus. Invisible radiographically, it is diagnosed endoscopically (if necessary).
Cl, chloride; HCl, hydrogen chloride; HCO_3, bicarbonate; K, potassium; Na, sodium.

TABLE 12.23 Supportive and Nonpharmacologic Therapies for Vomiting Episodes*

Disease	Therapy
All	Treat Cause: obstruction → operate; allergy → change diet (±steroids); metabolic error → Rx defect; acid peptic disease → H_2RAs, PPIs, etc.
Complications	
Dehydration	IV fluids, electrolytes
Hematemesis	Transfuse, correct coagulopathy
Esophagitis	H_2RAs, PPIs
Malnutrition	NG or NJ drip feeding useful for many chronic conditions
Meconium ileus	Gastrografin enema
DIOS	Gastrografin enema; balanced colonic lavage solution (e.g.,GoLytely)
Intussusception	Barium enema; air reduction enema
Hematemesis	Endoscopic: injection sclerotherapy or banding of esophageal varices; injection therapy, fibrin sealant application, or heater probe electrocautery for selected upper GI tract lesions
Sigmoid volvulus	Colonoscopic decompression
Reflux	Positioning; dietary measures (infants: rice cereal, 1 TBSP/ounce of formula)
Psychogenic components	Psychotherapy; tricyclic antidepressants; anxiolytics (e.g., diazepam: 0.1 mg/kg/t.i.d.-q.i.d. PO)

*If patient is acidotic, hyperkalemic, or in shock, see Table 12.24; adrenal crisis therapy outlined in Table 12.21.
DIOS, distal intestinal obstruction syndrome; GI, gastrointestinal; H_2RAs, histamine$_2$-receptor antagonists; IV, intravenous; NG, nasogastric; NJ, nasojejunal; PO, orally; PPIs, proton pump inhibitors; q.i.d, four times a day; TBSP, tablespoon; t.i.d, three times a day.

- blocking dopamine's inhibitory effect at the neuromuscular junction (domperidone, metoclopramide)
- stimulating the motilin receptor on gastric smooth muscle (erythromycin)
- substituting for acetylcholine's stimulatory effect at the neuromuscular junction (bethanechol)

In some settings, the diverse sites of action account for the useful additive effects of these drugs. Optimal therapy for vomiting caused by chemotherapy, for example, may include several agents in order to provide blockade of the multiple receptor types in the chemoreceptor trigger zone and elsewhere. Metoclopramide and ondansetron have been the most widely used general antiemetic agents.

TABLE 12.24 Vomiting Emergencies*

Drug/Symptoms	Poison†	Metabolic‡	Surgical	Neurologic	Liver Failure	Laboratory Studies
Shock	+	+	+			
Mental status change, lethargy, coma, seizure, psychosis	++	++		+++	+++	NH_3, head CT/MRI, glucose
Severe abdominal pain/distention	++	+	+++		+	Abdominal films
Acute liver dysfunction: jaundice, anicteric	++	++	+	+	+++	NH_3, PT
Respiratory: apnea, Kussmaul breathing	++	++	+	++	++	Blood gas; electrolytes; urinalysis, glucose
Other						
Bilious emesis		+	+++		+	Abdominal films
Silent abdomen			+++			
Hematemesis			+		++	Endoscopy

*An acutely ill child with vomiting needs:
Physical examination: especially vital signs, neurologic, funduscopic, abdominal (auscultation, peritoneal signs), rectal.
Laboratory tests: complete blood cell count, differential white blood cell count, platelets; sodium, potassium, chloride, carbon dioxide; glucose (Dextrostix); blood urea nitrogen, creatinine; liver function tests; amylase, lipase; blood gas; urinalysis.
If fever is present: cultures of blood, urine, cerebrospinal fluid (if mentation change), and stool (if diarrhea or hematochezia) are also needed.
If hematemesis is present: platelets, prothrombin time, and partial thromboplastin time also must be measured.
†See Tables 12.19 and 12.20.
‡See Tables 12.17 and 12.18.
CT, computed tomography; MRI, magnetic resonance imaging, NH_3, ammonia; PT, prothrombin time.
+, suggestive; ++, moderately suggestive; +++, highly suggestive.
Data from Mitchell LE, Risch N. The genetics of infantile hypertrophic pyloric stenosis. A reanalysis. *Am J Dis Child*. 1993;147:1203-1210; Rescorla FJ, Shedd FJ, Grosfeld JL, et al. Anomalies of intestinal rotation in childhood: Analysis of 447 cases. *Surgery*. 1990;108:710-716; and Seashore JH, Touloukian RJ. Midgut volvulus. An ever-present threat. *Arch Pediatr Adolesc Med*. 1994;148:43-46.

SUMMARY AND RED FLAGS

Vomiting and regurgitation are commonly encountered symptoms in children. Most commonly they are the result of acute, self-resolving illnesses, such as acute gastroenteritis. In infants, regurgitation caused by gastroesophageal reflux must be distinguished from other more serious causes. Symptoms suggesting vomiting emergencies are listed in Table 12.14 and Table 12.24. These are generally diseases that arise after surgery, are metabolic, or are caused by poisoning; liver failure and neurologic disorders are also included.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

General

Li BUK, Sferra TS. Vomiting. In: Wyllie R, Hyams JS, eds. *Pediatric Gastrointestinal Disease: Pathophysiology, Diagnosis, Management*. Philadelphia: WB Saunders; 1999:14-31.

Lilien LD, Srinivasan G, Pyati SP, et al. Green vomiting in the first 72 hours in normal infants. *Am J Dis Child*. 1986;140:662-664.

Martin TG, Burgess JL. *Dreisbach's Handbook of Poisoning*. 13th ed. London: Parthenon Publishing; 2001.

O'Neill JA, Rowe MI, Grosfield JL, et al. *Pediatric Surgery*. 5th ed. St. Louis: Mosby–Year Book; 1998.

Rollins MD, Shields MD, Quinn RJM, et al. Value of ultrasound in differentiating causes of persistent vomiting in infants. *Gut*. 1991;32:612-614.

Scriver CR, Beaudet AL, Sly WS, et al. *The Metabolic and Molecular Bases of Inherited Disease*. 7th ed. New York: McGraw-Hill Information Services; 1995.

Gastrointestinal Obstruction

Caniano DA, Beaver BL. Meconium ileus: A fifteen year experience with forty-two neonates. *Surgery*. 1987;102:699-703.

Champoux A, Del Beccaro M, Nazar-Stewart V. Recurrent intussusception: Risk features. *Arch Pediatr Adolesc Med*. 1994;148:474-478.

Depaepe A, Dolk H, Lechat MF, et al. The epidemiology of tracheo-oesophageal fistula and oesophageal atresia in Europe. *Arch Dis Child*. 1993;68:743-748.

Devane SP, Coombes R, Smith VV, et al. Persistent gastrointestinal symptoms after correction of malrotation. *Arch Dis Child*. 1992;67:218-221.

Ford EG, Senac MO, Srikanth MS, et al. Malrotation of the intestine in children. *Ann Surg*. 1992;215:172-178.

Hernanz-Schulman M. Imaging of neonatal gastrointestinal obstruction. *Radiol Clin North Am*. 1999;37:1163-1186.

Macdessi J, Oates RK. Clinical diagnosis of pyloric stenosis: A declining art. *BMJ*. 1993;306:553-555.

North American Society for Pediatric Gastroenterology and Nutrition. *J Pediatr Gastroenterol Nutr*. 2001;32(2):S1-S31.

Shulman RJ, Boyle JT, Colletti RB, et al. Use of cisapride in children. An updated medical position statement of the North American Society for Pediatric Gastroenterology and Nutrition. *J Pediatr Gastroenterol Nutr*. 2000;31:232-233.

Gastroesophageal Reflux

Albanese CT, Towbin RB, Ullman I, et al. Percutaneous gastrojejunostomy versus Nissen fundoplication for enteral feeding of the neurologically impaired child with gastroesophageal reflux. *J Pediatr*. 1993;123:371-375.

Booth IW. Silent gastro-oesophageal reflux: How much do we miss? *Arch Dis Child*. 1992;67:1325-1326.

Brown P. Medical management of gastroesophageal reflux. *Curr Opin Pediatr*. 2000;12:247-250.

Chidiac P, Alexander IS. Head retraction and respiratory disorders in infancy. *Arch Dis Child*. 1990;65:567.

Grill BB. Twenty-four-hour esophageal pH monitoring: What's the score? *J Pediatr Gastroenterol Nutr*. 1992;14:249-251.

Hoeffel JC, Nihoul-Fekete C, Schmitt M. Esophageal adenocarcinoma after gastroesophageal reflux in children. *J Pediatr*. 1989;115:259-261.

Kiely EM. Surgery for gastro-oesophageal reflux. *Arch Dis Child*. 1990;65:1291-1292.

Kinsbourne M, Oxon DM. Hiatus hernia with contortions of the neck. *Lancet*. 1964;283:1058-1061.

Orenstein SR. Prone positioning in infant gastroesophageal reflux: Is elevation of the head worth the trouble? *J Pediatr*. 1990;117:184-187.

Orenstein SR. Update on gastroesophageal reflux and respiratory disease in children. *Can J Gastroenterol*. 2000;14:131-135.

Orenstein SR, Izadnia F, Khan S. Gastroesophageal reflux disease in children. *Gastroenterol Clin North Am*. 1999;28:947-969.

Orenstein SR, Shalaby TM, DiLorenzo C, et al. The spectrum of pediatric eosinophilic esophagitis beyond infancy: A clinical series of 30 children. *Am J Gastroenterol*. 2000;95:1422-1430.

Vandenplas Y, Rudolph CD, Di Lorenzo C, et al. North American Society for Pediatric Gastroenterology Hepatology and Nutrition, European Society for Pediatric Gastroenterology Hepatology and Nutrition. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr*. 2009;49(4):498-547.

Other Etiologies

Barkin RM. Toxicologic emergencies. *Pediatr Ann*. 1990;19:629-633.

Bray GP. Liver failure induced by paracetamol. *BMJ*. 1993;306:157-158.

Buck ML, Grebe TA, Bond GR. Toxic reaction to salicylate in a newborn infant: Similarities to neonatal sepsis. *J Pediatr*. 1993;122:955-958.

Duane PD, Magee TM, Alexander MS, et al. Oesophageal achalasia in adolescent women mistaken for anorexia nervosa. *BMJ*. 1992;305:43.

Fleisher D, Matar M. Cyclic vomiting syndrome: A report of 71 cases and literature review. *J Pediatr Gastroenterol Nutr*. 1993;17:361-369.

Forbes D. Cyclic vomiting syndrome. In: Hyman PE, ed. *Pediatric Functional Gastrointestinal Disorders*. New York: Academy Professional Information Services; 1999:5.1-5.12.

Gordon GS, Wallace SJ, Neal JW. Intracranial tumours during the first two years of life: Presenting features. *Arch Dis Child*. 1995;73:345-347.

Harrington J, Gianos E, Stiefel M. Index of suspicion: Case 3. Diagnosis: Riley-Day syndrome (familial dysautonomia [FD]). *Pediatr Rev*. 2000;21:243, 246-247.

Li BUK, Balint JP. Cyclic vomiting syndrome: Evolution in our understanding of a brain-gut disorder. *Adv Pediatr*. 2000;47:117-160.

Rasquin-Weber A, Hyman PE, Cucchiara S, et al. Childhood functional gastrointestinal disorders. *Gut*. 1999;45(II):II60-II68.

Samuels J, Aksentijevich I, Torosyan Y, et al. Familial Mediterranean fever at the millennium: Clinical spectrum, ancient mutations, and a survey of 100 American referrals to the National Institutes of Health. *Medicine (Baltimore)*. 1998;77:268-297.

Therapy

Grunberg SM, Hesketh PJ. Control of chemotherapy-induced emesis. *N Engl J Med*. 1993;329:1790-1796.

Israel DM, Hassall E. Omeprazole and other proton pump inhibitors: Pharmacology, efficacy, and safety, with special reference to use in children. *J Pediatr Gastroenterol Nutr*. 1998;27:568-579.

Kulig K. Initial management of ingestions of toxic substances. *N Engl J Med*. 1992;326(25):1677-1681.

Pinkerton CR, Williams D, Wootton C, et al. 5-HT_3 antagonist ondansetron—An effective outpatient antiemetic in cancer treatment. *Arch Dis Child*. 1990;65:822-825.

13

Gastrointestinal Bleeding

Julia Fritz and Bernadette Vitola

Gastrointestinal (GI) bleeding in children can range from small amounts of blood in the stool, associated with milk protein allergy or anal fissure, to life-threatening hemorrhage, associated with portal hypertension or peptic ulcer disease. Severe bleeding is a true medical emergency and necessitates prompt diagnostic attention and appropriate management. *Hemodynamic stabilization of the patient with severe bleeding should always precede diagnostic studies.* An accurate history and thorough physical examination usually allow the physician to categorize the problem as mild or severe and to direct evaluation at the appropriate pace.

DEFINITIONS

Children with gastrointestinal bleeding generally present with hematemesis, hematochezia, or melena, although the clinical manifestation can be as subtle as evidence of occult blood loss. An **upper gastrointestinal bleed** is bleeding from the esophagus, stomach, or duodenum. Upper sources account for the majority of gastrointestinal bleeds in children. If the site of bleeding is distal to the ligament of Treitz, it is a **lower gastrointestinal bleed**. Blood passed per rectum can originate from either an upper or lower gastrointestinal source. Occult bleeding may occur from disorders at numerous sites.

Hematemesis. Vomited blood can be either red or the color of coffee grounds. Hematemesis is most commonly associated with an upper gastrointestinal bleed, although swallowed blood produces the same clinical picture. Bright red hematemesis suggests active bleeding that has not had prolonged contact with gastric secretions. When gastric secretions interact with the blood, the blood will darken in color as the iron oxidizes and leads to dark red or "coffee ground" emesis.

Hematochezia and melena. The presence of hematochezia (bright red blood) is generally associated with colonic bleeding, although it may result from a brisk upper bleed. Maroon stools from the rectum are generally associated with a lower gastrointestinal bleed. The presence of melena—passage of black, tarry stools—generally results from significant blood loss proximal to the ileocecal valve, including an upper gastrointestinal bleed. The color results from bacterial breakdown of the hemoglobin. *Up to 10-15% of upper gastrointestinal bleeds present with melena in the absence of hematemesis.* These patients are more likely to have a clinically significant bleed.

APPROACH TO GASTROINTESTINAL BLEEDING

The first step is to determine whether the problem is actually gastrointestinal bleeding. Many substances and nongastrointestinal sources may simulate gastrointestinal bleeding (Table 13.1). Stool guaiac and the modified guaiac (Gastroccult) test for emesis are used to determine the presence of blood. Recommendations from manufacturers are to avoid red meat, citrus fruits and juices, supplemental vitamin C in excess of 250 mg/day for 3 days prior to testing, and to avoid antacids for at least 60 minutes prior to testing. Nonsteroidal antiinflammatory drugs (NSAIDs) should be avoided for 1 week prior to testing and aspirin exposure should be minimized; however, it is uncertain whether these products affect the reliability of the test. In addition, although iron preparations may blacken stools, they do not lead to false-positive results. Female patients should be told not to collect test samples for 3 days after or during a menstrual period. To avoid potential false-positive or false-negative results, stool should be collected from diapers or from disposable collection devices rather than directly from toilet water. Finally, an alkali denaturation test, also known as the Apt-Downey or Apt test, should be performed when a breast fed infant vomits bright red blood or passes red bloody stools to distinguish whether it is maternal or fetal hemoglobin.

Once gastrointestinal bleeding is confirmed, the evaluation, differential diagnosis, and therapeutic interventions will depend on the age of the patient and whether the bleed is coming from the upper or the lower gastrointestinal tract (Tables 13.2, 13.3, and 13.4). A nasogastric (NG) tube may be placed in the appropriate patient when the source of bleeding is not clear. Bloody aspirate from the stomach is confirmation of upper gastrointestinal bleeding. The tube may then be used to lavage the stomach with warm saline. If aspirated saline clears after repeated lavage, the bleeding has likely stopped or is from a different source.

HEMATEMESIS AND MELENA: UPPER GASTROINTESTINAL BLEED

◆ History

Neonates who did not receive prophylactic vitamin K are at risk for hemorrhagic disease of the newborn (see Chapter 38) and additional perinatal factors may place them at risk for sepsis or other stress that could lead to gastritis. Infants who require intensive care may have trauma from an NG tube, and infants with neonatal umbilical vein catheterization or neonatal omphalitis are at risk for portal vein thrombosis and resultant later onset of esophageal varices. In older children, a recent history of vomiting, regurgitation, or abdominal pain suggests a mucosal lesion. Forceful, repeated vomiting may result in a Mallory-Weiss tear or prolapse gastropathy. Reactive gastritis can be due to medications such as NSAIDs as well as alcohol or ingestion of caustic substances. Providers must ask about recent bleeding such as epistaxis or dental procedures, which could lead to hematemesis without a gastrointestinal source of bleeding.

Information regarding chronic pulmonary disease, renal disease, bleeding disorders, and liver disease, including a history of jaundice, should be obtained in all children. Patients with cystic fibrosis are at risk not only for the development of esophageal varices caused by biliary cirrhosis but also for coagulopathies from vitamin K deficiency. They may also have hemoptysis, which can be misinterpreted as hematemesis. In patients with renal disease, uremia will cause platelet dysfunction, which may manifest as a gastrointestinal bleed. The family

(See *Nelson Textbook of Pediatrics,* p. 1766.)

TABLE 13.1 Mimics of Gastrointestinal Bleeding

Foodstuffs:
- Beets
- Blueberries
- Food coloring
- Gelatin
- Licorice
- Punch
- Red candy
- Spinach
- Tomato skins
- Watermelon

Medications:
- Bismuth
- Iron supplementation
- Rifampin

Bleeding from other locations:
- Epistaxis
- Hemoptysis
- Menses
- Recent dental work or tonsillectomy

Swallowed maternal blood in breast-fed or newborn infant
Munchausen (factitious disorder) syndrome by proxy
Factitious disorder

TABLE 13.2 Differential Diagnosis for Upper Gastrointestinal Bleeding

Infants	Milk protein sensitivity Trauma Esophagitis Gastritis Ulcer Infection—CMV, herpes, fungal Sepsis with DIC Vitamin K deficiency Anatomic anomalies (duplication) Vascular malformation Mallory-Weiss tear Prolapse gastropathy
Children	Esophagitis including pill ulceration Gastritis • NSAIDs • *Helicobacter pylori* Ulcer • Foreign body Stress Esophageal varices Hemobilia Vascular malformation • Dieulafoy lesion (artery that protrudes through mucosa) Anatomic anomaly Infection Sepsis with DIC Mallory-Weiss Tear Prolapse gastropathy

CMV, cytomegalovirus; DIC, disseminated intravascular coagulation; NSAIDs, nonsteroidal antiinflammatory drugs.

TABLE 13.3 Differential Diagnosis for Lower Gastrointestinal Bleeding

Infants	Milk protein sensitivity Anal fissure Infectious—*Salmonella, Shigella, Escherichia coli O157:H7, Campylobacter* species, *Yersinia* species, *Entamoeba histolytica,* CMV Ischemia—volvulus or necrotizing enterocolitis Sepsis with DIC Vitamin K deficiency Vascular malformation Hirschsprung enterocolitis Lympho-nodular hyperplasia Intussusception Trauma
Children	Milk and other protein sensitivity Anal fissure Infectious—above plus *Clostridium difficile* Medication • NSAIDs • Mycophenolate Intussusception Meckel diverticulum Juvenile polyp Inflammatory bowel disease Ischemia Typhlitis Vascular malformation Anatomic anomaly Henoch-Schönlein purpura Lymphonodular hyperplasia Trauma

CMV, cytomegalovirus; DIC, disseminated intravascular coagulation; NSAIDs, nonsteroidal antiinflammatory drugs.

history should address the presence of bleeding disorders, peptic ulcer disease, and possible *Helicobacter pylori* exposure.

◆ Physical Examination

Immediate attention must be given to signs of hypovolemia, anemia, or shock. An orthostatic change, such as a pulse rate increase of 20 beats/min or a drop in systolic blood pressure of more than 10 mm Hg when the patient changes from supine to standing is a sensitive index of significant volume depletion. Blood pressure may remain normal up to the point of circulatory collapse in children and a normal blood pressure should not be reassuring in the setting of other signs of hypovolemia such as tachycardia or delayed capillary refill.

In addition to close attention to changes in vital signs, a physical exam with emphasis on potential sources of bleeding is essential (Table 13.5). The oropharynx and nasal canals should be examined for lesions as the cause of bleeding. Palpation to evaluate organomegaly should begin at the iliac crests so as not to miss a hugely enlarged liver or spleen. A prominent venous pattern on the abdomen (Fig. 13.1), splenomegaly, and ascites may suggest portal hypertension. Tenderness and guarding indicate a significant inflammatory process.

In addition to assessing for pallor, cutaneous lesions may help determine the underlying cause of bleeding. Petechiae can indicate disseminated intravascular coagulation, hypersplenism, or another bleeding abnormality. Hyperpigmented lesions of the oral or anal mucosa may indicate Peutz-Jeghers disease. Cutaneous telangiectasia

TABLE 13.4 Causes of *Occult* Gastrointestinal Bleeding

Inflammatory Causes	**Infectious Causes**
Peptic esophagitis	Hookworm
Crohn disease	Strongyloidiasis
Ulcerative colitis	Ascariasis
Mild enterocolitis	Tuberculosis enterocolitis
Celiac disease	Amebiasis
Eosinophilic gastroenteritis	**Tumors and Neoplastic Causes**
Meckel diverticulum	Polyps
Solitary rectal ulcer	Lymphoma
Vascular Causes	Leiomyoma
Angiodysplasia and vascular ectasias	Lipoma
Gastroesophageal varices	Carcinoma
Congestive gastropathy	**Artificial Causes**
Hemangiomas	Hematuria
Drugs	Menstrual bleeding
Nonsteroidal antiinflammatory drugs	Nonspecific test positivity
Extragastrointestinal Causes	**Miscellaneous Causes**
Hemoptysis	Long-distance running
Epistaxis	Coagulopathies
Oropharyngeal bleeding	Factitious

Modified from Ahlquist DA. Approach to the patient with occult gastrointestinal bleeding. In: Yamada T, ed. *Textbook of Gastroenterology*. Philadelphia: JB Lippincott; 1991:620.

TABLE 13.5 Pertinent Physical Findings in Gastrointestinal Bleeding

Exam Finding	Associated Disorder
Splenomegaly Caput medusae	Portal hypertension and esophageal varices
Palmar erythema Spider angioma Jaundice	Liver disease
Hemangioma	Vascular malformations in gastrointestinal tract
Palpable purpura	Henoch-Schönlein purpura or other vasculitis
Hyperpigmented lesions of the oral or anal mucosa	Peutz-Jeghers syndrome (GI polyps)
Oral ulcers Perianal fistula Perianal skin tag Erythema nodosum Pyoderma gangrenosum	Inflammatory bowel disease

and hemangiomas may indicate such diseases as Osler-Weber-Rendu syndrome and ataxia-telangiectasia, or they may simply suggest a predisposition for vascular malformations. Palmar erythema, spider angioma, or jaundice suggests underlying liver disease. Scleral icterus may be subtle but can be the first sign of liver disease and may be more easily appreciated than jaundice in darker-skinned individuals.

FIGURE 13.1 Prominent venous pattern on the abdomen.

◆ Differential Diagnosis

In infants, esophagitis, gastritis, and ulcers are the most common causes of upper gastrointestinal bleeding. Esophagitis may be associated with dysphagia, irritability, and arching with feeds (see Chapter 12). Milk protein sensitivity should be considered as well, although it more often presents with blood in stool. Trauma or infection (such as cytomegalovirus, herpes simplex, or fungal) can cause mucosal irritation presenting as hematemesis. Anatomic abnormalities including duplication cysts or vascular abnormalities may also lead to hematemesis or melena in infants.

FIGURE 13.2 Endoscopic view of fundus showing area of prolapse gastropathy.

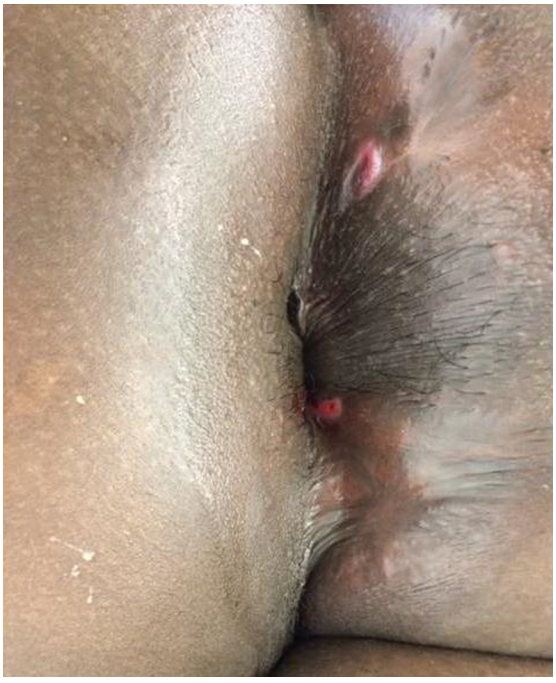


FIGURE 13.3 Skin tags and fistulas as in Crohn disease.

In older children, mucosal lesions remain common causes of bleeding. Mallory-Weiss tears are associated with repeated forceful vomiting from a variety of causes (e.g., acute gastroenteritis). The forcefulness of the vomiting causes a tear in the distal esophagus at the level of the lower esophageal sphincter. The history is generally one of frequent nonbloody vomiting that then becomes hematemesis. Prolapse gastropathy, caused by prolapse of gastric mucosa into the distal esophagus, can similarly occur after forceful vomiting and lead to hematemesis (Fig. 13.2). Reactive gastritis secondary to medication (NSAIDs) or infection (*H. pylori*) are also common causes of upper gastrointestinal bleeding. Children with known or unknown liver disease can develop esophageal varices that may lead to large-volume hematemesis and melena (or hematochezia if bleeding is brisk). Ulcers, although rare, can also lead to significant blood loss and may be related to *H. pylori* infection, stress such as surgery or burns, and foreign body ingestion, specifically button batteries, which can lead to significant bleeding.

HEMATOCHEZIA: LOWER GASTROINTESTINAL BLEED

◆ History

Chronicity of bleeding is essential to ascertain because infectious colitis may cause acute bloody diarrhea, while inflammatory bowel disease generally presents with a more prolonged history (see Chapter 11). Presence or absence of pain can also help distinguish between causes of bleeding. Severe, acute abdominal pain is often present in patients with vascular compromise, such as in intussusception, midgut volvulus, and bowel ischemia (e.g., Henoch-Schönlein purpura), while painless rectal bleeding suggests a Meckel diverticulum, polyp, or angiodysplasia. Growth failure is suggestive of inflammatory bowel disease, specifically Crohn disease; constipation points to the possibility of an anal fissure (see Chapter 16) or Hirschsprung disease with enterocolitis. Information regarding travel (either by the patient or by visitors), sick contacts, daycare exposure, camping, and antibiotic exposure may reveal potential infectious causes. Family history of polyps or colon cancer is important given the inherited polyposis syndromes, as is a family history of inflammatory bowel disease.

◆ Physical Examination

Physical exam in any patient with gastrointestinal bleeding must begin with assessment of hemodynamic status. In addition to a general exam, for patients with hematochezia, a rectal exam is important to evaluate for fissures as well as skin tags and fistulas, which may be seen in Crohn disease (Fig. 13.3). Local intense tenderness, fever, and erythema of the perianal area may suggest group A β-hemolytic streptococcus infection. Infants and toddlers may have a palpable right lower quadrant abdominal mass, which suggests intussusception. Skin examination may show purpura which, although not always present initially, is seen in Henoch-Schönlein purpura; it may also be seen in hemolytic uremic syndrome. Erythema nodosum or pyoderma gangrenosum is present in approximately 3% of children with inflammatory bowel disease and may correlate with disease severity.

◆ Differential Diagnosis

Anal fissures are probably the most frequent cause of streaks of bright red blood mixed with stool. The bleeding may be associated with hard bowel movements but may occur from straining with normal bowel movements. There is also an association with group A streptococcal perianal cellulitis and bleeding. Anal fissure may be a manifestation of milk protein allergy with resultant perianal inflammation and subsequent constipation to avoid painful defecation. More often, a milk protein allergy will present with specks of blood within the stool. There may be a history of increasing frequency and amount of blood and mucus in the stool. The infant may exhibit cramping with bowel movements and vomiting may be part of the presentation. Often there is a family history of food allergies. Milk protein allergy can be seen in infants fed cow's milk– or soy protein–based formulas, as well as in breast-fed infants. Ischemic bowel disease, including necrotizing enterocolitis and volvulus, may lead to rectal bleeding and an acutely ill, sick-appearing neonate or infant. Risk factors for necrotizing enterocolitis include prematurity, cardiac surgery, polycythemia, chronic diarrhea, and gastrointestinal malformations.

Infectious colitis is common in both infants and children and causes frequent, often watery, bloody bowel movements (see Chapter 11). There may be cramping pain before and during the bowel movement as a result of the colitis. Common pathogens include *Salmonella* and *Shigella* organisms, especially with dysentery type stools, but *E. coli* O157:H7, *Campylobacter* species, *Yersinia* species, and *Entamoeba histolytica* should also be considered. *Clostridium difficile* is a common cause of hematochezia in older children but is also found in healthy infants without causing disease due to lack of toxin receptors in the immature colon.

For young children, intussusception and Meckel diverticulum are common causes of hematochezia. The hallmark of intussusception is the presence of "currant jelly" stools associated with colicky abdominal pain, lethargy, or irritability. Meckel diverticulum occurs in 1-3% of the population and manifests by the age of 2 years in about 50% of patients. Bleeding results from mucosal ulceration secondary to secretion of gastric acid or pepsin from ectopic gastric or pancreatic tissue, respectively, in the tip of the diverticulum. It is usually brisk and painless with blood ranging from dark red to bright red.

Juvenile polyps also present with painless rectal bleeding but are uncommon in children under 1 year of age with peak incidence between ages 5 and 7 years. They are more common in boys and non-Caucasian races. Most juvenile polyps occur in the distal colon and may cause bleeding from autoamputation as they outgrow their blood supply. These polyps are generally benign but adenomatous polyps in children suggest an inherited disorder, such as familial adenomatous polyposis (FAP). Affected individuals with FAP are at significant risk for the development of colonic carcinoma and require repeated colonoscopies and, eventually, prophylactic colectomy and ileoanal pouch procedures.

In older children, inflammatory bowel disease becomes a more common cause of hematochezia. The rectal bleeding varies from occult to frank blood in the bowel movements. Blood is present in 100% of cases of ulcerative colitis but in only 30-50% of cases of Crohn disease. Inflammatory bowel disease is generally accompanied by fever, weight loss, and rectal bleeding (see Chapter 11).

Henoch-Schönlein purpura is a vasculitic syndrome that can cause bloody stools. It is often accompanied by cramping abdominal pain, purpuric rash (palpable purpura), joint swelling, scalp edema (infants and toddlers), and occasionally, nephritis (see Chapter 20).

OCCULT BLOOD LOSS

Occult blood loss most often presents as iron-deficiency anemia or may be detected during evaluation for abdominal pain, vomiting, diarrhea, or weight loss (see Table 13.4).

◆ Laboratory Evaluation

Initial laboratory evaluation should include a complete blood count with differential and platelet count, coagulation profile, and a comprehensive metabolic profile with total and direct bilirubin (Table 13.6). Patients with clinical signs of significant blood loss should have a blood typing with cross match sent. Guaiac testing can be performed on stool or emesis to confirm presence of blood. In patients with lower gastrointestinal bleeding, stool should be sent for analysis of infectious causes. Urinalysis may be useful in patients with hematochezia with suspicion for hemolytic uremic syndrome.

◆ Imaging

Radiographs

Abdominal radiographs should be obtained in all infants with acute hematochezia to look for pneumoperitoneum, pneumatosis intestinalis, or hepatic portal vein gas suggesting necrotizing enterocolitis. Flat plate films may also identify intussusception, volvulus, abdominal masses, or foreign bodies (Fig. 13.4). Upper gastrointestinal contrast studies can discern anatomic lesions, such as strictures, stenosis,

TABLE 13.6 Laboratory Findings Suggestive of a Diagnosis

Lab Finding	Significance
Hgb/HCT	Normal hemoglobin or hematocrit does not rule out significant bleed as it may take time to equilibrate
Low MCV	Chronic blood loss
Low platelets	HUS, hypersplenism (secondary to portal hypertension), ITP, DIC
Elevated prothrombin time	Liver disease, coagulation disorder, DIC
Increased BUN/Normal Cr	UGI bleed more likely
Increased BUN/Elevated Cr	HUS or HSP
Decreased albumin	IBD or liver disease
Elevated ESR/CRP	IBD
Elevated AST/ALT	Liver disease
Elevated bilirubin	Liver disease

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; DIC, disseminated intravascular coagulation; ESR, erythrocyte sedimentation rate; Hgb/HCT, hemoglobin/hematocrit; HSP, Henoch-Schönlein purpura; HUS, hemolytic uremic syndrome; IBD, inflammatory bowel disease; MCV, mean corpuscular volume; UGI, upper gastrointestinal.

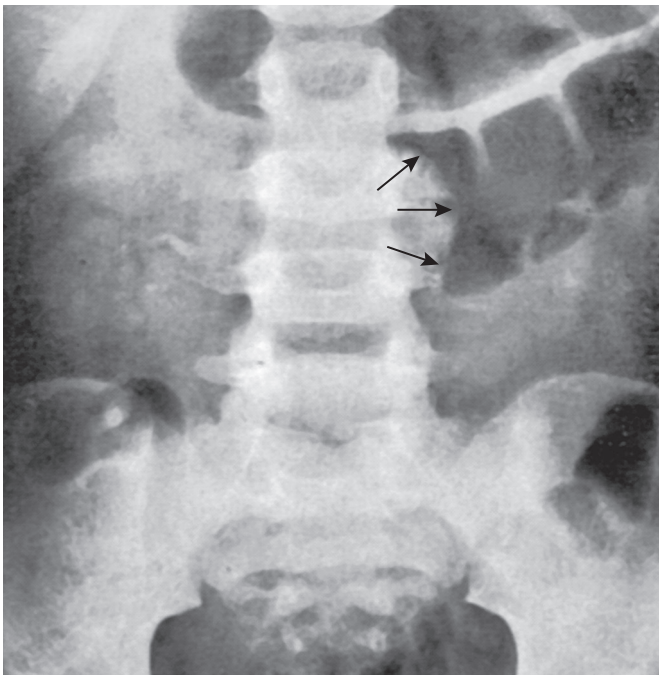


FIGURE 13.4 Flat plate film.

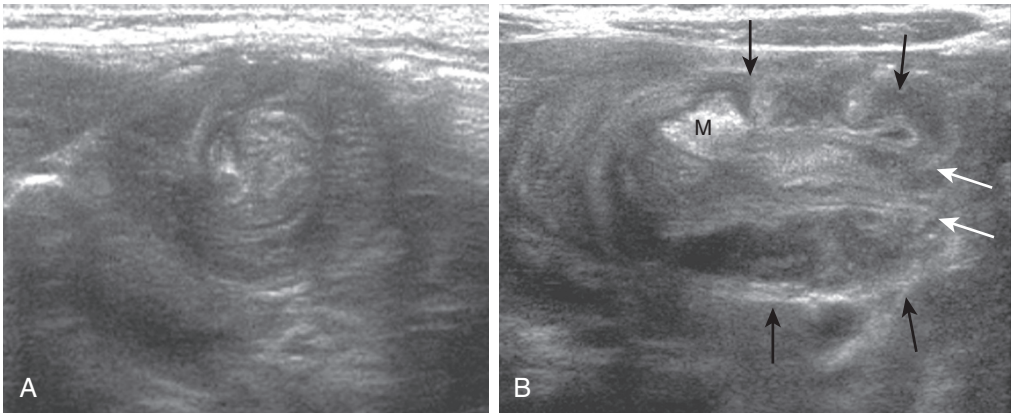


FIGURE 13.5 Abdominal ultrasound illustrating intususception. *A,* Transverse plane shows target-like appearance of bowel. *B,* Longitudinal plane shows inner bowel loops *(white arrows)* telescoping through outer bowel loops *(black arrows).* Edema of affected bowel causes hyperechoic mucosa *(M).*

atresias, malrotation, large ulcerations, and masses. Small bowel follow-through examination allows evaluation of the small bowel from the ligament of Treitz to the ileocecal valve. Areas of ulceration, mucosal thickening, and narrowing may be appreciated. An air or water soluble enema should be performed in infants and children in whom there is a concern of distal intestinal obstruction, such as intussusception (see Chapter 10). In cases of intussusception, the enema not only aids in diagnosis but may also be therapeutic. Crohn disease and ulcerative colitis may be suggested by results of this test, but endoscopy is necessary for histologic confirmation of these diagnoses.

Abdominal Ultrasound

An ultrasound may be useful in patients with suspected liver disease to evaluate for portal hypertension. It may also be used in potential cases of intussusception or suspected large vascular malformations (Fig. 13.5).

Computed Tomography

CT scans may be useful in evaluating possible anatomic anomalies and may reveal signs of inflammation related to infectious or inflammatory colitis. CT enterography can localize an *active* lower gastrointestinal bleed. Given the radiation exposure, the value of a CT over other diagnostic modalities must be considered.

Magnetic Resonance Enterography

MRE can be useful in cases of occult bleeding or in suspected and known inflammatory bowel disease to evaluate for areas of inflammation in the small bowel that may be causing blood loss. Patients must be awake and able to stay still through the prolonged study, which limits its utility in younger patients.

Angiography

Angiography may help identify the source of bleeding but is only sensitive for an active bleed at a rate of at least 0.5 mL/min. Nevertheless, angiography can identify extravasation of contrast in a Meckel diverticulum or the presence of vascular malformations of the bowel, which may be acquired or congenital. Therapeutic angiography can also be used to control gastrointestinal bleeding.

Nuclear Imaging

Nuclear medicine may determine the site of bleeding with minimal complications; it is associated with minimal radiation exposure and requires minimal sedation. Technetium 99m (99mTc) pertechnetate is rapidly taken up by gastric mucosa and it is useful in identifying sites of bleeding secondary to ectopic gastric mucosa. Gastric mucosa is found in 90% of bleeding Meckel diverticula, and in these patients the Meckel scan has a sensitivity of 94% and a specificity of 97% in the pediatric population (Fig. 13.6). False-negative results have been reported frequently because of insufficient gastric tissue mass, downstream washout of isotope, impaired blood supply, or suboptimal techniques. Positive identification may be improved by the administration of ranitidine to prevent excretion of pertechnetate from gastric tissue.

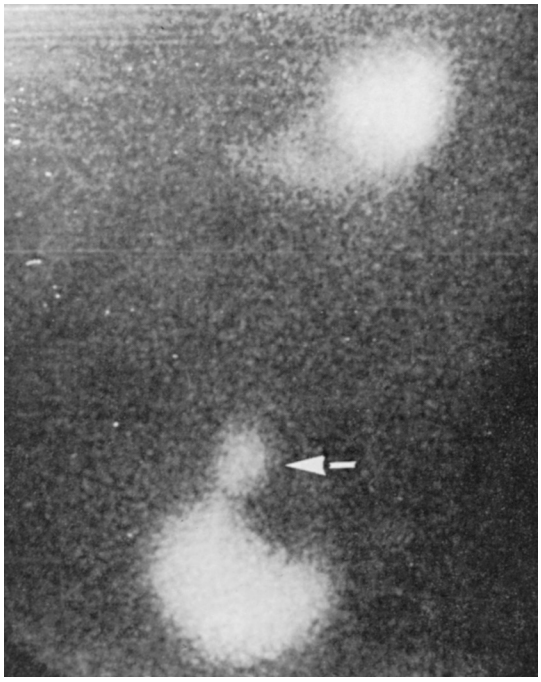


FIGURE 13.6 Positive Meckel scan. *Arrow* indicates abnormal area of increased uptake in lower abdomen above bladder, consistent with gastric mucosa containing Meckel diverticulum.

Bleeding scans are performed by intravenously injecting technetium sulfur colloid. The agent is distributed quickly and is rapidly taken up by the reticuloendothelial system. It can detect a rate of bleeding of 0.1 mL/min. However, because the technetium is taken up by the reticuloendothelial system, this may hinder the search for bleeding sites behind the liver or spleen. Finally, the clearance is very rapid, with a half-life of 2 minutes, which means that bleeding has to be occurring at the time of the scan.

The 99mTc pertechnetate–labeled red blood cell scan is a sensitive and accurate test for the localization of active bleeding. In cases of intermittent bleeding, a single injection of labeled cells allows repeated scans for up to 24 hours. It can detect as little blood as 0.5 mL/min.

◆ Imaging

Esophagogastroduodenoscopy (EGD) is the procedure of choice in identifying the site of upper gastrointestinal bleeding. EGD can also allow direct intervention at the bleeding site, as in the case of esophageal varices or a visible vessel in an ulcer crater. Endoscopic visualization of the stomach and duodenum should be performed even if the bleeding is thought to originate from esophageal varices. Of patients with proven esophageal varices, 50% may manifest bleeding from gastritis or peptic ulcer disease rather than the varices. Endoscopy, however, should not be performed until the patient is as hemodynamically stable as possible. Gastric lavage may be useful prior to upper endoscopy to remove any blood present in the stomach to allow for better views as well as to determine whether there is still active bleeding. Erythromycin can be given prior to endoscopy to accelerate gastric emptying and removal of blood from the stomach.

Lower gastrointestinal tract bleeding can also be evaluated endoscopically. Procedures frequently used in children include proctosigmoidoscopy and flexible colonoscopy. With the patient under appropriate sedation, lower gastrointestinal endoscopy allows for full exploration of the colon; identifies the presence of multiple lesions; allows for therapeutic intervention to bleeding lesions through electrocoagulation, laser therapy, or thermocoagulation; and allows for removal of bleeding lesions, such as polyps. Colonoscopy is indicated when there is melena or severe bleeding with no evidence of upper gastrointestinal lesions, when stools are guaiac-positive over a long time, and when examination of the terminal ileum is indicated to determine whether inflammatory bowel disease is present. One disadvantage is that large amounts of luminal blood obscure visualization of a lesion. Before lower gastrointestinal colonoscopy, intestinal lavage with oral administration of polyethylene glycol should be used to remove as much of the luminal blood and stool as possible.

Small bowel enteroscopy, or evaluation of the jejunum or proximal ileum, can be useful in the evaluation of occult bleeding. While its diagnostic yield varies by study, it allows for direct intervention if the source of bleeding is found. In addition, it has been employed intraoperatively to help identify lesions and guide surgical intervention.

Capsule Endoscopy

Wireless capsule endoscopy may be useful in patients with occult or apparent bleeding when other work-up, including an upper and lower endoscopy, have been negative. The patient swallows or has the capsule placed endoscopically and images are taken as the capsule passes through the small and large intestines, which can identify vascular malformations and other sources of bleeding (Fig. 13.7). The main risk is capsule retention and so children must be of a certain size and be evaluated for possible stricture prior to the study.

◆ Treatment

Resuscitation

The severity of bleeding determines the general guidelines for treatment. For severe bleeding, initial management reestablishes and maintains the intravascular volume. Subsequently, the site of blood loss must be determined and attempts made to stop the hemorrhage. Severe anemia also necessitates packed red blood cell transfusions after the intravascular volume deficit is corrected (Table 13.7).

Although parents tend to overestimate the amount of blood lost by their child, a major error in the management of gastrointestinal bleeding is underestimating blood loss. The hematocrit may remain unchanged initially, despite significant blood loss, and therefore is not a good indicator of significant bleeding. If orthostatic blood pressure changes or tachycardia are present, the initial goal of treatment should be to hemodynamically stabilize the patient, maintain the intravascular volume, and provide adequate oxygen delivery to the tissues. A second potential error is the failure to establish adequate intravenous (IV) access. The largest possible IV catheter must be rapidly placed in a child

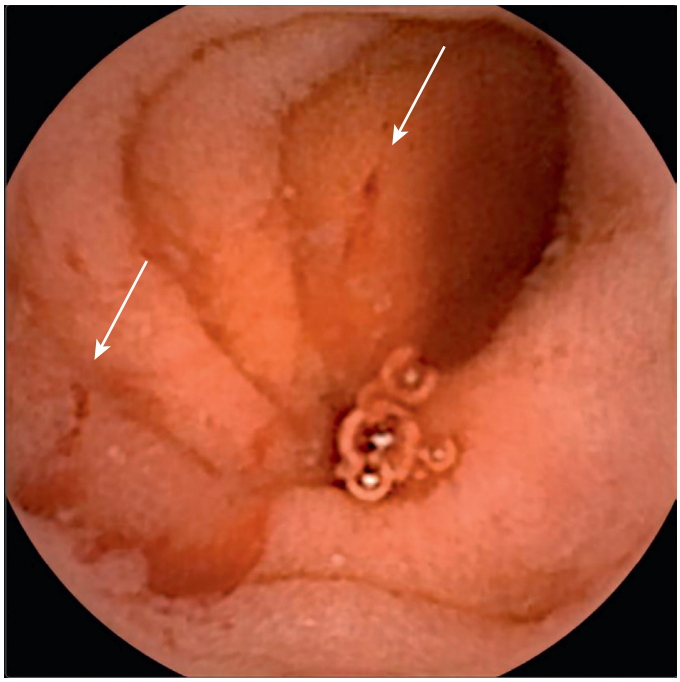


FIGURE 13.7 Capsule endoscopy image revealing jejunal bleeding from a vascular malformation in a patient who presented with anemia refractory to iron supplementation.

TABLE 13.7 Initial Management of Patients with Hypovolemia Secondary to Gastrointestinal Hemorrhage

1. Establish adequate intravenous (IV) access by placing 2 IV catheters.
   - Recommended catheter size:
     - Infant: 20 gauge
     - Child: 18 gauge
     - Adolescent: 16 gauge
2. Rapidly infuse saline or lactated Ringer solution, use smaller boluses and frequent monitoring in patients with suspected varices to avoid rapid increase in venous pressure and worsening of variceal bleed.
3. Carefully monitor pulse, blood pressure, and central venous pressure to avoid fluid overload.
4. Monitor urine output, skin perfusion, and orthostatic changes in pulse and blood pressure for early recognition of shock.
5. Transfuse with packed red blood cells to return oxygen-carrying capacity to normal.
6. Carefully record all fluids transfused, and estimate and record all recognized fluids lost.

Modified from Olson AD, Hillemeier AC. Gastrointestinal hemorrhage. In: Wyllie R, Hyams JS, eds. *Pediatric Gastrointestinal Disease*. Philadelphia: WB Saunders; 1993:253.

TABLE 13.8 Pharmacotherapy in Pediatric Gastrointestinal Bleeding*

Medication	Mechanism of Action/Indication	Dosage
Ranitidine	H_2-receptor antagonist, acid reducer	*IV:* ≤16 yr: 2-4 mg/kg/day divided every 6-8 hr (max dose: 50 mg/dose) >16 yr: 50 mg every 6-8 hr *Oral:* ≤16 yr: 4-8 mg/kg/day divided twice daily (max dose: 300 mg/day) >16 yr: 150 mg twice daily
Famotidine	H_2-receptor antagonist, acid reducer	*IV or PO:* ≤16 yr: 0.5 mg/kg/day nightly or divided twice daily (max dose 40 mg/day) >16 yr: 40 mg/day nightly or divided twice daily (max dose 40 mg/day)
Pantoprazole†	Proton pump inhibitor, acid reducer	*IV:* ≥2 yr: 0.8 or 1.6 mg/kg once daily (max dose: 80 mg/dose) *Oral:* <5 yr: 1.2 mg/kg/day once daily >5 yr: 20 or 40 mg once daily
Omeprazole†	Proton pump inhibitor, acid reducer	*Oral:* 5 kg to <10 kg: 5 mg once daily 10 kg to <20 kg: 10 mg once daily ≥20 kg: 20 mg once daily
Lasoprazole†	Proton pump inhibitor, acid reducer	*Oral:* ≤30 kg: 15 mg once daily >30 kg: 30 mg once daily
Sucralfate	Coats mucosal injury and binds bile acids to prevent further injury, inhibits pepsin in the presence of acid‡	*Oral:* 40-80 mg/kg/day divided every 6 hr (max dose 1000 mg/dose)
Octreotide	Somatostatin analog, selectively decreases splanchnic blood flow	*IV:* 1-2 μg/kg initial bolus followed by 1-2 μg/kg/hr continuous infusion (doses up to 4 μg/kg/hr have been used) Following endoscopic intervention may taper dose by 50% every 12 hr and discontinue when dose is 25% of initial dose

*Dosages listed are from *Pediatric Lexi-Comp* online formulary and do not apply to infants aged <3 mo. Evidence-based dosing of these medications is not well established.
†Proton pump inhibitors (PPIs) should not be administered in infants aged <1 yr without endoscopic evidence of acid-induced disease.
‡Use in conjunction with PPI may limit efficacy.

with active bleeding. Blood loss should be replaced immediately with a crystalloid solution, such as normal saline or lactated Ringer solution. Initially, a fluid push of 20 mL/kg should be given, although resuscitation should be performed cautiously in patients who may have portal hypertension as overly aggressive resuscitation raises the venous pressure and could worsen bleeding from varices. In these patients, small, repeated fluid boluses with close monitoring are preferred to large volume boluses. If blood loss continues and the patient appears to be at risk for hypovolemic shock, infusion of normal saline or colloid solutions (5% albumin) can be continued until blood is available. Plasma is indicated if coagulation factors are depleted. Once bleeding has stopped, transfusions of packed red blood cells should continue, to slowly raise the hematocrit to 30% (10 g/dL hemoglobin) (for patients with variceal bleeding the goal is instead hemoglobin of 8-9 g/dL). If continued blood loss necessitates multiple transfusions, fresh-frozen plasma and calcium should be given to replace coagulation factors and correct the hypocalcemia caused by the citrate in blood products. The platelet count in such patients must be monitored because thrombocytopenia may develop.

If a nasogastric tube is inserted, the tube size is determined by the child's age and size. A 12-French tube is used in infants and preschool children; a 14- or 16-French tube is appropriate for children of elementary school age or older. Gastric lavage should be undertaken with room-temperature normal saline. The color of the gastric lavage fluid gives the physician an indication of the rate of bleeding. Lavage returns that are bright red indicate significant ongoing bleeding; pink-tinged or brown flecks in the solution indicate less significant or minimal bleeding.

Maintaining a gastric pH of more than 4 is considered standard therapy for upper gastrointestinal mucosal bleeding. This can be accomplished with either H_2-receptor antagonists or proton pump inhibitors.

Vasoactive Agents

In patients with suspected variceal bleeding, a continuous infusion of octreotide may be started. This agent reduces splanchnic blood flow with minimal disturbance to other organs. It is safer than vasopressin but has not been shown to have benefit in nonvariceal bleeding. Customarily, a bolus of octreotide (1-2 μg/kg) is given over 5-10 minutes, and this is followed by a continuous infusion of 1 μg/kg/hr, although higher doses may be required. The infusion may help control the bleeding until definitive therapy (banding or sclerotherapy) is performed. After endoscopic intervention, octreotide infusions may be weaned slowly (every 12 hours) with close monitoring of the patient to ensure varices do not re-bleed. See Table 13.8 for additional pharmacotherapy.

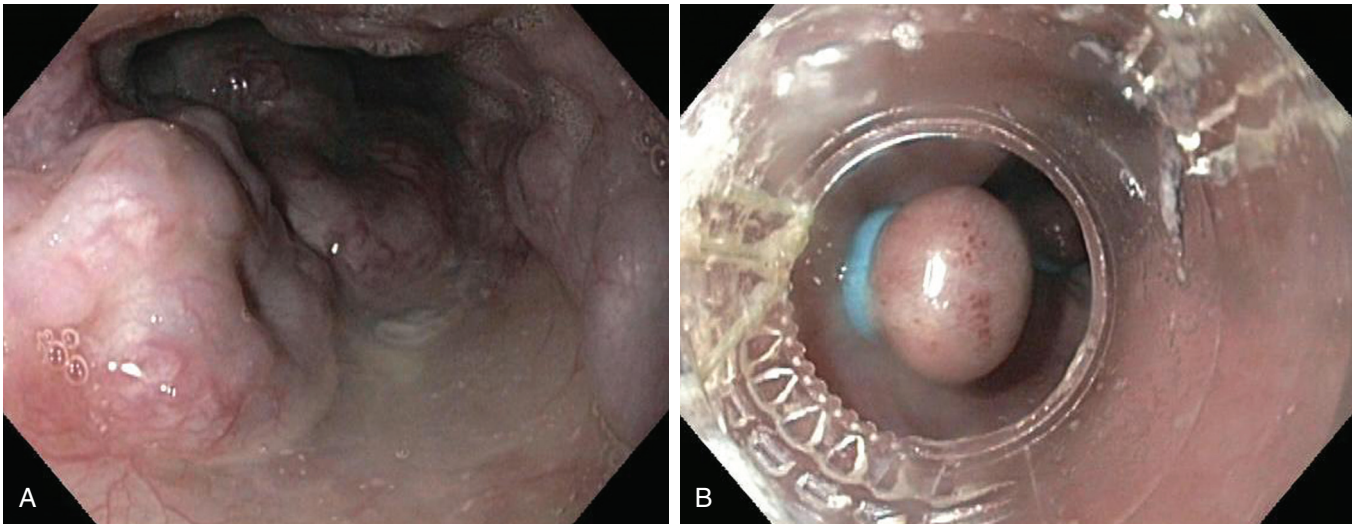


FIGURE 13.8 Variceal banding is the preferred method for treating esophageal varices. *A*, Grade 3 esophageal varices in patient with cirrhosis. *B*, View of varices after band application.

Endoscopic Modalities

Most patients with gastrointestinal bleeding will undergo upper and/or lower endoscopy for definitive diagnosis and treatment. For patients with mucosal lesions, such as ulcers or bleeding polyps, there are multiple therapeutic interventions available. Injection with a diluted epinephrine solution, thermal coagulation, laser photocoagulation, and endoscopic clips can be used to stop active bleeding. Vascular lesions may also be treated endoscopically. For patients with colitis, colonoscopy is used primarily to confirm diagnosis and extent of disease.

Variceal banding is the preferred method for treating bleeding esophageal varices (Fig. 13.8 *A* and *B*). Ideally, the banding takes place after good control of acute bleeding, affording the endoscopist an unobstructed view of the varices. Side effects of this therapy are minimal, and the procedure is repeated weekly to monthly until the varices are obliterated. Sclerotherapy is also effective in controlling the acute bleeding from esophageal varices and may be performed weekly to monthly until the varices resolve. In young children whose upper esophageal sphincter is too small for the endoscopic banding device to pass, sclerotherapy may be the only option. Complications include esophageal ulceration and esophageal stricture. A number of sclerosing agents (e.g., ethanolamine, sodium morrhuate, ethanol, tetradecyl sulfate) are efficacious in treating varices.

Surgical intervention is a definitive treatment for many of the anatomic anomalies causing gastrointestinal bleeding and may be performed in conjunction with endoscopy to identify the lesion. Vessel ligation may also be a necessary step in bleeding ulcers that cannot be controlled endoscopically.

Interventional Radiology

Selective embolization during angiography can be used to treat vascular malformations and to control bleeding from ulcers. The rate of complications from angiography is 2%, whether the procedure is diagnostic or therapeutic. In patients with intrahepatic portal hypertension with bleeding from gastrointestinal sites inaccessible to sclerotherapy or banding, coiling of varices or transjugular intrahepatic portosystemic shunting may be beneficial.

SUMMARY AND RED FLAGS

Gastrointestinal bleeding may occur anywhere along the gastrointestinal tract and can range from occult blood loss to massive hemorrhage. Approach to gastrointestinal bleeding begins with ensuring hemodynamic stability of the patient while obtaining a thorough history and physical exam to help determine upper versus lower source of bleeding. Red flags include hemodynamic instability that necessitates immediate attention. Laboratory, radiologic, and endoscopic evaluation are used for confirmation of diagnosis and potentially treatment.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Bishop PR, Nowicki MJ, Parker PH. Vomiting-induced hematemesis in children: Mallory-Weiss tear or prolapse gastropathy? *J Pediatr Gastroenterol Nutr*. 2000;30:436-441.

Brumbaugh DE, Colson SB, Sandoval JA, et al. Management of button battery-induced hemorrhage in children. *J Pediatr Gastroenterol Nutr*. 2011;52:585-589.

Chawla S1, Seth D, Mahajan P, et al. Upper gastrointestinal bleeding in children. *Clin Pediatr*. 2007;46:16-21.

Cohen SA, Klevens AI. Use of capsule endoscopy in diagnosis and management of pediatric patients, based on meta-analysis. *Clin Gastroenterol Hepatol*. 2011;9:490-496.

Davis JS1, Ryan ML, Fields JM, et al. Use of CT enterography for the diagnosis of lower gastrointestinal bleeding in pediatric patients. *J Pediatr Surg*. 2013;48:681-684.

de la Torre L, Carrasco D, Mora MA, et al. Vascular malformations of the colon in children. *J Pediatr Surg*. 2002;37:1754-1757.

Dotson JL1, Hyams JS, Markowitz J, et al. Extraintestinal manifestations of pediatric inflammatory bowel disease and their relation to disease type and severity. *J Pediatr Gastroenterol Nutr*. 2010;51:140-145.

Fox VL. Gastrointestinal bleeding in infancy and childhood. *Gastroenterol Clin North Am*. 2000;29:37-66.

Freedman SB, Stewart C, Rumantir M, et al. Predictors of clinically significant upper gastrointestinal hemorrhage among children with hematemesis. *J Pediatr Gastroenterol Nutr*. 2012;54:737-743.

Hood B, Bigler S, Bishop P, et al. Juvenile polyps and juvenile polyp syndromes in children: A clinical and endoscopic survey. *Clin Pediatr*. 2011;50:910-915.

Hwang JH, Fisher DA, Ben-Menachem T, et al. Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy. The role of endoscopy in the management of acute non-variceal upper GI bleeding. *Gastrointest Endosc*. 2012;75:6.

Kay MH, Wyllie R. Therapeutic endoscopy for nonvariceal gastrointestinal bleeding. *J Pediatr Gastroenterol Nutr*. 2007;45:157-171.

Kendrick ML, Buttar NS, Anderson MA, et al. Contribution of intraoperative enteroscopy in the management of obscure gastrointestinal bleeding. *J Gastrointest Surg*. 2001;5:162-167.

Konrad G1, Katz A. Are medication restrictions before FOBT necessary? Practical advice based on a systematic review of the literature. *Can Fam Physician*. 2012;58:939-948.

McKiernan PJ. Treatment of variceal bleeding. *Gastrointest Endosc Clin N Am*. 2001;11:789-812.

Melmed GY, Lo SK. Capsule endoscopy: Practical applications. *Clin Gastroenterol Hepatol*. 2005;3:411-422.

Molleston JP. Variceal bleeding in children. *J Pediatr Gastroenterol Nutr*. 2003;37:538-545.

Pant C, Sankararaman S, Deshpande A, et al. Gastrointestinal bleeding in hospitalized children in the United States. *Curr Med Res Opin*. 2014;30(6):1065-1069.

Sinha CK, Pallewatte A, Easty M, et al. Meckel's scan in children: A review of 183 cases referred to two paediatric surgery specialist centres over 18 years. *Pediatr Surg Int*. 2013;29:511-517.

Thakkar K, Fishman DS, Gilger MA. Colorectal polyps in childhood. *Curr Opin Pediatr*. 2012;24:632-637.

Xanthakos SA, Schwimmer JB, Melin-Aldana H, et al. Prevalence and outcome of allergic colitis in healthy infants with rectal bleeding: A prospective cohort study. *J Pediatr Gastroenterol Nutr*. 2005;41:16-22.

14

Hepatomegaly

Grzegorz W. Telega

Hepatomegaly occurs commonly in children as a feature of primary liver disease or as a result of systemic disorders involving the liver and other organs (Table 14.1). Because of congenital anomalies, inborn errors of metabolism, and perinatal infections, there may be a greater number of disorders manifesting with hepatomegaly during infancy than during any other time of life (Table 14.1). Common symptoms of hepatic dysfunction, such as fatigue, fever of unknown origin, pruritus, failure to thrive, confusion, change in mental status, and diarrhea are nonspecific. Hepatomegaly and jaundice are frequently the findings that lead to an evaluation for liver disease. Causes of hepatomegaly associated with jaundice are discussed in Chapter 15.

ASSESSMENT OF THE LIVER

An accurate assessment of liver size is an important initial step in evaluating a patient with possible liver disease. Considerable patience may be necessary to obtain the required information. The patient should lie down in a supine position with the knees flexed. The abdominal muscles should be relaxed as much as possible. The provider should become familiar with the sensation of pressure over the abdominal wall in the lower abdomen in order to detect the difference while transitioning over the liver edge. The examiner should also be sure that the lower border of a massively enlarged liver is not missed by failure to palpate below the umbilicus. The lower edge of the liver should be determined by palpation just lateral to the right rectus muscle. Careful palpation of the liver edge along the lower border is important as enlargement of the liver can be asymmetrical in chronic cirrhosis, in Budd-Chiari syndrome, and with liver tumors.

The lower edge of the liver is usually palpable in normal subjects with deep inspiration when it moves downward 1-3 cm. In the newborn, the liver edge may be palpable 2-3 cm below the right costal margin, but that distance is usually less than 2 cm by 4-6 months of age. In older children, the liver edge is usually not more than 1 cm below the right costal margin except on deep inspiration. The liver may be normally palpable in the midline several centimeters below the xiphoid.

Palpation should always be combined with percussion of the upper and lower boundaries of the liver. The upper edge of the liver is determined through percussion passing downward from the nipple line. The examiner may also define the lower edge through light percussion, moving upward from the umbilicus toward the costal margin. The anterior span of the liver is the difference between the highest and lowest points of hepatic dullness in the right midclavicular line.

In the scratch test the stethoscope is placed over the right lower costal area. The examiner then scratches the skin of the abdomen and uses auscultation to detect the lower liver edge by using the difference in sound transmission over solid liver and hollow intestine.

It is important to remember that physical examination has limitations. It may be difficult to detect the borders of the liver in patients with morbid obesity, ascites, pleural effusion, or extensive surgical scars. Physical examination determines only the external borders of the liver and does not truly measure liver volume. A downward, tongue-like projection of the right lobe—the Riedel lobe—is a normal anatomic variant that is more commonly found in girls. It is a common error to express liver size and to define hepatomegaly on the basis of only the liver edge felt below the right costal margin. The liver may be displaced downward in patients with pulmonary disease, particularly with hyperaeration of the lungs. It may be difficult in some cases to distinguish masses arising from the right kidney or adrenal gland from an enlarged liver.

Liver size changes with age in proportion to the body size (Table 14.2). At birth, the liver constitutes approximately 4% of body weight and normally occupies a larger portion of the abdominal cavity than it does later in life. Liver weight increases twofold by the end of the first year of life, triples by the age of 3 years, and is increased sixfold by the age of 9 years. In the adult, liver weight is approximately 12 times that in the neonate.

The consistency and surface of the liver should be noted, including whether the liver edge is sharp or rounded and whether the liver surface is soft, hard, or irregular. The liver edge is normally soft, fairly sharp, and nontender. Livers enlarged because of congestive heart failure or because of acute infiltration by inflammatory cells or tumor are firm, have a somewhat rounded edge, and have smooth surfaces. In cirrhosis, the liver is hard and may have an irregular surface and edge. Tenderness generally suggests an acute process, as rapid distention of the liver capsule causes pain.

Hepatomegaly may resolve rapidly when congestive heart failure is controlled, biliary obstruction is relieved, diabetes is better controlled, or when massive liver cell necrosis leads to collapse of the liver tissue.

◆ History and Physical Examination

Once the presence of hepatomegaly is established, the provider should focus on the aspects of the history and physical examination that will direct the diagnostic evaluation. Review of systems should focus on growth, achievement of developmental milestones, changes in mental status, vomiting, diarrhea, fevers, pruritus, easy bruising, bleeding, urine output, and abdominal distention. Obtaining a detailed family and travel history is important, as many conditions leading to hepatomegaly are genetic in nature or are a result of infections. The possibility of intentional or accidental drug intake should always be entertained. On physical examination, it is important to determine the presence or absence of jaundice, splenomegaly, ascites, change in mental status, tremors, neurologic abnormalities, fever, signs of malnutrition, prominent vascular patterns on the anterior abdominal wall (caput medusae, spider angiomas), arterial hypertension, hypotension, bruising, petechiae, hemangiomas, pallor, obesity, renal enlargement, masses outside of the liver, lymphadenopathy, muscle weakness, cyanosis, heart murmurs, tachypnea, tachycardia, abnormal eye exam (cataracts, Kayser-Fleischer ring), bone and joint abnormalities, and dysmorphic features. A pelvic exam in sexually active females may detect signs of

(See *Nelson Textbook of Pediatrics,* Fig. 304-4.)

TABLE 14.1 Causes of Hepatomegaly in Infants and Children

Infection and Inflammation
Viral hepatitis (hepatitis A, B, C, D, E; EBV; adenovirus, echovirus, TORCH)
Autoimmune hepatitis
Sepsis
Perinatal infections
Neonatal hemophagocytic lymphohistiocytosis (HLH)
Allograft rejection
Graft-versus-host disease
Systemic lupus erythematosus
Juvenile idiopathic arthritis
Primary sclerosing cholangitis
Systemic granulomatous disorders with hepatic involvement
Sarcoid
Tuberculosis
Hepatic abscess (bacterial and parasitic)
Parasitic infection
Visceral larva migrans
Schistosomiasis
Malaria
Liver flukes
Kupffer cell hyperplasia
Macrophage activation syndrome

Biliary Obstruction
Biliary atresia
Choledochal cysts
Stricture of common bile duct
Primary sclerosing cholangitis

Infiltration
Extramedullary hematopoiesis
Erythroblastosis fetalis
Thalassemias
Metastatic tumors
Neuroblastoma
Wilms tumor
Leukemia
Lymphoma
Hemophagocytic lymphohistiocytosis (HLH)

Storage/Metabolic Disease
α_1-Antitrypsin deficiency
Wilson disease
Infants of diabetic mothers
Glycogen storage disease
Galactosemia
Tyrosinemia
Cystic fibrosis
Gaucher disease
Niemann-Pick disease
Gangliosidoses
Hereditary fructose intolerance
Mucopolysaccharidoses
Amyloidosis
Hepatic porphyrias

Expansion of Extracellular Matrix
Cirrhosis
Fibrocystic disease (congenital hepatic fibrosis)

Steatosis
Malnutrition
Nonalcoholic steatohepatitis (obesity)
Neonatal iron storage disease
Cystic fibrosis
Parenteral nutrition
Diabetes mellitus
Hereditary fructose intolerance
Galactosemia
Wolman disease
Cholesterol ester storage disease
Mitochondrial hepatopathies
β-Oxidation defects
Medication toxicity (tetracycline, valproic acid)

Hepatic Malignancy/Tumor
Hepatoblastoma
Hepatocellular carcinoma
Hemangioma/hemangioendothelioma

Vascular Congestion
Congestive heart failure
Budd-Chiari syndrome
Venoocclusive disease

Cystic Disease
Fibrocystic disease
Autosomal dominant polycystic kidney disease
Isolated polycystic liver disease

EBV, Epstein-Barr virus; TORCH, toxoplasmosis, other infections, rubella, cytomegalovirus, herpes simplex virus.

TABLE 14.2 Normal Liver Span in Infants and Children

Age	Span (cm)
Preterm infant	4-5
Full-term infant	5-6.5
1-5 yr	6-7
5-10 yr	7-9
10-16 yr	8-10

a sexually transmitted infection, which can lead to Fitz-Hugh–Curtis syndrome.

◆ Pathophysiology

The pathophysiologic mechanisms underlying the enlargement of the liver are complex and heterogeneous. Hepatomegaly may reflect proliferation or enlargement or malfunction of one or more component structures of the liver, including liver parenchyma (hepatocytes), bile ducts (cholangiocytes, cysts), the reticuloendothelial system (Kupffer cells), interstitial tissue (stellate cells, collagen), blood (including hematopoietic cells), and blood vessels (endothelial cells). The liver also increases in size as a result of hepatic tumors, benign cysts, and infiltration of inflammatory or malignant cells.

The liver is particularly susceptible to injury not only from drugs and other exogenous toxins, but also from endotoxins that arise after the activation of inflammatory cells and the production of cytokines. Inborn errors of metabolism can be responsible for disturbances of liver structure and function and can produce hepatomegaly. The liver can be enlarged because of storage of glycogen, lipid, or glycolipids within the hepatocyte. In glycogen storage disease, the cytoplasm of enlarged hepatocytes is filled with dense pools of glycogen particles that displace other organelles. Steatosis is a frequent finding in diabetic or obese patients and is characterized ultrastructurally by large lipid inclusions, which may almost entirely fill the cytoplasm of hepatocytes. In lysosomal storage disorders such as Gaucher disease and Niemann-Pick disease, there is marked involvement of Kupffer cells with lysosomal inclusions characteristic of each disorder. Inclusions may also be present within hepatocytes; they contribute to hepatomegaly.

In many cases of biliary obstruction, such as biliary atresia, there may be significant hepatic enlargement, related in part to fibrosis and portal tract edema. As part of the liver's response to biliary obstruction, there may also be marked proliferation of small bile ductules that contribute to liver mass. Other conditions in which this could occur include choledochal cysts and common bile duct strictures.

The liver is the largest reticuloendothelial organ, and Kupffer cells, which are intensely phagocytic cells that line the sinusoids, constitute 15% of all the cells in the liver. In septicemia, hepatitis, and a number of other inflammatory conditions, hepatomegaly may result from proliferation and hyperplasia of Kupffer cells. Kupffer cells are involved in the cellular response to hepatocellular destruction. Kupffer cells also contribute to hepatomegaly in lysosomal storage disorders.

Resident stellate cells produce collagen, leading to fibrosis and eventually cirrhosis in response to injury of the liver from numerous causes, including infection, drug toxicity, and biliary obstruction. Hepatocellular injury can result in activation of stellate cells, which leads to the production of collagen and fibrosis. Fibrosis is a long-standing process, which may evolve over time to complete disruption of hepatic architecture and cirrhosis. Although an end-stage cirrhotic liver is often small, it may be significantly enlarged during the early stages of evolution. Congenital hepatic fibrosis is an inherited malformation of the liver characterized by the presence of broad bands of fibrous tissue and numerous distorted bile ducts and vascular structures. All of these abnormal components contribute to marked enlargement and hardening of the liver.

About 15% of the liver is occupied by sinusoidal and vascular structures. The liver is capable of rapid and massive enlargement in association with increased venous pressure. Distention of hepatic sinusoids can be present in congestive heart failure, constrictive pericarditis, or obstruction of hepatic venous outflow as a result of thrombosis or endothelial damage from drug toxicity (venoocclusive disease).

Since the liver serves as a secondary site of hematopoiesis, hepatomegaly can be caused by extramedullary hematopoiesis, particularly in young infants. Hepatomegaly can be the result of chronic inflammation, hemolysis, hemophagocytic lymphohistiocytosis (HLH), or bone marrow failure.

Hepatomegaly can occur as a result of cellular infiltration by inflammatory cells. Lymphocytic infiltrate is present in various forms of acute and chronic viral hepatitis, as well as in autoimmune hepatitis. Plasma cells may also be a prominent part of the infiltrate in autoimmune disease. Macrophages may also be observed, particularly in reaction to liver cell necrosis. The increase in liver size resulting from cellular infiltration may be balanced by loss of liver cell mass from liver cell necrosis or apoptosis.

Cellular infiltration of the liver may also occur in malignant disorders such as leukemia. A number of intraabdominal malignancies such as neuroblastoma may metastasize to the liver, producing hepatomegaly.

A variety of space-occupying lesions can lead to hepatomegaly. Cysts, either isolated or communicating with the biliary tract, tumors intrinsic to the liver, and hepatic abscesses can all be associated with hepatomegaly. Each must be differentiated by clinical features and defined more precisely by imaging studies.

EVALUATION OF THE CHILD WITH HEPATOMEGALY

Important historical or physical examination findings are noted in Tables 14.3 and 14.4.

◆ Laboratory Studies

Laboratory assessment of liver function in children with hepatomegaly is essential. Because of the large functional reserve of the liver, hepatomegaly may be the only indication of liver disease. The onset of symptoms such as jaundice and bleeding may be delayed long after laboratory evidence of disturbed liver function is evident. Patients with progressive liver disease, including those with chronic viral hepatitis, Wilson disease, or α_1-antitrypsin deficiency, may be asymptomatic for years or even decades. The pattern of liver test abnormalities may be helpful in suggesting whether the patient's liver disease is primarily hepatocellular or biliary in nature. Moreover, some laboratory studies, particularly when followed sequentially, may provide information about the synthetic, exocrine, metabolic (glucose, amino acids, lipids, detoxification) and endocrine (hyperaldosteronemia, vitamin D activation) liver function. Laboratory data provide input into several prognostic models used in assessment of the mortality risk and in evaluation for liver transplant.

All patients with hepatomegaly should have a complete metabolic panel (sodium, potassium, chloride, bicarbonate, creatinine, blood urea nitrogen (BUN), AST, ALT, albumin, glucose, lactate dehydrogenase (LDH), alkaline phosphatase, total bilirubin, total protein), fractionated bilirubin (conjugated and unconjugated bilirubin), complete blood count, urinalysis, prothrombin time (PT), partial thromboplastin time (PTT), and fibrinogen. D-dimers should also be tested in patients with suspected sepsis or thrombosis.

TABLE 14.3 Historical Features in the Diagnostic Evaluation of Hepatomegaly or Hepatosplenomegaly

Symptom	Diagnosis
Failure to thrive	Glycogen storage disease (infancy) types I, III, IV, IX, X Hereditary fructose intolerance Organic acidemias Wolman disease Cystic fibrosis Hemophagocytic lymphohistiocytosis Cholestatic liver disease
Fever	Acute and chronic hepatitis Systemic illness Hepatic abscess Hemophagocytic lymphohistiocytosis Viral infection
Diarrhea	Wolman disease Cholestatic liver disease
Peculiar odor	Organic acidemias Hepatic failure
Neurologic/psychiatric symptoms in older child	Wilson disease Porphyria Hyperammonemia (urea cycle disorders, organic acidemias) Drug intoxication/toxicity Hypoglycemia (glycogen storage disease, organic acidemias, β-oxidation defects)

Hepatocellular Injury

The concentrations of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are frequently studied to assess hepatocellular injury. The aminotransferases may be elevated as a result of hepatocyte necrosis induced by a number of infectious, inflammatory, or metabolic disorders or by drug toxicity. ALT is present in much lower concentration in most tissues other than the liver. AST is less specific, as it is present not only in liver but also in muscle and brain. Some patients with a systemic viral illness such as influenza may have acute rhabdomyolysis, which leads to a very marked increase in serum AST. Hemolysis may also lead to an elevation of this enzyme. Although in most cases of liver disease there is some elevation of aminotransferase values, significant liver disease (hepatic steatosis, hepatitis C infection, and many metabolic disorders) may be present even when these test results are normal. Aminotransferases do not reflect liver function and have little correlation with the specific diagnosis or prognosis.

Biliary Injury

Alkaline phosphatase and γ-glutamyltransferase (GGT) are expressed in the bile collecting system. Their elevation can occur in both intrahepatic and extrahepatic cholestasis. Alkaline phosphatase is found in several other tissues, including bone, small intestine, placenta, and kidney. Because children have a significant proportion of serum alkaline phosphatase activity originating from bone, this test may be of less value in the assessment of pediatric liver disease. Even minor bone trauma or vitamin D deficiency can lead to elevation of alkaline phosphatase. The tissue origin of alkaline phosphatase can be determined by fractionation of alkaline phosphatase isoenzymes. The normal newborn may have very high levels of GGT, up to 10 times the upper limit of normal for adults. Values of GGT for premature babies may be higher than those for term infants during the first weeks after birth. In comparison with other standard serum assays, that of GGT may be the most sensitive indicator of hepatobiliary disease, but it is not of value in determining a specific diagnosis. Nonetheless, the highest levels of GGT are found in biliary obstruction. GGT levels may be paradoxically normal or low in progressive familial intrahepatic cholestasis type 1 and 2 and in some inborn errors of bile acid metabolism.

Exocrine Function

Because bilirubin requires conjugation with glucuronic acid in the hepatocyte, excretion across the canalicular membrane, and unobstructed passage through the biliary tree, the serum concentration of conjugated bilirubin represents a test of exocrine liver function. It is important to remember that the pathophysiologic effects of cholestasis are more directly related to bile acid excretion. Insufficient bile acid levels in the intestinal lumen lead to fat malabsorption, fat-soluble vitamin deficiencies, and steatorrhea. Analysis of serum bile acid levels, vitamin A, 25-hydroxy vitamin D, vitamin E, PT/international normalized ratio (INR), and measurement of fecal fat may further define the extent of exocrine dysfunction (see Chapter 15).

Synthetic Function

Albumin is the principal serum protein synthesized by the liver and has a half-life in serum of approximately 20 days. A decrease in serum albumin concentration may result from decreased production by the liver caused by severe impairment of liver function or significant loss of liver parenchyma. Serum albumin may also be low because of loss into the urine or the gastrointestinal tract.

The liver plays a central role in the production of coagulation factors. The PT and PTT are reasonable tests of liver synthetic capacity once vitamin K deficiency has been excluded. All of the clotting factors except factor VIII are exclusively made by the hepatocyte. The half-life of several clotting factors is short (factor VII has a half-life of 3-5 hours), and so the PT rapidly reflects changes in hepatic synthetic function and serves as a prognostic indicator in patients with fulminant hepatic failure. Caution should be used in interpreting a prolonged PT or PTT as sepsis with disseminated intravascular coagulation may cause abnormalities.

Metabolic Function

Many tissues can break down glycogen or produce glucose-6-phosphate via the gluconeogenesis pathway for local energy production inside the cell. The liver is the only organ that is able to release glucose into circulation. Patients with hepatic failure, glycogen storage diseases, mitochondrial diseases, fatty acid β-oxidation defects, pyruvate metabolism defects, Krebs cycle and gluconeogenesis defects, organic acidurias, or hereditary fructose intolerance may be hypoglycemic. Blood glucose level determination is essential in the evaluation of hepatomegaly, particularly in patients with alterations in their mental status. In the majority of conditions, hypoglycemia is associated with ketosis and lactic acidosis. Hypoglycemia in the absence of or with low levels of ketones in the urine strongly suggests a fatty acid β-oxidation defect or a mitochondrial disorder. Blood gas (and anion gap), serum amino and urinary organic acids, lactate, pyruvate, acylcarnitines, acylglycines, cortisol, insulin, thyroid function, and adrenocorticotropic hormone (ACTH) as well as the ratios of total and esterified to free serum carnitine concentrations, should be determined in follow-up studies.

The urea cycle is a series of enzymatic reactions converting highly toxic ammonia into less toxic urea. Ammonia is a ubiquitous by-product of amino acid metabolism. The urea cycle takes place exclusively in the liver. In liver disease, impairment of the urea cycle can be caused by destruction of hepatocytes, metabolic block at the level of the urea cycle, organic acid catabolism defects, or

TABLE 14.4 Physical Signs in the Differential Diagnosis of Hepatomegaly

Sign	Differential Diagnosis
Asymmetric hepatomegaly	Tumor, cyst, abscess
Abdominal mass	Congenital hepatic fibrosis/polycystic kidneys Extrahepatic tumors (neuroblastoma, Wilms tumor) Choledochal cysts Adenoma Hepatoblastoma Hepatocellular carcinoma
Hepatic bruit	Hemangioendothelioma
Splenomegaly	Congenital infection Systemic infection (viral, bacterial, fungal) Cirrhosis Portal hypertension Lysosomal storage disease Lymphoma
Cutaneous hemangioma or telangiectasia	Hemangioendothelioma Hereditary hemorrhagic telangiectasia Cirrhosis (vascular spiders)
Coarse/dysmorphic facial features	Mucopolysaccharidosis GM_1 gangliosidosis Glycoproteinoses (sialidosis, mucolipidosis II) Disorders of protein glycosylation Glycogen storage disease type I Alagille syndrome Zellweger syndrome
Episodic acute encephalopathy/coma	Disorders of fatty acid β-oxidation Hyperammonemia (urea cycle disorders, organic acidemias) Mitochondrial disorders Some urea cycle disorders (arginosuccinate lyase deficiency) Drug toxicity
Skeletal deformities	Sialidosis (dysostosis multiplex) Mucopolysaccharidoses (dysostosis multiplex) Gaucher disease (marrow infiltration, deformities, fractures) Mucolipidosis II (restricted joint mobility)
Skin findings	
Papular acrodermatitis	Hepatitis B
Eczematoid rash	Histiocytosis
Neurodegeneration	Mucopolysaccharidoses (types IH, II, III) Gaucher disease types II and III GM_2 gangliosidosis Niemann-Pick disease types A, B, C Glycoproteinoses Mucolipidoses Disorders of protein glycosylation Peroxisomal disorders (Zellweger syndrome) Mitochondrial disorders
Hypotonia	Glycogen storage disease type II Peroxisomal disorders (Zellweger syndrome) Mitochondrial disorders Mucolipidoses
Malnutrition	Cystic fibrosis Steatosis
Virilization	Hepatoblastoma Nonalcoholic fatty liver (female)
Eye findings	
Cataracts	Galactosemia
Kayser-Fleischer rings	Wilson disease
Telangiectasias	Hereditary hemorrhagic telangiectasia
Iritis	Primary sclerosing cholangitis
Cherry red spot	Glycoproteinoses GM_2 gangliosidosis Niemann-Pick disease type B
Posterior embryotoxon	Acute hepatitis (viral, toxic, autoimmune) Congestion (heart failure, hepatic vein obstruction) Trauma (subcapsular hematoma, fracture, laceration) Abscess (hepatic, subphrenic) Cholangitis

mitochondrial electron transport defects. Shunting of portal blood in cirrhosis or in congenital portosystemic shunts permits large amounts of ammonia and other toxins to bypass the liver and reach the systemic circulation directly.

Hepatomegaly with an acute change in mental status should raise the possibility of a serious metabolic condition. Since both hypoglycemia and hyperammonemia can lead to severe and irreversible brain damage, correction of these abnormalities should be considered an emergency.

The liver is the main site of biosynthesis and processing of cholesterol, lipids, and lipoproteins. Liver disease may profoundly affect serum lipid and lipoprotein concentrations. In cholestatic liver disease there may be extreme elevations of free cholesterol and phospholipids. These abnormalities are accompanied by the presence of an abnormal low-density lipoprotein fraction called lipoprotein X. In end-stage liver disease and acute liver failure, serum cholesterol may be low.

Enzymatic analysis of cultured lymphocytes or hepatic tissue may aid in the diagnosis. Genetic diagnosis is possible in a number of these disorders.

Extrahepatic Involvement

High levels of unconjugated bilirubin suggest the possibility of a concurrent hemolytic disorder or may reflect inborn errors of conjugation (see Chapter 15).

Neutropenia can be associated with splenomegaly/hypersplenism from portal hypertension, glycogen storage disease type Ib, Shwachman-Diamond syndrome, hemophagocytic lymphohistiocytosis (HLH), sepsis, leukemia, and neuroblastoma.

Renal involvement can be reflected by elevated creatinine, inability to concentrate urine, or by Fanconi syndrome. This could raise suspicion for autosomal recessive polycystic kidney disease, tyrosinemia, glycogen storage disease type Ib, Wilson disease, hereditary fructose intolerance, or galactosemia.

◆ Imaging Studies

A plain film of the abdomen may initially suggest the possibility of hepatomegaly. Air may be seen within the portal venous system, a late finding in bowel infarction and necrosis, intraabdominal sepsis, and associated inflammatory bowel disease. Air may also be present within the biliary tree, especially in patients who have undergone recent biliary tract surgery or who have an enterobiliary fistula. Coarse calcifications may be found in hepatoblastoma and laminated calcifications in hepatocellular carcinoma. Subacute abscesses and echinococcal cysts may also contain calcium.

Ultrasonography is often the most useful initial imaging modality. It can assess gallbladder size, detect gallstones and sludge in the bile ducts and gallbladder, demonstrate ascites, and define cystic or obstructive dilatation of the biliary tree. Extrahepatic anomalies may also be detected. Mass lesions in the liver, including tumors, cysts, abscesses, vascular malformations, and hematomas, can be defined. Abnormal echogenicity may suggest diffuse parenchymal liver disease including fatty infiltration or fibrosis. Doppler studies may be used to differentiate between vascular and nonvascular structures. The study may be particularly useful for assessing portal hypertension, in which portal venous flow may be decreased or reversed.

Computed tomography (CT) with contrast provides useful information in differentiation of liver masses. CT angiograms and/or venograms are useful in defining the anatomy of vascular anomalies. Disadvantages of CT scans are the frequent need for sedation, potential renal toxicity of contrast, and risks from ionizing radiation.

Magnetic resonance imaging (MRI) provides additional information about liver anatomy. Magnetic resonance angiography (MRA) may be of value in assessing the vascularity of masses within the liver. Magnetic resonance cholangiography is commonly used to assess the biliary tract with visualization of details previously possible only with transhepatic or endoscopic retrograde cholangiography.

Hepatic scintigraphy can be useful for assessing the liver parenchyma and biliary tree. The most frequently performed study is hepatobiliary scintigraphy performed with a technetium 99m (^{99m}Tc)–labeled iminodiacetic acid derivative. Biliary imaging with this technique provides information about patency of the biliary tract and gallbladder. ^{99m}Tc–sulfur colloid scanning may be used in assessing a patient with a mass. ^{99m}Tc–sulfur colloid accumulates in Kupffer cells. Most malignant tumors, hemangiomas, abscesses, and cysts lack Kupffer cells and appear as "cold" spots on these scans. In contrast, a nodule taking up the isotope suggests a benign lesion containing Kupffer cells, such as a regenerative nodule of cirrhosis, fatty change, or focal nodular hyperplasia.

Liver Biopsy

Percutaneous, transjugular, or open-liver biopsy is one of the most important diagnostic tests in evaluating a child with hepatomegaly. Liver biopsy is essential in establishing a diagnosis and possibly prognosis in patients with chronic viral hepatitis, drug-induced liver disease, autoimmune hepatitis, and various metabolic disorders. Abnormal storage of material in hepatocytes or Kupffer cells and viral inclusions may also be found. Electron microscopy and immunohistochemical methods may aid in identification and localization of these abnormalities. Liver tissue may also be frozen for later biochemical or molecular analysis.

SPECIFIC ISSUES IN THE DIAGNOSIS AND TREATMENT OF HEPATOMEGALY

The clinical challenge in the evaluation of hepatomegaly is that there is a very broad differential with many relatively rare conditions. Tables 14.4 and 14.5 list some of the physical signs and laboratory abnormalities that may be associated with hepatomegaly. Table 14.6 lists a stepwise approach for devising the differential diagnosis and directing the investigation. The first goal is to identify potentially life-threatening conditions, to focus on emergency measures to manage immediate threats to life, and to prevent irreversible end-organ damage. The second goal is to identify potentially treatable disorders requiring timely interventions. Ultimately, the clinician should focus on other chronic conditions in order to establish the diagnosis and prognosis. Some disorders may be corrected by liver transplantation; such patients should be promptly referred to a transplant center for evaluation.

TABLE 14.5 Helpful Laboratory Abnormalities in the Evaluation of Hepatomegaly

Vacuolated white blood cells in peripheral smear	Wolman disease GM_1 gangliosidosis
Neutropenia	Glycogen storage disease type I Organic acidurias Shwachman-Diamond syndrome Hemophagocytic lymphohistiocytosis Sepsis Leukemia Neuroblastoma Portal hypertension (hypersplenism)
Hemolytic anemia	Wilson disease Autoimmune hepatitis Hemoglobinopathy (with extramedularry hematopoeisis)
Hypophosphatemia	Glycogen storage disease type I Hereditary fructose intolerance
Hypertriglyceridemia	Glycogen storage disease type I Hemophagocytic lymphohistiocytosis Nonalcoholic fatty liver
Elevated creatinine	Disorders of fatty acid β-oxidation Reye syndrome Congenital hepatic fibrosis/autosomal recessive polycystic kidney disease
Renal tubular dysfunction	Tyrosinemia Glycogen storage disease type I Hereditary fructose intolerance Wilson disease Galactosemia

Hepatomegaly in the Infant

Hepatomegaly in the neonate is commonly associated with liver dysfunction and jaundice (see Chapter 15). In infants, jaundice is a frequent presenting feature of liver disease rather than a later manifestation of advanced liver disease, as in the older child or adult. The majority of infants with cholestatic liver disease manifest the disease during the first month of life.

Changes in mental status, such as irritability or lethargy, poor feeding, and vomiting, are frequent symptoms in metabolic disorders. Urea cycle defects lead to hyperammonemia and acute encephalopathy associated with astrocyte swelling without axonal damage. Patients present with a change in mental status or ataxia. Severe or prolonged hyperammonemia ultimately leads to progressive irreversible changes in the brain characterized by cortical and brainstem gliosis and

TABLE 14.6 Evaluation of Patients with Hepatomegaly

Jaundice → (+)	See Chapter 15
(–)	
Prominent vomiting or altered sensorium → (+)	Disorders of mitochondrial fatty acid β-oxidation Reye syndrome Congenital lactic acidemias Disorders of gluconeogenesis Respiratory chain defects Organic acidemias Urea cycle defects Disorders of carbohydrate metabolism Glycogen storage disease types I and III Hereditary fructose intolerance* Fulminant hepatic failure
(–)	
Progressive neurologic deterioration → (+)	Peroxisomal disorders Zellweger syndrome* Lysosomal storage disease Niemann-Pick disease, Gaucher disease GM_1 gangliosidosis Mucopolysaccharidosis Wilson disease*
(–)	
Prominent elevation of serum aminotransferase levels → (+)	Acute hepatitis Chronic hepatitis B, C, and D Chronic drug-induced hepatitis* Autoimmune hepatitis* Wilson disease* α_1-Antitrypsin deficiency* Sclerosing cholangitis*
(–)	
Evidence of associated systemic disease → (+)	Cardiovascular disease, right-sided heart failure* Inflammatory bowel disease Collagen vascular disease Hematologic disorders Leukemia Familial hemophagocytic lymphohistiocytosis* Sickle cell disease Post–bone marrow transplantation status Diabetes mellitus Systemic infection Cystic fibrosis* Sarcoidosis
(–)	
Isolated hepatomegaly (with or without splenomegaly) → (+)	Hepatic tumors Fatty liver* Hepatic cysts Hepatic abscess Congenital hepatic fibrosis* Choledochal cyst Hepatic outflow obstruction* Glycogen storage disease type IV* Wolman disease* Cholesterol ester storage disease Niemann-Pick disease type B Gaucher disease (adult form)* Tyrosinemia*

*Disease that may result in cirrhosis.

neuronal atrophy. Symptomatology of galactosemia and tyrosinemia depends on the presence of nutritional substrates; thus irritability, lethargy, hepatomegaly, ascites, edema, and coagulopathy may manifest soon after feedings are initiated and evolve over the first weeks of life.

A profound impairment of hepatic synthetic function, often in excess of that expected for the degree of cholestasis, may be an early indication of metabolic liver disease. Hepatic failure may be present in mitochondrial disorders, including both mitochondrial DNA mutations and mitochondrial DNA depletion syndromes. Multiple organs (brain, heart, skeletal muscle) may be involved in addition to the liver. Affected patients often have lactic acidosis, hypoglycemia, hypertriglyceridemia, and an abnormal acylcarnitine profile.

Neonatal hemochromatosis may manifest with hepatic failure at birth. Patients with neonatal hemochromatosis may benefit from treatment with plasmapheresis and may require liver transplantation. Diagnosis of hemochromatosis also bears significance for future pregnancies. Hemochromatosis will develop in up to 80% of infants of mothers with a child diagnosed with hemochromatosis. As hemochromatosis is likely caused by maternal alloantibodies crossing the placenta and damaging the liver, the severity of hemochromatosis can be alleviated by prenatal administration of intravenous immunglobulin (IVIG).

A number of clinical features may provide clues about the cause of neonatal cholestasis. An enlarged liver with a firm or hard consistency is more commonly found in infants with extrahepatic bile duct obstruction or neonatal hemochromatosis. Congenital infection may be associated with low birthweight, hepatomegaly, microcephaly, purpura, and chorioretinitis. Dysmorphic facial features may be seen in association with chromosomal abnormalities and with Alagille syndrome. Congenital malformations, including cardiac anomalies, polysplenia, intestinal malrotation, and situs inversus, may be found in the syndromic form of biliary atresia. In the **polysplenia syndrome**, a midline liver may be palpable in the hypogastrium. The spleen may also be enlarged with infection or as a result of portal hypertension. Hepatomegaly, as well as a mass in the right upper quadrant, may be felt in infants with a choledochal cyst. Infants may present with hepatomegaly, cholestasis, and sometimes hepatic failure related to infection. Cytomegalovirus, herpes simplex virus, enteroviruses, echovirus, coxsackievirus and parvovirus B19 are sometimes isolated from infants with cholestasis and hepatomegaly. Hepatomegaly and cholestasis can also be associated with bacterial sepsis, syphilis, tuberculosis, and toxoplasmosis. α_1-Antitrypsin deficiency can present as hepatomegaly associated with cholestasis in infants.

Infants with **storage diseases** can present with isolated hepatomegaly or hepatosplenomegaly and few other symptoms in the early stages. Hepatomegaly is a feature of these disorders because of a pathologic accumulation of undegraded or partially degraded macromolecules. The mucopolysaccharidoses, the lipid storage diseases, the mucolipidoses, and glycoprotein storage disease are examples of these disorders. The clinical features of lysosomal storage diseases are determined by where the deficient enzyme is expressed and the rate of accumulation of the abnormal material. Hepatomegaly in the neonate can occur in Gaucher disease, Niemann-Pick disease type A, and Wolman disease. Neonatal hepatosplenomegaly and jaundice may occur in Niemann-Pick disease type C. Progressive neurologic dysfunction may occur later. Hepatosplenomegaly accompanied by coarse facial features and skeletal abnormalities is present in infants with the GM_2 gangliosidoses and mucopolysaccharidoses. Significant liver disease may occur in some of these disorders, leading to chronic liver failure and cirrhosis. On the basis of clinical features and manifestations, specific enzymatic activities may be determined in peripheral white blood cell culture or in cultured skin fibroblasts to establish a precise diagnosis. Treatment options are limited for most of these disorders. Enzyme replacement with recombinant β-glucocerebrosidase is effective in treating patients with Gaucher disease without neurologic involvement. Although of limited efficacy, bone marrow transplantation has been used in patients with several of these disorders, including the mucopolysaccharidoses and Gaucher disease.

Hepatomegaly is one of the most common findings in glycogen storage disorders. A common feature of **glycogen storage disorders (GSD)** is inefficient release of glucose from glycogen stores; this can lead to hypoglycemia when fasting. Since brain energy metabolism heavily depends on the availability of glucose, severe hypoglycemia can lead to metabolic strokes, irreversible brain damage, and death.

Hepatomegaly in the Child and Adolescent

Hepatomegaly in the child or adolescent may be an isolated finding on a routine physical examination or may be associated with many other clinical features related to systemic disease or impaired liver function.

Steatohepatitis

Fatty liver disease in the child and adolescent is associated with childhood obesity. An increase in serum ALT value is found in 6% of overweight children and 10% of obese children. A large number of U.S. adolescents may have fatty infiltration of the liver (**nonalcoholic steatohepatitis**). Nonalcoholic steatohepatitis should be suspected in any obese child with hepatomegaly and/or abnormal liver test results. Nonalcoholic steatohepatitis is more prevalent in Hispanic patients. Many of these children have features of metabolic syndrome, such as insulin resistance, arterial hypertension, and elevated serum cholesterol and triglyceride levels. In overweight children presenting with hepatomegaly and liver dysfunction, nonalcoholic steatohepatitis should be the primary diagnostic consideration, but other disorders, such as autoimmune hepatitis and chronic viral hepatitis, must be ruled out. Imaging studies, including ultrasonography, MRI, and CT, may suggest altered composition of the liver consistent with steatosis. Liver biopsy is the definitive diagnostic test and should be considered in patients with persistently abnormal aminotransferases. The purpose of the biopsy is to establish the diagnosis of nonalcoholic steatohepatitis, rule out other conditions and evaluate the degree of steatosis, inflammation, and fibrosis. Steatohepatitis can progress to cirrhosis and chronic liver failure. Steatohepatitis is associated with increased mortality from cardiovascular disease and liver cancer. Obese patients with steatohepatitis should be enrolled in a weight-management program. Medications such as vitamin E and metformin could be considered.

Viral Hepatitis

Acute viral hepatitis should be considered in the child with hepatomegaly and liver dysfunction. The patient may be acutely ill with sudden onset of fever, anorexia, nausea, and vomiting. Jaundice may occur, but many children with acute viral hepatitis are anicteric. On physical examination, varying degrees of tender hepatomegaly may be defined. Hepatitis is confirmed by an elevation in serum aminotransferase levels. Hepatitis may be caused by hepatotropic viruses (hepatitis A, B, C, D, or E) or by other viral infections that can involve the liver, such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), adenovirus, enterovirus, and echovirus. Serodiagnosis of all of these infections is possible. The evaluation for various forms of hepatitis should include anti–hepatitis A virus immunoglobulin M (IgM), hepatitis B surface antigen, anti–hepatitis B core antibody, anti–hepatitis C antibody, CMV IgM or CMV polymerase chain reaction (PCR), and EBV serologic profile or EBV PCR. Therapy is available for hepatitis B, hepatitis C, and CMV hepatitis. Hepatitis B or C have the potential to evolve to cirrhosis over many years. Table 14.7 presents the main causes of chronic hepatitis in children. Chronic hepatitis B infection is defined

TABLE 14.7 Causes of Chronic Liver Disease in Children

- Autoimmune hepatitis
  - Type 1 (anti–smooth muscle antibody, antinuclear antibody positive)
  - Type 2 (anti–liver-kidney microsomal antibody)
- α_1-Antitrypsin deficiency
- Wilson disease
- Primary sclerosing cholangitis (overlap syndrome with autoimmune hepatitis)
- Viral hepatitis
  - Hepatitis B
  - Hepatitis C
  - Hepatitis D
- Drugs

by persistently elevated serum levels of hepatitis B DNA. Hepatitis C is an indolent infection with the potential to evolve to cirrhosis over several decades. However, some children, particularly when co-infected with human immunodeficiency virus, may have more rapidly progressive liver disease. Chronic hepatitis C infection is defined by the persistent presence of hepatitis C RNA in serum. As new antiviral agents are becoming available, eradication of hepatitis C is possible in the majority of adult patients though there are no clinically tested pediatric protocols currently.

Toxins

All patients presenting with hepatomegaly and liver dysfunction should be questioned about recent exposure to medications or environmental toxins. Acute and chronic hepatitis can be caused by a number of different medications such as isoniazid and methyldopa. Treatment of drug- or toxin-related liver injury is mainly supportive. Contact with the offending agent should be avoided. Corticosteroids may have a role in immune-related injury, as may occur with phenytoin. *N*-acetylcysteine therapy, by stimulating glutathione synthesis, is effective in preventing hepatotoxicity when administered within 16 hours after an overdose of acetaminophen and appears to improve survival in patients with severe liver injury even 36 hours after toxin ingestion. Liver injury in most cases is completely reversible when the hepatotoxic drug is withdrawn. With continued use of certain drugs, such as methotrexate, the effects of hepatotoxicity may proceed insidiously to cirrhosis.

Alpha-1-Antitrypsin Deficiency

Children and adolescents with α_1-antitrypsin deficiency may present with manifestations of chronic liver disease or cirrhosis with evidence of portal hypertension. Liver biopsy may show a chronic hepatitis with varying degrees of fibrosis. The diagnosis is established by determination of the α_1-antitrypsin phenotype (phenotypes ZZ and SZ cause liver disease) and may be confirmed by liver biopsy. Periportal hepatocytes demonstrate periodic acid–Schiff–positive diastase-resistant intracytoplasmic globules. Immunocytochemical studies confirm that this material is the abnormal α_1-antitrypsin. There is no specific treatment other than to manage the complications of cirrhosis, cholestasis, and portal hypertension. Patients with α_1-antitrypsin deficiency are at increased risk of hepatocellular carcinoma. Liver transplantation is curative, though the majority of the patients with α_1-antitrypsin deficiency do not require liver transplantation.

Wilson Disease

Wilson disease is a metabolic disorder that may manifest with hepatic disease in childhood, ranging from asymptomatic hepatomegaly (with or without splenomegaly) to subacute or chronic hepatitis or fulminant hepatic failure. Initial manifestations of Wilson disease may include portal hypertension, ascites, edema, and esophageal hemorrhage. Wilson disease can also present with extrahepatic symptoms, such as hemolytic anemia, movement disorders, or mood disorders. Wilson disease is due to mutations in a copper-transporting P-type adenosine triphosphatase, which leads to a failure of biliary copper excretion and a progressive accumulation of copper in the liver and other organs. Lipid peroxidation, particularly of mitochondrial membranes, results from copper overload leading to the functional alterations in the liver and the brain. A low serum ceruloplasmin level suggests the diagnosis of Wilson disease. Serum copper levels may also be elevated, and urinary copper excretion is high, often up to 1000 µg or more per day. The diagnosis is confirmed with a quantitative determination of copper in a liver-biopsy specimen. Treatment of Wilson disease involves chelation and urinary excretion of the excess copper. The most frequently employed agents are penicillamine and trientin. In response to chelation therapy, urinary copper excretion increases markedly, and this is associated with a gradual clinical improvement. Liver transplantation may be required for treatment of fulminant Wilson disease or in patients with decompensated cirrhosis.

Autoimmune Liver Disease

Several forms of autoimmune liver disease may also manifest with hepatomegaly during childhood and adolescence. Autoimmune hepatitis is defined as a continuing inflammatory process manifested by elevated aminotransferase concentrations and a number of circulating autoantibodies. The severity at presentation is highly variable; affected children may have only biochemical evidence of liver disease, may have stigmata of chronic liver disease, or may present in hepatic failure. In 25-30% of patients with autoimmune hepatitis, particularly children, the illness may mimic acute viral hepatitis; however, in most patients, the onset is insidious. The patient may be asymptomatic or have fatigue, malaise, behavioral changes, anorexia, and amenorrhea. Months or even years may pass before a liver problem is recognized with onset of jaundice or bleeding. There is a high association with extrahepatic disorders, including arthritis, vasculitis, nephritis, thyroiditis, celiac disease, inflammatory bowel disease and Coombs-positive anemia.

Laboratory studies in autoimmune hepatitis reveal a moderate elevation, usually less than 1000 IU/L, of serum aminotransferase activities. Serum bilirubin levels are commonly 2-10 mg/dL. Serum alkaline phosphatase activity is normal or only slightly increased. A diagnosis of autoimmune hepatitis may initially be suggested by marked polyclonal elevations of serum gamma globulin levels. Characteristic patterns of serum autoantibodies may be present. The most common is formation of non–organ-specific antibodies such as anti-actin (smooth muscle), and antinuclear antibodies (**type 1 autoimmune hepatitis**). In this variant of autoimmune hepatitis, most patients present between 10 and 20 years of age. High titers of a liver-kidney microsomal antibody can be detected in **type 2 autoimmune hepatitis** that usually affects children between the ages of 2 and 14 years. Liver biopsy is useful in confirming the diagnosis and assessing the degree of liver damage. Cirrhosis may be present at the time of diagnosis in children.

Immunosuppressive medications are necessary to treat autoimmune hepatitis. Corticosteroid therapy, with or without low doses of azathioprine, improves the clinical, biochemical, and histologic features in most patients and prolongs transplant-free survival in most patients with severe disease.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis is an autoimmune disorder with the focus of injury being the biliary tract. The disorder may be difficult to

(See *Nelson Textbook of Pediatrics,* p. 1961.)

distinguish from autoimmune hepatitis, and some patients have an overlap syndrome with features of both disorders. Hepatomegaly is frequently present. Patients may be asymptomatic or have jaundice, pruritus, or abdominal pain. Although serum aminotransferase levels are elevated, there is more striking elevation of serum alkaline phosphatase, 5'-nucleotidase, and GGT activities. **Inflammatory bowel disease** occurs in 50-75% of patients and may manifest at any time in the course of the liver disease. MR cholangiography reveals beading and irregularity of the intrahepatic and extrahepatic bile ducts. There is no definitive treatment. The course of the disorder is slowly progressive and eventually necessitates liver transplantation.

Acquired Immunodeficiency Syndrome

Hepatobiliary manifestations are common in patients with acquired immunodeficiency syndrome (AIDS). Hepatomegaly may be present, caused by a heterogeneous group of issues that includes viral hepatitis, opportunistic infections, medication-induced hepatic injury, malnutrition, peliosis hepatis, AIDS cholangiopathy, and neoplasms. Pathologic features that are most typical of pediatric AIDS include giant cell transformation and diffuse parenchymal lymphoplasmacytic infiltrates, the latter being associated with lymphoid interstitial pneumonitis.

Other Infections

Hepatosplenomegaly and anicteric hepatitis have been reported with cat-scratch disease, typhoid, brucellosis, tularemia, syphilis, Lyme disease, leptospirosis, Rocky Mountain spotted fever, Q fever, tuberculosis, and actinomycosis.

Fitz-Hugh–Curtis Syndrome

Fitz-Hugh–Curtis syndrome is a perihepatitis associated with acute salpingitis. Symptoms and signs include acute onset of severe right upper quadrant abdominal pain, friction rub over the anterior liver surface, and physical signs of pelvic inflammatory disease on pelvic examination (see Chapter 18).

Hepatic Abscess

A pyogenic, fungal, or parasitic hepatic abscess is an unusual infection in children. Common clinical findings are fever, abdominal pain, and hepatomegaly, with or without tenderness.

Pyogenic abscesses occur most frequently in infants who have had sepsis or umbilical infections. Cases in older children are usually associated with underlying host-defense defects, particularly human immunodeficiency virus, chronic granulomatous disease, and leukemia, or with occurrence of previous blunt trauma to the liver. Pyogenic abscess may follow an episode of appendicitis. Liver abscess may also occur in previously healthy children. *Staphylococcus aureus* and enteric and anaerobic bacteria are common etiologic agents. Liver function test results are commonly normal. Ultrasonography or CT scan confirms the presence and number of lesions. Echogenic debris or gas may be seen.

Amebiasis occurs in clusters in the southern United States, with person-to-person transmission in association with poor sanitation and crowding. Amebic abscess follows portal invasion by the parasite. The diagnosis is established by demonstrating a positive result on enzyme-linked immunosorbent assay for antibody to *Entamoeba histolytica* or by finding trophozoites or cysts in the stool. Toxocariasis and echinococcosis are caused by abortive infection of the liver in humans with the natural parasite of dogs or cats. The diagnosis is confirmed by specific serologic profiles.

Endocrine Disorders

Hepatomegaly and mild elevations of aminotransferase levels and bilirubin are common in hypothyroidism and are occasionally observed in hyperthyroidism. An enlarged liver is often found in patients with diabetes mellitus, particularly those with severe or poorly controlled diabetes, mainly as a result of excessive glycogen deposition. An extreme, rare case of this process is represented by **Mauriac syndrome**, which is characterized by dwarfism, obesity, moon facies, hypercholesterolemia, and marked hepatomegaly. Patients with acromegaly can also have mild to severe hepatomegaly as part of a generalized visceromegaly associated with the disease.

Liver Tumors

Liver tumors are the third most common solid abdominal tumors, after neuroblastoma and Wilms tumor (see Chapter 17). Hepatic metastatic disease can also occur with many childhood neoplasms, most frequently neuroblastoma, leukemia, and lymphoma. The primary tumor location is usually known.

Benign liver tumors account for 33% of cases of primary hepatic tumors. Benign liver tumors include hemangioendotheliomas, mesenchymal hamartomas, focal nodular hyperplasia, and adenomas. Malignant tumors include hepatoblastoma, hepatocellular carcinoma, and undifferentiated embryonal cell sarcoma. Of all hepatic neoplasms, hepatoblastoma, hepatocellular carcinoma, and infantile hemangioendothelioma are the 3 most common, accounting for 65% of cases. Most hepatic tumors are asymptomatic or may manifest with abdominal distention, abdominal pain, weight loss, vomiting, or diarrhea. Any hepatic mass can present with acute abdominal pain caused by hemorrhage into the tumor or peritoneal cavity.

Hemangioendotheliomas are the most common benign hepatic tumors. Nearly 95% of all hemangioendotheliomas manifest in the first year of life. Congestive heart failure due to hyperdynamic circulation may be present in 10-15% of cases. In addition to hepatomegaly, anemia and hemangiomas of the skin, lungs, lymph nodes, pancreas, retroperitoneum, intestine, or bone may be seen with hepatic hemangioendothelioma. Liver ultrasound shows a hyperechogenic mass frequently associated with increased vascular flow on Doppler evaluation. MRI or CT with intravenous contrast can be useful to further define the mass if sonographic evaluation is not conclusive.

Typically, a mesenchymal hamartoma, which consists of multiple cysts filled with serous fluid separated by myxomatous stroma, has no capsule. Of mesenchymal hamartomas, 70% manifest in the first 2 years of life. Hepatic adenoma is a rare benign tumor of the liver. Oral contraceptives, diabetes mellitus, glycogen storage disease, portosystemic shunts, and androgen therapy for Fanconi anemia increase the risk of adenoma.

Focal nodular hyperplasia (FNH) is caused by nodular regeneration of the liver around a focal scar of the liver parenchyma. FNH is seen predominantly in females and may occur at all ages. FNH is more common in patients who have congenital portosystemic shunts (Abernethy anomaly).

The majority of patients with **hepatoblastoma** present before 2 years of age and 90% by the age of 4. **Hepatocellular carcinoma,** and less commonly, undifferentiated embryonal sarcoma occur primarily in older children. Hepatocellular carcinoma is associated with hereditary tyrosinemia, ataxia-telangiectasia, glycogen storage disease type I, chronic hepatitis B or hepatitis C, α_1-antitrypsin deficiency, autoimmune hepatitis, and familial cholestatic cirrhosis. Serial screening with periodic liver sonograms is indicated for patients with these diseases. If nodules are identified, the nature of the mass can be clarified with CT with contrast (triphasic CT) or MRI with contrast.

Serum α-fetoprotein (AFP) is the most useful marker of malignant liver tumors; 80-90% of hepatoblastomas and 60-90% of hepatocellular carcinomas are positive. The serum AFP level is normal in mesenchymal hamartoma, focal nodular hyperplasia, and adenoma. The diagnosis is confirmed by needle biopsy, usually with CT guidance.

(See *Nelson Textbook of Pediatrics,* p. 2479.)

TABLE 14.8 Red Flags Suggesting Serious Liver Disease in a Patient with Hepatomegaly

History
- History of prolonged hyperbilirubinemia in infancy
- History of neurologic or psychiatric disease
- Previous blood transfusion, intravenous drug use
- Past history of hepatitis
- Delayed puberty
- Gastrointestinal bleeding
- Family history of chronic liver or kidney disease

Physical Examination
- Hard or nodular liver
- Splenomegaly
- Ascites
- Prominent abdominal venous pattern
- Growth retardation
- Muscle wasting
- Digital clubbing
- Palmar erythema
- Spider angiomata
- Arthritis
- Papular acrodermatitis
- Kayser-Fleischer rings
- Mental status changes
- Asterixis

Laboratory Test Results
- Prolonged prothrombin time
- Hypoglycemia
- Decreased serum albumin

Hepatic Cysts

The origin of solitary cysts is unknown. They are probably the sequelae of intrahepatic hemorrhage. **Peliosis hepatis**, characterized by multiple blood-filled spaces of varying sizes within the liver parenchyma, can be a complication of long-term treatment with anabolic steroids. Hepatomegaly, often with tenderness, may be present before any evidence of liver biochemical abnormality is evident.

Choledochal cysts are defined as congenital dilation or outpouching of large bile ducts. Though the majority of choledochal cysts are diagnosed in the first year of life, later presentation is possible. Choledochal cysts are associated with an increased risk of ascending cholangitis and cholangiocarcinoma; thus they should be surgically removed.

Congenital hepatic fibrosis is almost universally associated with autosomal recessive polycystic kidney disease (ARPKD). Approximately 40% of patients with congenital hepatic fibrosis have involvement of large bile ducts, which can be visualized by MR cholangiogram as multiple cystic dilations of the intrahepatic bile ducts (Caroli disease). **Caroli disease** is associated with an increased risk of ascending cholangitis and sepsis, particularly in patients who underwent kidney transplantation for ARPKD. Recurrent cholangitis in patients with ARPKD can be an indication for combined liver/kidney transplantation.

Hepatic Venous Outflow Obstruction

Hepatic venous outflow obstruction is classified into 3 categories on the basis of the level of obstruction. Obstruction can occur at the level of hepatic venules (venoocclusive disease), hepatic veins (Budd-Chiari syndrome), or suprahepatic vena cava. Hepatic venous outflow obstruction manifests with acute ascites and tender hepatomegaly. Abdominal pain, distention, and splenic enlargement may be prominent. Elevation of the aminotransferases or serum bilirubin level are present in the acute stage.

The pathologic hallmark of **venoocclusive disease** is occlusion of central and sublobular hepatic veins by intimal edema and fibrosis. The illness classically follows ingestion of plants that contain a toxic pyrrolizidine alkaloid, which can be present in bush teas and herbal medicines. Venoocclusive disease may also occur as a hepatic response to irradiation and induction for bone marrow transplantation. A familial form of venoocclusive disease associated with immunodeficiency has also been reported. The clinical diagnosis is based on either the McDonald (modified Seattle) or Jones (Baltimore) criteria. The McDonald criteria require the presence of 2 features from hepatomegaly with right-upper quadrant pain, total bilirubin of 34.2 μmol/L or more (normal range <20 μmol/L), and ascites or unexplained weight gain >2% of baseline. The Jones criteria require a total bilirubin of 34.2 μmol/L or more and presence of at least 2 of the following: hepatomegaly, ascites, and weight gain >5% of baseline.

Budd-Chiari syndrome develops in a variety of conditions that predispose to thrombosis, including intake of oral contraceptives, pregnancy, previous trauma, tumor invasion, cirrhosis, inflammatory bowel disease, collagen vascular disease, protein C deficiency, sickle cell anemia, polycythemia vera, and lymphoproliferative disorders. Membranous obstruction of the suprahepatic vena cava is the most common cause of suprahepatic outflow obstruction. However, thrombosis of the suprahepatic vena cava can occur in any condition that may precipitate Budd-Chiari syndrome. Diagnostic evaluation begins with pulsed Doppler sonography of the hepatic vessels. CT angiogram can further define the anatomy of the outflow obstruction. Liver biopsy in hepatic outflow obstruction reveals a characteristic pattern of sinusoidal dilatation with centrilobular congestion. Cirrhosis is a poor prognostic sign.

SUMMARY AND RED FLAGS

Hepatomegaly that is persistent suggests a chronic illness, which with time may produce serious morbidity or mortality, despite an initial well appearance of the patient. It is important to determine whether the hepatomegaly is a result of a specific liver disease or whether it is part of a generalized systemic illness. Red flags include signs of acute hepatic failure (coma, hemorrhage), developmental delay, failure to thrive, and those noted in Table 14.8.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

General Review

Wolf AD, Lavine JE. Hepatomegaly in neonates and children. *Pediatr Rev*. 2000;21:303-310.

Clinical Assessment of Liver Size

Konus OL, Ozdemir A, Akkaya A, et al. Normal liver, spleen, and kidney dimensions in neonates, infants, and children: Evaluation with sonography. *AJR Am J Roentgenol*. 1998;171:1693-1698.

Naveh Y, Berant M. Assessment of liver size in normal infants and children. *J Pediatr Gastroenterol Nutr*. 1984;3:346-348.

Noda T, Todani T, Watanabe Y, et al. Liver volume in children measured by computed tomography. *Pediatr Radiol*. 1997;27:250-252.

Weisman LE, Cagle N, Mathis R, et al. Clinical estimation of liver size in the normal neonate. *Clin Pediatr (Phila)*. 1982;21:596-598.

Younoszai MK, Mueller S. Clinical assessment of liver size in normal children. *Clin Pediatr (Phila)*. 1975;14:378-380.

Biochemical Studies of Liver Function and Injury

D'Agata ID, Balistreri WF. Evaluation of liver disease in the pediatric patient. *Pediatr Rev*. 1999;20:376-390.

Rosenthal P. Assessing liver function and hyperbilirubinemia in the newborn. *Natl Acad Clin Biochem Clin Chem*. 1997;43:228-234.

Neonatal Cholestasis

Bezerra JA, Balistreri WF. Cholestatic syndromes of infancy and childhood. *Semin Gastrointest Dis*. 2001;12:54-65.

Fischler B, Papadogiannakis N, Nemeth A. Aetiological factors in neonatal cholestasis. *Acta Paediatr*. 2001;90:88-92.

Jacquemin E, Hadchouel M. Genetic basis of progressive familial intra hepatic cholestasis. *J Hepatol*. 1999;31:377-381.

Nio M, Ohi R, Hochman JA, et al. Biliary atresia. *Semin Pediatr Surg*. 2000;9:177-186.

Suchy FJ. Approach to the infant with cholestasis. In: Suchy FJ, Sokol RJ, Balistreri WB, eds. *Liver Disease in Children*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2001:187-194.

Thompson RJ, Azevedo RA, Galoppo C, et al. European Society for Paediatric Gastroenterology, Hepatology and Nutrition. Cholestatic and metabolic liver diseases: Working Group report of the second World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr*. 2004;39(2):S611-S615.

Zerbini MC, Gallucci SD, Maezono R, et al. Liver biopsy in neonatal cholestasis: A review on statistical grounds. *Mod Pathol*. 1997;10:793-799.

Viral Hepatitis

Chang MH. Natural history of hepatitis B virus infection in children. *J Gastroenterol Hepatol*. 2000;15(suppl):E16-E19.

Gollan JL, Gollan TJ. Wilson disease in 1998: Genetic, diagnostic and therapeutic aspects. *J Hepatol*. 1998;1:28-36.

Hochman JA, Balistreri WF. Viral hepatitis: Expanding the alphabet. *Adv Pediatr*. 1999;46:207-243.

Jonas MM. Viral hepatitis. From prevention to antivirals. *Clin Liver Dis*. 2000;4:849-877.

Metabolic Liver Disease

McGovern MM, Mistry PK. The lysosomal storage diseases. In: Suchy FJ, Sokol RJ, Balistreri WB, eds. *Liver Disease in Children*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2001:687-700.

Perlmutter DH. Alpha-1-antitrypsin deficiency. *Semin Liver Dis*. 1998;18:217-225.

Rashid M, Roberts EA. Nonalcoholic steatohepatitis in children. *J Pediatr Gastroenterol Nutr*. 2000;30:48-53.

Roy A, Finegold MJ. Hepatic neoplasia and metabolic diseases in children. *Clin Liver Dis*. 2010;14(4):731-746.

Saudubray JM, Martin D, de Lonlay P, et al. Recognition and management of fatty acid oxidation defects: A series of 107 patients. *J Inherit Metab Dis*. 1999;22:488-502.

Sokol RJ, Treem WR. Mitochondria and childhood liver diseases. *J Pediatr Gastroenterol Nutr*. 1999;28:416.

Autoimmune Liver Disease

Gregorio GV, Portmann B, Karani J, et al. Autoimmune hepatitis/sclerosing cholangitis overlap syndrome in childhood: A 16-year prospective study. *Hepatology*. 2001;33:544-553.

Roberts EA. Primary sclerosing cholangitis in children. *J Gastroenterol Hepatol*. 1999;14:588-593.

Yachha SK, Srivastava A, Chetri K, et al. Autoimmune liver disease in children. *J Gastroenterol Hepatol*. 2001;16:674-677.

Liver Tumors

Stocker JT. An approach to handling pediatric liver tumors. *Am J Clin Pathol*. 1998;109:S67-S72.

Stocker JT. Hepatic tumors in children. *Clin Liver Dis*. 2001;5:259-281.

Miscellaneous Disorders Causing Hepatomegaly

D'Agata ID, Jonas MM, Perez-Atayde AR, et al. Combined cystic disease of the liver and kidney. *Semin Liver Dis*. 1994;14:215-228.

Gentil-Kocher S, Bernard O, Brunelle F, et al. Budd-Chiari syndrome in children: Report of 22 cases. *J Pediatr*. 1988;113:30-38.

Rubbia-Brandt L. Sinusoidal obstruction syndrome. *Clin Liver Dis*. 2010;14(4):651-668.

15

Jaundice

Grzegorz W. Telega

Jaundice, the yellow discoloration of skin and sclerae, results when the serum level of bilirubin, a pigmented compound, is elevated. Jaundice is not evident until the total serum bilirubin is at least 2-2.5 mg/dL in children out of the neonatal period.

Bilirubin is formed from the degradation of heme-containing compounds, particularly hemoglobin (Fig. 15.1). Microsomal heme oxygenase, located principally in the reticuloendothelial system, catabolizes heme to biliverdin, which is then reduced to bilirubin by biliverdin reductase. This unconjugated bilirubin (UCB) is lipophilic and cannot be eliminated via the kidney because of its insolubility in water. It can easily cross cell membranes and the blood-brain barrier. UCB is transported bound primarily to albumin. A receptor on the hepatocyte surface facilitates bilirubin uptake. Bilirubin is then conjugated with glucuronic acid by bilirubin uridine diphosphate glucuronosyltransferase (UDPGT). UDPGT can be induced by a variety of drugs (e.g., narcotics, anticonvulsants, and contraceptive steroids) and by bilirubin itself. Enzyme activity is decreased by restriction of calorie and protein intake.

Conjugated bilirubin (CB) is a polar, water-soluble compound. It is excreted from the hepatocyte to the canaliculi, through the biliary tree, and into the duodenum. Once CB reaches the colon, bacterial hydrolysis converts CB to urobilinogen. A small amount of urobilinogen is reabsorbed and returned to the liver via enterohepatic circulation or excreted by the kidneys. The remainder is converted to stercobilin and excreted in feces. In neonates, β-glucuronidase in the intestinal lumen hydrolyzes CB to UCB, which is then reabsorbed and returned to the liver via the enterohepatic circulation.

Hyperbilirubinemia can result from alteration of any step in this process. Hyperbilirubinemia can be classified as conjugated (direct) or unconjugated (indirect), depending on the concentration of CB in the serum. Conjugated and unconjugated are more accurate terms, because "direct" and "indirect" refer to the van den Bergh reaction, used for measuring bilirubin. In this assay, the unconjugated fraction is determined by subtracting the direct fraction from the total and, therefore, is an indirect measurement. The direct fraction includes both conjugated bilirubin and Δ-bilirubin, an albumin-bound fraction. Conjugated hyperbilirubinemia exists when more than 20% of the total bilirubin or more than 2 mg/dL is conjugated. If neither criterion is met, the hyperbilirubinemia is classified as unconjugated.

Unconjugated hyperbilirubinemia can be caused by any process that results in increased production, decreased delivery to the liver, decreased hepatic uptake, decreased conjugation, or increased enterohepatic circulation of bilirubin. The primary concern in patients with high levels of unconjugated bilirubin is kernicterus, resulting from the neurotoxicity of UCB across the blood-brain barrier mostly in the basal ganglia, pons, or cerebellum. This is a concern primarily in neonates.

Conjugated hyperbilirubinemia can occur due to hepatocellular dysfunction, biliary obstruction, and abnormal excretion of bile acids or bilirubin.

DIAGNOSTIC STRATEGIES

The causes of jaundice in the neonate and older infant are not the same as the causes of jaundice in the older child or adolescent (Figs. 15.2 and 15.3). The approach to the problem varies with age.

Bilirubin

In any patient with jaundice, the total serum bilirubin should be fractionated, as the differential diagnosis of unconjugated hyperbilirubinemia is distinct from that of conjugated hyperbilirubinemia (see Figs. 15.2 and 15.3). On occasion, hemolysis interferes with some assays and may result in a falsely elevated conjugated fraction. This can be problematic with specimens obtained by heelstick or fingerstick. If the clinical picture is consistent with unconjugated hyperbilirubinemia, the assay should be repeated with a venous sample.

Aminotransferases

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are frequently used as markers of hepatocellular injury. AST is expressed in mitochondria of the liver and cytosol of red blood cells and muscles; thus it is not specific for liver injury. Since ALT is less abundant outside of the liver, an increased ALT level is more suggestive of liver disease. Levels of both are markedly elevated (>5- to 10-fold normal) with hepatocellular injury caused by hepatitis, hepatotoxicity, ischemia, genetic or metabolic liver disorders. Elevation of AST in excess of ALT suggests extrahepatic source of injury. With acute biliary obstruction, there are initial sharp increases in ALT and AST levels and a rapid decline in 12-72 hours as obstruction is relieved. In chronic cholestasis, aminotransferases are usually only mildly elevated. With hepatocellular injury, ALT and AST levels tend to remain more significantly elevated longer. In acute liver failure a rapid decline in ALT and AST levels with worsening coagulopathy is a poor prognostic factor.

It is important to remember that aminotransferases reflect cell injury, not liver function. *There is no correlation between the severity of the liver dysfunction and the degree of elevation of ALT and AST levels.* Temporal trends in serum aminotransferase levels are useful in monitoring disease activity in chronic viral and autoimmune hepatitis.

Alkaline Phosphatase

Alkaline phosphatase is an enzyme found in bile ducts, bone, intestine, placenta, and tumors. Elevations in the serum alkaline phosphatase level occur with hepatobiliary disease but also normal growth, healing

(See *Nelson Textbook of Pediatrics,* p. 872.)

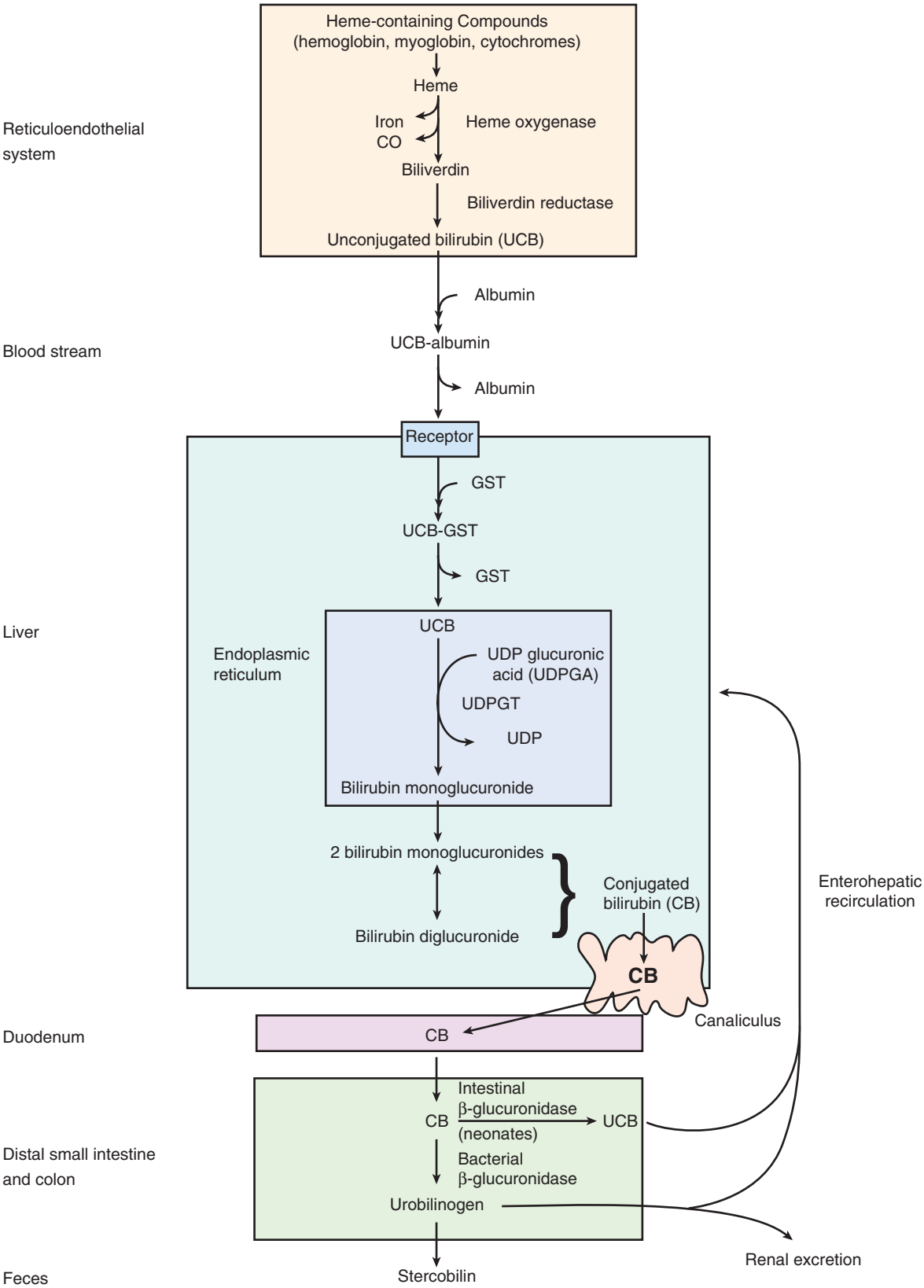


FIGURE 15.1 Bilirubin production and metabolism. CB, conjugated bilirubin; CO, carbon monoxide; GST, glutathione S-transferase B; UCB, unconjugated bilirubin; UDP, uridine diphosphate; UDPGA, uridine diphosphate glucuronic acid; UDPGT, uridine diphosphate glucuronosyltransferase. (Modified from Gourley GR. Jaundice. In: Wyllie R, Hyams JS, eds. *Pediatric Gastrointestinal Disease: Pathophysiology, Diagnosis, Management.* 2nd ed. Philadelphia: WB Saunders; 1999:89.)

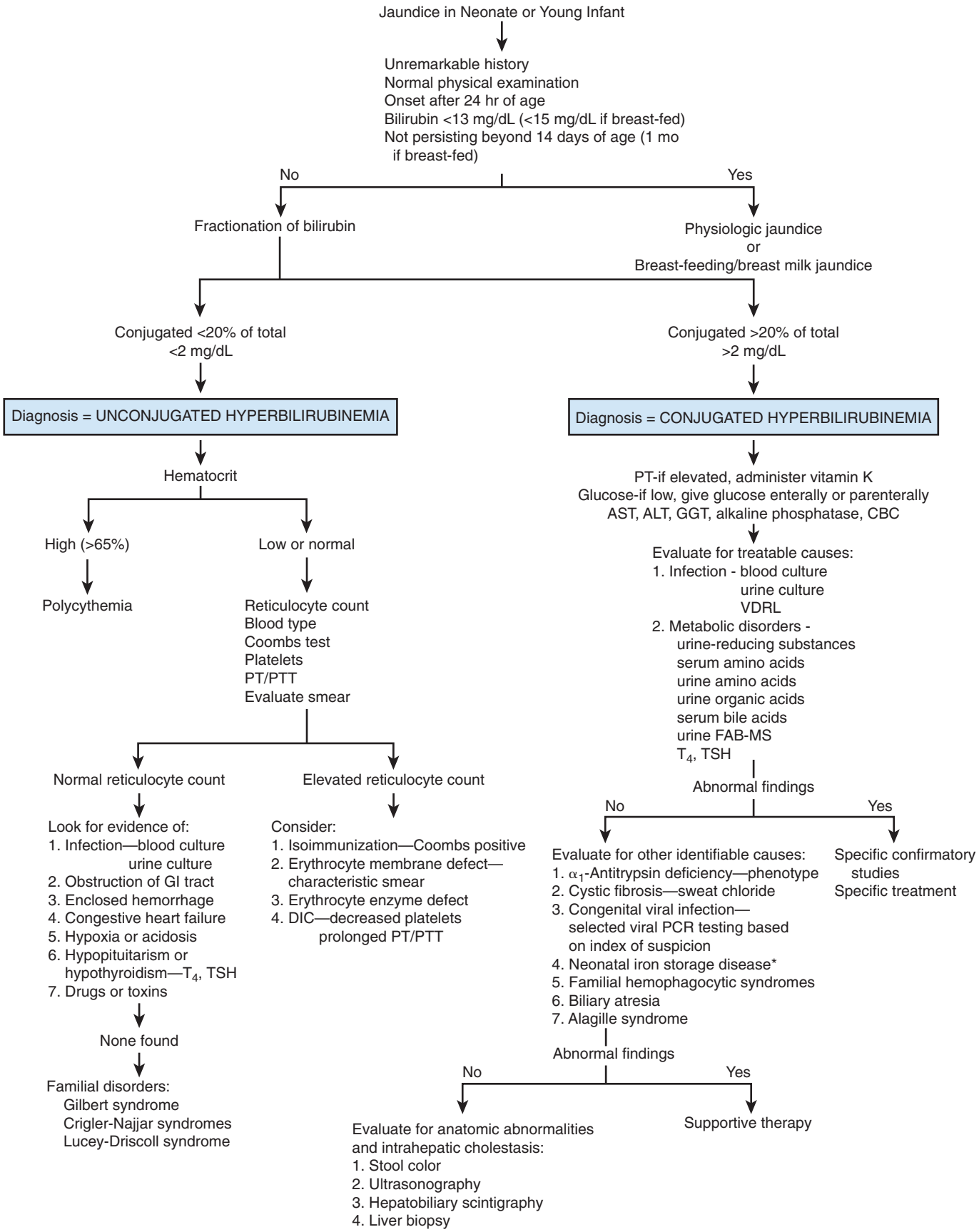


FIGURE 15.2 Diagnostic approach to the neonate or infant with hyperbilirubinemia. *Also called congenital alloimmune hepatitis or neonatal hemachromatosis. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; DIC, disseminated intravascular coagulation; FAB-MS, fast atom bombardment mass spectrometry; GGT, γ-glutamyltransferase; GI, gastrointestinal; PT, prothrombin time; PTT, partial thromboplastin time; T_4, thyroxine; TSH, thyroid-stimulating hormone; VDRL, Venereal Disease Research Laboratory.

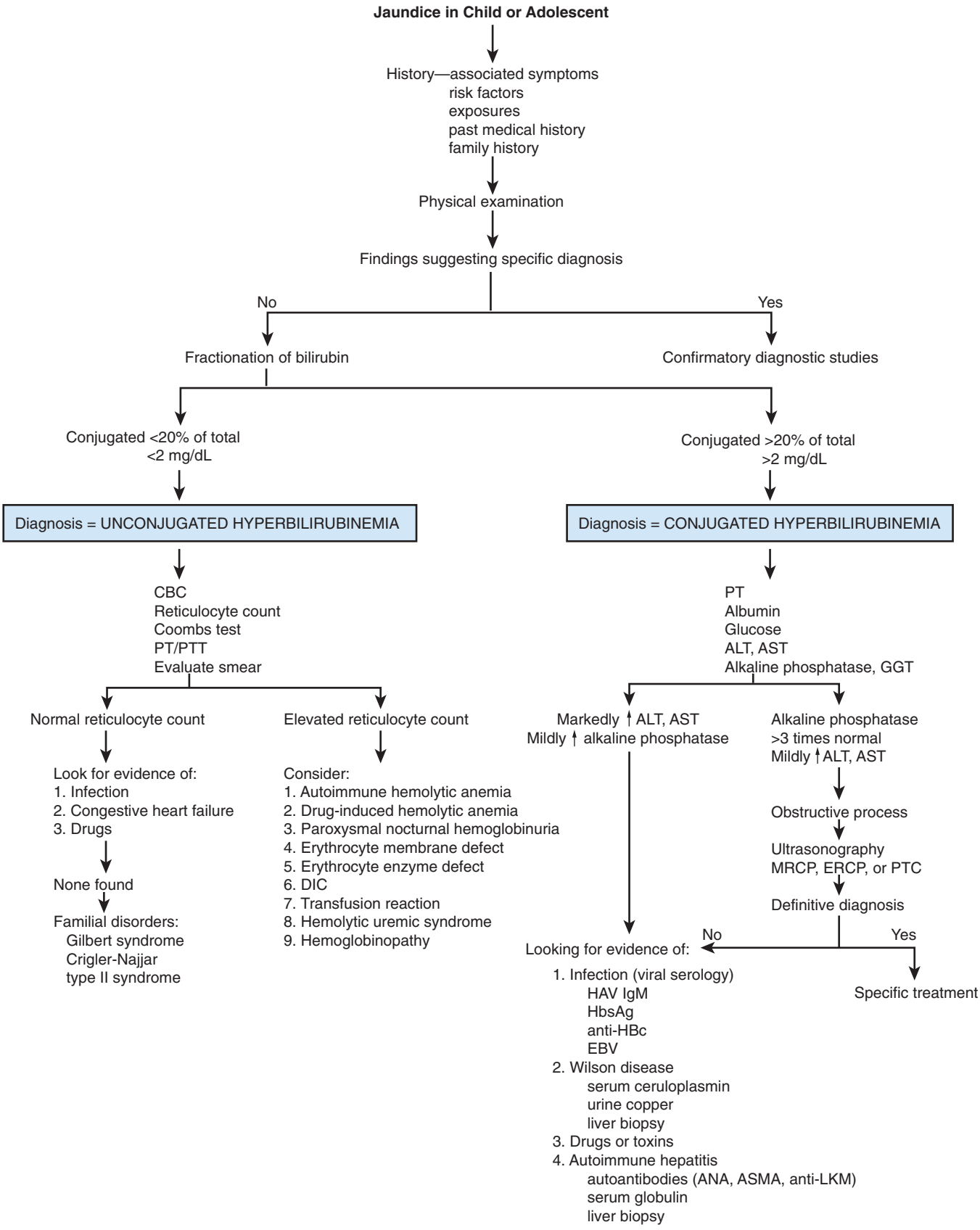


FIGURE 15.3 Diagnostic approach to the child or adolescent with hyperbilirubinemia. ALT, alanine aminotransferase; ANA, antinuclear antibody; ASMA, anti–smooth muscle antibody; AST, aspartate transaminase; CBC, complete blood count; DIC, disseminated intravascular coagulation; EBV, Epstein-Barr virus; ERCP, endoscopic retrograde cholangiopancreatography; GGT, γ-glutamyltransferase; HAV, hepatitis A virus; HBc, hepatitis B core; HBsAg, hepatitis B surface antigen; IgM, immunoglobulin M; LKM, liver-kidney microsomal; MRCP, magnetic resonance cholangiopancreatography; PT, prothrombin time; PTC, percutaneous transhepatic cholangiography; PTT, partial thromboplastin time.

fractures, vitamin D deficiency, bone disease, pregnancy, and malignancy. Fractionation of the alkaline phosphatase isoenzymes can help to determine its site of origin. A mild increase can be seen transiently in normal individuals. In the evaluation of conjugated hyperbilirubinemia, an alkaline phosphatase level of greater than 3 times normal indicates cholestasis; a milder elevation is more consistent with hepatocellular disease.

γ-Glutamyltransferase

The γ-glutamyltransferase (GGT) level is more specific for biliary tract disease than are ALT and AST levels. GGT elevations are inducible by alcohol and certain drugs, including phenytoin and phenobarbital. GGT is found in a variety of tissues and can be elevated in chronic pulmonary disease, renal failure, and diabetes mellitus. The GGT concentration is most helpful in confirming that an elevated alkaline phosphatase level is a result of liver disease rather than bone disease and in differentiating familial cholestatic syndromes.

Bile Acids

Serum bile acids are a very sensitive measure of cholestatic disease. Bile acid levels may be elevated before an increase in bilirubin. Levels are generally very high in primary cholestasis and biliary obstruction but only mildly increased (more than twice normal) in hepatocellular disease. Bile acids should be measured while fasting.

Albumin

Albumin is produced in the liver, and levels can reflect hepatic synthetic function. Serum albumin levels can be useful in monitoring progression of chronic liver disease and in discriminating an acute illness from a previously unrecognized chronic disorder. Hypoalbuminemia can also be secondary to nephrotic syndrome or a protein-losing enteropathy. Due to a long half-life (20 days), albumin is of limited use in assessing synthetic dysfunction in acute liver failure.

Prothrombin Time

Prothrombin time (PT) is the best marker of hepatic synthetic function, as most clotting factors are produced in the liver. It is important not only to measure the PT but also to document the response to parenteral administration of vitamin K because vitamin K deficiency may be an alternative explanation of the elevation of the PT. With severe hepatocellular injury, there is little improvement in the PT. Disseminated intravascular coagulation and thrombosis of a major blood vessel should not be overlooked as the cause of a prolonged PT.

Ultrasonography

Ultrasound studies are useful, noninvasive, relatively inexpensive diagnostic tools for the evaluation of liver disease. Ultrasonography provides information on the size and consistency of the liver and spleen and anatomic abnormalities of the biliary tree, gallstones, and hepatic masses such as cysts, tumors, or abscesses. Dilated intrahepatic ducts may indicate extrahepatic obstruction; however, the absence of dilatation on ultrasonography cannot exclude obstruction, and further studies are required for definitive diagnosis. The utility of ultrasonography is limited in obese patients and in patients with excessive bowel gas. Doppler ultrasonography also demonstrates dynamic flow in hepatic blood vessels and the portal vein; it can identify vascular anomalies of the liver and suggest presence of portal hypertension.

Scintigraphy

Hepatobiliary scintigraphy can aid in the diagnosis of biliary atresia. In a healthy individual, hepatic uptake and excretion of the radionuclide via the biliary system are prompt. When there is an injury to the hepatocyte, the uptake of radionuclide by the liver is diminished; however, the tracer should eventually be visualized in the intestinal tract. With obstructive processes, such as biliary atresia, uptake should be relatively normal unless the problem has been present long enough to have caused hepatocellular injury; however, there is no excretion into the intestinal tract. Administration of phenobarbital (5 mg/kg/day) for 5 days before the study may increase bile flow and thus can increase the diagnostic accuracy. Unfortunately, a significant percentage of patients with intrahepatic cholestasis and neonatal hepatitis do not demonstrate biliary excretion, and further evaluation is needed; thus final diagnosis is delayed. In patients with high level of suspicion for biliary atresia (acholic stools, high GGT), liver biopsy and percutaneous cholangiogram provide a faster and more direct way to reach the diagnosis.

Computed Tomography

Computed tomography (CT) is useful for identifying mass lesions within the liver and when there are technical problems with ultrasonography. CT with contrast can be used to define nature of liver tumors. CT angiography can define the anatomy of portal and hepatic circulation. CT has limited value in the evaluation of biliary anatomy.

Magnetic Resonance

MR studies provide valuable information regarding the anatomy of the liver. Since many imaging protocols can be used depending on the purpose of the study, contacting a radiologist prior to ordering the study is recommended. Cost and frequent need for sedation make MR evaluation the tool for secondary evaluation after screening imaging with ultrasound leaves diagnostic questions. MR imaging can demonstrate storage of heavy metals, such as iron in neonatal iron storage disease. MR with contrast can define the nature of liver tumors. MR angiography is useful in studying the vascular system, including the vascular supply of tumors. MR cholangiopancreatography (MRCP) visualizes abnormalities of the intrahepatic and extrahepatic biliary tree and is also quite useful in evaluating the pancreatic duct system. At this point resolution of MRCP is inadequate to diagnose biliary atresia. Unlike endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC), MRCP is noninvasive.

Endoscopic Retrograde Cholangiopancreatography

ERCP is performed for the evaluation of biliary anatomy. Unlike MRCP, ERCP is both diagnostic and potentially therapeutic for common duct stones and for strictures. Complications of the procedure include cholangitis and pancreatitis. ERCP is recommended for evaluation of biliary tree when therapeutic intervention is likely.

Percutaneous Transhepatic Cholangiography

PTC can be used as an alternative to ERCP as a diagnostic and therapeutic tool in evaluating the biliary tree. Under ultrasound guidance, a needle is passed through the liver and into the biliary tree, and contrast material is injected. If obstruction is identified, biliary drainage, if required, can be performed at the same time. PTC is contraindicated if there is marked ascites or irreversible coagulopathy. The complications of PTC include bleeding, pneumothorax, infection, and bile leakage.

Liver Biopsy

Percutaneous liver biopsy is often necessary to determine the cause of conjugated hyperbilirubinemia. In some instances, a specific pattern of injury, such as paucity of bile ducts or bile duct proliferation, may be evident. In other cases, specific markers of disease may be identified (the distinctive inclusions in α_1-antitrypsin deficiency) or measured

(metabolic enzyme activity). Ultrasound-guided biopsy is useful when a specific lesion needs to be evaluated or if there is abnormal anatomy of the liver. An open biopsy may be necessary when a large sample of tissue is needed or when there are contraindications to the percutaneous approach, such as ascites or coagulopathy. Transjugular liver biopsy can reduce the risk of bleeding in patients with coagulopathy. The complications of liver biopsy are the same as those for PTC.

JAUNDICE IN THE NEONATE AND INFANT

◆ History

Evaluation of the infant with jaundice starts with a thorough history, including age at onset and duration of jaundice (see Fig. 15.2). In the neonate, the causes of jaundice range from a benign, self-limited process associated with immaturity of bilirubin excretion (physiologic jaundice) to life-threatening biliary atresia or metabolic disorders (galactosemia, fructosemia, tyrosinemia). In older infants, there are fewer benign explanations for jaundice. For example, physiologic jaundice generally resolves by 1-2 weeks of age, and jaundice associated with breast milk usually resolves by the time the infant is 1 month old.

Acholic stools usually indicate obstruction of the biliary tree; however, nonpigmented stools can be seen with severe hepatocellular injury. The clinician should document the presence or absence of acholic stool in every infant evaluated for jaundice. The center of the stool should be examined because the outside may be lightly pigmented from sloughed jaundiced cells of the intestinal tract. Delayed passage of meconium may be secondary to cystic fibrosis or Hirschsprung disease. Delayed passage of stools, by itself, can lead to increased enterohepatic circulation of bilirubin.

Clues to the diagnosis of hyperbilirubinemia are often found in the prenatal and perinatal history (Table 15.1). Maternal infections that can be transmitted to the fetus or neonate, such as syphilis, toxoplasmosis, cytomegalovirus (CMV), hepatitis B, enterovirus, herpes simplex, and human immunodeficiency virus, are rare causes of cholestatic liver disease in the neonate. Prenatal growth pattern should be carefully evaluated. Perinatal infections such as CMV, rubella, and toxoplasmosis can present with intrauterine growth restriction. Premature infants are prone to higher bilirubin levels and more prolonged hyperbilirubinemia; they are also more likely to have risk factors for hyperbilirubinemia, such as delayed enteral feedings, require parenteral nutrition, and have perinatal insults with hypoxia and acidosis.

Delay of feeding can contribute to both conjugated and unconjugated hyperbilirubinemia; this effect is usually transient and should not be overinterpreted. Breast-feeding is associated with higher levels of unconjugated bilirubin and a longer duration of jaundice than in formula-feeding. Even when diagnosis of breast milk jaundice is likely, conjugated bilirubin should be checked because it provides an easy screening tool for liver disorders, including biliary atresia. Galactosemia does not manifest in the infant who receives a lactose-free formula. Hereditary fructose intolerance is not clinically apparent until the infant ingests fluids or solids containing fructose or sucrose. Infants with metabolic disorders often present with a history of vomiting, lethargy, and poor feeding. Vomiting may also be a symptom of intestinal obstruction including malrotation/volvulus.

The family history can often provide direction to the evaluation, particularly with some of the less common hereditary disorders. This can include most of the metabolic disorders, hemolytic diseases, and disorders associated with intrahepatic cholestasis (Tables 15.2 and 15.3).

TABLE 15.1 Diagnostic Clues in the Evaluation of Infants with Jaundice

Symptom	Possible Diagnosis
Prenatal/Perinatal Findings	
Polyhydramnios	Intestinal atresia
In utero growth restriction	Cytomegalovirus; rubella; toxoplasmosis
Vomiting/poor feeding	Metabolic disorders
Delayed passage of meconium	Cystic fibrosis; Hirschsprung disease
Constipation, hypotonia, hypothermia	Hypothyroidism
Maternal preeclampsia	HELLP: fatty acid oxidation disorders
Microphallus	Hypopituitarism associated with SOD
Intrahepatic cholestasis of pregnancy	PFIC type 2 and 3
Repeated affected neonates	Alloimmune hepatitis
Characteristic Facies	
Narrow cranium, prominent forehead, hypertelorism, epicanthal folds, large fontanel	Zellweger syndrome
Triangular face with broad forehead, hypertelorism, deep-set eyes, long nose, pointed mandible	Alagille syndrome
Microcephaly	Congenital viral infections
Ophthalmologic Findings	
Cataracts	Galactosemia; rubella
Chorioretinitis	Congenital infections
Nystagmus with hypoplasia of optic nerve	Hypopituitarism with septo-optic dysplasia (SOD)
Posterior embryotoxon	Alagille syndrome
Perinatal Infections	
Syphilis	Syphilis
Toxoplasmosis	Toxoplasmosis
Cytomegalovirus	Cytomegalovirus
Hepatitis B	Hepatitis B
Herpes simplex	Herpes simplex
Enterovirus	Enterovirus
Human immunodeficiency virus	HIV infection
Renal Disease	
RTA	Tyrosinemia
RTA	Galactosemia
Congenital hepatic fibrosis	ARPKD
Alagille syndrome	Alagille syndrome
Arthrogyposis	RTA–cholestasis syndrome

HELLP, hemolysis, elevated liver enzymes, low platelets; PFIC, progressive familial intrahepatic cholestasis; ARPKD, autosomal recessive polycystic kidney disease; RTA, renal tubular acidosis.

TABLE 15.2 Differential Diagnosis of Unconjugated Hyperbilirubinemia in Neonates and Infants

Physiologic Jaundice

Breast-Feeding/Breast Milk Jaundice

Polycythemia
- Diabetic mother
- Fetal transfusion (maternal, twin)
- Intrauterine hypoxemia
- Delayed cord clamping
- Congenital adrenal hyperplasia
- Neonatal thyrotoxicosis

Hemolysis
- Isoimmune
  - Rh incompatibility
  - ABO incompatibility
  - Other (M, S, Kidd, Kell, Duffy)
- Erythrocyte membrane defects
  - Hereditary spherocytosis
  - Hereditary elliptocytosis
  - Infantile pyknocytosis
- Erythrocyte enzyme defects
  - Glucose-6-phosphate dehydrogenase
  - Pyruvate kinase
  - Hexokinase
  - Other
- Hemoglobinopathy
  - Thalassemia
- Sepsis
- Hemangioma
- Congenital erythropoietic porphyria

Infection

Intestinal Obstruction
- Pyloric stenosis
- Intestinal atresia
- Hirschsprung disease
- Cystic fibrosis

Enclosed Hematoma (Cephalohematoma, Ecchymoses)

Congestive Heart Failure

Hypoxia

Acidosis

Hypothyroidism or Hypopituitarism

Drugs/Toxins
- Maternal oxytocin
- Vitamin K
- Antibiotics
- Phenol disinfectants
- Herbs

Familial Disorders of Bilirubin Metabolism
- Gilbert syndrome
- Crigler-Najjar syndrome types I and II
- Lucey-Driscoll syndrome

Modified from Balistreri WF. Liver disease in infancy and childhood. In: Schiff ER, Sorrell MF, Maddrey WC, eds. *Schiff's Diseases of the Liver.* 8th ed. Philadelphia: Lippincott-Raven; 1999:1364.

◆ Physical Examination

With increasing levels of bilirubin, neonatal icterus becomes more extensive, spreading in a cephalopedal direction. **Pallor** may indicate hemolytic disease. **Petechiae** alert the clinician to thrombocytopenia, possible sepsis, congenital infections, or severe hemolytic disease.

Dysmorphic face can be present in Zellweger syndrome or Alagille syndrome (see Table 15.1). The characteristic facies of Alagille syndrome may not be recognizable until later in childhood. Microcephaly that accompanies jaundice is associated with congenital viral infections.

An **ophthalmologic examination** can demonstrate a variety of abnormalities. Cataracts are seen in galactosemia and rubella. Chorioretinitis accompanies congenital infections (toxoplasmosis, syphilis, rubella, CMV, herpes simplex virus). Nystagmus with hypoplasia of the optic nerve suggests hypopituitarism associated with septo-optic dysplasia. Posterior embryotoxon is found in Alagille syndrome.

A **heart murmur** may be caused by an underlying congenital heart disease, which may be associated with Alagille syndrome, one of the trisomies, and syndromic forms of biliary atresia (polysplenia syndrome). Heart disease that results in hepatic ischemia or congestion can be a cause of conjugated or unconjugated hyperbilirubinemia.

Hepatomegaly, splenomegaly, and ascites may be caused by both hepatic and nonhepatic etiologies, but they always require evaluation as they are not associated with physiologic or breast milk jaundice.

Microphallus can be associated with septo-optic dysplasia and hypopituitarism.

◆ Differential Diagnosis

When a neonate has jaundice, a thorough history, including the obstetric history, and physical examination should provide most of the information necessary to determine whether the condition represents physiologic jaundice (see Fig. 15.2). A total and fractionated bilirubin measurement should be performed if there is any question about the diagnosis of physiologic jaundice.

Physiologic and Breast Milk Jaundice

In neonates, increased bilirubin production is caused by the normally increased neonatal red blood cell mass and the decreased life span of the red blood cells (80 vs 120 days). Albumin binding is decreased because of lower albumin concentrations and diminished binding capacity, which results in decreased transport of UCB to the liver with increased deposition in tissues. Uptake of bilirubin by the hepatocytes during the 1st weeks of life is defective. Low levels of glutathione S-transferase B decrease intracellular binding, which may impede the transport of UCB to the endoplasmic reticulum. Conjugation is impaired by decreased activity of UDPGT. Secretion into the canaliculi is impaired. There is increased enterohepatic circulation of unconjugated bilirubin as a result of increased concentrations of β-glucuronidase in the intestinal lumen and as a result of decreased intestinal bacterial flora, leading to diminished urobilinogen formation (see Fig. 15.1).

These features contribute in varying degrees to **physiologic jaundice**, characterized by a peak bilirubin level of less than 13 mg/dL on

TABLE 15.3 Differential Diagnosis of Conjugated Hyperbilirubinemia in Infants

Obstructive/Anatomic Disorders
Biliary atresia
Choledochal cyst
Caroli disease (cystic dilatation of intrahepatic ducts)
Congenital hepatic fibrosis
Neonatal sclerosing cholangitis
Bile duct stenosis
Spontaneous bile duct perforation
Anomalous choledochopancreaticoductal junction
Cholelithiasis
Inspissated bile or mucous
Mass or neoplasia

Infections
Bacterial (gram negative) sepsis
Urinary tract infection
Listeriosis
Syphilis
Toxoplasmosis
Tuberculosis
Cytomegalovirus
Herpesvirus (herpes simplex, herpes zoster, human herpesvirus 6)
Rubella virus
Hepatitis B virus
Human immunodeficiency virus (HIV)
Coxsackievirus
Echovirus
Parvovirus B19
Adenovirus
Measles

Metabolic Disorders
α_1-Antitrypsin deficiency
Cystic fibrosis
Citrin deficiency
Neonatal hemochromatosis (neonatal iron storage disease)

Endocrine Disorders
Panhypopituitarism
Hypothyroidism

Disorders of Carbohydrate Metabolism
Galactosemia
Hereditary fructose intolerance (fructosemia)
Glycogen storage disease type IV

Disorders of Amino Acid Metabolism
Tyrosinemia
Hypermethioninemia

Disorders of Lipid Metabolism
Wolman disease
Cholesterol ester storage disease
Farber disease
Niemann-Pick disease
Beta-oxidation defects
Gaucher disease

Disorders of Bile Acid Synthesis and Metabolism
Primary Enzyme Deficiencies
3β-Hydroxy-Δ^5-C_{27}-steroid dehydrogenase/isomerase
Δ^4-3-Oxosteroid 5β-reductase
Oxysterol 7α-hydroxylase

Secondary
Zellweger syndrome (cerebrohepatorenal syndrome)
Infantile Refsum disease
Smith-Lemli-Opitz syndrome
Other enzymopathies
Mitochondrial disorders (respiratory chain)

Intrahepatic Cholestasis
Alagille syndrome (arteriohepatic dysplasia)
Nonsyndromic paucity of intrahepatic bile ducts
Progressive familial intrahepatic cholestasis (PFIC)
- Type 1: Byler disease
- Type 2: Defect in the bile salt export pump
- Type 3: Defect in canalicular phospholipid transporter

Benign recurrent intrahepatic cholestasis
Greenland familial cholestasis (Nielsen syndrome)
North American Indian cirrhosis
Hereditary cholestasis with lymphedema (Aagenaes syndrome)

Toxin- or Drug-Related
Cholestasis associated with total parenteral nutrition
Chloral hydrate
Home remedies/herbal medicines
Venoocclusive disease

Miscellaneous
Idiopathic neonatal hepatitis
Autoimmune hemolytic anemia with giant cell hepatitis
Shock or hypoperfusion (including cardiac disease)
Intestinal obstruction
Langerhans cell histiocytosis
Neonatal lupus erythematosus
Dubin-Johnson syndrome
North American Indian childhood cirrhosis
Trisomies (18, 21)
Congenital disorders of glycosylation
Kabuki syndrome
Donahue syndrome (leprechaunism)
Arthrogryposis, cholestatic pigmentary disease, renal dysfunction syndrome
Familial hemophagocytic lymphohistiocytosis

Modified from Balistreri WF. Liver disease in infancy and childhood. In: Schiff ER, Sorrell MF, Maddrey WC, eds. *Schiff's Diseases of the Liver.* 8th ed. Philadelphia: Lippincott-Raven; 1999:1370; Suchy FJ. Approach to the infant with cholestasis. In: Suchy FJ, Sokol RJ, Balistreri WF, eds. *Liver Disease in Children.* 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2001:188.

postnatal days 3-5, a decrease to normal by 2 weeks of age, and a conjugated fraction of less than 20%. In premature, breast-fed infants of diabetic mothers and in Asian and Native American infants, the peak is higher and lasts longer. Conjugated bilirubin should be checked if there is any question of the nature of jaundice.

Breast-feeding has been associated with an increased incidence of unconjugated hyperbilirubinemia outside the expected range (>13 mg/dL). Jaundice of this level may occur in 10-25% of breast-fed infants, in contrast to 4-7% of formula-fed infants. It can occur within the 1st 5 days of life and is referred to as "early" or "breast-feeding" jaundice. Breast-feeding jaundice is seen in infants who are not feeding adequately and may be dehydrated or malnourished. In a second group of breast-fed infants, the jaundice develops slowly, occurring after the 1st week of life, and peaks between the 2nd and 3rd weeks of life at 10-20 mg/dL. This is referred to as "late" or "breast milk" jaundice. The precise cause of increased bilirubin levels in this latter setting has not been established; alternative theories include inhibition of glucuronosyltransferase activity and increased enterohepatic circulation of UCB. Kernicterus appears to be very rare but has been reported in association with breast-feeding. No treatment is necessary for physiologic jaundice. Practices that support breast-feeding, such as rooming-in on the maternity ward and frequent feedings, decrease the risk for breast-feeding jaundice. If the bilirubin exceeds 20 mg/dL in the breast-fed infant, discontinuing breast-feeding for 24 hours results in a decreased bilirubin level. Phototherapy or exchange transfusion may also be needed.

If there are any **red flags,** uncertainty about the diagnosis (Table 15.4), or if treatment is being considered, the hyperbilirubinemia should be investigated further, including fractionation of the bilirubin. Any abnormality identified by history or physical examination is a matter of concern.

Unconjugated Hyperbilirubinemia

The differential diagnosis of unconjugated hyperbilirubinemia in the neonate and infant is presented in Table 15.2. Unless abnormalities in the history and physical examination direct the evaluation more specifically, hematologic evaluation, which may identify causes of increased bilirubin production, should be performed. This includes a complete blood count with examination of the smear, a reticulocyte count, a direct Coombs test, and blood typing (mother and infant).

Polycythemia. Neonatal polycythemia, defined as a hematocrit greater than 65% by venipuncture, can be caused by maternal diabetes, maternal-fetal or twin-twin transfusion, intrauterine hypoxemia, endocrine disorders, and delayed cord clamping (see Table 15.2). Polycythemia results in increased bilirubin production because of the increased red blood cell mass.

TABLE 15.4 Red Flags in the Evaluation of Infants with Jaundice

Onset
<24 hr of age
>2 wk of age

Bilirubin

Conjugated
>20% of total or >2 mg/dL

Total
>13 mg/dL formula-fed
>14-15 mg/dL breast-fed

Course
Increases by >5 mg/dL/day
Persists beyond 14 days of age

Prenatal History
Maternal infection
Maternal diabetes mellitus
Maternal drug use
Polyhydramnios
Intrauterine growth restriction

Delivery
Prematurity
Perinatal asphyxia
Small for gestational age

Feeding
Delayed enteral feeding
Vomiting
Poor feeding
Associated with change in formula

Stools
Acholic
Delayed passage of meconium

Family History
Jaundice
Anemia
Liver disease
Splenectomy
Cholecystectomy

Physical Examination
Ill-appearing
Pallor
Petechiae
Hematoma or ecchymoses
Chromosomal stigmata
Abnormal facies
Microcephaly
Cataracts
Chorioretinitis
Nystagmus
Optic nerve hypoplasia
Posterior embryotoxon
Heart murmur
Hepatosplenomegaly (or isolated hepatomegaly or splenomegaly)
Ascites
Acholic stools
Dark urine
Microphallus

Hemolytic disorders. Reticulocytosis, unconjugated hyperbilirubinemia, and an increased nucleated red blood cell count, with either a low or normal hematocrit, suggest hemolysis. This can result from isoimmunization; erythrocyte membrane, hemoglobin or enzyme defects; or sepsis with disseminated intravascular coagulation. Some causes of isoimmunization have low reticulocyte counts because the antibody binds to these precursor cells. Rarer causes of hemolysis include hemangiomas and congenital erythropoietic porphyria.

Isoimmune hemolytic disease. In this group of disorders, maternal antibodies (immunoglobulin G) to the infant's erythrocytes cross the placenta, resulting in red blood cell destruction. The administration of anti-D gamma globulin (Rh_O[D] immune globulin [RhoGAM]) after delivery to women who are Rh-negative has reduced the incidence of Rh sensitization and erythroblastosis fetalis. If a woman has been sensitized, the fetus can be monitored with serial amniocenteses. If necessary, intrauterine transfusion can then be performed to prevent the sequelae of severe hemolysis, which include fetal and neonatal anemia, edema, hepatosplenomegaly, and circulatory collapse or stillbirth of an infant with hydrops fetalis. If the problem has not been recognized prenatally, the infant with Rh incompatibility presents with pallor, hepatosplenomegaly, and rapidly developing jaundice.

The diagnosis is confirmed by demonstrating that the infant is Rh-positive, that the direct Coombs test result is positive, and that maternal antibody is coating the infant's red blood cells. These test results are modified with in utero transfusions with Rh-negative cells. Depending on the degree of hemolysis, postnatal phototherapy, and/or exchange transfusion may be required.

ABO blood type incompatibility causes a less severe form of isoimmune hemolytic disease with a less rapid development of jaundice. It is more common in infants with blood type A or B who are born to mothers with blood type O. Hemolysis develops in 50% of sensitized infants; of these infants, 50% have a bilirubin level greater than 10 mg/dL. In addition to showing anemia, reticulocytosis, and spherocytes on the smear, the direct Coombs test result is weakly positive, and the indirect Coombs test result is positive. In rare cases, other minor blood group antibodies can also cause hemolysis.

Erythrocyte membrane defects. Red blood cell membrane defects are relatively uncommon causes of unconjugated hyperbilirubinemia. There is often a family history of hemolysis, transfusions, cholecystectomy for bilirubin stones, or splenectomy. Hemolysis results from fragility of the red blood cell membrane. When the defect is present in infancy, there are anemia, jaundice, and splenomegaly, and the smear is often characteristic (e.g., spherocytosis or elliptocytosis). Spherocytes are also seen with ABO incompatibility. All membrane defects yield negative results of the Coombs tests.

Erythrocyte enzyme defects (see Chapter 37). Glucose-6-phosphate dehydrogenase (G6PD) deficiency is common. Jaundice is seen more frequently in persons with a Mediterranean or Far Eastern ancestry who have a complete absence of the enzyme. In these individuals, hemolysis can occur without a precipitant. In African-American patients, the disease is generally less severe, and hemolysis is rare without exposure to a drug, toxin, or infection that causes an oxidant stress. G6PD deficiency can manifest as neonatal jaundice on day 2 or 3 after birth; alternatively, it may not manifest until later in childhood, when jaundice is associated with an acute hemolytic crisis. The diagnosis of G6PD deficiency is confirmed by documenting deficiency of the enzyme in red blood cells.

Numerous deficiencies of enzymes in the glycolytic pathway have been identified. Pyruvate kinase deficiency is the most common of these rare disorders. Most of these disorders are thought to have an autosomal recessive mode of transmission and have been identified in only a small number of individuals. They all result in hemolysis. The time of manifestation depends on the degree of hemolysis.

Other considerations. If the hematocrit is normal and there is no evidence of hemolysis or a consumptive process, other explanations for unconjugated hyperbilirubinemia should be sought. Blood and urine cultures rarely identify infectious etiologic agents if the patient is otherwise clinically normal. Vomiting, abdominal distention, and delayed passage of meconium suggest obstruction of the gastrointestinal tract and should be further investigated by imaging. Clinical examination should also identify cephalohematoma, ecchymoses, heart failure, hypoxia, and acidosis. Thyroxine and thyroid-stimulating hormone levels should be obtained or checked from the state neonatal screening program to look for evidence of hypothyroidism or hypopituitarism.

Drugs, administered to either mother or neonate, and toxins should be identified by careful record review. Examples include oxytocin, excess vitamin K in premature infants, some antibiotics, and phenol disinfectants used in nurseries. Use of herbal remedies should also be investigated.

In the evaluation process, it is important to remember that the division of causes into hemolytic and nonhemolytic is an arbitrary one. For example, drugs, infection, and G6PD deficiency can contribute to both hemolytic and nonhemolytic neonatal jaundice. In addition, the cause of jaundice can be multifactorial.

Familial disorders of bilirubin metabolism

Gilbert syndrome. Gilbert syndrome is a benign condition that occurs in up to 8% of the population. A familial incidence is reported in 15-40% of cases. Gilbert syndrome is a heterogeneous group of disorders that have in common at least a 50% decrease in UDPGT activity as a result of a defect in the gene responsible for this enzyme. In 20-30% of individuals with Gilbert syndrome, there is also a decrease in hepatocyte bilirubin uptake. Affected individuals are generally asymptomatic and may not present with jaundice until the 2nd or 3rd decade of life. Gilbert syndrome may be responsible for some cases of neonatal jaundice. Mild jaundice with a bilirubin level up to 7 mg/dL can occur transiently with fatigue, exercise, fasting, febrile illness, and alcohol ingestion in older patients. Except for showing an increased indirect bilirubin level, all laboratory studies are normal. The diagnosis is generally a clinical one but can be confirmed by documenting a twofold to threefold rise in unconjugated bilirubin during a 24-hour fast.

Crigler-Najjar syndrome. Crigler-Najjar syndrome types I and II (also known as Arias syndrome) are rare autosomal recessive conditions caused by mutations (different alleles from those of Gilbert syndrome) in the gene coding for UDPGT. Crigler-Najjar syndrome type I is characterized by marked hyperbilirubinemia (20-40 mg/dL) in the neonatal period in an otherwise healthy infant. Among untreated infants, kernicterus is universal, and affected individuals usually die with severe neurologic problems. Because UDPGT is undetectable, there is no conjugated bilirubin in the bile or serum, and the bile is colorless. There is no decrease in serum UCB levels during phenobarbital administration. The only therapies are exchange transfusion, intensive phototherapy, and liver transplantation.

The onset of Crigler-Najjar syndrome type II is usually at birth, although it can be in late childhood. There is less than 5% of the normal UDPGT activity. Bile contains bilirubin monoglucuronides. Bilirubin levels, generally 8-25 mg/dL, respond to phenobarbital administration with a significant decrease. Neurologic disease is rare.

Lucey-Driscoll syndrome. Lucey-Driscoll syndrome is a transient familial neonatal hyperbilirubinemia that appears in the 1st few days of life and resolves by 2-3 weeks of age. This results from inhibition of

UDPGT by a substance that has been found in both maternal and infant serum. The bilirubin level can rise to greater than 60 mg/dL in untreated infants, resulting in severe neurotoxicity. The condition is treated with exchange transfusion.

Therapy. Treatment of unconjugated hyperbilirubinemia depends on the degree of elevation of bilirubin. Considerable controversy exists over which level is toxic and when treatment should be initiated. Because it is lipid soluble, unconjugated bilirubin can diffuse into the central nervous system, which results in neurologic toxicity. Most authorities agree that kernicterus does not occur below a bilirubin level of 20-30 mg/dL in the healthy, full-term infant without evidence of hemolysis. Kernicterus may occur at lower bilirubin levels in premature or sick neonates.

Treatment options include phototherapy and exchange transfusion. Phototherapy produces a reduction of bilirubin by 1-2 mg/dL in 4-6 hours by causing the photoisomerization and photodegradation of unconjugated bilirubin to more water-soluble forms that are more readily excreted in bile and urine. Potential complications include retinal damage, diarrhea, and dehydration. Phototherapy is begun at levels below that for exchange transfusion (~5 mg/dL less) or during preparations for an exchange transfusion.

Exchange transfusion with blood cross-matched against that of the mother is indicated for severe hyperbilirubinemia. This decision must be based not only on the bilirubin level but also, as important, on the infant's age and clinical condition. In full- or near-term infants (>2000 g in weight) with evidence of hemolysis, exchange transfusion is indicated if the serum unconjugated bilirubin level is higher than 25-30 mg/dL or if the bilirubin level does not rapidly respond to phototherapy. Signs of kernicterus (i.e., a high-pitched cry, gaze paralysis, fever, lethargy, and opisthotonic posture) warrant exchange transfusion, no matter what the bilirubin level.

Neonatal Conjugated Hyperbilirubinemia

Potential causes of conjugated hyperbilirubinemia in the neonate and infant are extensive (see Table 15.3). It is important to first evaluate the infant for potentially treatable problems (Table 15.5) and institute specific therapy that prevents significant morbidity and may be lifesaving. Fig. 15.2 outlines a diagnostic approach when the clinical presentation has not suggested a likely diagnosis.

Common to all of these conditions is the potential for **hypoprothrombinemia**. If the PT is prolonged, the infant should be treated with intravenous vitamin K to avoid spontaneous hemorrhage, particularly intracranial. Depending on the degree of hepatocellular damage, vitamin K may not correct the PT. This is worrisome and mandates prompt evaluation for the underlying cause of neonatal liver failure or extrahepatic causes of coagulopathy. Interpretation of PT should be based on neonatal norms, as normal PT is higher in newborns, particularly in premature newborns versus older infants. Even with a normal PT at the outset, infants with conjugated hyperbilirubinemia should be on oral fat-soluble vitamin supplementation until their cholestasis resolves.

Hypoglycemia is another danger that is associated with diseases that cause severe hepatic dysfunction, metabolic disorders as well as with hypopituitarism. The infant may be relatively asymptomatic despite significant hypoglycemia. The serum glucose level can be measured before a feeding. If hypoglycemia is present, the infant should receive frequent feedings, continuous feedings, or intravenous dextrose infusions. Glucose level should always be the part of the evaluation of conjugated hyperbilirubinemia.

Hyperammonemia can be present in severe liver dysfunction and metabolic liver disorders. Ammonia should be checked on infants with lethargy or with a change in mental status.

TABLE 15.5 Conditions Not to Miss in Infants with Conjugated Hyperbilirubinemia

Priorities
Hypoprothrombinemia
Hypoglycemia
Extrahepatic biliary atresia
Infections
Sepsis
Urinary tract infection
Syphilis
Toxoplasmosis
Herpes simplex virus
Endocrine Disorders
Hypopituitarism
Hypothyroidism
Metabolic Disorders
Galactosemia
Hereditary fructose intolerance (fructosemia)
Tyrosinemia
Other
Neonatal hemochromatosis
Bile acid abnormalities
Choledochal cyst
Intestinal obstruction
Familial hemophagocytic syndromes
Heart disease
Toxins

Serum levels of aminotransferases, GGT, and alkaline phosphatase, in addition to a complete blood count, should be included in the initial evaluation.

Obstructive/anatomic abnormalities, idiopathic cholestasis, and idiopathic neonatal hepatitis

Biliary atresia. Untreated biliary atresia is lethal, and only prompt diagnosis and surgical treatment can prevent mortality. Biliary atresia accounts for approximately 30% of cases of neonatal cholestasis seen at major referral centers. It occurs in 1 in 8000-15,000 live births. It is the result of a progressive inflammatory process leading to obliteration of the lumen of the extrahepatic duct. It is the leading indication for liver transplantation in the pediatric population. Infants are less often icteric from birth and more often develop jaundice at 2-6 weeks of age. Infants are usually full term and initially appear healthy except for jaundice, dark urine, and acholic stools. The family history usually is negative for liver disease. There appear to be 2 forms of biliary atresia:

1. In the "embryonic" or "fetal form," which occurs in 15-30% of cases, there is no jaundice-free period. There are often associated defects, including cardiac defects, polysplenia, malrotation, and situs inversus.
2. In the "perinatal form," there may be a jaundice-free interval after resolution of the normal physiologic jaundice, and there are no associated anomalies.

At the time of presentation, infants with biliary atresia may have an enlarged, firm liver. Pruritus, splenomegaly, and ascites can

develop with advanced disease. The work-up should be performed expeditiously; it is important to identify biliary atresia early because the success of surgical establishment of drainage is correlated with early age at surgery. Surgery performed before the infant is 2 months old carries an approximately 80% rate of success in terms of obtaining some bile flow. This rate decreases to about 20% for surgery performed in patients older than 3 months. Diagnostic work-up includes evaluation of other identifiable causes of neonatal cholestasis including CMV infection, α_1-antitrypsin deficiency, hypothyroidism, and other anatomic abnormalities of the biliary tree. Combination of conjugated hyperbilirubinemia, acholic stools, and elevated GGT should trigger prompt evaluation for biliary atresia. An ultrasound study helps exclude other treatable anatomic abnormalities, such as a choledochal cyst. The gallbladder is usually absent or collapsed in infants with biliary atresia. Liver biopsy and percutaneous cholangiogram should follow if no alternative cause of jaundice is identified. Characteristic findings on liver biopsy are periportal edema and fibrosis, bile duct proliferation, and bile duct plugs. Some centers utilize hepatobiliary scintigraphy, which demonstrates uptake of tracer but no excretion into the duodenum if biliary atresia is present. However this study can lead to delay in diagnosis (requires pretreatment with phenobarbital) and can be inconclusive in hepatic dysfunction due to poor uptake of the tracer.

The diagnosis is confirmed by intraoperative cholangiography at the time of surgery. The surgical procedure, a portoenterostomy, is that initially described by Kasai. The porta hepatis is transected, and a loop of intestine is brought up to drain the bile ducts. In a small percentage of patients (5-15%), a discrete distal lesion is identified, and the surgery is curative. Those in whom bile drainage is not established require early liver transplantation. In the majority of patients, surgery is palliative, allowing time before liver transplantation is needed; overall and post-transplant mortality are significantly reduced with timely Kasai procedure.

The important, potentially life-threatening complication of the Kasai procedure is **bacterial ascending cholangitis**. Febrile patients with biliary atresia need to be promptly evaluated for causes of fever. If no alternative source of fever is identified, they should be evaluated for cholangitis.

Most of the patients with biliary atresia remain cholestatic despite the Kasai procedure; thus they require supplementation with MCT oil (or MCT-enriched formulas) and fat-soluble vitamins. Portal hypertension with splenomegaly, esophageal varices, and ascites can develop over time in many patients with biliary atresia. Due to significant risk of complications and frequent need for liver transplant, patients with biliary atresia should be followed in centers with pediatric transplant/hepatology expertise.

Alagille syndrome. Alagille syndrome is characterized by the abnormal development of multiple organs related to defective JAG-1/NOTCH-2 signaling. The most important clinical feature is a marked reduction in the number of interlobular bile ducts. Jaundice may have its onset in the neonatal period or may not appear until later in childhood. Additionally, patients with Alagille syndrome can have unusual facies (a triangular face with broad forehead, widely spaced and deep-set eyes, a long nose, and a pointed mandible), vertebral arch defects (butterfly vertebrae, hemivertebrae, decreased interpedicular distance), posterior embryotoxon (ocular), and cardiac anomalies (ranging from peripheral pulmonic stenosis to complex congenital heart disease). Renal anomalies, pancreatic insufficiency, and growth retardation, are present in some patients (Table 15.6). This appears to be a progressive phenomenon and may not be readily recognizable in neonates. By the age of 4-6 months, pruritus develops and can be severe. Xanthomas appear in association with a markedly elevated cholesterol level.

TABLE 15.6 Extrahepatic Manifestations of Alagille Syndrome

Cardiac
Peripheral pulmonary stenosis
Tetralogy of Fallot
Ventricular septal defect
Atrial septal defect
Aortic coarctation
Pulmonary atresia
Skeletal
Short stature
Butterfly vertebrae
Fused vertebrae
Rib anomalies
Spina bifida occulta
Thin cortical bones
Ocular
Posterior embryotoxon
Axenfeld anomaly
Optic disc drusen
Shallow anterior chamber
Microcornea
Vascular
Renal artery stenosis
Intracranial bleeding
CNS malformations
Other
Renal developmental abnormalities
Renal tubulopathies
Pancreatic exocrine and endocrine insufficiency
High-pitched voice
Microcolon

From Mieli-Vergani G, Hadzic N. Biliary atresia and neonatal disorders of the bile ducts. In: Wyllie R, Hyams JS, Kay M, eds. *Pediatric Gastrointestinal and Liver Disease*. 4th ed. Piladelphia: Elsevier/Saunders; 2011:749.

Alagille syndrome has an autosomal dominant transmission with highly variable expression. Often other family members are recognized as being affected when an infant is brought to medical attention. There is a high proportion of sporadic cases (up to 70%) with de novo mutations in the *JAG-1* gene responsible for this syndrome. Mutations of the NOTCH-2 receptor can result in a similar clinical picture though they are less common than *JAG-1* mutations. The diagnosis is confirmed by liver biopsy. Symptoms often improve over time. There is a 20-25% rate of mortality from serious cardiac or liver disease.

There is a nonsyndromic form of bile duct paucity with cholestasis caused by bile duct paucity but not associated with clinical or genetic mutations characteristic of Alagille syndrome. The prognosis for this form is less favorable.

Choledochal cysts. Manifestations include conjugated hyperbilirubinemia with jaundice, vomiting, acholic stools, and hepatomegaly

in the neonate. Alternatively, choledochal cysts can manifest with jaundice, abdominal pain, and a right upper quadrant mass in the older child. There are five anatomic types of cystic dilatations of the extrahepatic or intrahepatic bile ducts. The diagnosis is made by ultrasound studies and confirmed by MR cholangiography or intraoperative cholangiography. Treatment involves surgical excision. Cholangitis may occur postoperatively. If the cyst is not fully excised, carcinoma can develop in the residual cyst tissue.

Treatable infections

Bacterial infection. An infant may, in rare cases, appear clinically well, with jaundice as the only sign of a bacterial infection. Blood and urine cultures should be obtained in infants with unexplained conjugated hyperbilirubinemia. Infection is less likely to be missed in the symptomatic infant who presents with poor feeding, lethargy, vomiting, temperature instability, apnea, bradycardia, or shock. *Escherichia coli* is the most common organism identified in either sepsis or urinary tract infection (often with bacteremia) when jaundice is present. The hyperbilirubinemia may be caused by endotoxin-mediated canalicular dysfunction. Less often, other gram-negative bacilli or *Listeria*, *Staphylococcus*, or *Streptococcus* species may be identified as the causative agent. Although sepsis accounts for only a small percent of the cases of neonatal cholestasis, it is easily diagnosed and treated.

Herpes simplex. Herpes simplex causes a severe neonatal infection that usually manifests at 7-14 days of age with lethargy, poor feeding, a vesicular rash (in 60-70% of patients), jaundice, hepatomegaly, temperature instability, encephalitis, and coagulopathy. The diagnosis is made by identification of the virus in skin lesions through direct fluorescent antibody staining or polymerase chain reaction of herpes simplex DNA in blood and cerebrospinal fluid. Treatment is with intravenous acyclovir. Among infants with disseminated infection, the mortality rate is 15-35%.

Enteroviruses. Maternal infection at the time of delivery may result in severe enteroviral disease in the infant within 1-7 days of birth. Manifestations are similar to that of herpes simplex virus except a macular rash. Severe hepatitis, carditis, or encephalitis or a sepsis picture may develop. Diagnosis is made through polymerase chain reaction or viral culture. Treatment strategies include intravenous immunoglobulin (IVIG) and pleconaril.

Cytomegalovirus infection. CMV infection is common, but 90% of affected infants are asymptomatic at birth. In the severely affected infant with vertical transmission, CMV can manifest within the 1st 24 hours after birth with intrauterine growth restriction, conjugated hyperbilirubinemia, hemolytic anemia, thrombocytopenic purpura, and hepatosplenomegaly. Often an infant with low birthweight presents with microcephaly, periventricular calcifications, and chorioretinitis. The diagnosis can be made by obtaining urine specimens for culture.

Treatment includes the use of ganciclovir and possibly CMV immunoglobulin. The liver disease resolves in most patients, but neurologic sequelae are common. Postnatal acquisition from CMV-positive blood transfusion may produce a sepsis syndrome and hepatitis.

The findings of CMV in a cholestatic infant without other features of congenital CMV infection should not stop the search for other causes of cholestasis, particularly biliary atresia.

Hepatitis B. Hepatitis B infection manifests with jaundice in fewer than 5% of perinatal infections. Perinatal transmission is high when mothers are chronic carriers who are seropositive for hepatitis B e antigen or when they acquire acute infection in the last trimester. Most infants are asymptomatic, but there is a high incidence of subsequent chronic infection. Perinatal infection can be prevented with hepatitis B immune globulin and vaccination. It is important to identify mothers who are seropositive for hepatitis B surface antigen (HBsAg); identification requires universal screening.

Syphilis. Congenital syphilis remains a problem despite maternal screening. With severe infection, the infant has fever, a diffuse macular-papular rash, hepatosplenomegaly, edema, anemia, and periostitis, in addition to jaundice. Nontreponemal serologic tests (Venereal Disease Research Laboratory) may be routinely performed on cord blood. If the result is positive, the diagnosis should be confirmed on serum from the infant. Confirmation requires a positive specific test for syphilis such as the immunoglobulin M (IgM) or immunoglobulin G fluorescent treponemal antibody. Treatment is with intravenous penicillin for 10-14 days.

Toxoplasmosis. If toxoplasmosis is suspected on clinical grounds, IgM titers should be obtained, or the placenta should be examined histologically. Most infected infants are asymptomatic. Infants with severe congenital infection may have hydrocephaly or microcephaly, intracranial calcifications, chorioretinitis, aseptic meningitis, jaundice, purpura, and hepatomegaly. Postnatal treatment consists of pyrimethamine and sulfadiazine; folinic acid is added to prevent folate deficiency.

Treatable metabolic disorders. Many metabolic disorders are part of the universal newborn screening program in developed countries. The clinician needs to be aware of which disorders are and which are not screened for in a particular country or state. Even in the presence of universal neonatal screening for metabolic disorders, the test may be falsely negative, particularly if the newborn was tested too early, was premature or underwent transfusions before the test was performed. In countries with robust neonatal screening programs, repeating newborn screen may be an easy and cost-effective 1st step in evaluation for possible metabolic disease. Other useful screening modalities include: urine-reducing substances (galactosemia), serum amino acids, ammonia level, urine organic acids, quantitative serum bile acids, qualitative analysis of urinary bile acids by fast atom bombardment mass spectrometry (FAB-MS), the thyroxine level, and the thyroid-stimulating hormone level, succinyl-acetone (thyrosinemia), triglycerides, lactate, pyruvate, and acyl carnitines (mitochondrial disorders).

Galactosemia. Galactosemia, a life-threatening disorder, can easily be detected. It is an autosomal recessive disorder with deficiency of galactose-1-phosphate uridyltransferase, which is required for conversion of galactose to glucose. As a result, galactose-1-phosphate accumulates; this compound is thought to be hepatotoxic. Once lactose (glucose-galactose) is introduced into the infant's diet, vomiting, diarrhea, jaundice, hepatomegaly, and cataracts develop. Affected infants often present with *E. coli* sepsis in the 1st weeks of life.

Laboratory evaluation may demonstrate elevations of aminotransferase levels, a prolonged PT, hemolytic anemia, and aminoaciduria. The urine yields positive findings for reducing substances (galactose) if the infant is receiving a lactose-containing formula or breast milk. The diagnosis can be confirmed by documenting deficiency of the enzyme in erythrocytes or leukocytes. Transfusions may cause false-negative results. Treatment consists of eliminating galactose from the diet.

Hereditary fructose intolerance (**fructosemia**) is an uncommon disorder; it can manifest with hepatic failure in an infant exposed to fructose or sucrose in formula, juice, fruit, or medications. A thorough diet history in relation to the onset of jaundice is often the key to this diagnosis. Prompt removal of fructose, sucrose, and sorbitol from the diet is essential.

Tyrosinemia is diagnosed from serum amino acid levels and urine organic acid levels. Elevated urinary succinylacetone is pathognomonic. Treatment involves the dietary restriction of phenylalanine,

(See *Nelson Textbook of Pediatrics,* p. 1723.)

(See *Nelson Textbook of Pediatrics,* p. 1590.)

methionine, and tyrosine and the use of 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione) to prevent the formation of toxic metabolites. Liver transplantation may still be required.

Disorders of bile acid metabolism typically are suggested by conjugated hyperbilirubinemia with low or normal GGT and low or normal total bile acid levels. They can be detected by bile acid FAB-MS analysis of urine. Treatment of some forms of bile acid synthetic disorder is possible with oral cholic acid supplementation.

Other identifiable infectious and metabolic causes of cholestasis

α_1-Antitrypsin deficiency. An α_1-antitrypsin protein immunoelectrophoresis can detect an α_1-antitrypsin deficiency, which is the most common inherited cause of neonatal cholestasis. Deficiency occurs in 1 in 1600-2000 live births. α_1-Antitrypsin is a protease inhibitor that is synthesized in the liver and inactivates neutrophil proteases. The normal α_1-antitrypsin phenotype, MM, is found in 80-90% of the population. There are numerous allelic variants. Liver disease is associated with the ZZ phenotype and sporadically with other variants. The exact mechanism of liver injury is unclear, and there is variability in expression so that clinically significant liver disease develops in only 10-15% of individuals with the ZZ phenotype. There is also great variability in manifestation. Commonly, the disorder manifests in early infancy with prolonged conjugated hyperbilirubinemia, failure to thrive, acholic stools, hepatomegaly, and possibly ascites. However, it may not manifest until later childhood or even adulthood. Manifestations in older individuals include jaundice, hepatosplenomegaly, ascites, portal hypertension with varices, chronic hepatitis, cryptogenic cirrhosis, or, rarely, hepatocellular carcinoma. The diagnosis is established by serum phenotyping (ZZ). Treatment is supportive. Some individuals do very well with minimal liver dysfunction. Others have progressive liver disease, requiring transplantation. α_1-Antitrypsin deficiency can enhance hepatotoxicity of hepatotoxic drugs. All individuals with α_1-antitrypsin deficiency should be aware of the potential for lung disease when they are older.

Cystic fibrosis. As many as one third of infants with cystic fibrosis may have evidence of liver involvement, frequently cholestasis. The incidence is increased among infants with meconium ileus. The diagnosis can be confirmed with a sweat chloride test or by detecting the abnormal gene. Although the cholestasis resolves, the infant with cystic fibrosis can develop problems including focal biliary cirrhosis, multilobular cirrhosis, fatty liver, obstruction of the common duct, cholelithiasis, sclerosing cholangitis, and, rarely, cholangiocarcinoma.

Hypothyroidism and hypopituitarism. Jaundice can be a manifestation of both hypothyroidism and hypopituitarism. Hypopituitarism may manifest with hypoglycemia, microphallus, and signs of hypothyroidism in addition to jaundice. Wandering nystagmus is present when hypopituitarism is associated with septo-optic dysplasia. Treatment of the underlying endocrinopathy leads to resolution of the liver disease.

Progressive Familial Intrahepatic Cholestasis

Progressive familial intrahepatic cholestasis (PFIC) is a group of disorders related to defective transport of bile acids (Table 15.7). PFIC is clinically suggested by presence of cholestasis in absence of physical damage to the bile ducts. GGT is normal except for PFIC type 3. The molecular defects for 3 PFIC types involve molecules expressed on the canalicular membrane of the hepatocyte. All types of PFIC are inherited in an autosomal recessive manner. PFIC results in progressive cholestasis and pruritus, leading to cirrhosis and end-stage liver disease. PFIC type 1 has low or normal serum γ-glutamyltransferase (GGT) and high serum concentrations of bile acids. The defect of the *FIC-1* gene, which encodes a P-type adenosine triphosphatase (ATP8B1), is involved in phospholipid translocation in the enterocytes and

TABLE 15.7 Progressive Familial Intrahepatic Cholestasis

	PFIC 1	PFIC 2	PFIC 3
Transmission	Autosomal recessive	Autosomal recessive	Autosomal recessive
Chromosome	18q21-22	2q24	7q21
Gene	*ATP8B1/F1C1*	*ABCB11/BSEP*	*ABCB4/MDR3*
Protein	FIC1	BSEP	MDR3
Location	Hepatocyte, colon, intestine, pancreas; on apical membranes	Hepatocyte canalicular membrane	Hepatocyte canalicular membrane
Function	ATP-dependent aminophospholipid flippase; unknown effects on intracellular signaling	ATP-dependent bile acid transport	ATP-dependent phosphatidylcholine translocation
Phenotype	Progressive cholestasis, diarrhea, steatorrhea, growth failure, severe pruritus	Rapidly progressive cholestatic giant cell hepatitis, growth failure, pruritus	Later-onset cholestasis, portal hypertension, minimal pruritus, intraductal and gallbladder lithiasis
Histology	Initial bland cholestatic; coarse, granular canalicular bile on EM	Neonatal giant cell hepatitis, amorphous canalicular bile on EM	Proliferation of bile ductules, periportal fibrosis, eventually biliary cirrhosis
Biochemical features	Normal serum GGT; high serum, low biliary bile acid concentrations	Normal serum GGT; high serum, low biliary bile acid concentrations	Elevated serum GGT; low to absent biliary PC; absent serum LPX; normal biliary bile acid concentrations
Treatment	Biliary diversion, ileal exclusion, liver transplantation, but post-OLT diarrhea, steatorrhea, fatty liver	Biliary diversion, liver transplantation	UDCA if residual PC secretion; liver transplantation

ATP, adenosine triphosphate; BSEP, bile salt export pump; EM, electron microscopy; GGT, γ-glutamyltransferase; LPX, lipoprotein X; OLT, orthotopic liver transplantation; PC, phosphatidylcholine; PFIC, progressive familial intrahepatic cholestasis; UDCA, ursodeoxycholic acid.
From Suchy FJ, Sokol RJ, Balistreri WF, eds. *Liver Disease in Children.* 3rd ed. New York: Cambridge University Press; 2007.

canalicular membrane of the hepatocyte. In addition to cholestasis, patients have chronic secretory diarrhea. PFIC 1 can also be associated with sensorineural hearing loss and pancreatitis.

Patients with PFIC type 2 also exhibit cholestasis, normal serum GGT, and high levels of serum bile acids. A PFIC 2 disorder is caused by defective function of the bile salt export pump (BSEP) protein, encoded by the *ABCB11* gene. Since BSEP is expressed only in hepatocytes, symptoms are limited to cholestatic liver disease.

Patients with PFIC type 3 have high serum GGT and cholesterol levels. They demonstrate symptoms later in life and reach end-stage liver disease at a later age. PFIC type 3 is caused by a defect in the *ABCB4* gene, which encodes a phospholipid transporter (MDR3) in the canalicular membrane and results in low biliary phospholipid levels.

Except in cases necessitating liver transplantation, chronic biliary diversion and ursodeoxycholic acid therapy may reduce pruritus and improve liver function. In **benign recurrent intrahepatic cholestasis (BRIC)**, homozygous or compound heterozygous mutations of respective genes *(ATP8B1, ABCB11, ABCB4)* develop a milder form of cholestatic liver disease, which generally does not progress to end-stage liver disease. In patients with BRIC jaundice, pruritus or fat malabsorption symptoms can be triggered by pregnancy, toxins, and medications.

Idiopathic neonatal hepatitis. Idiopathic neonatal hepatitis is a descriptive term rather than a specific disease entity. The diagnosis is made by exclusion of other causes of cholestasis, particularly biliary atresia. The infant with neonatal hepatitis is more likely to be premature or small for gestational age. Acholic stools are uncommon but can occur when the hepatitis is severe. In 5-15% of cases, there is a familial incidence. Hepatobiliary scintigraphy demonstrates delayed uptake, but there is usually excretion into the duodenum unless the hepatitis is severe. In this case, intraoperative cholangiography may be required. Biopsy findings include panlobular disarray indicative of severe hepatocellular disease, inflammatory infiltrate in the portal areas, focal hepatocellular necrosis, multinucleated giant cells, and increased extramedullary hematopoiesis.

Treatment is supportive. The outcome is variable and is better for infants with sporadic (nonfamilial) cases; of such infants, approximately 60% recover, 10% have chronic liver disease, and 30% die without liver transplantation. The percentages for recovery and death are reversed (30% and 60%, respectively) in familial cases.

Treatment of cholestasis. Some interventions are essential for all infants with cholestasis. Malabsorption of fats and fat-soluble vitamins occurs as a result of a decreased concentration of bile salts in the intestinal lumen. Affected infants should be given a formula containing medium-chain triglycerides (MCTs), which are better digested and absorbed in the absence of bile acids. Even with MCT supplementation, many patients will require caloric intake in excess of 150 kcal/kg/day to maintain growth. Due to organomegaly and ascites, weight alone may overestimate nutritional status. Proper monitoring of growth requires a routine anthropometric evaluation of skinfold and mid-arm circumference. Some affected infants require supplemental nasogastric feedings. Supplemental vitamins A, D, E, and K are given to prevent symptoms of vitamin deficiency visual problems, rickets, neuropathy, and coagulopathy, respectively. Fat-soluble vitamin levels need to be monitored. Pruritus is often severe and is not readily treatable. Several medications have been tried, including ursodeoxycholic acid, antihistamines, cholestyramine, phenobarbital, and rifampin. Ursodeoxycholic acid is beneficial in some infants with cholestasis, and helps to improve bile excretion, thus reducing serum bile acid levels. Biliary diversion has been effective in some cases. Ascites can be managed with sodium restriction and diuretics.

JAUNDICE IN THE CHILD AND ADOLESCENT

◆ History

Chronic fatigue, though nonspecific, is a common symptom of liver disease and should trigger at least a basic evaluation including aminotransferases even in the absence of overt jaundice. Myalgias, nausea, vomiting, and fever are often seen in patients with viral hepatitis or autoimmune hepatitis. **Acute biliary obstruction** is signaled by right upper quadrant pain, vomiting, fever, and acholic stools in addition to jaundice. Neurologic and psychiatric symptoms may be among the manifestations of Wilson disease. Autoimmune hepatitis may be accompanied by manifestations of other autoimmune disorders.

The child's age at the onset of symptoms may be helpful. Wilson disease commonly manifests in school-aged children and adolescents. Similarly, autoimmune hepatitis is most prevalent in school-aged children and adolescents with female predominance. A thorough history should include past and present use of prescription, over-the-counter (e.g., acetaminophen), and street drugs. Many medications have been associated with hepatobiliary damage; others, with hemolysis. Drug abuse is a risk factor for viral hepatitis and human immunodeficiency virus. Adolescents in particular should be asked about alcohol use.

Symptoms of cholestasis such as jaundice, dark urine, steatorrhea, symptoms of fat-soluble vitamin deficiency, failure to thrive, and pruritus should be explored in detail.

Information about exposure to viral hepatitis, either by travel to an endemic area or during an outbreak, should be pursued. There is a high transmission rate in daycare centers.

The patient's medical history should be reviewed because some chronic illnesses are associated with specific hepatobiliary complications. These should include acquired immunodeficiency syndrome, cystic fibrosis, heart disease, renal disease, hemolytic disorders, autoimmune disorders, celiac disease, and inflammatory bowel disease.

A family history of inheritable disorders, such as Wilson disease, autosomal recessive polycystic kidney disease, Alagille syndrome, or spherocytosis, is informative. Less specific but still useful clues are a history of autoimmune disorders, jaundice, anemia, cholecystectomy, or splenectomy in other family members.

◆ Physical Examination

Some patients present with previously unidentified chronic liver disease. The clinician should focus on signs of portal hypertension: spider angiomas, palmar erythema, dilated abdominal veins, ascites, and splenomegaly with a small liver. Cutaneous excoriation as evidence of pruritus, xanthomas, and jaundice support cholestasis. Clubbing of digits may suggest hepatopulmonary syndrome. A large, tender liver is suggestive of acute viral hepatitis or congestive heart failure. A small liver may be found in patients with severe hepatitis or cirrhosis. A tender gallbladder is indicative of choledocholithiasis or cholecystitis. Abnormal neurologic findings, including tremor, fine motor incoordination, clumsy gait, and choleriform movements, suggest Wilson disease. A slit-lamp examination should be included to look for the Kayser-Fleischer rings (a brownish discoloration at the periphery of the cornea) of Wilson disease.

◆ Differential Diagnosis

Unconjugated Hyperbilirubinemia

Most causes of unconjugated hyperbilirubinemia in the child and adolescent are secondary to hemolysis (Table 15.8) (see Chapter 37). A complete blood count with evaluation of the smear, reticulocyte count, and Coombs test can differentiate hemolytic from nonhemolytic disorders.

TABLE 15.8 Differential Diagnosis of Unconjugated Hyperbilirubinemia in Childhood and Adolescence

Increased Bilirubin Production

- Autoimmune hemolytic anemia
  - Idiopathic
  - Secondary
    - Infection (viral, mycoplasma)
    - Diseases with autoantibody production
    - Immunodeficiency
    - Malignancy
- Drug-induced hemolytic anemia
- Paroxysmal nocturnal hemoglobinuria
- Erythrocyte membrane defects
  - Hereditary spherocytosis
  - Hereditary elliptocytosis
- Erythrocyte enzyme defects
  - Glucose-6-phosphate dehydrogenase
  - Pyruvate kinase
  - Hexokinase
  - Other
- Hemoglobinopathy
  - Sickle cell disease
  - Thalassemia
- Hemolytic uremic syndrome
- Sepsis with disseminated intravascular coagulation
- Reabsorption of hematoma
- Transfusion reaction

Decreased Uptake, Storage, or Metabolism

- Congestive heart failure
- Sepsis
- Acidosis
- Gilbert syndrome
- Crigler-Najjar syndrome type II
- Prolonged fasting
- Drugs
- Portacaval shunt

Erythrocyte membrane defects (spherocytosis) and enzyme defects (pyruvate kinase deficiency, G6PD) may not be apparent until childhood or adolescence. Acquired autoimmune hemolytic anemia is characterized by pallor, abdominal pain, fever, and dark urine in addition to jaundice. Laboratory studies document anemia and reticulocytosis. The direct Coombs test result is positive. Hemolytic anemia can be associated with infection, immunodeficiency, malignancy, hemolytic uremic syndrome, or other autoimmune disorders, such as systemic lupus erythematosus, rheumatoid arthritis, thyroid disorders, and autoimmune hepatitis.

Unconjugated hyperbilirubinemia can be caused by congestive heart failure and infection should in such circumstances extrahepatic symptoms, cardiac failure, or sepsis dominate the picture. If no other explanation is found, Gilbert syndrome or Crigler-Najjar syndrome type II should be considered.

Conjugated Hyperbilirubinemia

In the child with conjugated hyperbilirubinemia, the PT and the albumin, glucose, AST, ALT, GGT, and alkaline phosphatase levels should be measured. Albumin and PT determinations provide evidence of hepatocyte synthetic function. Hypoglycemia is another marker of severity of hepatocellular damage. This is important in considering how quickly the evaluation should proceed or how closely the patient should be monitored. Patients with coagulopathy, hyperammonemia, encephalopathy, or hypoglycemia should be admitted to the hospital and observed very closely. PT should be repeated after a dose of parenteral vitamin K to differentiate synthetic liver failure from a vitamin K deficiency. Hypoglycemia should be corrected with frequent meals or intravenous dextrose.

Obstruction. The relative elevation of AST/ALT and alkaline phosphatase levels in the context of the clinical picture determines the likelihood of an obstructive cause. Although obstructions occur less commonly in children than in adults, it is important not to miss correctable causes of obstruction that, if left untreated, can cause hepatocellular damage. These patients usually have markedly elevated alkaline phosphatase and minimally elevated AST and ALT levels. They should be evaluated promptly with ultrasonography and possibly with MRCP, ERCP, or PTC. The possible causes of obstruction are listed in Table 15.9.

Gallstones. Gallstones are particularly common in children with hemolytic disorders, such as sickle cell disease, thalassemia, erythrocyte membrane defects, erythrocyte enzyme defects, and autoimmune hemolytic anemia. The mean age at presentation is 12 years. Gallstones are also associated with anatomic abnormalities of the biliary tract, cystic fibrosis, ileal dysfunction, obesity, parenteral nutrition, sepsis, prematurity, and pregnancy. Stones may be found incidentally on abdominal radiographs or ultrasound studies in asymptomatic individuals. Alternatively, gallstones may manifest with symptoms of biliary colic: nausea, vomiting, right upper quadrant or nonspecific abdominal pain and jaundice. Ultrasonography is a very sensitive diagnostic test. Treatment for symptomatic patients is cholecystectomy. ERCP can be used to remove common bile duct stones.

Primary sclerosing cholangitis. Primary sclerosing cholangitis (PSC) is characterized by focal dilatation and stenosis of the intrahepatic or extrahepatic bile ducts with surrounding fibrosis resulting from an inflammatory process. It can manifest from early childhood through adulthood. In adults, it is frequently associated with inflammatory bowel disease, especially ulcerative colitis. PSC may precede the onset of inflammatory bowel disease by many years. It can occur in the absence of any underlying condition. The onset may be insidious with fatigue and pruritus being the only symptoms. Steathorrhea, weight loss, and symptoms of fat-soluble deficiency can be present in some patients. Abdominal pain, fever, and jaundice may signify ascending cholangitis with bacterial infection complicating PSC. Diagnostic evaluation includes ultrasound studies, which may show dilated ducts. MR cholangiography can provide a detailed anatomy of the biliary tree and is more sensitive than an ultrasound. ERCP or PTC do not provide an advantage in diagnosing PSC but are useful, minimally invasive procedures that can be performed if the dominant stricture is identified and biliary obstruction can be improved by dilation and/or stent placement. PTC can progress to cirrhosis with ultimate liver failure. Cholangiocarcinoma complicates PTC in 10-15% of adults. No medical therapy has been shown to improve outcomes in PSC; thus treatment is supportive focused on management of cholestasis. Liver transplantation is available as curative intervention once disease progresses to end-stage liver disease.

TABLE 15.9 Differential Diagnosis of Conjugated Hyperbilirubinemia in Childhood and Adolescence

Autoimmune Hepatitis

Anatomic/Obstructive

Gallstones
Primary sclerosing cholangitis
Choledochal cyst
Bile duct stenosis
Anomalies of the choledochopancreaticoduodenal junction
Pancreatitis
Caroli disease
Congenital hepatic fibrosis
Tumor
- Hepatic
- Biliary
- Pancreatic
- Duodenal

Infection

Non–A-E hepatitis
Hepatitis A
Hepatitis B
Hepatitis C
Hepatitis D
Hepatitis E
Epstein-Barr virus
Cytomegalovirus
Human herpesvirus 6
Herpes simplex virus
Varicella-zoster virus
Enteroviruses
Measles
Human immunodeficiency virus
Leptospirosis
Sepsis/shock
Liver abscess

Metabolic Disorders

Wilson disease
Cystic fibrosis
Cholesterol ester storage disease
Alpers syndrome
α_1-Antitrypsin deficiency

Drug or Toxin

Drugs*

Chlorpromazine
Hormones (estrogens, androgens)
Antibiotics (amoxicillin-clavulanate, dicloxacillin, erythromycin, sulfonamides, tetracycline)
Anticonvulsants (carbamazepine, phenytoin, valproate)
Acetaminophen
Alcohol
Halothane
Isoniazid
Antineoplastics

Toxins

Amanita phalloides (mushroom)
Insecticides
Carbon tetrachloride
Phosphorus
Herbal teas

Total Parenteral Nutrition

Intrahepatic Cholestasis

Benign recurrent intrahepatic cholestasis
Progressive familial intrahepatic cholestasis type 3

Miscellaneous

Dubin-Johnson syndrome
Rotor syndrome
Budd-Chiari syndrome
Systemic lupus erythematosus
Indian childhood cirrhosis
Cardiovascular
Ischemia
Congestive heart failure
Cardiomyopathy
Oncologic
Leukemia
Langerhans cell histiocytosis
Lymphoma
Graft-versus-host disease
Venoocclusive disease
Sickle cell disease with intrahepatic sickling
Hemophagocytic lymphohistiocytosis
Heat stroke
Navajo neuropathy

*Many other drugs have been implicated in the etiology of conjugated hyperbilirubinemia; these are the most commonly cited.

Multiple **biliary strictures** have also been found in association with Langerhans cell histiocytosis, congenital hepatic fibrosis, autosomal recessive polycystic kidney disease, following ischemic/hypoxic injury, and in immunodeficiency states.

Overlap syndrome with features of both sclerosing cholangitis and autoimmune hepatitis and autoimmune cholangitis with inflammation focused on small bile ducts has been described as variants of the disease. In those conditions, response to immunosuppressive therapy is better than in PSC but worse than in autoimmune hepatitis.

Infection. Infections are a common cause of jaundice in the child and adolescent. The most important step is to evaluate patients for

synthetic liver failure and for signs of chronicity (portal hypertension, growth failure, risk factors for blood-borne or sexually transmitted disorders). Patients with synthetic liver failure should be referred for urgent evaluation by the liver transplant center.

Diagnostic work-up should focus on potentially treatable disorders (CMV, hepatitis B, and C), disorders preventable for contacts (hepatitis A). Screening for common community-acquired disorders such as EBV, adenovirus, or enterovirus is optional. In the absence of an identifiable viral agent, idiopathic acute hepatitis can be diagnosed only after the complete resolution of abnormal bilirubin and aminotransferases is documented. If abnormalities persist, a work-up for chronic liver diseases should be initiated.

Hepatitis A. Hepatitis A virus (HAV) infection is usually anicteric or asymptomatic in children younger than 5 years of age. However, in almost 66% of infected patients between 5 and 17 years of age, a symptomatic illness with jaundice develops. Two to 7 days before the onset of jaundice, there is a flulike illness with symptoms that can include malaise, headache, myalgias, anorexia, vomiting, diarrhea, right upper quadrant pain, and fever. Some children present with cough and coryza. The urine becomes dark, and jaundice and pale or acholic stools develop. Aminotransferase levels are 10-100 times normal. The diagnosis is confirmed by an HAV IgM study. Children generally recover within 2 weeks. On occasion, fulminant hepatitis develops from HAV infection. Small percentages develop either a relapsing or protracted cholestatic illness lasting up to 8 months. There is no carrier state or chronic illness.

HAV is an enterovirus of the picornavirus group. Transmission is by the fecal-oral route, which may include contaminated water and food, especially shellfish. The greatest fecal excretion is before the onset of jaundice when the disease has not yet been recognized (Fig. 15.4). Transmission rates are high in daycare centers and institutions with developmentally delayed children. The incubation period is 15-40 days. After exposure, infection can be prevented in 85-90% of cases by giving intramuscular immunoglobulin to contacts within 2 weeks of exposure. Hepatitis A vaccine is available for long-term prophylaxis.

Hepatitis B. Hepatitis B virus (HBV) is a DNA virus that is transmitted through blood products, shared needles, and sexual contact; vertically during childbirth; and from occupational exposure. Infection in the newborn can be prevented by administration of hepatitis B immunoglobulin within 12 hours of birth and a series of 3 hepatitis B vaccinations. HBV infection is diagnosed mostly in children from countries with high prevalence of hepatitis B and no effective immunization or perinatal screening program. In developed countries, hepatitis B should be suspected in children born from mothers with preexisting hepatitis B or mothers with no prenatal care. Hepatitis B risk factors in adolescents include intravenous (IV) drug use and unprotected sex. The majority of children with hepatitis B are asymptomatic; few develop symptoms of acute or chronic hepatitis. Extrahepatic symptoms of arthritis, polyarteritis, urticaria, and nephritis from circulating immune complexes can be present. HBsAg is the first antigenic marker to appear; it disappears after 1-3 months if HBV resolves (Fig. 15.5). Hepatitis B surface antibody (anti-HBs) is a protective antibody that develops after immunization or resolution of infection. In patients whose infections resolve, there is a window of 2-6 weeks between the disappearance of HBsAg and the appearance of anti-HBs. During this window, anti-HBc or HBV DNA may be the only evidence of infection with HBV. Hepatitis B e antigen (HBeAg) correlates with viral replication. HBV DNA is a measure of viral replication. Screening for infection is made with HBsAg and anti-HBc. Although acute HBV infection is rarely a severe illness, fulminant hepatic failure develops in up to 1% of patients. Chronic infection, defined as the persistence of HBsAg for at least 6 months, occurs in 90% of infected neonates, 25-50% of infected children younger than 5 years, and 5-10% of infected adults. Children with chronic active hepatitis B can be treated with interferon α 2b or antiviral agents.

Hepatitis C. Acute hepatitis C virus (HCV) infection is often mild and usually subclinical. Jaundice is unusual. Chronic infection develops in 40-60% of affected children, in contrast with up to 80% of infected adults, and can progress to cirrhosis. Screening for hepatitis uses anti-HCV antibodies, and infection is confirmed via polymerase chain reaction (PCR) for HCV RNA. Transmission may be parenteral due to IV drug use or exposure to blood, or sexual or vertical transmission is also possible. Elimination of hepatitis C is possible with directly acting antiviral agents. The treatment regimen is selected based on

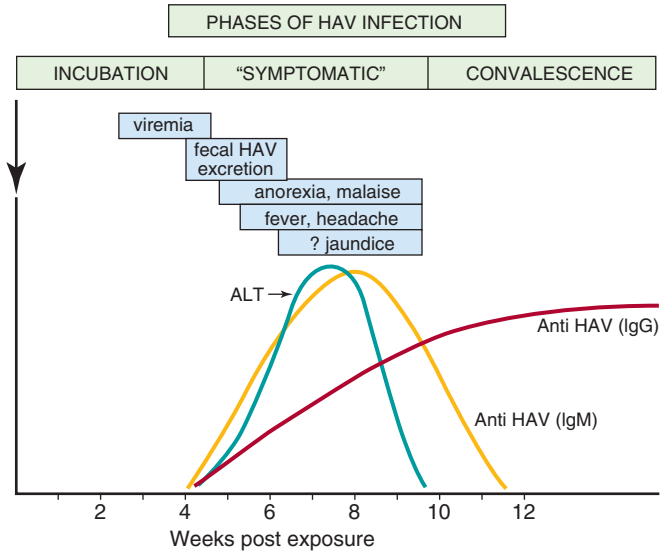


FIGURE 15.4 Typical course of hepatitis A virus (HAV) infection. ALT, alanine aminotransferase; IgG, immunoglobulin G; IgM, immunoglobulin M. (From Balistreri WF. Viral hepatitis. *Pediatr Clin North Am.* 1988;35:640.)

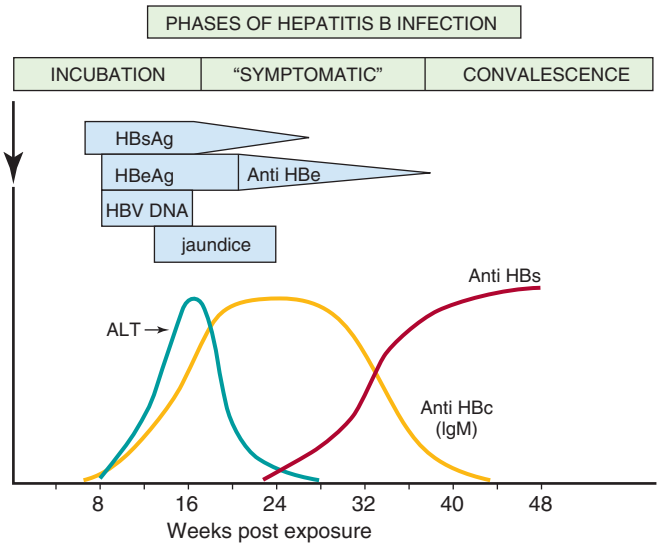


FIGURE 15.5 Typical course of acute hepatitis B virus (HBV) infection. ALT, alanine aminotransferase; HBc, hepatitis B core; HBe, hepatitis B e; HbeAg, hepatitis B e antigen. HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen; IgM, immunoglobulin M. (From Balistreri WF. Viral hepatitis. *Pediatr Clin North Am.* 1988;35:647.)

hepatitis C genotype. It is a rapidly evolving area; however, pediatric experience with direct-acting antiviral regimens is limited.

Hepatitis D. Hepatitis D virus (HDV) infection can occur only in the presence of HBV as either a co-infection or a superinfection. Its route of transmission is parenteral. As with HBV, it can become chronic. The diagnosis is confirmed by the presence of HDV antibody.

Hepatitis E. Hepatitis E (HEV) infection is similar to HAV in its manifestation and mode of transmission. It is a self-limited illness with no chronic state. However, fulminant hepatitis may occur in up to 20% of cases. Serologic diagnosis can be made by finding antibodies to HEV.

Epstein-Barr virus. Epstein-Barr virus infection can mimic HAV, HBV, or HCV infection. Often there is an exudative pharyngitis and lymphadenopathy. Fatal hepatic necrosis can occur. This is rare, but it is of particular concern in the immunocompromised host. The diagnosis is confirmed by elevation of Epstein-Barr virus PCR.

Cytomegalovirus hepatitis can be symptomatic particularly in infants. Hepatitis is usually self-limited. Ganciclovir can be used as treatment in severe cases.

Other viruses. Other viruses including herpes simplex, human herpesvirus 6, parvovirus B19, and norovirus can also cause hepatitis, particularly in the immunosuppressed patient.

Wilson disease. Wilson disease is an autosomal recessive disorder of copper metabolism. As a result of ATP7B mutation, copper cannot be excreted and it accumulates in the liver, which causes hepatic steatosis and necrosis. Copper is then released into the circulation and is ultimately deposited in the central nervous system, kidneys, and cornea. The hepatic manifestation predominates in childhood; a neuropsychiatric manifestation becomes more common later, in adolescence and adulthood. The liver involvement may manifest as acute hepatitis, fulminant hepatic failure, chronic hepatitis, cirrhosis, or asymptomatic elevation of serum aminotransferases. Neurologic symptoms such as dysarthria, clumsiness, tremor, and mood disorders may or may not be present. In the kidney, the result is tubular dysfunction; in the cornea, the result is Kayser-Fleischer rings. Hemolysis can be present as a result of copper toxicity. The diagnosis is supported by documenting a low serum ceruloplasmin level, high urinary copper excretion, and increased hepatic copper concentrations on liver biopsy. D-Penicillamine or trientin chelate copper can successfully treat Wilson disease. Dietary restriction of copper can aid treatment. Wilson disease requires lifelong therapy. Wilson disease is a potentially lethal treatable disorder that should be promptly diagnosed. Patients presenting with synthetic liver failure should be promptly referred for liver transplant evaluation.

Drugs and toxins. Numerous drugs and toxins are associated with hepatic injury (see Table 15.9) and should be considered in the evaluation of jaundice. The reaction can be idiosyncratic or dose related. In the latter case, this may be associated with either accidental or purposeful overdose. The manifestation can be that of acute hepatitis, fulminant hepatic failure, or cholestatic disease, depending on the drug.

Autoimmune hepatitis. Autoimmune hepatitis (AIH) is a common cause of chronic liver injury (Table 15.10). The most frequent course is insidious with fatigue as a dominant symptom. Autoimmune hepatitis can present acutely with malaise, anorexia, nausea, vomiting, and jaundice. Autoimmune disorders such as arthritis, thyroiditis, vasculitis, nephritis, hemolytic anemia, or diabetes mellitus are often associated with AIH. Autoimmune hepatitis may be associated with inflammatory bowel disease. Laboratory studies demonstrate elevated aminotransferase levels, mild hyperbilirubinemia, and hypergammaglobulinemia. ANA, actin, or anti–smooth muscle antibody is present in type 1 AIH, whereas anti–liver-kidney microsomal antibody is found in type 2 AIH (see Table 15.10).

Liver biopsy is required for diagnosis. Characteristic findings are plasma cells and an inflammatory infiltrate expanding the portal area and moderate to severe piecemeal necrosis. Treatment consists of steroids and azathioprine.

TABLE 15.10 Classification of Autoimmune Hepatitis

Variable	Type 1 Autoimmune Hepatitis	Type 2 Autoimmune Hepatitis
Characteristic autoantibodies	Antinuclear antibody* Smooth-muscle antibody* Antiactin antibody† Autoantibodies against soluble liver antigen and liver-pancreas antigen‡ Atypical perinuclear antineutrophil cytoplasmic antibody	Antibody against liver-kidney microsome type 1* Antibody against liver cytosol type 1* Antibody against liver-kidney microsomal type 3
Geographic variation	Worldwide	Worldwide; rare in North America
Age at presentation	Any age	Predominantly childhood and young adulthood
Gender of patients	Female in ~75% of cases	Female in ~95% of cases
Association with other autoimmune diseases	Common	Common§
Clinical severity	Broad range, variable	Generally severe
Histopathologic features at presentation	Broad range, mild disease to cirrhosis	Generally advanced
Treatment failure	Infrequent	Frequent
Relapse after drug withdrawal	Variable	Common
Need for long-term maintenance	Variable	~100%

*The conventional method of detection is immunofluorescence.
†Tests for this antibody are rarely available in commercial laboratories.
‡This antibody is detected by an enzyme-linked immunosorbent assay.
§Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy is seen only in patients with type 2 disease.
From Krawitt EL. Autoimmune hepatitis. *N Engl J Med.* 2006;354:54-66.

(See *Nelson Textbook of Pediatrics,* p. 1939.)

SUMMARY AND RED FLAGS

In evaluating the older child or adolescent with jaundice, it is important to determine whether the condition represents a hepatobiliary problem, a hematologic disorder, or a systemic illness. If there is conjugated hyperbilirubinemia, it is essential to evaluate for severe dysfunction, as manifest by, prolonged PT, hyperammonemia, encephalopathy, and hypoglycemia. Coagulopathy, encephalopathy, or hypoglycemia can signify hepatic failure, which mandates early intervention.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

General

Kelly DA, ed. *Diseases of the Liver and Biliary System in Children*. 3rd ed. Oxford, West Sussex: UK Wiley-Blackwell; 2008.

Suchy FJ, Sokol RJ, Balistreri WF, eds. *Liver Disease in Children*. 4th ed. Cambridge, UK: Cambridge University Press; 2014.

Diagnostic Strategies

Gubernick JA, Rosenberg HK, Ilaslan H, et al. US approach to jaundice in infants and children. *Radiographics*. 2000;20:173-195.

Jensen MK, Biank VF, Moe DC, et al. HIDA, percutaneous transhepatic cholecysto-cholangiography and liver biopsy in infants with persistent jaundice: can a combination of PTCC and liver biopsy reduce unnecessary laparotomy? *Pediatr Radiol*. 2012;42(1):32-39.

Pal S, Curley A, Stanworth SJ. Interpretation of clotting tests in the neonate. *Arch Dis Child Fetal Neonatal Ed*. 2015;100(3):F270-F274.

Rosenthal P. Assessing liver function and hyperbilirubinemia in the newborn. *Clin Chem*. 1997;43:228-234.

Neonatal Jaundice

Andres JM. Neonatal hepatobiliary disorders. *Clin Perinatol*. 1996;23:321-352.

Dennery PA, Seidman DS, Stevenson DK. Neonatal hyperbilirubinemia. *N Engl J Med*. 2001;344:581-590.

Jacquemin E, Lykavieris P, Chaoui N, et al. Transient neonatal cholestasis: Origin and outcome. *J Pediatr*. 1998;133:563-567.

Watchko JF. Vigintiphobia revisited. *Pediatrics*. 2005;115(6):1747-1753.

Alagille Syndrome, Primary Intrahepatic Cholestasis

Alissa FT, Jaffe R, Shneider BL. Update on progressive familial intrahepatic cholestasis. *J Pediatr Gastroenterol Nutr*. 2008;46(3):241-252.

Balistreri WF. Inherited disorders of bile acid transport or synthesis. *Gastroenterol Hepatol*. 2007;3(5):343-345.

Turnpenny PD, Ellard S. Alagille syndrome: pathogenesis, diagnosis and management. *Eur J Hum Genet*. 2012;20:251-257.

α_1-Antitrypsin Deficiency

Francavilla R, Castellaneta SP, Hadzic N, et al. Prognosis of alpha-1-antitrypsin deficiency–related liver disease in the era of paediatric liver transplantation. *J Hepatol*. 2000;32:986-992.

Silverman EK, Sandhaus RA. Clinical practice. Alpha1-antitrypsin deficiency. *New Engl J Med*. 2009;360(26):2749-2757.

Biliary Atresia

Chardot C, Carton M, Spire-Bendelac N, et al. Prognosis of biliary atresia in the era of liver transplantation: French national study from 1986 to 1996. *Hepatology*. 1999;30:606-611.

Khalil BA, Perera MT, Mirza DF. Clinical practice: management of biliary atresia. *Eur J Pediatr*. 2010;169(4):395-402.

McKiernan PJ, Baker AJ, Kelly DA. The frequency and outcome of biliary atresia in the UK and Ireland. *Lancet*. 2000;355:25-29.

Crigler-Najjar Syndromes

Fox IJ, Chowdhury JR, Kaufman SS, et al. Treatment of the Crigler-Najjar syndrome type I with hepatocyte transplantation. *N Engl J Med*. 1998;338:1422-1426.

Hardikar W. Genes for jaundice. *J Paediatr Child Health*. 1999;35:522-524.

Cystic Fibrosis

Shapira R, Hadzic N, Francavilla R, et al. Retrospective review of cystic fibrosis presenting as infantile liver disease. *Arch Dis Child*. 1999;81:125-128.

Erythrocyte Enzyme Defects

Kaplan M, Hammerman C. Severe neonatal hyperbilirubinemia: A potential complication of glucose-6-phosphate dehydrogenase deficiency. *Clin Perinatol*. 1998;25:575-590.

Nathan DG, Orkin SH, eds. *Nathan and Oski's hematology of infancy and childhood*. 5th ed. Philadelphia: WB Saunders; 1998.

Gilbert Syndrome

Burchell B, Hume R. Molecular genetic basis of Gilbert's syndrome. *J Gastroenterol Hepatol*. 1999;14:960-966.

Monaghan G, McLellan A, McGeehan A, et al. Gilbert's syndrome is a contributory factor in prolonged unconjugated hyperbilirubinemia of the newborn. *J Pediatr*. 1999;134:441-446.

Lucey-Driscoll Syndrome

Arias IM, Wolfson S, Lucey JF, et al. Transient familial neonatal hyperbilirubinemia. *J Clin Invest*. 1965;44:1442-1450.

Lucey JF, Arias IM, McKay RJ. Transient familial neonatal hyperbiliru-binemia. *Am J Dis Child*. 1960;100:787-789.

Physiologic and Breast Milk Jaundice

Gartner LM, Lee K-S. Jaundice in the breastfed infant. *Clin Perinatol*. 1999;26:431-445.

Jaundice in Older Children and Adolescents

Balistreri WF. Liver disease in infancy and childhood. In: Schiff ER, Sorrell MF, Maddrey WC, eds. *Schiff's Diseases of the Liver*. 8th ed. Philadelphia: Lippincott-Raven; 1999:1357-1512.

Autoimmune Hemolytic Anemia

Ware RE, Rosse WF. Autoimmune hemolytic anemia. In: Nathan DG, Orkin SH, eds. *Nathan and Oski's Hematology of Infancy and Childhood*. 5th ed. Philadelphia: WB Saunders; 1998:499-522.

Autoimmune Hepatitis

Manns MP, Czaja AJ, Gorham JD, et al. Diagnosis and management of autoimmune hepatitis. *Hepatology*. 2010;51(6):2193-2213.

Mieli-Vergani G, Vergani D. Immunological liver diseases in children. *Semin Liver Dis*. 1998;18:271-279.

Drugs

Lee W. Drug-induced hepatotoxicity. *N Engl J Med*. 1995;333:1118-1127.

Zimmerman HJ. *Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 1999.

Gallstones

Rescorla FJ. Cholelithiasis, cholecystitis, and common bile duct stones. *Curr Opin Pediatr*. 1997;9:276-282.

Hepatitis

Balistreri WF. Viral hepatitis. *Pediatr Clin North Am*. 1988;35:637-669.

Debray D, Cullufi P, Devictor D, et al. Liver failure in children with hepatitis A. *Hepatology*. 1997;26:1018-1022.

Duchon J, Zachariah P. TORCH infections. *Clin Perinatol*. 2015;42(1):77-103.

Kemmer NM, Miskovsky EP. Hepatitis A. *Infect Dis Clin North Am*. 2000;14:605-615.

Petta S, Craxi A. Current and future HCV therapy: do we still need other anti-HCV drugs? *Liver Int*. 2015;35(suppl 1):4-10.

Ryder SD, Beckingham IJ. Acute hepatitis. *BMJ*. 2001;322:151-153.

Trepo C, Chan HL, Lok A. Hepatitis B virus infection. *Lancet*. 2014;384(9959):2053-2063.

Primary Sclerosing Cholangitis

Debray D, Pariente D, Urvoas E, et al. Sclerosing cholangitis in children. *J Pediatr*. 1994;124:49-56.

Roberts EA. Primary sclerosing cholangitis in children. *J Gastroenterol Hepatol*. 1999;14:588-593.

Williamson KD, Chapman RW. Primary sclerosing cholangitis. *Dig Dis*. 2014;32(4):438-445.

Wilschanski M, Chait P, Wade JA, et al. Primary sclerosing cholangitis in 32 children: Clinical, laboratory, and radiographic features with survival analysis. *Hepatology*. 1995;22:1415-1422.

Wilson Disease

Loudianos G, Gitlin JD. Wilson's disease. *Semin Liver Dis*. 2000;20:353-364.

Wilson DC, Phillips MJ, Cox DW. Severe hepatic Wilson's disease in preschool-aged children. *J Pediatr*. 2000;137:719-722.

16

Constipation

Joshua Noe

Constipation is defined symptomatically as the infrequent passage of hard stools, straining while passing a stool, or pain associated with the passage of a hard stool. The range of normal defecation patterns in children is widely variable, though in general, formula-fed infants may have 4-5 stools per day in the 1st weeks of life while breast-fed infants usually pass softer and more frequent stools. Stool frequency in both gradually decreases to 1-2 per day by 1 year of age. Most children aged 1-4 years have 1 or 2 daily bowel movements, with a range of 3 daily bowel movements to 1 bowel movement every other day.

Constipation is classified broadly either as functional or as secondary to underlying conditions, such as anatomic abnormalities, metabolic disorders, neurologic dysfunction, or medication effects (Table 16.1). The majority of childhood constipation is functional. The Rome III Criteria for Functional Gastrointestinal Disorders defines **functional constipation** in 2 age groups as noted in Tables 16.2 and 16.3.

Changes in diet, such as formula changes or the addition of solid foods, may lead to transient constipation in infants. Minor illnesses, including infectious diarrhea, can subsequently result in episodic constipation as well. More long-standing constipation is often secondary to inadequate intake of dietary fiber, fluid, or both. The evaluation of constipation involves first determining whether the change in the frequency or consistency of stools is secondary to functional constipation or is related to an underlying organic disorder. This determination is based on identifying historical features and examination findings that suggest an underlying disorder and prompt further investigation.

PHYSIOLOGY OF NORMAL DEFECATION AND CONSTIPATION

Fecal continence and physiologic defecation are dependent on the **anal inhibitory reflex**, which is in turn dependent on the proper structure and function of the internal and external anal sphincters and the pelvic floor. The **internal anal sphincter** is an involuntary muscle that is contracted at rest. When a bolus of stool distends the rectum, the internal anal sphincter relaxes. This process generally results in the child sensing the need to defecate. The **external anal sphincter** and the **puborectalis muscle** of the pelvic floor, under voluntary control, contract upon rectal distention, respectively closing the anus and decreasing the rectoanal angle, thus allowing the child to hold stool until it is socially convenient to defecate. Voluntary relaxation of the puborectalis muscle and the external anal sphincter straightens the anorectal angle and allows the child to stool. In situations where there is **encopresis** secondary to **overflow incontinence**, the child typically consciously withholds stool by refusing to relax the external anal sphincter in the setting of a relaxed internal anal sphincter. Over time, the child is not able to keep the external anal sphincter fully contracted and stool leaks out of the anal canal. The presence of overflow incontinence is an important indicator that the anal inhibitory reflex is likely intact, as patients with anatomic or neurologic abnormalities of the distal colon and internal anal sphincter are unable to reflexively relax the internal anal sphincter to allow for the passage of stool.

Patients with chronic constipation have physiologic abnormalities upon anorectal manometric evaluation. The most consistent abnormality is blunted rectal sensation, rendering the patient unable to feel the bolus of stool in the rectum. Other findings include incomplete relaxation of the internal anal sphincter and paradoxical contraction of the external sphincter during attempted defecation. Patients who have paradoxical anal contraction are less likely to respond to routine medical therapy or may be more likely to have recurrent constipation if treatment is withdrawn.

DATA COLLECTION AND ASSESSMENT

◆ History

Functional constipation may be distinguished from secondary causes of constipation by assessing the age of symptom onset, the stool consistency, and the presence of associated signs or symptoms.

The age at symptom onset differentiates disease processes that are congenital versus those that are acquired. Failure to pass meconium within the first 48 hours of life suggests a diagnosis of **Hirschsprung disease**; however, up to 50% of patients with Hirschsprung disease will pass meconium prior to this. In addition to Hirschsprung disease, constipation in the 1st month of life or a history of constipation since infancy suggests organic causes (Table 16.4). The appearance of symptoms beyond infancy suggests acquired organic constipation or functional constipation.

Stool consistency in constipation can differ by etiology. Functional constipation tends to produce large, bulky stools, whereas constipation secondary to Hirschsprung disease or other organic etiologies tends to produce harder, pebble-like, or ribbon-like stools. Stool consistency may be objectively rated via use of the **Bristol stool scale** (Fig. 16.1), and can be used to follow response to therapy.

The assessment of associated signs and symptoms should include evaluating for a history of blood in the stool, as well as for the presence of urinary symptoms. Bright red blood on the surface of the stool suggests an anal fissure indicative of straining, which is seen in approximately 25% of patients with constipation. Blood on the periphery of the stool may suggest pathology in the distal colon or anorectal vault.

Urinary symptoms may take the form of either retention or incontinence. Retention may be secondary to congenital or acquired abnormalities in the neurologic regulation of bladder voiding and may be associated with similar abnormalities in the regulation of defecation. Alternately, retention may be secondary to urinary tract outflow obstruction, which is secondary to a large stool burden. Incontinence may be due to a large stool mass distending the rectum and placing pressure on the posterior bladder wall, or may indicate overflow incontinence in the setting of a neurogenic bladder. Urinary retention is also seen in patients with chronic intestinal pseudoobstruction and is thought to be secondary to autonomic dysregulation.

(See *Nelson Textbook of Pediatrics*, p. 868.)

TABLE 16.1 Causes of Constipation in Infants and Children

Functional
Faulty diet (poor fiber intake, excessive cow's milk, inadequate nutrition)
Inadequate fluid intake
Situational
Depression
Familial-constitutional

Anatomic
Anterior anal displacement
Ectopic anus
Anal stenosis
Malrotation
Colonic anomalies (rectocele, duplications)
Stricture (postsurgical, sequelae of inflammatory disorders)
Painful anorectal lesions (fissures, dermatitis, abscess)
Abnormal abdominal musculature (prune belly, gastroschisis)
Intestinal neoplasm, extraintestinal pelvic mass (teratoma)

Endocrine
Hypothyroidism
Panhypopituitarism
Diabetes mellitus

Genetic/Metabolic
Hypercalcemia
Metal intoxication (lead, arsenic, mercury)
Dehydration
Cystic fibrosis: meconium ileus equivalent
Hypokalemia
Acute intermittent porphyria
Blue diaper syndrome
Hereditary coproporphyria
Rubinstein-Taybi syndrome
Williams syndrome (hypercalcemia)

Infectious
Typhoid
Infant botulism
Chagas disease

Abnormal Innervation/ Neurologic
Aganglionosis
Hirschsprung disease
Neural dysgenesis (pseudo-obstruction syndromes)
Hyperganglionosis
Myotonic dystrophy
Cerebral palsy

Neurologic/Spinal Cord Lesions
Spina bifida and spina bifida occulta
Tethered cord
Spinal cord tumors
Traumatic lesions

Psychologic
Anorexia nervosa
Depression

Medications
Anticonvulsants
Antacids (aluminum and calcium)
Iron
Barium
Opiates (codeine, diphenoxylate–atropine sulfate [Lomotil], loperamide [Imodium])
Antidepressants
Anticholinergics
Phenothiazines
Vincristine
Calcium channel blockers
Bismuth
Clonidine
Antihistamines
Diuretics

Other
Milk protein–induced anal inflammation and fissure formation
Celiac disease
Collagen vascular disease (SLE, mixed connective tissue disease, scleroderma)
Amyloidosis

SLE, systemic lupus erythematosus.

TABLE 16.2 Functional Constipation: Infant/Toddler

Diagnostic criteria Must include 1 mo of **at least two** of the following in infants up to 4 yr of age:
1. Two or fewer defecations per week
2. At least one episode/week of incontinence after the acquisition of toileting skills
3. History of excessive stool retention
4. History of painful or hard bowel movements
5. Presence of a large fecal mass in the rectum
6. History of large-diameter stools, which may obstruct the toilet

Accompanying symptoms may include irritability, decreased appetite, and/or early satiety. The accompanying symptoms disappear immediately following passage of a large stool.

From Rome III Diagnostic Criteria for Functional Gastrointestinal Disorders. 2006(Appendix A):895. Available at: http://www.romecriteria.org/assets/pdf/19_RomeIII_apA_885-898.pdf.

TABLE 16.3 Functional Constipation: Child/Adolescent

*Diagnostic criteria** Must include **two or more** of the following in a child with a developmental age of at least 4 yr with insufficient criteria for diagnosis of IBS:
1. Two or fewer defecations in the toilet per week
2. At least one episode of fecal incontinence per week
3. History of retentive posturing or excessive volitional stool retention
4. History of painful or hard bowel movements
5. Presence of a large fecal mass in the rectum
6. History of large diameter stools, which may obstruct the toilet

*Criteria fulfilled at least once per week for at least 2 mo prior to diagnosis.
IBS, irritable bowel syndrome.
From Rome III Diagnostic Criteria for Functional Gastrointestinal Disorders. 2006(Appendix A):897. Available at: http://www.romecriteria.org/assets/pdf/19_RomeIII_apA_885-898.pdf.

TABLE 16.4 Causes of Constipation During the Neonatal Period

Meconium plug (rule out cystic fibrosis)
Meconium ileus (rule out cystic fibrosis)
Hirschsprung disease
Intestinal pseudoobstruction
Anteriorly displaced anus
Ectopic anus
Anal stenosis
Imperforate anus
Spina bifida
Hypothyroidism
Hypercalcemia
Neuronal intestinal dysplasia types A and B
Medications (opioids, paralytic agents, magnesium)

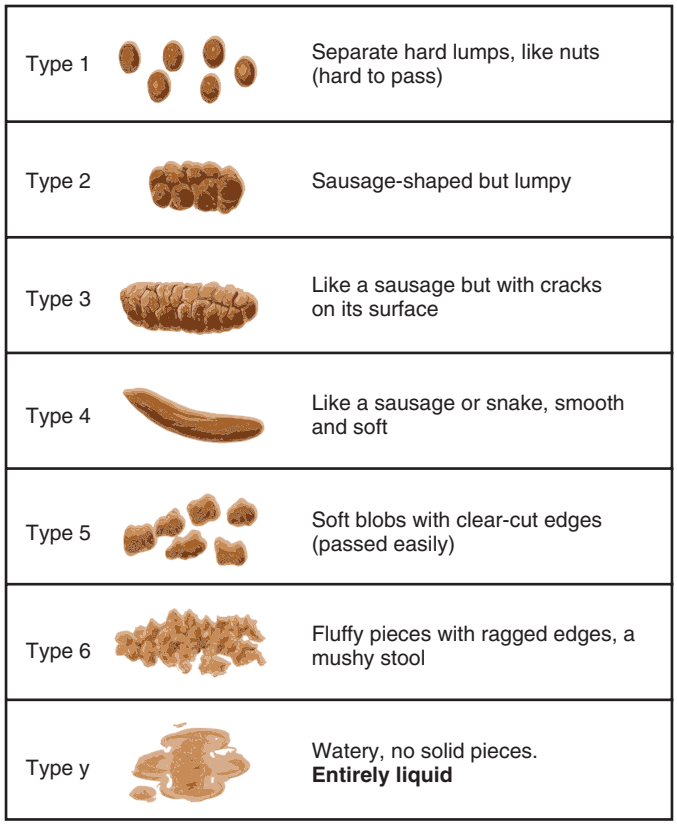


FIGURE 16.1 The Bristol stool chart allows for qualitative comparisons of stool consistency in the setting of both constipation and diarrhea.

TABLE 16.5 Historical and Physical Findings Suggestive of Organic Etiologies of Constipation

Symptoms or History	Physical Findings
Acute Signs	Severe abdominal distension
Delayed passage of meconium (after 48 hr of life)	Pelvic mass (e.g., sacral teratoma)
Fever, vomiting, or diarrhea	Lumbosacral dimple, hair tuft or lipoma, or deviation of the gluteal cleft
Rectal bleeding (unless attributable to an anal fissure)	Anal scars
Severe abdominal distension	Anteriorly displaced anus
Chronic Signs	Patulous anus (i.e., low resting sphincter tone)
Constipation present from birth or early infancy	Perianal fistula
Ribbon stools (very narrow in diameter)	High anal canal tone with empty rectum
Urinary incontinence or bladder disease	Explosive expulsion of stool after digital examination of the rectum
Weight loss or poor weight gain	Absent anal wink
Delayed growth (e.g., decreasing height percentiles)	Absent cremasteric reflex
Extraintestinal symptoms (especially neurologic deficits)	Decreased lower extremity tone or strength
Congenital anomalies or syndrome associated with Hirschsprung disease (e.g., Down syndrome)	Abnormal lower extremity deep tendon reflex: absence of delay in relaxation phase
Family history of Hirschsprung disease	Abnormal thyroid gland
	Extreme fear during the anal inspection

Modified from Tabbers MM, DiLorenzo C, Berger MY, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr.* 2014;58(2):258.

Abdominal pain is common in constipated patients; when present, it is often mild, nonspecific, and periumbilical. Older children may describe discomfort in the lower abdomen and a history of relief of pain after a stool is passed. Appetite is often diminished. A diary recording the passage of stools, the timing of meals, and the onset of abdominal pain over a period of several days to a few weeks can aid in the diagnosis of constipation and in monitoring of therapy. The personal medical history and the family history may reveal illnesses and conditions associated with constipation (Table 16.5; see Table 16.1).

The child's behavior during defecation should be noted. A history of straining, as an index of difficulty in defecation, can be misinterpreted by parents, who often view a child's efforts to withhold stool as efforts to pass a bowel movement. Parents often describe a toddler who hides in a corner, with stiffened straight legs, or who may lean into the wall or hold onto a table while "straining." More often, these actions represent attempts at withholding stool. The young child, having become constipated, passes a painful stool. Passage of a large, painful stool may be associated with an anal fissure. If a fissure is present, a small amount of blood is usually passed with the stool. The child associates the passage of stools with pain and tries to prevent further painful episodes by withholding fecal matter. This behavior results in the formation of even larger, harder stools, which are painful to pass, thus establishing a link between pain and defecation that perpetuates the cycle. Children with stool retention may go 3-5 days without defecating. Enuresis and encopresis may occur.

◆ Physical Examination

Abnormal growth patterns should alert the physician to the possibility of underlying organic disease, such as hypothyroidism or celiac disease (see Table 16.5). Abdominal examination is usually benign; there may be some mild tenderness in the left lower quadrant on palpation of a segment of bowel that is full of stool. Stool may be palpable through the abdominal wall in the sigmoid and descending colon. On occasion, a large, firm fecal mass extends from the symphysis pubis to the umbilicus, which may mimic findings of an abdominal malignancy.

The spine and sacral area should be examined closely. A tuft of hair, a dimple, or a palpable defect or mass in this area should prompt consideration of **spina bifida occulta** or a **tethered spinal cord**. Sensory and motor function should be assessed. The presence of a normal **anal wink**, as elicited by gentle stroking of the perianal skin with a sharp object, such as a wooden tongue blade or the corner of a small package of lubricant, gives evidence of intact lumbosacral innervation. Presence of a normal **cremasteric reflex** in males also gives evidence of intact lumbosacral innervation. The cremaster muscle, innervated by the genitofemoral nerve of the lumbar plexus, typically contracts when the observer brushes a finger along the upper surface of the inner thigh, resulting in withdrawal superiorly of the ipsilateral testis.

The perianal area should be examined for evidence of fissures suggestive of the passage of large, hard stools. The examination is facilitated if an assistant gently spreads the patient's buttocks apart while the examiner illuminates the area. Soiling in the undergarments may indicate fecal impaction with overflow incontinence. The anus should be located in relation to the other perineal structures to assess for anatomic or structural anomalies, such as **anterior displacement of the anus** (Fig. 16.2). The anus is typically situated in the center of the

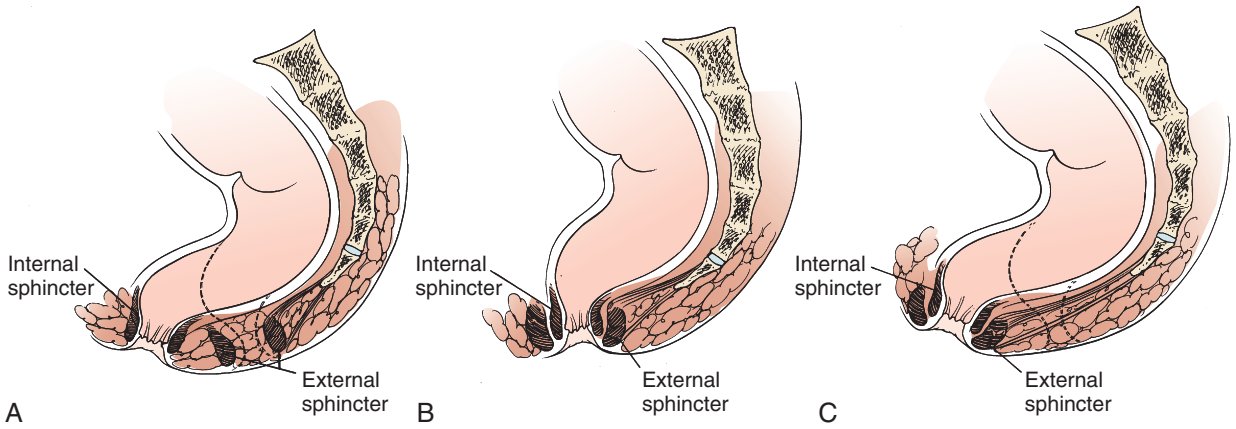


FIGURE 16.2 *A,* Anterior ectopic anus. *B,* Normal anal anatomy. *C,* Anterior anal displacement.

slightly hyperpigmented skin surrounding the anal sphincter. An anteriorly displaced anus is indicated by an abnormal **anal position index (API)**, which is defined as the ratio of the distance between the anus and the posterior aspect of the genitals (the fourchette in females and scrotum in males), to the distance between the coccyx and the posterior genitals. Measurements may be obtained using calipers or by placing clear plastic tape adjacent to the landmarks and marking with a pen, and then subsequently measuring the distance on the tape. The normal API for females is 0.45 ± 0.15, and for males is 0.54 ± 0.14.

Digital examination is indicated in the evaluation of infantile constipation, if the cause or degree of constipation is unclear, or if there are signs of organic disease. The examiner should note the patency and tone of the anus. High tone and an empty rectal vault may suggest Hirshsprung disease. If the aganglionic segment is short enough, withdrawal of the finger might result in an explosive release of stool as the finger acts as a dilator to reach the dilated, ganglion-containing segment. Conversely, a dilated rectal vault with a large stool impaction is more suggestive of functional constipation with withholding behavior. In a cooperative patient, the examiner can ask the patient to bear down against their finger as if attempting to push out stool, which should result in relaxation of the anal canal. Patients who have paradoxical contraction of their anal canal upon this request may have **functional dyssnergia**, a condition in which the patient's pelvic floor fails to relax upon attempted defecation.

◆ Diagnostic Evaluation

Routine laboratory evaluation is usually not helpful in the evaluation of constipation, though it is indicated if a metabolic abnormality is suspected on the basis of the history or physical examination. Endocrinologic disturbances, such as hypothyroidism, can be associated with constipation. If **celiac disease** (see Chapter 11) is a consideration, serum anti–tissue transglutaminase immunoglobulin A (IgA) antibody levels should be assessed. A total IgA level should be performed concomitantly to exclude IgA deficiency confounding interpretation. If the patient does have IgA deficiency, anti–tissue transglutaminase IgG levels or esophagogastroduodenoscopy with duodenal biopsies can be performed. Stool studies may be obtained to exclude infection if indicated by the history.

Plain films of the abdomen are rarely necessary, although if obtained may demonstrate stool in the large bowel. This information is occasionally useful in the case of a child with complaints of diarrhea whose symptoms are due to fecal impaction and overflow of liquid stools. Suspected Hirschsprung disease is evaluated radiographically via a liquid contrast enema. Neurologic symptoms are evaluated with magnetic resonance imaging of the spine and/or brain, particularly to assess for evidence of spinal dysraphism or a tethered cord. Concerns for intestinal dysmotility may be evaluated with a **Sitz marker study**, in which the patient swallows a capsule of radiopaque circular markers and undergoes serial abdominal radiographs to determine the distribution of the markers. After 3 days, any markers that have not yet been evacuated in the stool should be located in the rectum. The presence of markers more proximally in the gastrointestinal tract suggests enteric nervous system or neuromuscular pathology (e.g., chronic intestinal pseudoobstruction).

A rectal motility evaluation may be helpful in the diagnosis and management of chronic constipation. **Anorectal manometry** can be used to evaluate the integrity of the muscles and the innervation of the defecatory mechanism. Determining the sensory threshold provides valuable diagnostic information: patients who cannot detect a balloon filled with 120 mL of air usually have encopresis. Hirschsprung disease is unlikely if reflexive relaxation of the internal anal sphincter occurs in the presence of rectal distention. Manometry and **electromyography** document the presence of paradoxical contraction of the external anal sphincter on attempted defecation. Anorectal manometry can also be used as a therapeutic modality in biofeedback therapy in patients with constipation and encopresis and in patients with paradoxical external anal sphincter contraction. **Total colonic motility** is performed by placing a catheter in the colon to monitor pressures from the rectum to the cecum. Motility tracings reveal information about the function of the colon that is useful in diagnosis and treatment, particularly if surgical options need to be explored.

DIFFERENTIAL DIAGNOSIS

The algorithmic approach to the evaluation of delayed passage of meconium in neonates is presented in Fig. 16.3. An algorithmic approach to the evaluation of pediatric constipation is presented in Fig. 16.4.

Hirschsprung Disease

Congenital aganglionic megacolon, or Hirschsprung disease, is a common cause of neonatal intestinal obstruction, occurring in approximately 1:5000-1:15,000 live births, with a male-to-female ratio of about 4:1. The disease is rare in premature births, may be familial, and is associated with trisomy 21, Waardenburg syndrome, multiple endocrine neoplasia type 2A syndrome, and piebaldism. The absence of ganglion cells in both the Meissner (submucosal) plexus and the Auerbach (myenteric) plexus results in an inability of the involved segment of bowel to relax in response to distention from the presence of stool. In the newborn, passage of meconium is often delayed beyond 48 hours after birth. Most affected patients

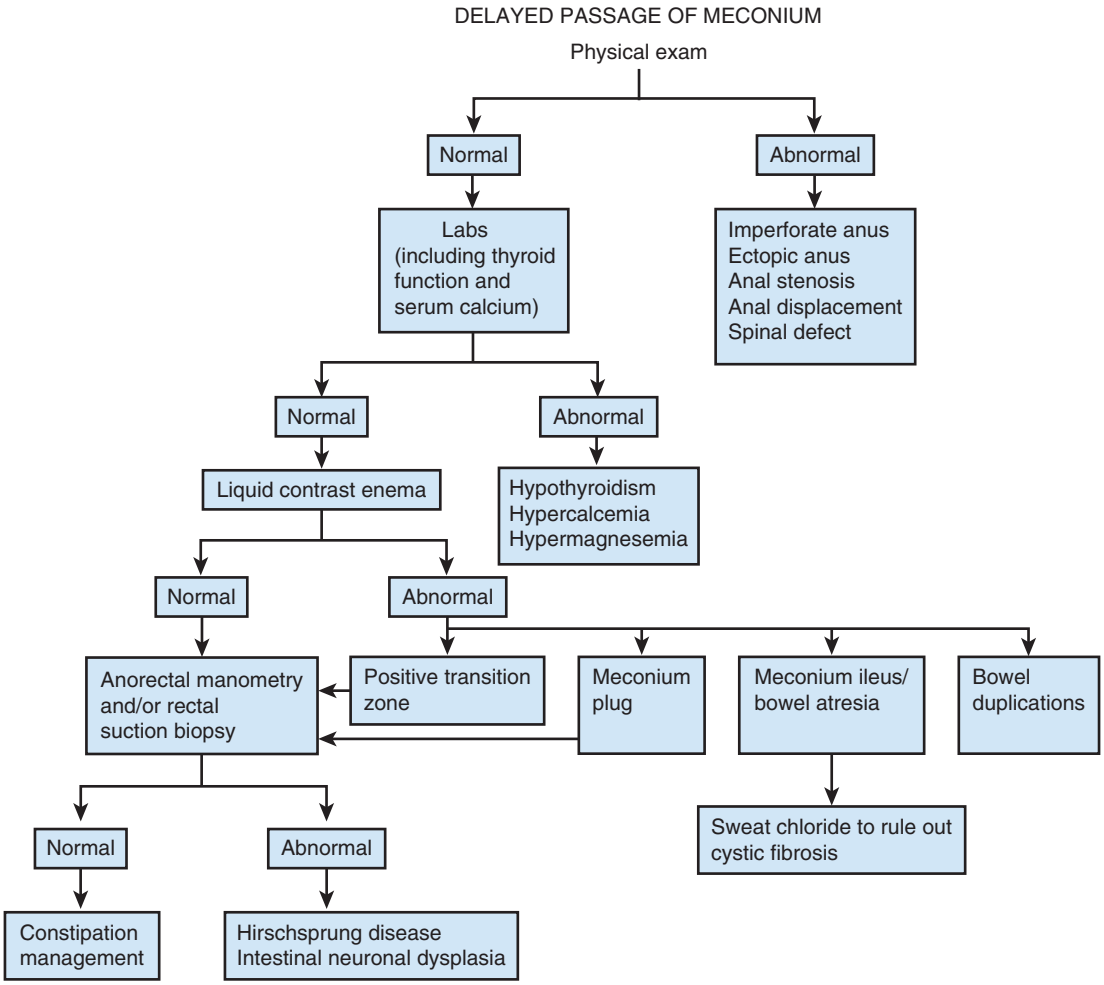


FIGURE 16.3 Algorithmic approach to the differential diagnosis of delayed passage of meconium.

are diagnosed during infancy; 50% are diagnosed in the 1st months of life, 75% by 3 months, and 80% by the end of the 1st year. Diagnosis may be delayed into childhood and, in rare cases, into adolescence or even adulthood in some patients with ultrashort-segment disease. These patients complain of constipation; manifestations usually start in infancy. Differentiating Hirschsprung disease from functional constipation may be challenging in older patients or in those with short-segment disease (Table 16.6). Other conditions that may mimic Hirschsprung disease include other abnormalities of intestinal innervation such as chronic intestinal pseudoobstruction and hyperganglionosis.

The lesion begins at the internal anal sphincter and extends continuously into the rectum or the rectosigmoid in 75-80% of cases. In 10% of cases, there is total colonic aganglionosis; in another 10%, there is variable involvement of the small intestine in addition to total colonic disease. Delayed passage of meconium is the most common manifestation in the neonate, followed by lower intestinal obstruction (distention, bile-stained emesis), obstipation (no stools), failure to thrive, or, in rare cases, intestinal perforation. Meconium plug syndrome may be an initial presentation. In addition, if stool is passed immediately after a rectal examination is performed in an obstipated or constipated patient, Hirschsprung disease should be suspected.

A plain abdominal film occasionally reveals distention of the normally innervated bowel proximal to the affected segment. The most useful radiographic test, though, is a liquid contrast enema, which may demonstrate a small-caliber rectum with a transition in the rectosigmoid to the dilated, obstructed, normal proximal colon. Patients undergoing contrast enema should not undergo preparatory bowel evacuation procedures, which decrease test specificity, particularly in short-segment disease. A delayed lateral radiograph performed 24 hours after the barium enema aids in identifying a transition zone in the sigmoid colon.

Anorectal manometry is a valuable diagnostic procedure if radiographic procedures are unrevealing. Normal internal anal sphincter relaxation with transient rectal distention rules out Hirschsprung disease. Paradoxical contraction of the internal anal sphincter suggests an absence of ganglion cells and is most common in Hirschsprung disease. Absence of relaxation has been noted in premature infants, in neonates with infection or sepsis, and in thyroid aplasia; normal function is seen after appropriate therapy. The sensitivity and specificity of this test varies somewhat among the different age groups (children versus infants versus neonates). This test has a sensitivity that ranges from 0.79 to 0.90, a specificity ranging from 0.97 to 1.00, and a positive predictive value of 0.94-1.00.

A definitive diagnosis of Hirschsprung disease requires histologic confirmation of the absence of ganglion cells; such confirmation may be accomplished by a simple submucosal suction biopsy, which may be performed in the physician's office. Suction biopsy excludes the diagnosis if ganglion cells are present. However, there may be a 10% false-negative rate. A full-thickness rectal biopsy procedure is reserved for infants with bowel obstruction and for older children with abnormal rectal motilities and inconclusive suction biopsies.

Complications of undiagnosed Hirschsprung disease include **acute toxic megacolon** or infectious enterocolitis, most frequently caused by

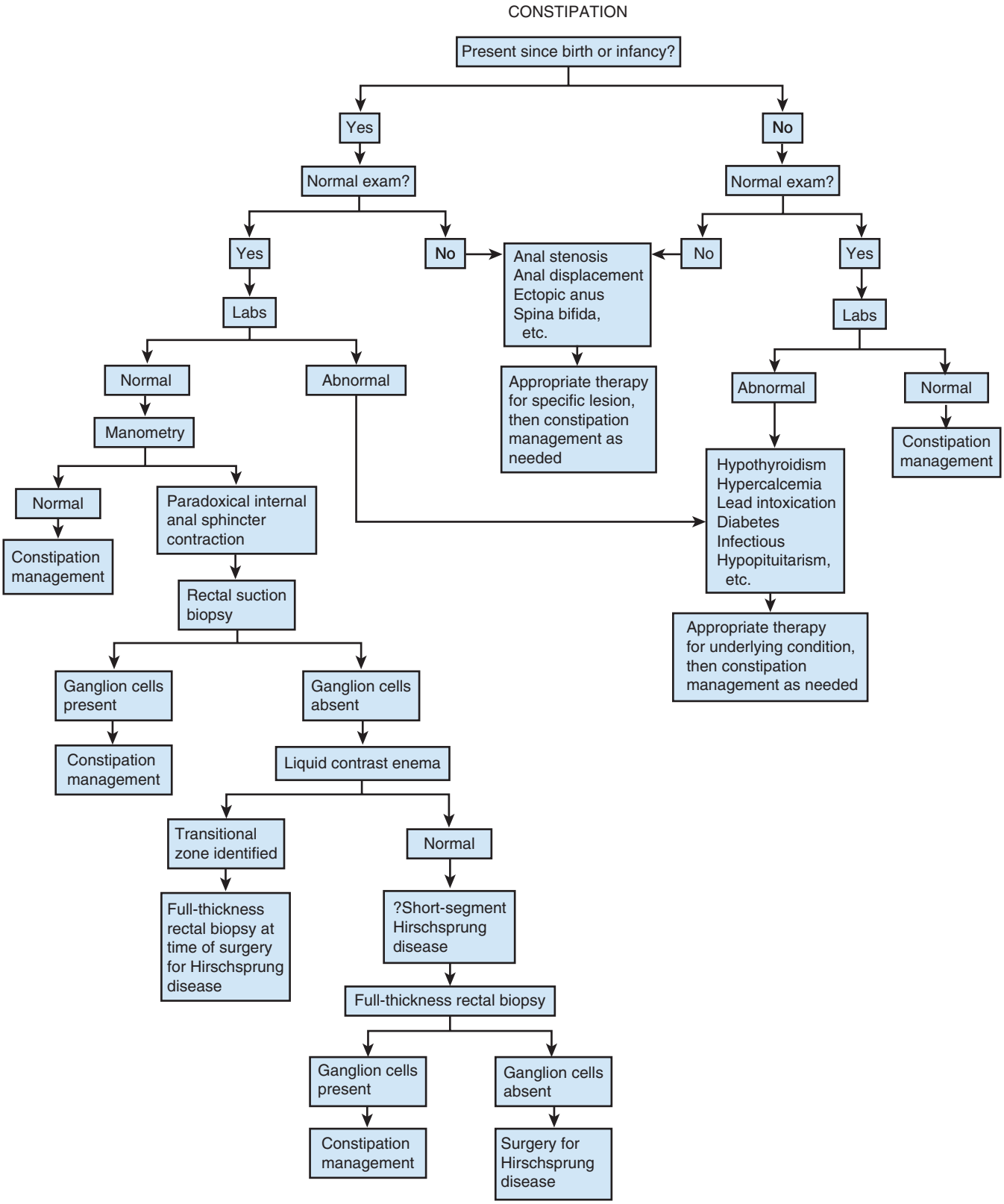


FIGURE 16.4 Algorithmic approach to the diagnosis of constipation.

TABLE 16.6 Distinguishing Hirschsprung Disease from Functional (Acquired) Constipation

	Functional Constipation	Hirschsprung Disease*
History		
Gender of patient	Male	Male
Onset of constipation	After 2 yr of age	At birth
Prevalence	1-3% of boys	1:5000-1:15,000
Encopresis	Common	Very rare
Forced bowel training	Usual	None
Stool size	Very large	Small, ribbon-like
Enterocolitis	None	Possible
Abdominal pain	Common	Rare except with obstruction, toxic megacolon, or enterocolitis
Failure to thrive	Uncommon	Common
Examination		
Abdominal distention	Variable	Common
Poor growth	Rare	Common
Anal tone	Patulous	Tight
Rectal examination	Stool in ampulla	Ampulla empty
Malnutrition	Absent	Possible
Laboratory		
Barium enema	Massive amounts of stool, no transition zone	Transition zone, delayed evacuation (>24 hr)
Rectal biopsy	Normal	No ganglion cells; ↑ acetylcholinesterase staining
Anorectal manometry	Distention of the rectum causes relaxation of the internal sphincter	No sphincter relaxation

*Note that ultrashort-segment Hirschsprung disease may have clinical features of functional (acquired) megacolon (e.g., constipation).
Modified from Behrman RE, ed. *Nelson Textbook of Pediatrics.* 16th ed. Philadelphia: Saunders; 2000:1140.

Staphylococcus aureus or *Clostridium difficile*. Therapy for these complications includes correcting electrolyte abnormalities (hypokalemia), broad-spectrum parenteral antibiotics, bowel rest, rectal tube placement, and if needed, emergency cecostomy or colectomy. Treatment for Hirschsprung disease is surgical resection of the affected segment of bowel and various strategies for an ileal or colonic rectal pull-through procedure.

Chronic Intestinal Pseudoobstruction

This disorder is characterized by manifestations of intestinal obstruction without an identifiable anatomic lesion and may be secondary to an intestinal **neuropathy** or **myopathy**. Congenital cases may be sporadic or inherited, in either autosomal dominant or recessive patterns.

Congenital disease often presents in the 1st months of life. Patients may be born prematurely and may have associated malrotation. Manifestations include abdominal distention, emesis, constipation, growth failure, and pain; diarrhea is less common. Diagnosis is based on the clinical manifestations in the absence of identifiable anatomic obstruction, as well as on motility studies that quantify abnormal bowel transit. Full-thickness intestinal biopsy should be reserved for severe or refractory cases, and care should be taken to pursue biopsy only if the patient is undergoing another indicated intraabdominal procedure, as biopsy in these patients increases the risk of postoperative adhesions and acquired obstruction.

Anterior Anal Displacement

There are two forms of displacement of the anus (see Fig. 16.2). In **anterior ectopic anus**, the anal canal and the internal anal sphincter are displaced anteriorly in the perineum as a unit and are separated from the external anal sphincter, which remains posterior in its usual position. On physical examination, it may be possible to elicit an external sphincter anal wink in the usual location, posterior to the opening of the anal canal. Rectal examination often reveals a sharp posterior angulation in the anal canal. In **anterior anal displacement**, the entire normal anal unit is located in the anterior perineum. Both entities are found more commonly in females. Symptoms of constipation often begin in the neonatal period and are related to the difficulty in expelling stool through a canal that is angled anteriorly. If the displacement is severe enough to cause symptoms, surgical correction may be necessary to relocate the anus and relieve the obstruction.

Anal Stenosis

The diagnosis of **anal stenosis** may be delayed beyond the neonatal period, especially if the degree of stenosis is not severe. Any portion of the anal canal or the entire canal may be involved. The diagnosis can be made by digital examination or by endoscopy. Constipation is caused by fecal retention secondary to outlet obstruction. Treatment is by dilatation or anorectal myectomy.

Imperforate Anus

Imperforate anus is usually diagnosed in the neonatal nursery. Passage of meconium is delayed or is noted to take place through an abnormal location as a result of the presence of a fistula (e.g., rectovaginal, rectovesicular, or rectoperineal). Treatment is surgical; the actual procedure depends on the level and the extent of the defect.

Spina Bifida and Spina Bifida Occulta

Defecation disturbances, most frequently constipation, are common in patients with spina bifida and spina bifida occulta, especially if the defect involves the lumbosacral spine. The spinal and nerve root defects result in poor functioning of the terminal bowel. Voluntary external sphincter control and rectoanal sensation are most often diminished or absent, and the degree of difficulty with defecation is related to the degree and the extent of the injury.

Most patients can achieve an acceptable level of continence via an individualized bowel regimen. Dietary fiber, stool softeners, suppositories, and enema continence catheters are treatment options. Biofeedback and pudendal nerve stimulation are successful in some patients. In most patients, a combination of treatment modalities allows social continence to be achieved and dramatically improves the patient's quality of life. Treatment of patients with spinal or nerve injury or dysfunction from other causes is similar.

Metabolic Diseases

The appropriate laboratory tests should be performed to rule out the various metabolic and endocrinologic conditions that may manifest with constipation (see Table 16.1). The most important of

(See *Nelson Textbook of Pediatrics*, p. 1806.)

(See *Nelson Textbook of Pediatrics*, p. 3409.)

these conditions is hypothyroidism. In routine neonatal screening, hypothyroidism manifesting solely with constipation is rarely seen. It should be suspected in any infant presenting with constipation and a history of prolonged neonatal jaundice.

Neurologic Disease

Children with neurologic disease may have constipation for many reasons, including poor intestinal motility, lack of dietary fiber, and poor awareness of rectal vault distention with stool retention. Any illness affecting the spinal cord or sacral nerves, degenerative muscle diseases, cerebral palsy, and demyelinating diseases can result in constipation.

Medication-Related Constipation

A complete medication history may reveal substances that can cause constipation (see Table 16.1).

ENCOPRESIS

Idiopathic constipation is much more common than Hirschsprung disease. Long-standing constipation leads to **encopresis**, the deposition of stools in the undergarments or other unorthodox locations that persists or occurs beyond the age that is considered culturally appropriate for achieving continence. In some cultures, delayed bowel training up to the age of 6 years is normal. It is generally accepted in the United States that healthy children should be bowel trained by the age of 4 years.

Encopresis is related to the chronic withholding of stool. As the fecal mass accumulates, it causes rectal distention, increases rectal compliance, and eventually results in blunted or absent sensitivity of the rectum to the presence of liquid stool passing around a firm fecal mass. Children with encopresis usually pass small stools and do not completely empty the rectum. Periodically, they pass huge stools, which may block the toilet. It is important to specifically question the patient or parents regarding these massive stools because this information is frequently not volunteered.

Encopresis has been incorrectly considered a symptom or manifestation of psychiatric illness. It was thought that the patient retained stools either consciously or subconsciously as a way to rebel against, please, or anger caretakers. Although encopresis may be seen in association with emotional and behavioral problems, it is usually the result of painful defecation followed by a pattern of stool withholding, leading to chronic constipation, overflow encopresis, and possibly poor relations with peers as a result of fecal soiling. In the few patients in whom encopresis is truly a manifestation of psychiatric disease, there is often no stool retention, and the prognosis for fecal continence with therapy is poor.

Idiopathic constipation with or without encopresis may compress the bladder by a dilated rectum, thus causing stasis and urinary tract infections.

SUMMARY AND RED FLAGS

Constipation is a common concern in infants and young children. A detailed history of bowel patterns identifies many children with normal bowel movements whose parents need reassurance. The majority of patients who do have constipation have functional constipation. The history should include a review of all medications and a search for an associated chronic disease, such as a metabolic or neurologic disease. This complete history, combined with a careful physical examination, including the spine and sacral area, the location of the anus, and a digital rectal examination, should alert the physician to the need for further evaluation. Red flags include onset in the neonatal period, growth failure, and prolonged jaundice in the neonatal period. Distinguishing features associated with Hirschsprung disease are listed in Table 16.6.

REFERENCES

A bibliography is available at ExpertConsult.com.

(See *Nelson Textbook of Pediatrics,* p. 1807.)

REFERENCES

Baker DD, Liptak GS, Colletti RB, et al. Constipation in infants and children: evaluation and treatment. *J Pediatr Gastroenterol Nutr*. 1999;29:612-626.

Bennett WE Jr, Heuckeroth RO. Hypothyroidism is a rare cause of isolated constipation. *J Pediatr Gastroenterol Nutr*. 2012;54:285-287.

Croffie JM, Davis MM, Faught PR, et al. At what age is a suction rectal biopsy less likely to provide adequate tissue for identification of ganglion cells? *J Pediatr Gastroenterol Nutr*. 2007;44:198-202.

Davari HA, Hosseinpour M. The anal position index: a simple method to define the normal position of the anus in the neonate. *Acta Paediatr*. 2006;95:877.

Di Lorenzo C. Pediatric anorectal disorders. *Gastroenterol Clin North Am*. 2001;30:269.

Drossman DA. Bowel patterns among subjects not seeking health care. *Gastroenterology*. 1982;83:529-534.

Drossman DA. *The functional gastrointestinal disorders and the Rome III process*. 2006;130:1377-1390.

Ghosh A, Griffiths DM. Rectal biopsy in the investigation of constipation. *Arch Dis Child*. 1998;79:266-268.

Gidrewicz D, Potter K, Trevenen CL, et al. Evaluation of the ESPGHAN Celiac Guidelines in North American pediatric population. *Am J Gastroenterol*. 2015;110:760-767.

Granada C, Loveless M, Justice T, et al. Tethered cord syndrome in the pediatric-adolescent gynecologic patient. *J Pediatr Adolesc Gynecol*. 2014; pii S1083-3188. [Epub ahead of print].

Jung PM. Hirschsprung's disease: one surgeon's experience in one institution. *J Pediatr Surg*. 1995;30:646-651.

Khatib M, Baker RD, Ly EK, et al. The presenting pattern of pediatric celiac disease. *J Pediatr Gastroenterol Nutr*. 2015. [Epub ahead of print].

Lapointe SP, Rivet C, Goulet O, et al. Urological manifestations associated with chronic intestinal pseudo-obstructions in children. *J Urol*. 2002;168(4 Pt 2):1768-1770.

Lembo AJ, Ullman SP. Constipation. In: Feldman M, Friedman LS, Sleisenger MH, eds. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease*. Philadelphia: WB Saunders; 2002:181-210.

Loening-Baucke V. Chronic constipation in children. *Gastroenterology*. 1993;105:1557-1564.

Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. *Gastroenterology*. 2006;130:1480-1491.

Lund JN, Scholefield JH. Aetiology and treatment of anal fissure. *Br J Surg*. 1996;83:1335-1344.

Metaj M, Laroia N, Lawrence RA, et al. Comparison of breast- and formula-fed normal newborns in time to first stool and urine. *J Perinatol*. 2003;23:624-628.

Proctor ML, Traubici J, Langer JC, et al. Correlations between radiographic transition zone and level of aganglionosis in Hirschsprung's disease: Implications for surgical approach. *J Pediatr Surg*. 2003;38:775-778.

Tabbers MM, DiLorenzo C, Berger MY, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr*. 2014;58:258.

van den Berg MM, Benninga MA, Di Lorenzo C. Epidemiology of childhood constipation: a systematic review. *Am J Gastroenterol*. 2006;101:2401-2409.

Weaver LT. The bowel habit of young children. *Arch Dis Child*. 1984;59:649-652.

Weaver LT. The bowel habit of milk-fed infants. *J Pediatr Gastroenterol Nutr*. 1988;7:568-571.

17

Abdominal Masses

John C. Densmore and Emily M. Densmore

An abdominal mass or abdominal fullness in a child usually becomes apparent when it enlarges enough to be visualized during bathing or palpable on physical examination. Masses may arise from intraperitoneal, retroperitoneal, or abdominal wall locations and emanate from both solid and hollow viscera (Figs. 17.1 and 17.2). An abdominal mass may prove life threatening (e.g., malignant neoplasm, splenic sequestration crisis in sickle cell disease), arise from congenital malformation or disorganized development (e.g., mesenteric cyst, enteric duplication), or be benign or correctable nonoperatively (fecaloma). Hepatomegaly and splenomegaly often represent systemic illnesses such as infection, hemolysis, storage disease, or malignancy. A child with an abdominal mass requires a prompt and thorough work-up with testing guided by history, physical examination findings, age, and gender. Early surgical referral may assist in this work-up following a directed screening approach.

DIAGNOSTIC STRATEGIES

◆ Clinical History

A child's age, gender, and thorough clinical history help to identify the most likely disease category (Tables 17.1 and 17.2). The duration and character of associated symptoms are important for narrowing the differential diagnosis (e.g., fatigue, fever, appetite changes, vomiting, stooling history, weight loss, night sweating, character and frequency of pain, hematuria, flushing, palpitations, lower extremity swelling, lymph nodal prominence, and jaundice). A history of abdominal trauma should be elicited, as solid organ injuries may result in hematoma, seroma, persistent pseudocyst, or arteriovenous malformation. Infectious disease may have sequelae of cyst, lymphadenopathy, or intraabdominal abscess. Some systemic diseases (e.g., glycogen storage, hereditary spherocytosis), genetic syndromes (e.g., Beckwith-Wiedemann, Peutz-Jeghers, familial adenomatous polyposis), and anomalies (aniridia with Wilms tumor, isolated hemihypertrophy with neuroblastoma and Wilms tumor) are associated with intraabdominal tumors. A family and sexual history are also pertinent, particularly in adolescent females. Modern prenatal imaging frequently identifies congenital malformations and neoplasms, requiring postnatal imaging and surgical assessment.

◆ Physical Examination

A complete physical exam should be performed in children with abdominal masses. Attention should be paid to the general condition of the child and to signs of metastatic disease. Enlarged lymph nodes and their locations should be noted, the skin inspected, and the lungs and heart auscultated. Extremities should be evaluated for evidence of swelling, venous phlegmasia, or evidence of embolic disease. Genitourinary exam should make note of any inappropriate virilization, testicular changes, and hymenal patency in the case of a female with a low pelvic mass. In addition, a neurologic examination may reveal signs of nervous system involvement. The eyes should be carefully inspected for periorbital ecchymosis, proptosis, squint, opsoclonus-myoclonus syndrome, heterochromia of the iris, Horner syndrome, and scleral icterus. The patient's blood pressure must be determined and may be elevated in patients with Wilms tumor, neuroblastoma, or pheochromocytoma.

To successfully perform abdominal palpation in a child, the physician must approach the patient calmly and gently, as the most reliable exams are completed in cooperative and relaxed children. Enlarged organs may be missed in a struggling child who does not lie quietly. When cooperation proves difficult in an infant, the examining hand should be placed and remain static on the abdomen and the exam completed between cries or as the child calms in the parent's arms. Creative play is sometimes necessary, with the use of pacifiers or bottles to distract the child from the exam. Re-examination after voiding or defecating elucidates contributions of constipation and urinary retention in the child's presentation.

The abdominal quadrants should be examined systematically (Table 17.3; Figs. 17.1 and 17.2). With the patient in the supine position, the symmetry of the abdomen should be inspected, and any visible masses or the presence of ascites should be noted. A very enlarged spleen is frequently visible, with fullness of the left side of the abdomen. The presence of tense fluid-filled hernias or prominent periumbilical veins as sequelae of portal hypertension should be noted. The mass should be localized, and its size, shape, texture, mobility, tenderness, and relation to midline noted. The umbilical position is a useful marker of abdominal asymmetry.

Signs of peritoneal inflammation must be sought (see Chapter 10). Dull visceral pain conducted by slow C nerve fibers may be reported for inflammatory processes in the vascular distributions of the celiac, superior mesenteric, and inferior mesenteric arteries and referred to the epigastrium, umbilical region, or hypogastrium, respectively. When the inflamed process contacts the peritoneum, peritoneal fast A nerve fibers allow discrete localization of sharp pain to the abdominal wall. Ultrasound is often a very useful adjunct in the evaluation of an abdominal mass and is often available at the bedside.

Approximately half of abdominal masses in older children are caused by enlargement of the liver or spleen, or both. The liver is normally palpated in the right upper quadrant and epigastrium extending 1-2 cm below the costal margin. The inferior hepatic margin may be palpated in a thin child, is usually nontender, and moves with respiration. Detection of liver edge by auscultation using skin scratches has been proven unreliable and has been supplanted by the use of readily available ultrasound. The spleen is located in the left upper quadrant and is nonpalpable in most healthy children. To locate an enlarged spleen, the examiner must begin palpation in the patient's right iliac fossa (to avoid missing a grossly enlarged spleen or liver with

(See *Nelson Textbook of Pediatrics*, p. 1766.)

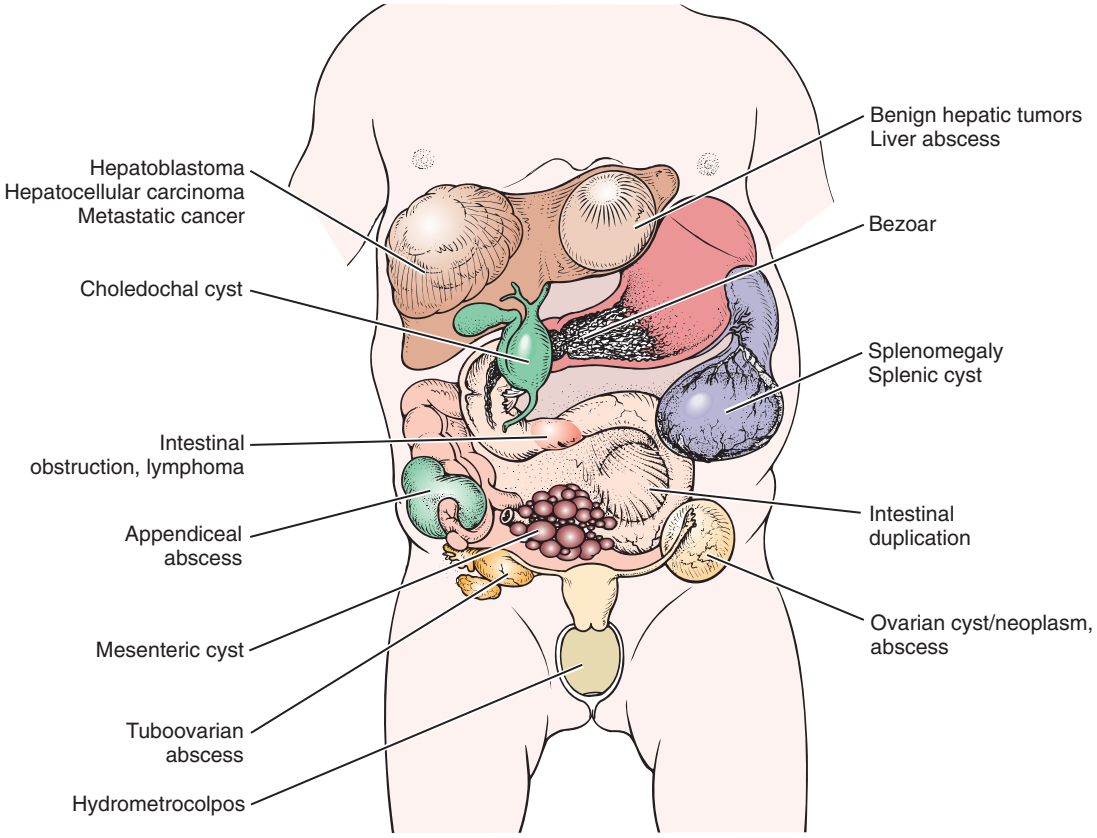


FIGURE 17.1 Location of select intraabdominal tumors and masses.

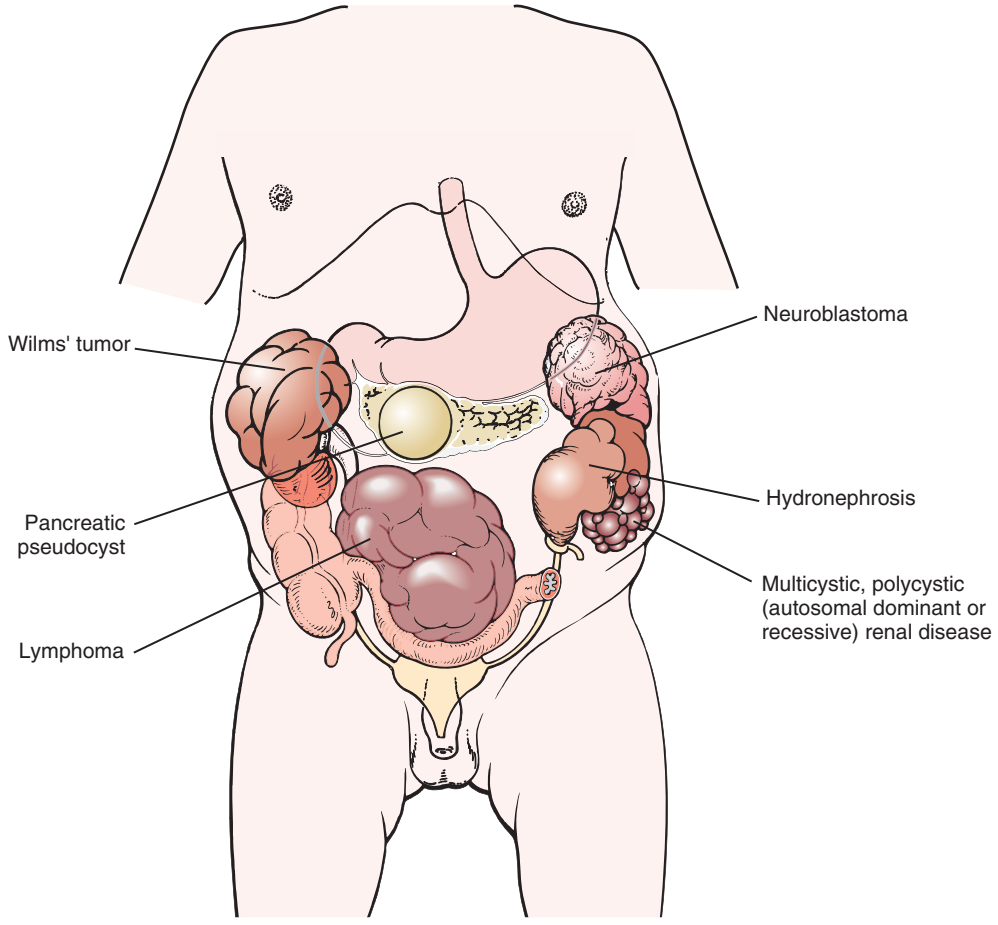


FIGURE 17.2 Location of select retroperitoneal tumors and masses.

TABLE 17.1 Stepwise Evaluation of an Abdominal Mass

Clinical History
Age and gender
General symptoms
Pain
Gastrointestinal symptoms
Urogenital symptoms
Pulmonary symptoms
Family history
Sexual history
Weight loss
Travel

Physical Examination
General condition
Lymph nodes
Associated physical findings
Cachexia

Abdominal Palpation
Quadrant of the abdomen
Organ most likely to be affected
Characteristics (soft or hard, mobile or nonmobile, crosses midline, moves with respiration, tender)

Ultrasonography
Location
Solid or cystic

Depending on the Clinical Suspicion, Evaluation Can Be Continued with One or More of the Following:
Laboratory studies: CBC, urinalysis, tumor markers
Imaging studies: plain radiography of chest and abdomen, contrast radiography of the gastrointestinal tract, computed tomography, magnetic resonance imaging, angiography, scintigraphy

TABLE 17.2 Age-Related Etiology of Abdominal Masses

Age	Benign	Malignant
Neonate (0-1 mo)	Congenital hydronephrosis Cystic kidney disease Intestinal duplication Mesenteric/omental cyst Neurogenic bladder Ovarian cyst Renal vein thrombosis Choledochal cyst Mesoblastic nephroma Meconium ileus Hematoma (adrenal, hepatic, splenic)	Neuroblastoma
Infant (0-1 yr)	Intestinal duplication Mesenteric/omental cyst Ovarian cyst Mesoblastic nephroma Liver hamartomas Hepatic cavernous hemangioma Liver hemangioendothelioma Teratoma Intussusception Hepatosplenomegaly Choledochal cyst Megacolon	Neuroblastoma Hepatoblastoma Wilms tumor (rare) Teratoma
Child	Mesenteric/omental cyst Choledochal cyst Appendiceal abscess	Neuroblastoma (2-10 yr) Hepatoblastoma Wilms tumor Leukemia Lymphoma
Adolescent	Bezoar Hematocolpos Hydrometrocolpos Pregnancy Inflammatory bowel disease Retroperitoneal hematoma (hemophilia)	Neuroblastoma (11-16 yr) Hepatocellular carcinoma Ovarian neoplasm Lymphoma

extension of the left hepatic lobe into the splenic area in the left upper quadrant); the examiner's right hand should move toward the patient's left upper quadrant to find the spleen's lower pole or medial border. The examiner's left hand is placed in the patient's left flank, and gentle displacement of the thoracic cage toward the examiner's right hand often displaces the spleen forward enough to make it appreciable. The spleen has a rounded tip and should move downward with inspiration and is more superficial than a renal mass. It is equally important for the examiner to palpate the spleen as it is for the spleen to "touch" the examiner during its descent with inspiration. Overaggressive palpation may push the spleen away, whereas gentle or light palpation permits the examiner to feel the spleen's edge passively. The characteristic notch in the medial or inferior border may not be palpable when the spleen is enlarged only a few centimeters, but the notch's presence usually clearly distinguishes an enlarged spleen from other abdominal masses on the examination alone. Because the extent to which the spleen extends below the costal margin depends heavily on the patient's position, the extent of the spleen below the costal margin should be measured with the patient in the supine position. Measurement from the left costal margin to the lower pole of the spleen defines the splenic axis. Ordinarily, the long axis of the spleen is along the length of the 10th rib. As it enlarges, it extends medially and downward. Masses in the left upper quadrant, especially left renal masses, may be difficult to distinguish from an enlarged spleen. In general, the presence of the splenic notch helps identify the mass as a spleen, but nodular masses, such as Wilms tumors of the kidney, neuroblastomas, and retroperitoneal teratomas may masquerade as splenomegaly. Many enlarged spleens are not palpable on physical examination because of their relationship to other organs and the thoracic cage. Hyperinflation of lungs (as occurs in asthma, bronchiolitis, ipsilateral pneumothorax) may make a normal-sized liver or spleen palpable.

Flank masses are the next most frequent, particularly in newborn to toddler-aged children. Renal masses extend caudally, are fixed with respiration, and cause abdominal asymmetry. Lower abdominal masses are most commonly caused by constipation or urinary retention. These may be functional or secondary to neurogenic dysfunction. A perforated appendix with resulting abscess formation may create a tender right lower quadrant mass. Ovarian or uterine tumors often grow undetected in the pelvis until large enough to exit the pelvis as a large palpable abdominal mass.

◆ Laboratory and Imaging Studies

Screening laboratory data, including complete blood count with differential and cell morphology, measurements of serum electrolytes, urinalysis, urine pregnancy test when appropriate, and inflammatory markers, are broadly applicable. Liver function tests, serum amylase,

TABLE 17.3 Location and Nature of Abdominal Masses

Organ	Congenital	Benign	Malignant	Acquired
Liver and biliary tract	Hemangioma Choledochal cyst	Hemangioendothelioma Hamartoma	Hepatoblastoma Lymphoma Leukemia Hepatocellular carcinoma	Abscess Hematoma Parasitic disease Hydrops of the gallbladder
Spleen		Cyst	Sarcoma	Splenomegaly (e.g., mononucleosis)
Kidney	Hydronephrosis Cystic disease Duplication		Wilms tumor	Hematoma
Adrenal gland	Neuroblastoma		Neuroblastoma	Hematoma
Stomach	Duplication Teratoma	Leiomyoma Inflammatory pseudotumor	Leiomyosarcoma Adenocarcinoma	Bezoar
Intestines	Duplication Megacolon	Lymphangioma Hemangioma	Carcinoma Lymphoma	Appendiceal abscess Intussusception Obstipation
Mesentery		Mesenteric/omental cyst		Inflammatory bowel disease Parasitic disease Tuberculosis
Pancreas		Cyst	Carcinoma	Pseudocyst
Uterus	Hydrometrocolpos	Myoma	Rhabdomyosarcoma	Pregnancy
Ovaries	Cyst Teratoma	Cyst Cystic teratoma Cystic adenoma Granulosa cell tumor	Yolk sac tumor Embryonal carcinoma Dysgerminoma Choriocarcinoma	Tuboovarian abscess
Bladder	Urachal cyst Posterior urethral valve	Inflammatory pseudotumor	Rhabdomyosarcoma	Urinary retention
Retroperitoneum	Presacral teratoma Anterior myelomeningocele	Ganglioneuroma	Neuroblastoma	Psoas abscess Aortic aneurysm
Abdominal wall	Hernia Omphalocele Gastroschisis	Hemangioma	Rhabdomyosarcoma	Hematoma Rectus sheath hematoma Abscess

tumor marker levels (Table 17.4), and renal function tests are often important initial objective data points.

Plain abdominal radiographs may reveal tumor calcifications, organomegaly, excess fecal load, and mass effect upon intestines. Views in at least 2 different positions should be obtained to appreciate ascites or intestinal obstruction. As a screening modality, ultrasonography is a highly efficient, low-cost, and widely available test. It is noninvasive, nonirradiating, and can give detailed information on the location, vascularity, and nature of the mass and adjacent structures (Fig. 17.3). The most widely used axial imaging technique is computed tomography (CT) (Fig. 17.4), followed by magnetic resonance imaging (MRI). These modalities often provide radiologic diagnosis, are invaluable for surgical planning, and are unhampered by bowel gas, a common limitation of ultrasound. MRI pulse sequences have evolved to discriminate between primary malignant, metastatic, and hamartomatous liver lesions.

TABLE 17.4 Tumor Markers

Tumor	Tumor Markers
Neuroblastoma	Urinary catecholamines LDH Ferritin Neuron-specific enolase
Wilms tumor	Erythropoietin
Hepatoblastoma, pancreatoblastoma, yolk sac tumors	α-Fetoprotein
Germ cell tumors	β-hCG

hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase

SPLENOMEGALY

Unlike many other abdominal masses, splenomegaly is usually secondary to another process; it can be caused by diseases that result in hyperplasia of the lymphoid and reticuloendothelial systems (infections, connective tissue, inflammatory disorders), infiltrative disorders (Gaucher disease, leukemia, lymphoma, histiocytosis, hemophagocytic lymphohistiocytosis), hematologic disorders (thalassemia, hereditary spherocytosis), and conditions that cause distention of the sinusoids whenever there is increased pressure in the portal or splenic veins (portal hypertension) (Table 17.5). In addition, palpable spleens in children and adolescents are not always indicative of disease. A palpable spleen (≤2 cm below the left costal margin) is a normal finding in a child younger than 3 years and may be a normal finding in an older child. Up to 15% of full-term neonates, 10% of children, and 3% of college freshmen have palpable spleens unassociated with an increase in lymphoreticular malignancy and with equivalent health. Painful splenomegaly generally follows stretching of the splenic capsule with rapid enlargement of the spleen. Malfixed spleens may undergo torsion,

(See *Nelson Textbook of Pediatrics*, p. 2408.)

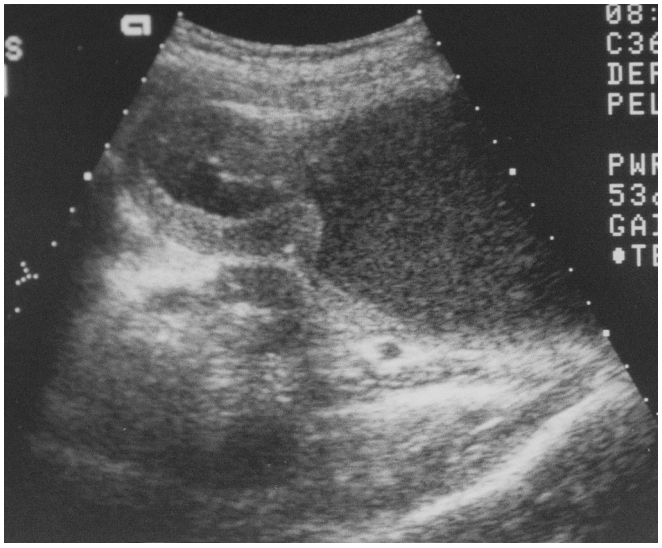


FIGURE 17.3 An ultrasonic longitudinal view of the pelvis reveals hydrometrocolpos. The uterus and cervix are readily seen superior to the large collection of fluid in the vagina located at the right of the image.

FIGURE 17.4 Computed tomogram revealing a large Wilms tumor replacing the right kidney. Notice that the renal cortex, enhanced by contrast medium, is splayed out around the mass. This characteristic helps differentiate Wilms tumor from neuroblastoma, which would displace a normal-appearing kidney.

presenting the upper pole to the abdominal wall as a prominent painful abdominal mass. Splenic enlargement that is noted not in the context of an acute illness (i.e., it is noted incidentally, for instance on a well child examination or check up) is more likely to be caused from a chronic process such as a storage disease than splenomegaly that is noted in the context of an acute illness. Acute onset of splenomegaly is most characteristic of an acute infection or a rapidly progressive malignancy (acute leukemia, lymphoma). **Chronic splenomegaly** (present for ≥1 month) is much more likely to represent a chronic process, such as storage diseases, congestive processes (portal hypertension, congestive heart failure), hemolysis, chronic infection or inflammation.

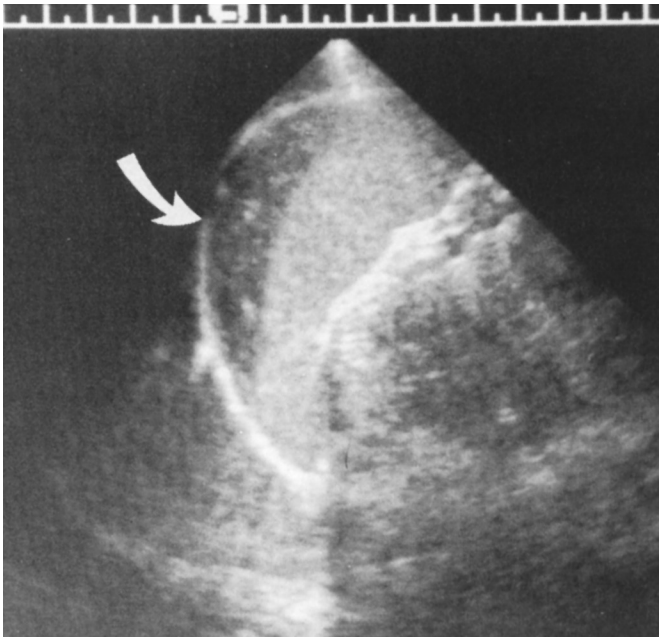


FIGURE 17.5 The subcapsular splenic hematoma *(arrow)* in a 15-year-old boy who had been in an automobile accident was best seen on coronal scans through the left intercostal spaces.

History

Birth and medical history, including transplacentally acquired infections, especially congenital syphilis, are often associated with splenic enlargement. History of a neonatal umbilical venous catheter, perhaps accompanied by occult portal venous injury or thrombosis, may progressively obstruct the extrahepatic portal vein, leading to congestive splenomegaly. Causative previous infections include hepatitis, mononucleosis, and malaria. Liver disease may lead to portal hypertension, which may in turn lead to splenomegaly. Congestive heart failure and associated congenital cardiac malformations have an increased risk of splenic malformation and splenomegaly. Abdominal trauma may acutely produce a splenic hematoma (Fig. 17.5) or may be followed by development of a chronic splenic pseudocyst.

A family history of anemia, transfusions, early biliary stones, cholecystectomy, and splenectomy may indicate hemolytic anemia. Identification of Mediterranean (thalassemia, glucose-6-phosphate dehydrogenase [G6PD] deficiency), African (sickle cell disease, G6PD deficiency), southern Asian (thalassemia, G6PD deficiency), or Ashkenazi Jewish (storage disease) ancestry in patients with splenomegaly is helpful in identifying an inherited process.

Systemic symptoms, such as fever or weight loss, are seen in many disorders that manifest splenomegaly, particularly infections, malignancies, and inflammatory or granulomatous processes, such as hemophagocytic lymphohistiocytosis (HLH) and sarcoidosis. When fever is acute in onset, infection is most likely. Chronic fever, often gradual in onset and not associated with chills, is more likely to be caused by inflammatory processes (systemic lupus erythematosus [SLE], juvenile idiopathic arthritis [JIA], sarcoidosis, Langerhans cell histiocytosis), or tumors (lymphomas, especially Hodgkin disease, or leukemia). Exposure to infectious agents or a travel history that might result in exposure to infectious agents unusual for the patient's community (malaria, leishmaniasis, schistosomiasis, trypanosomiasis for U.S. citizens with a travel history to an endemic country) should be determined. Social and behavioral issues of parents, children, and adolescents heavily affect certain risks and exposures. Sexual encounters and intravenous

TABLE 17.5 Differential Diagnosis of Splenomegaly by Pathophysiology

Anatomic Lesions
Cysts, pseudocysts
Hamartomas
Polysplenia syndrome
Hemangiomas and lymphangiomas
Hematoma or rupture (traumatic)
Peliosis

Hyperplasia Caused by Hematologic Disorders
*Acute and Chronic Hemolysis**
Hemoglobinopathies (sickle cell disease in infancy with or without sequestration crisis and sickle variants, thalassemia major, unstable hemoglobins)
Erythrocyte membrane disorders (hereditary spherocytosis, elliptocytosis, pyropoikilocytosis)
Erythrocyte enzyme deficiencies (severe G6PD deficiency, pyruvate kinase deficiency)
Immune hemolysis (autoimmune and isoimmune hemolysis)
Paroxysmal nocturnal hemoglobinuria

Chronic Iron Deficiency
Extramedullary Hematopoiesis
Myeloproliferative diseases: CML, juvenile CML, myelofibrosis with myeloid metaplasia, polycythemia vera
Osteopetrosis
Patients receiving granulocyte and granulocyte-macrophage colony-stimulating factors

Infections†
Bacterial
Acute sepsis: *Salmonella typhi, Streptococcus pneumoniae, Haemophilus influenzae* type b, *Staphylococcus aureus*
Chronic infections: infective endocarditis, chronic meningococcemia, brucellosis, tularemia, cat-scratch disease
Local infections: splenic abscess (*S. aureus,* streptococci, less often *Salmonella* species, polymicrobial infection), pyogenic liver abscess (anaerobic bacteria, gram-negative enteric bacteria), cholangitis

*Viral**
Acute viral infections, especially in children
Congenital CMV, herpes simplex, rubella
Hepatitides A, B, and C; CMV
EBV
Viral hemophagocytic syndromes: CMV, EBV, HHV-6
HIV

Spirochetal
Syphilis, especially congenital syphilis
Leptospirosis

Rickettsial
Rocky Mountain spotted fever
Q fever
Typhus

Fungal/Mycobacterial
Miliary tuberculosis
Disseminated histoplasmosis
South American blastomycosis
Systemic candidiasis (in immunosuppressed patients)

Parasitic
Malaria
Toxoplasmosis, especially congenital
Toxocara canis, Toxocara cati (visceral larva migrans)
Leishmaniasis (kala-azar)
Schistosomiasis (hepatic-portal involvement)
Trypanosomiasis
Fascioliasis
Babesiosis

Immunologic and Inflammatory Processes*
Systemic lupus erythematosus
Rheumatoid arthritis
Mixed connective tissue disease
Systemic vasculitis
Serum sickness
Drug hypersensitivity, especially to phenytoin
Graft-versus-host disease
Sjögren syndrome
Cryoglobulinemia
Amyloidosis
Sarcoidosis
Autoimmune lymphoproliferative syndrome
Post-transplant lymphoproliferative disease
Large granular lymphocytosis and neutropenia
Histiocytosis syndromes
Hemophagocytic syndromes (nonviral, familial)

Malignancies
Primary: leukemia (acute, chronic), lymphoma, angiosarcoma, Hodgkin disease, mastocytosis
Metastatic

Storage Diseases
Lipidosis (Gaucher disease, Niemann-Pick disease, infantile GM1 gangliosidosis)
Mucopolysaccharidoses (Hurler, Hunter-type)
Mucolipidosis (I-cell disease, sialidosis, multiple sulfatase deficiency, fucosidosis)
Defects in carbohydrate metabolism: galactosemia, fructose intolerance, glycogen storage disease type IV
Sea-blue histiocyte syndrome
Tangier disease
Wolman disease
Hyperchylomicronemia type I, IV

Congestive*
Heart failure
Intrahepatic cirrhosis or fibrosis
Extrahepatic portal (thrombosis), splenic, and hepatic vein obstruction (thrombosis, Budd-Chiari syndrome)

*Common.
†Chronic or recurrent infection suggests underlying immunodeficiency.
CML, chronic myelogenous leukemia; CMV, cytomegalovirus; EBV, Epstein-Barr virus; G6PD, glucose-6-phosphate dehydrogenase; HHV-6, human herpesvirus 6; HIV, human immunodeficiency virus.

and illicit drug exposure may expose patients to hepatitis, cytomegalovirus, and human immunodeficiency virus (HIV). Sexual abuse may place even young children at risk, and it may be difficult to elicit an accurate history.

A review of systems in a patient with splenomegaly should elucidate related conditions. Pallor suggests anemia (hemolysis, bone marrow infiltration, hypersplenism); purpura and petechiae suggest thrombocytopenia (bone marrow failure, autoimmune disorder, hypersplenism, bone marrow infiltration); and jaundice or conjunctival icterus suggest hemolytic anemia, liver dysfunction, or both. Rashes caused by a variety of acute and chronic infections (SLE, JIA, infective endocarditis, HLH) and hemangiomata that are part of a systemic process involving the spleen may provide clues to splenic disease. Dyspnea, cough, orthopnea, and fatigue suggest respiratory disease (Langerhans cell histiocytosis or sarcoidosis), anemia, congestive heart failure, or malignancy (Hodgkin disease). Diarrhea caused by *Salmonella* infection or inflammatory bowel disease may be accompanied by splenic enlargement. Abdominal pain accompanied by splenomegaly may be attributable to acute splenic capsule distention or caused by coincident gallstones, hepatitis, or trauma. Joint pain resulting from SLE, JIA, and other autoimmune inflammatory diseases may be associated with splenomegaly. Bone pain is a feature of bone marrow infiltrative processes, particularly leukemia or neuroblastoma. Poor vision in an infant with splenomegaly suggests osteopetrosis (with deafness) or uveitis-iritis (sarcoidosis, JIA). Loss of developmental milestones occurs with storage diseases. Myasthenia gravis may in rare cases be accompanied by splenomegaly.

◆ Physical Examination

Nutritional status and growth parameters provide clues to disorders that affect the patient's metabolic state and tissue oxygenation. Poor nutrition (as evidenced by such problems as weight loss and failure to thrive) in a child with splenomegaly suggests malignancy, chronic hemolysis, immunodeficiency or chronic infection, a metabolic disorder, or liver disease. Pallor, petechiae, purpura, icterus, hemangiomata, septic emboli to the skin, infiltrative lesions (leukemia cutis, solid tumors), seborrhea, or eczema (as occurs in Langerhans cell histiocytosis and immunodeficiency) should be noted. Cherry-red retinal spots or cloudy corneas suggest storage diseases. Conjunctival pallor, scleral icterus, fundal hemorrhages, evidence of sinus infection or otitis media, condition of gingivae, and evidence of salivary gland enlargement should be noted. The clinician should look for signs of heart failure or new or changing murmurs, which suggest valvular or other structural heart disease or endocarditis. Any distress, rales, rhonchi, or suggestions of pneumonia or asthma should be noted. Abdominal distention, prominent veins on the abdomen, hepatomegaly, fluid wave, tenderness, or rebound should be noted, as should specific characteristics and size of the spleen itself. A hard or nodular spleen suggests malignancy or chronic hemolysis. A tender spleen suggests either acute enlargement or infection, or both. A spleen that is more than 5 cm below the left costal margin is usually not transient and represents significant disease. Arthritis, splinter hemorrhages, and poor bone growth (as occurs in storage diseases and osteopetrosis) should be noted. Size, texture, mobility, tenderness, and distribution of lymph nodes should be noted. Enlarged (>1 cm), firm, fixed lymph nodes are suggestive of lymphoma or leukemia. Tender, enlarged lymph nodes are suggestive of more common infections. Developmental delay suggests chronic infection, immunodeficiency, or storage diseases.

Approach to the Child with Splenomegaly

The most common cause of splenomegaly in childhood is viral infection, which should induce only moderate splenomegaly (<5 cm below the left costal margin) that is transient, lasting less than 4-6 weeks. Other common causes include autoimmune disorders and destruction of abnormal blood cells (such as brisk hemolysis). The approach to the child with splenomegaly is affected by several key factors, each of which indicates the probability of significant disease necessitating diagnosis and intervention (Fig. 17.6*A* and *B*).

◆ Laboratory Investigation

Table 17.6 summarizes key diagnostic laboratory investigations.

Complete Blood Cell Count

A complete blood count is the first test indicated in all patients with undiagnosed splenomegaly. This count provides extensive information about hematologic, infectious, and inflammatory processes, and the result may be abnormal in patients with hypersplenism caused by portal hypertension.

Leukocyte Count and Differential. Elevation or decrease in the number of total white blood cells (WBCs), the neutrophil count, and the lymphocyte count and the presence of abnormal cells (atypical lymphocytes, blasts) should be noted. Viral infection is the most common cause of splenomegaly in children, and atypical lymphocytosis may be a clue. Viral infections may be associated with an increased (early) or decreased WBC count. Most significant bacterial infections produce neutrophilia and reactive changes in the neutrophils. Infections with intracellular bacteria or some viruses may produce neutropenia. Leukemia can manifest with an increased or decreased total WBC count. The presence of blasts is confirmatory, but they are not always present.

Hemoglobin, Erythrocyte Morphology, and Reticulocyte Count. Hemolytic anemia may be unsuspected without examination of the blood smear and the reticulocyte count. Malarial parasites may be seen on the blood smear but may be missed unless a thick preparation is examined. Clues found on the blood smear include spherocytes (present in hereditary spherocytosis and hemolytic anemias); elliptocytes (present in hereditary elliptocytosis); polychromasia, poikilocytes, and fragmented cells (present in hemolytic anemias); sickled cells with target cells, spherocytes, and nucleated red blood cells (present in sickle cell anemia and variants); and microcytosis, hypochromia (present in thalassemias), and Howell-Jolly bodies (present in splenic dysfunction).

Platelet Count. Thrombocytopenia (<150,000 platelets/mm^3) may be caused by decreased platelet production or increased platelet destruction. Production is diminished in conditions characterized by bone marrow infiltration (leukemia, neuroblastoma). Increased destruction accompanies immunologic processes, drug reactions, HLH, and viral infections. Thrombocytosis (>400,000 platelets/mm^3) often accompanies iron deficiency or acute infection as an acute-phase reactant.

Pancytopenia. Pancytopenia implies bone marrow dysfunction, bone marrow infiltration, or portal hypertension with hypersplenic destruction (increased sequestration and lysis by splenic macrophages) of all the formed elements of the blood. A bone marrow aspiration and biopsy should be performed in any child with splenomegaly and pancytopenia. Tests of liver function, including prothrombin time and albumin, are indicated.

Erythrocyte Sedimentation Rate

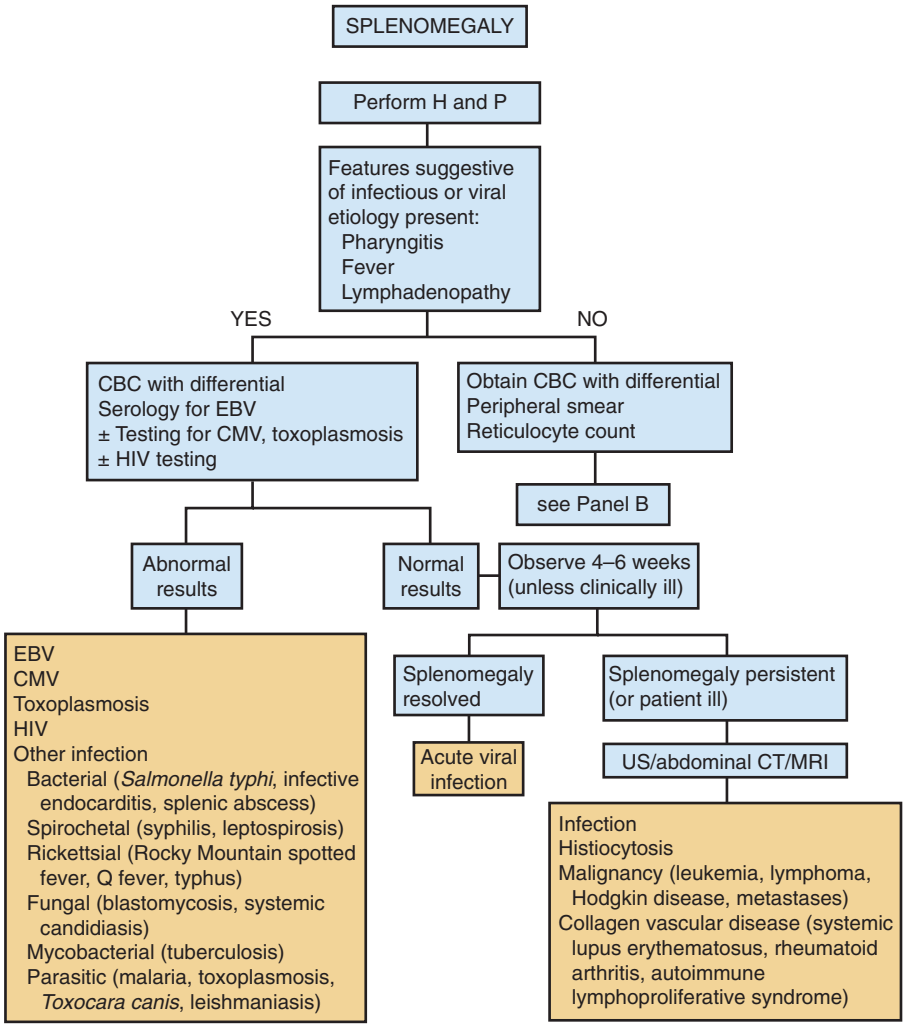
Elevation of erythrocyte sedimentation rate (ESR) is nonspecific but suggests infection, especially bacterial, mycobacterial, or fungal infection, or an inflammatory process, such as JIA, HLH, or SLE. The ESR may be normal despite significant inflammation. The C-reactive protein level may be elevated when the ESR is normal.

(See *Nelson Textbook of Pediatrics*, p. 2409.)

TABLE 17.6 Summary of Laboratory Investigations for Suspected Diagnosis with Splenomegaly

Suspected Diagnosis	Tests to Be Performed
Hemolysis	CBC, reticulocyte count, blood smear, serum bilirubin measurement, Coombs test, osmotic fragility study, RBC enzyme assays, hemoglobin electrophoresis
Infection	CBC, differential, blood cultures, viral studies (EBV, CMV, HIV), toxoplasmosis, TB test, malaria test
Liver disease	Liver function tests, albumin measurement, prothrombin time, α_1-antitrypsin, serum copper, ceruloplasmin
Portal hypertension	Liver function tests; albumin measurement; prothrombin time; ultrasonography/CT of portal veins, liver, and spleen
Immunologic and inflammatory disease	ESR; C3, C4, antinuclear antibody, rheumatoid factor measurements; urinalysis; blood urea nitrogen, serum creatinine, and immunoglobulins measurements
Infiltrative disease	Bone marrow aspiration, CT, enzyme assay for Gaucher disease, tests as indicated for other storage diseases

CBC, complete blood count; CMV, cytomegalovirus; CT, computed tomography; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; RBC, red blood cell; TB, tuberculosis.



A

FIGURE 17.6 *A* and *B,* Approach to the child with splenomegaly. CBC, complete blood count; CMV, cytomegalovirus; CT, computed tomography; EBV, Epstein-Barr virus; G6PD, glucose-6-phosphate dehydrogenase; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; RBC, red blood cell; US, ultrasonography. (From Pomeranz A, Sabnis S, Busey S, et al. *Splenomegaly: Pediatric Decision-Making Strategies*. 2nd ed. Philadelphia: Elsevier; 2016:106-109.)

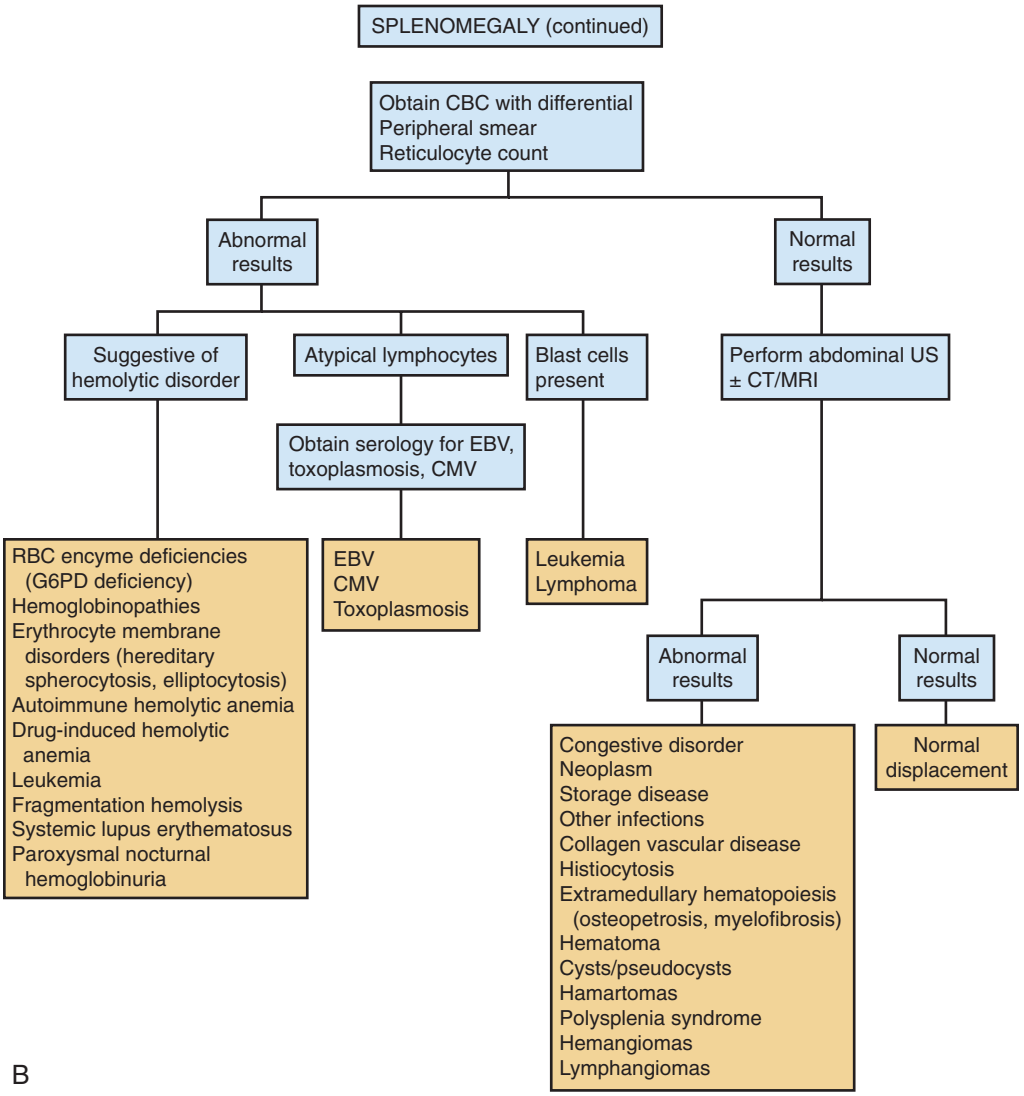


FIGURE 17.6, cont'd

Liver Function Tests

Liver function tests are indicated if splenomegaly is significant (>2 cm) or persists longer than 1 month. Portal hypertension is often asymptomatic until hepatic fibrosis is far advanced. Liver synthetic function (albumin, prothrombin time, fibrinogen), direct bilirubin levels, and transaminase levels should be assessed.

Immunologic Evaluation

Immunologic evaluation is needed when autoimmune disorders (JIA, SLE) or immunodeficiency disorders (inherited or acquired) are suspected. This assessment includes measurements of antinuclear antibody titer, immunoglobulin levels, and immunoglobulin subclass levels; tests of neutrophil function; and measurements of T-cell subclasses. Repeated infections stimulate the immune system and may cause splenomegaly.

Viral Antibody Titers

Viral antibody titers for Epstein Barr virus and cytomegalovirus should be obtained when a mononucleosis syndrome is present, especially when splenomegaly persists. The results of these tests rarely affect management but may permit a presumptive diagnosis of a self-limited process to be made, and they may preclude more invasive tests such as imaging and/or bone marrow examination. Toxoplasmosis should also be considered. Primary infection with HIV frequently causes splenomegaly. Acute infection with HIV may not be noted on screening labs; therefore additional testing may be required.

Cultures

Bacterial, fungal, and other cultures may be necessary and are dictated by the suspected infection.

Bone Marrow Examination

Bone marrow examination is appropriate for diagnosing infiltrative processes (acute leukemia and other malignancies), storage disorders (Gaucher disease, Niemann-Pick disease, sea-blue histiocyte syndrome), HLH, and some infections that may be difficult to diagnose from other tissues (disseminated histoplasmosis, miliary tuberculosis, bacterial endocarditis, and other chronic infections, especially in immunocompromised patients).

◆ Imaging

Imaging of the spleen has several roles but should be performed selectively. It is useful for the confirmation of splenic size, assessment of splenic architecture, and evaluation of other organs involved in the differential diagnosis. It can be useful in determining whether there are other abdominal masses that suggest widespread involvement by tumor, and if there is silent portal hypertension.

The choice of imaging depends on the questions to be asked. Ultrasonography has been the preferred method of imaging as it is used to assess size, perfusion, and to visualize cysts and other lesions. Guidelines are available for the upper limit of normal splenic length (measured as the greatest longitudinal distance between the dome of the spleen and the tip). Dopplerflow ultrasonography can detect portal hypertension.

CT of the spleen can define focal lesions (Fig. 17.7) and nonfocal enlargement, as well as evaluate the splenic and portal veins and the vasculature of the spleen. Less common in children than in adults, splenic cysts and pseudocysts may manifest with palpable spleens (Fig. 17.8). Both CT and ultrasonography identify such cysts well, and they also image the pancreas. Pancreatitis is a common cause of splenic cysts. Subcapsular hematoma can also be visualized by ultrasonography. Splenic lacerations are seen well on CT (Fig. 17.9). Persistent splenomegaly after systemic infections may be caused by splenic abscesses, which are visualized with ultrasonography (Fig. 17.10). CT is an alternative imaging procedure for each of these problems.

FIGURE 17.7 Abdominal computed tomographic scan of a 15-year-old with fever, weight loss, and orthopnea. The diagnosis was Hodgkin disease. The spleen shows hypoechoic lesions, typical of lymphoma.

SPLENECTOMY

Surgery plays an important role in the management of splenomegaly due to congenital hemolytic anemia. Laparoscopic splenectomy procedures have been demonstrated to significantly decrease sequestration events in both hereditary spherocytosis and sickle cell disease. Partial splenectomy outcomes are durable in 5 year followup with only a 4.8% failure rate according to the congenital hemolytic anemia registry. The use of partial splenectomy may be helpful in hereditary spherocytosis where total splenectomy has been associated with pulmonary artery hypertension, thrombosis, and overwhelming postsplenectomy sepsis. Pediatric surgeons initiated nonoperative approaches for the management of splenic lacerations resulting from trauma. The American Association for the Surgery of Trauma grading scales for splenic injury have been employed to prospectively follow outcomes in stable pediatric trauma patients. Patients with grade I-II lacerations are confined to bed for 24 hours, and those with grade III-V lacerations are confined to bed for 48 hours with restriction of activity for grade plus 2 weeks postinjury. Even for the highest grades of injury, the need for splenectomy due to hemorrhage and clinical deterioration is less than 5%.

NEUROBLASTOMA

Neuroblastoma is the most common extracranial solid malignancy in childhood. It accounts for 10% of all childhood tumors and 15% of pediatric cancer deaths. The incidence of neuroblastoma is approximately 10.2 per million U.S. children under age 15 and is more common in boys than in girls (1.2:1). The tumor affects primarily children younger than 8 years, and more than 50% occur in children older than 2 years of age.

It arises from neural crest cells forming primitive sympathetic innervation. Seventy-five percent of the tumors are abdominal, and 65% of these originate in the adrenal medulla or lumbar sympathetic ganglia. The biology of neuroblastoma is exceptionally heterogeneous as mature lesions, particularly in neonates, may regress spontaneously or mature into more benign forms of ganglioneuroblastoma or ganglioma. Unpredictably, other lesions may degenerate despite intensive chemotherapy. As a derivative of sympathetic ganglia, this tumor produces catecholamines (90%) and expresses surface disialoganglioside

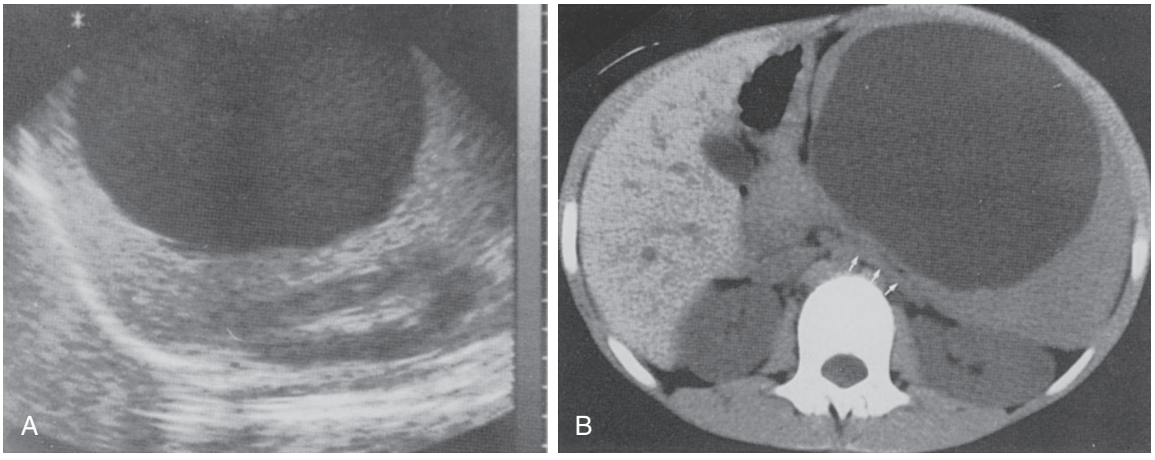


FIGURE 17.8 The large epidermoid cyst of the spleen in a boy, shown on ultrasonography *(A)*, is shown by computed tomographic scan *(B)* to compress the left renal vein *(arrows)*. The boy presented with varicocele.

(See *Nelson Textbook of Pediatrics*, p. 2411.)

(See *Nelson Textbook of Pediatrics*, p. 2461.)

2 (GD2). These features are exploited via MIBG scans and GD2 epitope-directed immunotherapy. Neuroblastomas evade T and NK cells and exploit inflammatory macrophages to enhance survival. MYCN, X-linked alpha thalassemia/mental retardation syndrome (ATRX), anaplastic lymphoma receptor tyrosine kinase (ALK), and paired like homeobox 2b (PHOX2B) mutations have been recognized among neuroblastomas.

Toddlers present with progressive abdominal distention or abdominal discomfort. The mass is retroperitoneal and tends to encase rather than displace other viscera. Catecholamine production by the tumor occasionally results in flushing, sweating, and irritability. Vasoactive intestinal polypeptide, also produced by the tumor, may cause **secretory diarrhea** rarely. A variety of neurologic symptoms (**opsoclonus-myoclonus**) may also be seen, as may weight loss and anorexia. Most patients have metastases at the time of diagnosis, mainly to regional and distant lymph nodes, bone marrow and bone cortex, the orbit, the liver, and occasionally the lungs. Signs and symptoms related to metastases include bone pain, proptosis, and skin lesions.

Diagnostic studies must define relative anatomy and size of the tumor, determine regional invasion, metastatic disease, function, and ultimately histologic features. In 90% of patients, high levels of catecholamines and their detectable metabolites (homovanillic and vanillylmandelic acid) are found in spot urine samples. Twenty-four-hour urine collections show no additional sensitivity. Other serum markers include lactate dehydrogenase, ferritin, and neuron-specific enolase. In 50% of cases, a plain radiograph shows finely stippled tumor calcifications and displacement of gas-filled bowel loops. Ultrasonography confirms its solid nature and position in relation to the kidney. CT or MRI should be completed with arterial and venous phase contrast prior to biopsy or resection (Fig. 17.11). Axial imaging may reveal any intraspinal extension of the tumor or its metastases. Bone marrow metastases are detected by bone marrow aspiration. Technetium 99m (Tc-99m) bone scans can be used to detect cortical bone lesions and are necessary for staging. Metaiodobenzylguanidine (MIBG) scans are utilized to detect remote metastatic disease.

Surgical resection is the primary treatment of localized neuroblastoma. Two exceptions to this rule currently exist—neonates with stage 4S disease (primary lesion, cutaneous, hepatic, and/or bone marrow metastases) and infants under 6 months of age with stage 1 small adrenal tumors (<16 mL). In these cases careful observation may be employed with intervention for disease progression. Adjuvant chemotherapy and radiotherapy are employed postoperatively, depending on

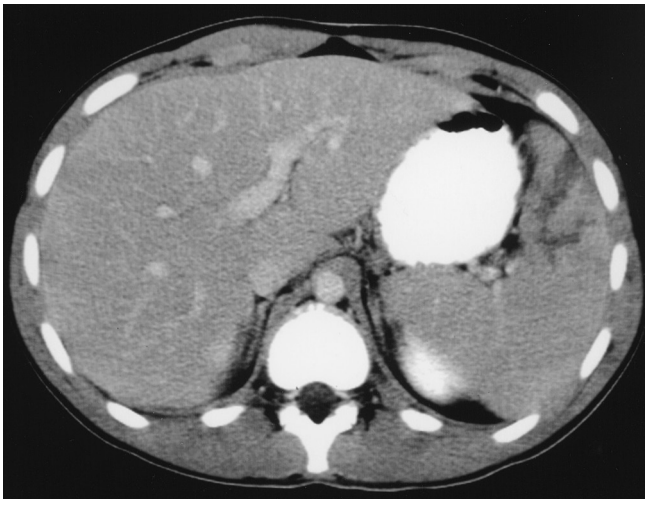


FIGURE 17.9 Splenic laceration that resulted from trauma in a 15-year-old boy.

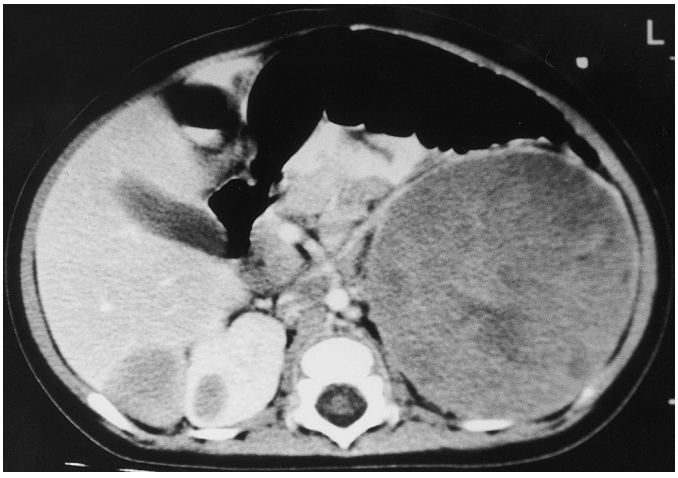


FIGURE 17.11 Computed tomogram of a left adrenal neuroblastoma reveals metastatic disease in the right kidney and liver. The patient, in whom the disease was diagnosed before 1 year of age, died of the disease.

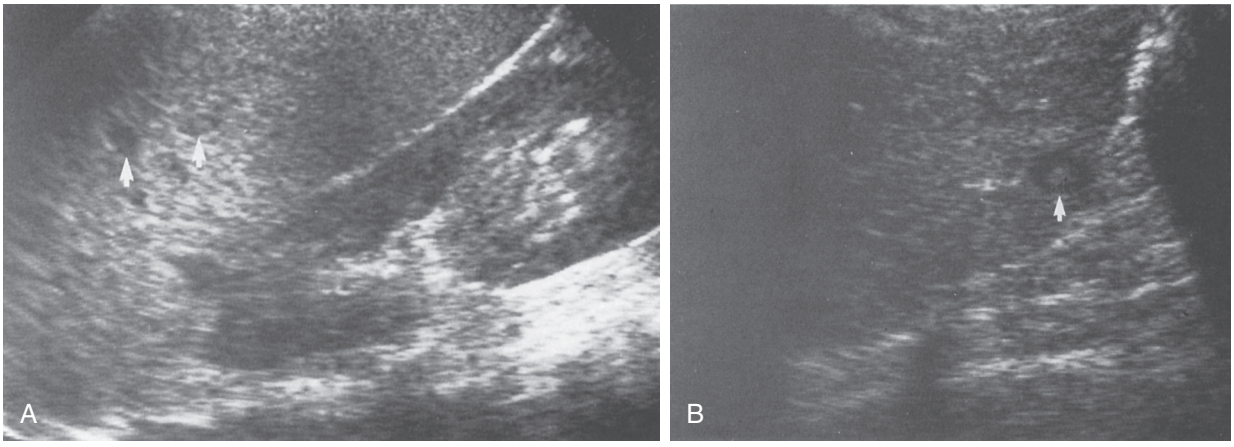


FIGURE 17.10 A 10-year-old girl had been treated for acute myelogenous leukemia. She had taken multiple antibiotics for recurrent infections. Unremitting fevers then developed. Candidiasis was strongly suspected, and ultrasonography was requested. Two weeks after the clinical suspicion of candidiasis was raised, obvious focal defects *(arrows)* could be seen within the spleen *(A)* and liver *(B)*.

the stage of the disease. For initially unresectable tumors, a diagnostic open biopsy or a needle biopsy is performed, preferably retroperitoneally. Bone marrow aspiration findings, necessary for staging, may demonstrate classic small, round blue cells forming rosettes. For large encasing tumors surrounding major vasculature, neoadjuvant chemotherapy may be employed following biopsy and prior to resection. This strategy has been shown to improve resectability, the goal being to achieve greater than 90% tumor volume reduction at resection. In high-risk neuroblastoma, at least 4 cycles of high-dose chemotherapy precede resection, followed by postoperative radiation therapy, autologous stem cell rescue, and continued chemotherapy. The use of differentiating agents, such as retinoic acid, is indicated in high-risk disease. Interleukin 2 (IL-2), granulocyte macrophage colony-stimulating factor (GM-CSF), and anti-GD2 therapy are being used in high-risk protocols as well. Staging is based on the regional extension of the tumor, the level of metastatic disease, and the degree of resection. The outcome of the patient is determined primarily by the child's age, tumor stage, histologic classification, MYCN amplification, and 11q deletions. Hyperploid DNA is associated with a lower stage and better prognosis (contrary to most other tumors). Five year survival for infants is 90% and for older children is 62-68%.

RENAL MASSES

The most common causes of a renal mass in neonates and infants are congenital **hydronephrosis** and congenital **multicystic-dysplastic kidney** (often unilateral). In older infants and toddlers, Wilms tumor (nephroblastoma) emerges as the leading cause. Ultrasonography immediately reveals whether the mass is solid or cystic, thus directing further investigation. An ectopic or horseshoe midline kidney may also be palpable.

Congenital Hydronephrosis

Hydronephrosis secondary to ureteropelvic obstruction due to aberrant renal artery or adhesion may result in a flank mass discovered in the neonatal period or in later childhood. It is more common in boys and on the left side. The most common presenting symptom in infants is an abdominal mass or urinary tract infection. In older children, distention of the renal pelvis may cause intermittent pain, and hematuria may occur following minor abdominal trauma.

The diagnosis is confirmed with ultrasonography. A voiding cystourethrogram excludes ureterovesical reflux and posterior urethral valves (in boys). Diuretic renal scintigraphy is useful to demonstrate degree of obstruction and relative renal function. Treatment consists of pyeloplasty with resection of the obstruction and, if necessary, parts of the distended renal pelvis.

Prenatally diagnosed hydronephrosis can be detected in up to 5% of pregnancies and rarely requires fetal intervention (Fig. 17.12). Postnatally, infants with unilateral neonatal hydronephrosis will spontaneously resolve in over 90% of cases, with higher rates of intervention required in infants with bilateral hydronephrosis, ureteric dilatation >12 mm, and bladder thickening.

Cystic Abnormalities of the Kidney

A unilateral multicystic-dysplastic kidney usually manifests as a flank mass in the newborn. Ultrasonography, MRI, or CT demonstrates a cystic kidney with absence of renal parenchyma and decreased function and readily allow for evaluation of the contralateral kidney. Treatment usually consists of surgical excision, as a dysplastic kidney increases the child's risk for hypertension, urinary tract infection, malignant transformation, and pain. Alternatively, select patients without recurrent infection, hypertension, or severe proteinuria and with small lesions may be managed nonoperatively and followed long-term.

In the more serious case of **autosomal recessive infantile polycystic disease**, both kidneys are affected. The kidneys are filled with thousands of small cysts derived from the collecting tubules. The clinical manifestation varies, depending on the degree of renal failure. Unfortunately, almost 50% of patients experience severe renal insufficiency before the age of 15 years. The neonatal form is fatal without renal transplantation. Abdominal ultrasonography discloses the cystic nature of the condition, and diuretic renal scintigraphy shows

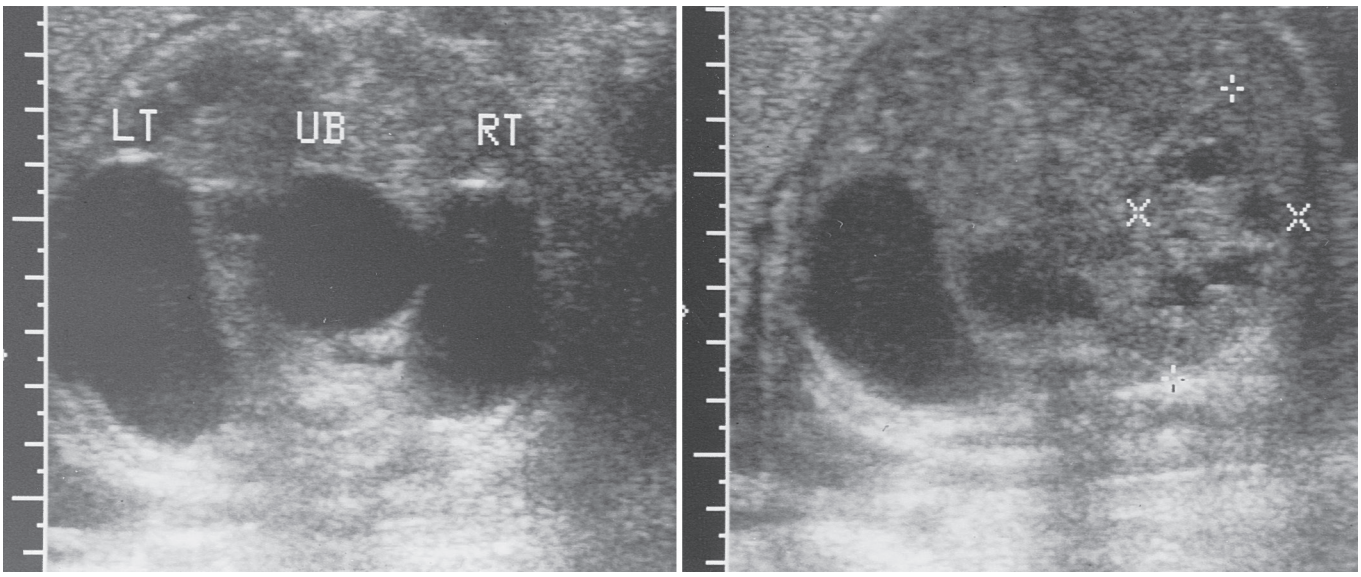


FIGURE 17.12 Fetal ultrasonography showing bilateral hydronephrosis. *A,* The urinary bladder (UB) is seen between the two dilated renal pelvises (LT and RT). *B,* The renal cortex is seen on the right side of the same fetus, between the two Xs.

symmetrically diminished function. Following peritoneal dialysis, renal transplantation is the definitive management.

Wilms Tumor (Nephroblastoma)

Wilms tumor (WT) is an embryonal renal neoplasm, one of the most common childhood abdominal malignancies. The estimated incidence is close to 1 in 15,000 live births, with a male-to-female ratio of 0.9:1. The mean age at diagnosis is 3.5 years, and at least 90% of the patients present before the age of 8 years. Between 4% and 10% of children have bilateral disease with a mean age of 2.5 years. Associated conditions include aniridia, hemihypertrophy, genitourinary anomalies, and Beckwith-Wiedemann syndrome. Wilms tumor arises in precursor lesions called nephrogenic rests, which may be intra- or extralobar and usually spontaneously regress. The tumor suppressor gene *WT1* (11p13) and the transcription factor *WT2* (11p15) are associated with Wilms pathogenesis. Germline mutations in these genes induce Wilms-associated syndromes (Denys-Drash, Wilms tumor–aniridia–genitourinary malformation–mental retardation). Microscopic hematuria is present in about 30% of patients. In rare cases, obstruction of the left renal vein may induce a left-sided varicocele via the gonadal vein. Other less common symptoms or signs include anemia, polycythemia, weight loss, hypertension, or frank hematuria.

In this age group, the most useful imaging modality is a CT scan of the abdomen with arterial and venous phase contrast due to the speed of the study and high resolution afforded for surgical planning (Fig. 17.13). The location, size, resectability of the tumor, presence of local tumor invasion, and infiltration of the renal vein and inferior vena cava are assessed. Metastatic or bilateral disease must be ruled out. Differentiation of Wilms tumor from neuroblastoma on axial imaging is based on whether the renal pelvis is splayed by an intrinsic renal mass or simply displaced by a suprarenal mass. In Wilms tumor, lung metastases from the renal vein and inferior vena cava infiltration may be present, whereas bone metastases are rare; these features distinguish it from neuroblastoma. In some cases, however, the overwhelming size of the tumor may obfuscate radiologic differentiation between Wilms tumor and neuroblastoma. A chest CT scan should be completed.

Treatment includes a transabdominal nephrectomy with early ligation of the renal vein to avoid tumor mobilization. Chemotherapy and radiotherapy are added postoperatively, depending on the stage and histologic features of the tumor. For very large or complex tumors, especially those with extension of the tumor into the renal vein, inferior vena cava, and right atrium, preoperative chemotherapy has been employed in selected patients following tumor biopsy. In cases of bilateral disease, partial resection with nephron-sparing surgery is employed. For children with excessive loss of functional renal parenchyma, transplantation is an option.

Tumor staging is based on radiographic evaluation (metastatic disease) and intraoperative findings (tumor size, extrarenal extension of the tumor, tumor spillage, status of local lymph nodes). The stage determines the prognosis and treatment of the disease. Survival depends on the prognostic factors, cytogenetics, the histologic features of the tumor, and the age of the patient. Younger patients have a better prognosis. Most children have either stage I or stage II disease (regional extension of the tumor but complete surgical removal), and most cases of Wilms tumor have favorable histologic features. Overall, the 5-year survival rate for favorable histology tumors exceeds 90%, with steadily decreasing chemotherapeutic toxicity and radiation exposure. The late complications of therapy for Wilms tumor include the development of acute myelogenous leukemia, short stature, and congestive heart failure.

FIGURE 17.13 An exophytic Wilms tumor noted incidentally on a computed tomogram obtained for trauma.

LIVER TUMORS

Hepatomegaly or a hepatic mass may be caused by infection (hepatitis, abscess, cyst), storage disease, extramedullary hematopoiesis, as well as by benign or malignant lesions. Primary liver tumors are uncommon in children, but when they occur, 66% are malignant. Hepatoblastomas predominate, followed by hepatocellular carcinoma, mesenchymoma, and rarely sarcoma.

Hepatic abscesses are caused by pathogens such as *Staphylococcus aureus*, anaerobic bacteria, or *Escherichia coli*. Chronic granulomatous disease, appendicitis, or immunocompromised state may predispose a child to this complication. Amebic infection of the liver caused by *Entamoeba histolytica* and parasite infestation with *Echinococcus* species may also lead to abscess formation in tropical climates. Abscesses are treated with appropriate antibiotics and percutaneous drainage, only rarely requiring surgical intervention.

Benign tumors can be of either mesenchymal or epithelial origin. Mesenchymal tumors include disorders such as hamartomas, cavernous hemangiomas, and infantile hemangioendotheliomas in young children. These conditions manifest as asymptomatic abdominal masses. Hemangiomas, particularly diffuse ones, may be difficult to resect and should be managed nonoperatively unless complications develop. Hamartomas, which usually manifest in the 1st year of life, should be resected. Epithelial lesions include focal nodular hyperplasia, hepatic adenoma, and nonparasitic solitary or multiple cysts.

The initial radiographic evaluation for liver masses should include plain abdominal radiography to detect calcifications and the mass effect, and ultrasonography to determine the origin, size, and echogenicity of the tumor. In addition, an abdominal CT or MRI scan can be obtained to define the exact localization and extent of the tumor (Fig. 17.14). MRI is more capable of discerning hamartomatous versus malignant lesions than CT scan, especially using EOVIST, a gadolinium agent preferentially taken up by hepatocytes. Angiography is often useful for determining resectability. Chest radiography or CT is used to determine the presence of pulmonary metastases.

Hepatoblastoma

Hepatoblastoma is the most common primary liver tumor in children under 3 years of age affecting 1.5 million/year, and it is twice as common in boys as in girls. Premature birth and very low birthweight are associated with increased risk. The most common presentation is a child with a palpable abdominal mass, occasionally associated with anemia, nausea, vomiting, weight loss, or abdominal pain. An unusual

(See *Nelson Textbook of Pediatrics,* p. 2479.)

FIGURE 17.14 Magnetic resonance image showing a liver hamartoma in a 13-month-old boy. Note the excellent visualization of the blood vessels. The child presented with abdominal distention, poor appetite, and decreased activity. The liver was nontender and was palpated 15 cm below the costal margin. Operative resection was successful.

manifestation is precocious puberty resulting from tumor secretion of human chorionic gonadotropin. Elevated levels of serum α-fetoprotein are seen in about 90% of cases, and this feature is helpful in the post-therapy monitoring of disease activity. Ultrasonography, MRI, or CT (Fig. 17.15) may be used to image the lesion and assign a PRETEXT (PRETreatment EXTent of Disease) stage. Designed by the International Childhood Liver Tumor Strategy Group (SIOPEL), PRETEXT classifies tumors into 4 risk groups based upon the number of contiguous uninvolved liver segments as well as metastatic, portal venous, or systemic venous invasion (Fig. 17.16). The goal is to accurately predict resectable lesions and plan for transplantation when appropriate without the complications associated with attempted resection in all cases, as surgical resection of hepatoblastoma is the mainstay of therapy. Biopsy and neoadjuvant chemotherapy are undertaken in unresectable lesions, and axial imaging is repeated. Hepatic transplantation may be undertaken when lesions remain unresectable in the absence of metastatic disease. Incompletely resected lesions have a poor prognosis. Pretreatment variables associated with survival are the extent of the tumor, histologic classification, and the presence of metastases.

Hepatocellular Carcinoma

Hepatocellular carcinoma, more common in adults, usually occurs in an already diseased liver, such as that found after hepatitis B or C virus infection, tyrosinemia, galactosemia, biliary atresia, or cirrhosis. It is rare in younger children and has a peak incidence between the ages of 10 and 15 years. The tumor manifests as a painful abdominal mass; in more than 65% of patients, it is unresectable. In these cases and in the absence of metastatic disease, liver transplantation should be considered. The diagnostic evaluation, staging, and treatment of hepatocellular carcinoma are similar to those of hepatoblastoma.

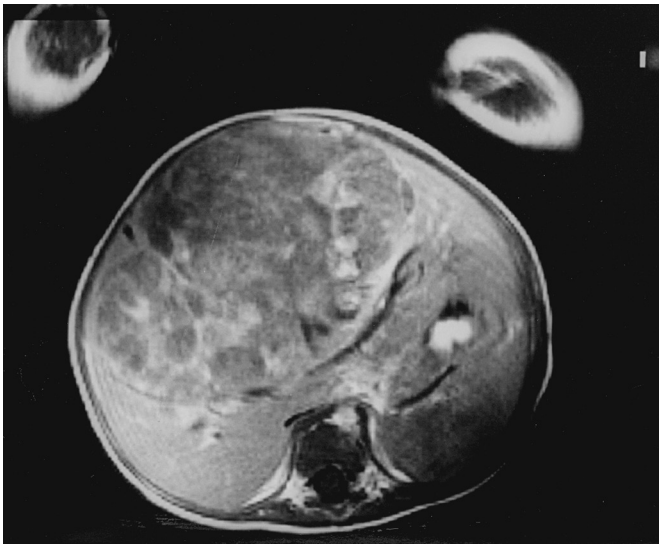


FIGURE 17.15 Computed tomogram of a hepatoblastoma in an 8-month-old girl. The child presented with hepatomegaly, increased abdominal girth, weight loss, and lethargy. The voluminous tumor occupies a large part of the upper abdominal cavity.

CONGENITAL DILATATION OF THE BILE DUCTS

Any congenital cystic dilatation of the bile ducts is commonly called choledochal cyst. There are several anatomic varieties of this condition, and the cause remains unknown. The most common choledochal cyst is seen when the common bile duct is grossly dilated (Todani type I, Fig. 17.17). However, the size varies, and the child may remain asymptomatic for many years. About 20% of patients present with the classic triad of jaundice, pain, and a right upper quadrant abdominal mass. Obstructive jaundice may result from coincident gallstones, manifesting in pruritus, dark urine, and acholic stools.

Ultrasonography reveals the location, size, and nature of the cyst. If there is any doubt about its origin, magnetic resonance cholangiopancreatography (MRCP) or liver-phase CT scan (Fig. 17.18) may be used to outline the biliary tract and help differentiate it from other lesions such as duodenal duplication. Treatment consists of resection of the cyst and drainage of the hepatic duct into an intestinal segment (Fig. 17.19). Incomplete resection of at least the mucosa of the affected portion of the biliary tree predisposes the patient to the development of cholangiocarcinoma, which is a 20-30% lifetime risk in this population.

INTESTINAL AND PANCREATIC MASSES

Appendiceal Phlegmon and Abscess

Either delayed manifestation (walled off by mesentery) or delayed diagnosis of acute appendicitis may enable the development of a right lower quadrant mass after perforation as the inflamed tissues amalgamate into a phlegmon. Further maturation of this process may lead to an abscess. Diagnosis is often facilitated by the history, which can differentiate from many other causes of abdominal mass by the recent (days to weeks) history of fever associated with abdominal pain and nausea. Antibiotic therapy may mask the diagnosis of appendicitis. CT

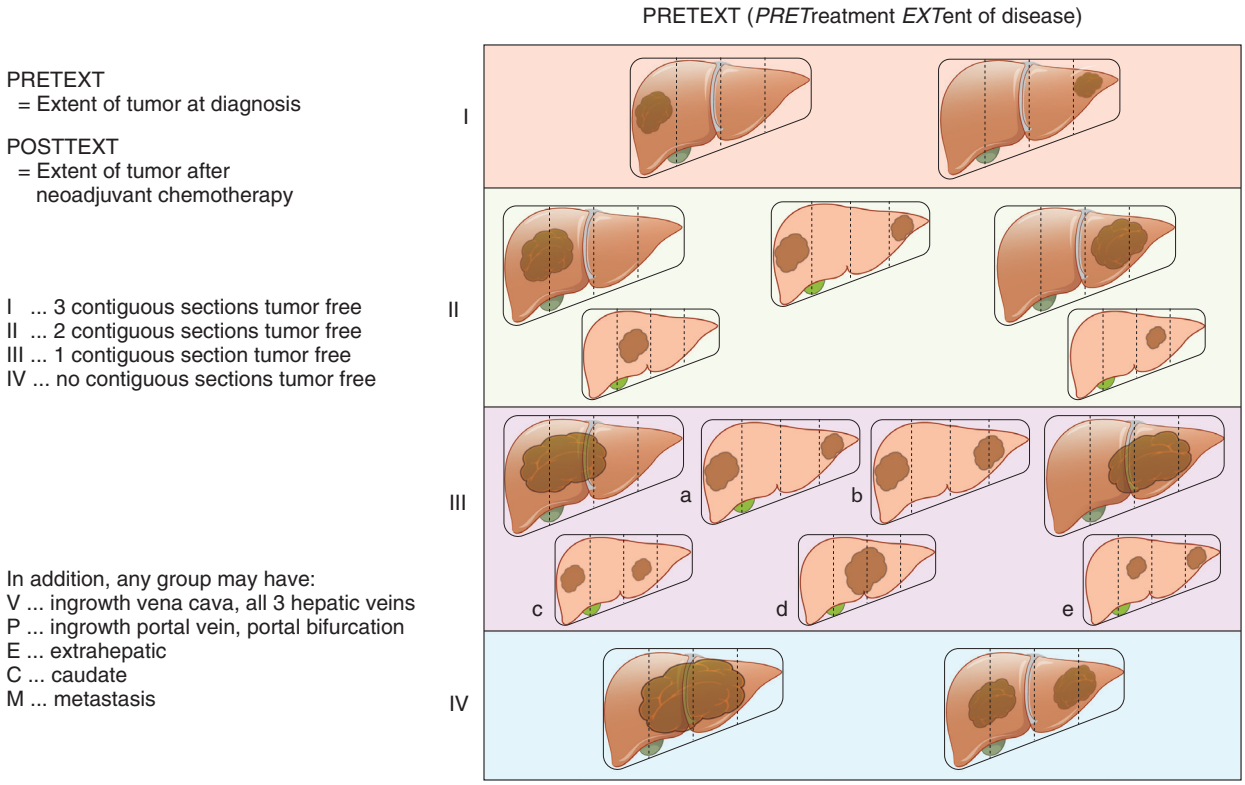


FIGURE 17.16 PRETEXT classification of hepatic tumors. Staging considers number of uninvolved contiguous liver segments. (From Meyers R, Aronson D, Zimmermann A. Malignant liver tumors. In: Coran A, ed. *Pediatric Surgery*. 7th ed. Philadelphia: Saunders; 2012:463-482.)

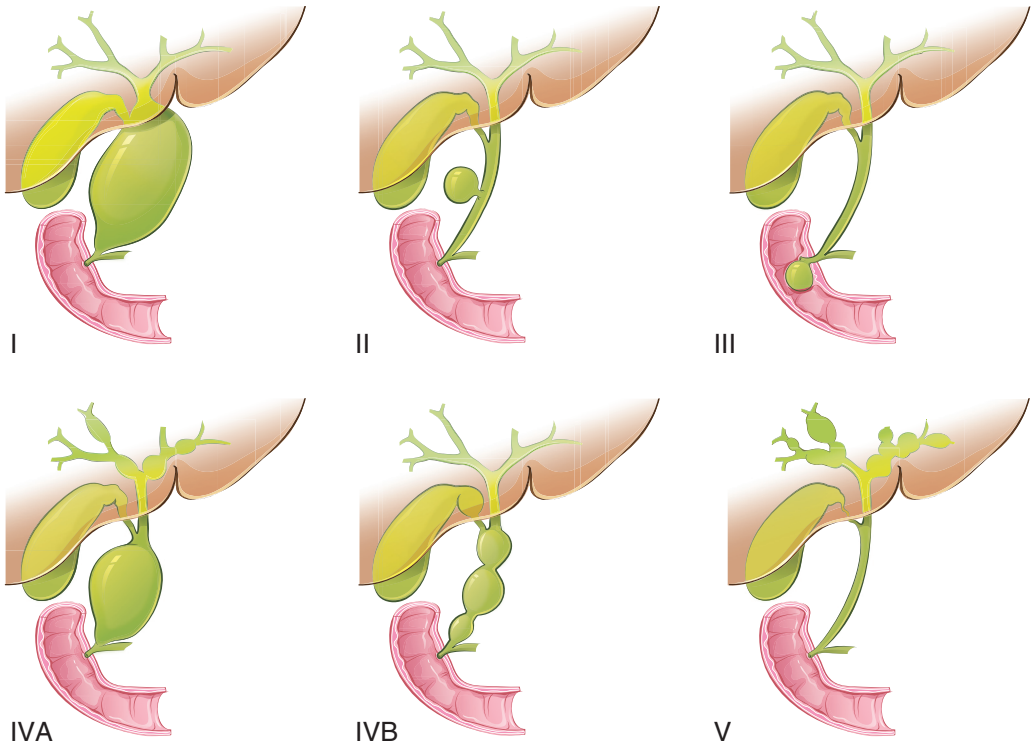


FIGURE 17.17 Todani classification of choledochal cysts. (From Michaelis S, Kalache K. Biliary anomalies. In: Copel J, ed. *Obstetric Imaging*.1st ed. Philadelphia: Saunders; 2012:114-120; redrawn from Callen PW. *Ultrasonography in Obstetrics and Gynaecology*. 5th ed. Philadelphia: Saunders; 2008.)

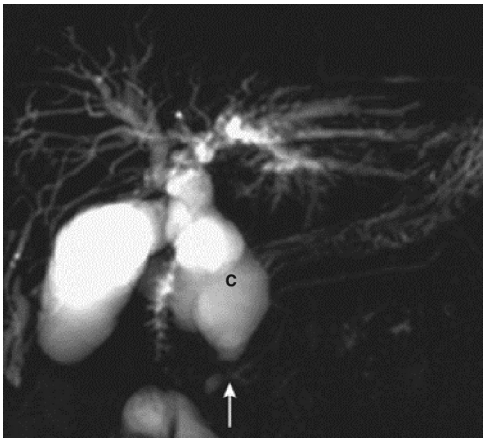


FIGURE 17.18 Manetic resonance cholangiopancreatography demonstrating a pediatric Todani type I choledochal cyst *(C)* and common bile duct–pancreatic duct junction *(arrow)*. (From Lim J, Kim K, Choi D. Biliary tract and gallbladder. In: Haaga J, Dogra V, Forsting M, et al., eds. *CT and MRI of the Whole Body*. 5th ed. Philadelphia: Mosby; 2009:1373-1453.)

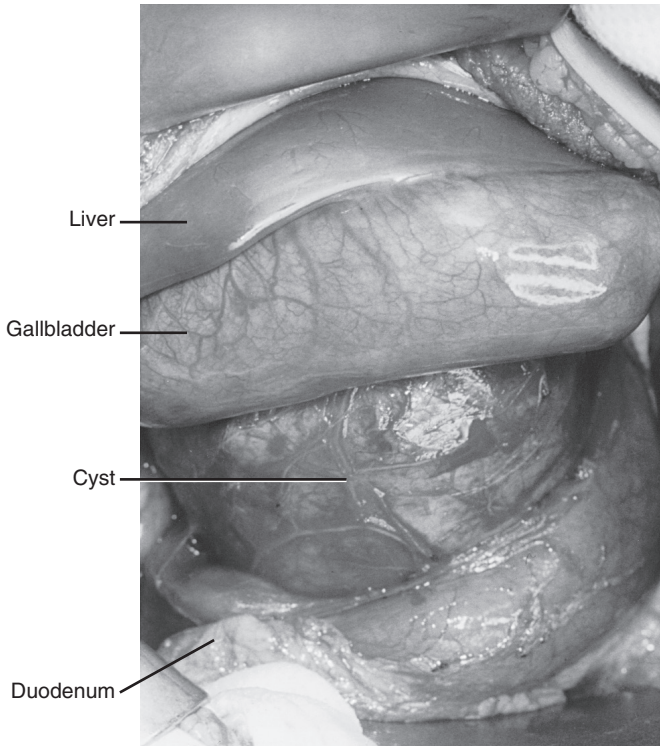


FIGURE 17.19 Operative photograph of a choledochal cyst between the gallbladder and the duodenum, displacing both.

scan is warranted in this circumstance because of the desirability of treating an abscess by percutaneous aspiration and antibiotics (Fig. 17.20). Interval appendectomy in an uninflamed field may be performed safely 6-8 weeks later. This approach is not appropriate for either suspected uncomplicated acute appendicitis or for diffuse peritonitis.

Bezoar

Children with mental illness or developmental delay occasionally eat their own hair (trichotillomania) or other indigestible material (e.g., persimmon peel). Ninety percent of these patients are girls, usually in their teens. A **trichobezoar** (hair) or a **phytobezoar** (vegetable matter) forms in the stomach and causes partial gastric outlet obstruction. Gastric bezoars may massively distend the stomach and extend into the small intestine. If hair manages to pass the stomach, it collects in the duodenum and causes biliary tract obstruction; if it collects in the ileum, it may lead to intestinal obstruction.

The clinical picture is characterized by poor appetite, vague abdominal discomfort, and intolerance to solid foods. Physical examination reveals loss of hair on the scalp and a movable mass in the epigastrium. Abdominal radiographs will show gastric outlet or intestinal obstruction. Axial imaging subsequently demonstrates the size and location. The bezoar may be removed endoscopically, but operative removal is often required. Bacterial counts within a bezoar are high, and operative removal is associated with a high rate of postoperative infection.

FIGURE 17.20 A large appendiceal abscess with a calcified fecalith. The abscess was drained percutaneously and treated with antibiotics. Interval appendectomy was performed 8 weeks later.

Duplications

Duplications of the gastrointestinal tract occur anywhere from the esophagus to the anus and are either cystic or tubular. The more common cystic duplications are lined with endothelium and are enclosed in a muscular wall common with the adjacent intestinal segment. Tubular duplications are located on the mesenteric side of the bowel and are either blind or in communication with the bowel. The lining is usually that of the adjacent intestine but may be heterotopic, such as gastric mucosa in a duplication of the small bowel.

Duplications are often detected prenatally. When discovered, they should be resected after birth as volvulus has been seen as early as 2 postnatal weeks. In older children, the manifestations depend on the size and location of the malformation. Many intra-abdominal duplications manifest as an asymptomatic, palpable mass but may also cause pain, intestinal obstruction, hemorrhage, or volvulus. Ultrasonography differentiates the cystic nature of duplications from solid tumors and also demonstrates the intimate association between the duplication and the bowel wall. Treatment consists of resection of the duplication alone or, more commonly, along with the part of the gut from which the duplication arose, depending on the anatomic location and amount of shared wall and blood supply (Fig. 17.21).

Neoplasms of the Gastrointestinal Tract

Neoplasms of the gastrointestinal tract of children are rare. The symptoms are often nonspecific, and diagnosis tends to be delayed.

FIGURE 17.21 Operative photograph of the typical appearance of an intestinal duplication.

FIGURE 17.22 Computed tomographic scan of the abdomen in an 11-year-old boy, showing a mesenteric cyst in the transverse mesocolon.

A gastric teratoma may appear as an epigastric mass, while gastric leiomyosarcomas or leiomyomas manifest with bleeding. Non-Hodgkin lymphoma is the most common malignant tumor of the small intestine and may act as a lead point for **intussusception**. Other malignant tumors of the small intestine include leiomyosarcoma, angiosarcoma, and carcinoid tumor. These conditions also occur in the large intestine. Carcinoid tumors are most commonly found in the appendix, where they can cause obstruction and lead to appendicitis. The colon is the most common site for the rare adenocarcinoma of the gastrointestinal tract in children. Colon adenocarcinoma in children is usually nonsyndromic, mucinous in nature (80%), and often at an advanced stage upon discovery. Benign neoplasms of the small and large intestine include hemangiomas, lymphangiomas, leiomyomas, and polyps. Malignant neoplasms and most benign neoplasms should be resected.

Mesenteric, Omental, and Retroperitoneal Cysts

Benign cysts located in the omentum or mesentery can be simple or multilocular, and contain clear serous fluid. They arise from a developmental abnormality of the lymphatic system that results in lymphatic obstruction. Most of these cysts are diagnosed during the 1st 5 years of life. They may be asymptomatic for years or manifest with a distended abdomen, abdominal mass, intestinal obstruction, volvulus, or abdominal pain. The abdomen is usually nontender with a mobile mass. In contrast to ascites, the flanks do not bulge when a child with an abdominal cyst is in the supine position.

A plain abdominal radiograph shows intestinal gas displaced forward in the case of a mesenteric cyst and backward in the case of an omental cyst. Small amounts of calcification may be seen in the wall of the cyst. Ultrasonography, MRI, or CT further elucidates the nature, size, and location of the cyst (Fig. 17.22). An ovarian, pancreatic, or choledochal cyst or an intestinal duplication may be difficult to differentiate from a mesenteric or omental cyst. Cerebrospinal fluid from a **ventriculoperitoneal shunt** or lumbar drain fails to be resorbed because of scarring of the peritoneum, leading to a "CSFoma" (Fig. 17.23), which also may be mistaken for a mesenteric or omental cyst. Treatment of these lesions consists of surgical marsupialization or extirpation, occasionally requiring segmental small bowel resection. Retroperitoneal lymphatic malformations are amenable to percutaneous sclerotherapy with good results.

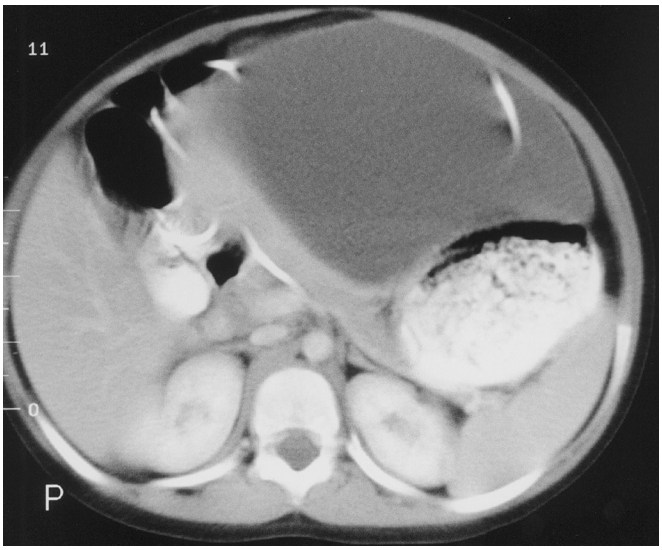


FIGURE 17.23 A large fluid collection associated with a ventriculoperitoneal shunt ("CSFoma").

Pancreatic Pseudocyst and Neoplasms

Pancreatic tumors are rare in children and are cystic or solid, benign or malignant. Young children and infants may have pancreaticoblastoma. Functional neoplasms arise from the islet cells, and the clinical manifestation is not of an abdominal mass but rather is characterized by the effects of the endocrine substances secreted by the tumor (e.g., hypoglycemia caused by insulinoma). Tumors arising from the acinar or ductal parts of the pancreas are nonfunctional and usually manifest as an abdominal mass. They may be benign (cystadenoma) or malignant (adenocarcinoma). Embryonic pluripotent cells may give rise to solid pseudopapillary tumors, accounting for less than 5% of all pediatric pancreatic masses. Metastases are common in pancreatic neoplasms given the frequent delay in diagnosis. Diagnosis is aided by ultrasonography, endoscopy, CT or MRI and, in cases of suspected endocrine tumors, by measurements of active hormones. Both benign and malignant tumors should be surgically resected. A 35 year review

FIGURE 17.24 Torsion of an ovarian teratoma in a 5-year-old girl. The child presented with acute abdominal pain and a movable mass. A preoperative radiograph showed calcified material in the mass.

TABLE 17.7 Red Flags

1. Lower Abdominal Mass in Girls
May be an indication of pregnancy, imperforate hymen, torsion of ovarian tumor, tuboovarian abscess

2. Appendiceal Abscess
Can often appear as a small bowel obstruction in younger children, in whom the diagnosis is often missed

3. Nonmobile Mass
Is suggestive of malignancy

4. Skeletal Pain or Pathologic Fracture
Is suggestive of metastatic disease (neuroblastoma) or lymphoma

5. Sudden Increase in Size of Clothing
May represent a mass or ascites

6. Left-Sided Varicocele
May be a consequence of a left-sided Wilms tumor

7. Systemic Signs of Weight Loss, Fever, Night Sweats, Anorexia, Petechiae, Anemia
Should trigger concern for malignancy, inflammatory bowel disease, or atypical infections

of malignant non-MEN pancreatic tumors in children at one center revealed only 17 cases. Eighty percent of patients were alive at follow-up, significantly better than adult counterpart data.

A pancreatic pseudocyst lacks epithelial lining and is the result of pancreatitis or pancreatic blunt trauma. Often, there is a symptom-free interval of several weeks or months between the trauma and the appearance of symptoms. The cause of pancreatic pseudocyst in the absence of trauma should prompt investigation of causes of recurrent pancreatitis including pancreas divisum and mutations in *PRSS1* and *SPINK1* genes, allowing inappropriate release of pancreatic trypsin. Typical signs and symptoms are nausea, abdominal pain, and an epigastric mass. Ultrasonography and axial imaging locate the cyst and identify any displacement of the bowel. The cysts usually resolve spontaneously; however, if they do not, they should be drained percutaneously or into the gastrointestinal tract.

OVARIAN TUMORS

Ovarian tumors in children are uncommon, with an incidence of about 25 in 100,000 children's hospital admissions. They must be considered in any girl with lower abdominal pain, an abdominal mass, or precocious puberty. They manifest at any age from birth to adulthood but occur slightly more frequently in children at an average of 13 years of age. The risk of malignancy increases with age. Cystic tumors are more common than solid tumors, and the majority of masses are benign. An ovarian lesion may also be the presenting manifestation of other metastatic diseases, such as neuroblastoma or rhabdomyosarcoma. Malignant gonadal tumors (dysgerminoma, gonadoblastoma) may be seen in girls with gonadal dysgenesis and boys with cryptorchidism. Other causes of lower abdominal mass in a girl include pregnancy and imperforate hymen, which leads to hydrocolpos or hydrometrocolpos.

Diagnosis is made by ultrasonography, which provides information on the size, consistency, location, perfusion, and wall characteristics of the tumor. Abdominal radiography may reveal calcifications. CT can locate local or distant metastases. Endocrinopathies are present in 5-10% of children with ovarian tumors, so consideration of the anterior pituitary–adrenal–gonadal axis is warranted. Levels of tumor markers, such as α-fetoprotein, β-human chorionic gonadotropin (β-hCG), CA-125, and inhibin A should be considered, especially in older children with masses >8 cm, inappropriate virilization, or other concerns for operative findings consistent with epithelial cancer.

A simple cyst may appear in a neonate as a mobile abdominal mass or may even be detected incidentally by ultrasonography. Small cysts (generally <6 cm) can be monitored with ultrasonography and should spontaneously disappear. Larger cysts should be excised, because they can undergo torsion. The symptoms of ovarian torsion in an older child simulate those of appendicitis or ectopic pregnancy (Fig. 17.24).

All other tumors of the ovaries should be excised, whether benign (cystic teratoma, cystic adenoma, granulosa cell tumor) or malignant (endodermal sinus tumor, yolk sac tumor, embryonal carcinoma, malignant teratoma, adenocarcinoma, dysgerminoma, choriocarcinoma). Great care should be taken to spare as much of the adnexa as possible to preserve future fertility. Depending on the histologic appearance and stage, most malignant lesions should be treated postoperatively with chemotherapy. Survival depends on the nature of the lesion; however, with the exception of highly malignant tumors such as endodermal sinus tumors and embryonal carcinoma, the prognosis is good.

SUMMARY AND RED FLAGS

Although the discovery of an abdominal mass in a child is of great concern, the prognoses of most congenital masses are excellent. Splenomegaly is often a manifestation of acute and benign common viral infections in children. Red flags for splenomegaly include chronicity, a positive family or travel history, pancytopenia, and signs of disease in addition to splenomegaly (weight loss, pallor, jaundice, fever, malaise, petechiae). Additional red flags for abdominal masses are listed in Table 17.7. With modern diagnostic techniques and advanced multimodal therapy, the prognoses for malignant tumors continue to improve.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Diagnostic Strategies

Cope Z. The prevention and early diagnosis of the acute abdomen. *Br Med J*. 1929;1:6-9.

Splenomegaly

Atichartakarn V, Chuncharunee S, Yamwong S, et al. Pulmonary artery pressure correlates directly with spleen volume in non-splenectomized hemoglobin E/beta-thalassemia patients. *Acta Haematol*. 2013;130(3):172-175.

Brandow AM, Camitta BM. Splenomegaly. In: Kliegman RM, ed. *Nelson Textbook of Pediatrics*. 20th ed. Elsevier; 2016:2408-2410.

Buesing KL, Tracy ET, Kiernan C, et al. Partial splenectomy for hereditary spherocytosis: a multi-institutional review. *J Pediatr Surg*. 2011;46(1):178-183.

Das A, Bansal D, Ahluwalia J, et al. Risk factors for thromboembolism and pulmonary artery hypertension following splenectomy in children with hereditary spherocytosis. *Pediatr Blood Cancer*. 2014;61(1):29-33.

Dervan LA, King MA, Cuschieri J, et al. Pediatric solid organ injury operative interventions and outcomes at Harborview Medical Center, before and after introduction of a solid organ injury pathway for pediatrics. *J Trauma Acute Care Surg*. 2015;79(2):215-220.

Di Rocco M, Andria G, Deodato F, et al. Early diagnosis of Gaucher disease in pediatric patients: proposal for a diagnostic algorithm. *Pediatr Blood Cancer*. 2014;61(11):1905-1909.

Ebaugh FG Jr, McIntyre OR. Palpable spleen. A ten year follow-up. *Ann Intern Med*. 1979;90:130-131.

Emond AM, Collis R, Darville D, et al. Acute splenic sequestration in homozygous sickle cell disease: Natural history and management. *J Pediatr*. 1985;107:201-206.

Hilmes MA, Strouse PJ. The pediatric spleen. *Semin Ultrasound CT MR*. 2007;28(1):3-11.

Klopfenstein KJ, Grossman NJ, Fishbein M, et al. Cavernous transformation of the portal vein: A cause of thrombocytopenia and splenomegaly. *Clin Pediatr*. 2000;39:727-730.

McIntyre OR, Ebaugh FG Jr. Palpable spleens in college freshmen. *Arch Intern Med*. 1967;66:301-306.

Megremis SD, Vlachonikolis IG, Tsilimigaki AM. Spleen length in childhood with US: normal values based on age, sex, and somatometric parameters. *Radiology*. 2004;231(1):129-134.

Motyckova G, Steensma DP. Why does my patient have lymphadenopathy or splenomegaly? *Hematol Oncol Clin North Am*. 2012;26(2):395-408, ix.

Munolini F, Merlob J, Ashkenazi S, et al. Palpable spleens in newborn term infants. *Clin Pediatr*. 1985;24:197-198.

Murphy EE, Murphy SG, Cipolle MD, et al. The pediatric trauma center and the inclusive trauma system: Impact on splenectomy rates. *J Trauma Acute Care Surg*. 2015;78(5):930-933, discussion 933-934.

Pomeranz A, Sabnis S, Busey S, et al. *Splenomegaly. Pediatric Decision-Making Strategies*. 2nd ed. Philadelphia: Saunders; 2016:106-109.

Pozo AL, Godfrey EM, Bowles KM. Splenomegaly: investigation, diagnosis and management. *Blood Rev*. 2009;23(3):105-111.

Rice HE, Englum BR, Rothman J, et al. Splenectomy in Congenital Hemolytic Anemia Consortium. Clinical outcomes of splenectomy in children: Report of the Splenectomy in Congenital Hemolytic Anemia Registry. *Am J Hematol*. 2015;90(3):187-192.

Tamato SG, Rickman LS, Mathews WC, et al. Examiner dependence on physical diagnostic tests for the detection of splenomegaly: A prospective study with multiple observers. *J Gen Intern Med*. 1993;8:69-75.

Neuroblastoma

Cheung NK, Dyer MA. Neuroblastoma: developmental biology, cancer genomics and immunotherapy. *Nat Rev Cancer*. 2013;13:397-411.

Kushner BH, Modak S, Kramer K, et al. Striking dichotomy in outcome of MYCN-amplified neuroblastoma in the contemporary era. *Cancer*. 2014;120:2050-2059.

Nuchtern JG, London WB, Barnewolt CE, et al. A prospective study of expectant observation as primary therapy for neuroblastoma in young infants: a Children's Oncology Group study. *Ann Surg*. 2012;256:573-580.

Renal Masses

Babu R, Sai V. Postnatal outcome of fetal hydronephrosis: implications for prenatal counselling. *Indian J Urol*. 2010;26:60-62.

Farmer DL. Urinary tract masses. *Semin Pediatr Surg*. 2000;9:109-114.

Liu DB, Armstrong WR, Maizels M. Hydronephrosis: prenatal and postnatal evaluation and management. *Clin Perinatol*. 2014;41:661-678.

Psooy K. Multicystic dysplastic kidney in the neonate: the role of the urologist. *Can Urol Assoc J*. 2010;4:95-97.

Ulman I, Jayanthi VR, Koff SA. The long-term follow-up of newborns with severe unilateral hydronephrosis initially treated nonoperatively. *J Urol*. 2000;3:1101-1105.

Wilms Tumor

Davidoff AM. Wilms tumor. *Adv Pediatr*. 2012;59:247-267.

Gadd S, Huff V, Huang CC, et al. Clinically relevant subsets identified by gene expression patterns support a revised oncogenic model of Wilms tumor: a Children's Oncology Group Study. *Neoplasia*. 2012;14:742-756.

Grundy PE, Green DM, Dirks AC, et al. Clinical significance of pulmonary nodules detected by CT and not CXR in patients treated for favorable histology Wilms tumor on National Wilms Tumor Studies-4 and -5: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2012;59:631-635.

Kieran K, Anderson JR, Dome JS, et al. Lymph node involvement in Wilms tumor: results from National Wilms Tumor Studies 4 and 5. *J Pediatr Surg*. 2012;47:700-706.

Liver Tumors

Chiorean L, Cui XW, Tannapfel A, et al. Benign liver tumors in pediatric patients - Review with emphasis on imaging features. *World J Gastroenterol*. 2015;21:8541-8561.

Czauderna P, Lopez-Terrada D, Hiyama E, et al. Hepatoblastoma state of the art: pathology, genetics, risk stratification, and chemotherapy. *Curr Opin Pediatr*. 2014;26:19-28.

Humphries PD, Sebire NJ, Siegel MJ, et al. Tumors in pediatric patients at diffusion-weighted MR imaging: apparent diffusion coefficient and tumor cellularity. *Radiology*. 2007;245:848-854.

Malogolowkin MH, Katzenstein HM, Meyers RL, et al. Complete surgical resection is curative for children with hepatoblastoma with pure fetal histology: a report from the Children's Oncology Group. *J Clin Oncol*. 2011;29:3301-3306.

Meyers RL, Tiao G, de Ville de Goyet J, et al. Hepatoblastoma state of the art: pre-treatment extent of disease, surgical resection guidelines and the role of liver transplantation. *Curr Opin Pediatr*. 2014;26:29-36.

Congenital Dilatation of the Bile Ducts

Edil BH, Cameron JL, Reddy S, et al. Choledochal cyst disease in children and adults: a 30-year single-institution experience. *J Am Coll Surg*. 2008;206:1000-1005, discussion 1005-1008.

Intestinal and Pancreatic Masses

Casanova M, Collini P, Ferrari A, et al. Solid-pseudopapillary tumor of the pancreas (Frantz tumor) in children. *Med Pediatr Oncol*. 2003;41:74-76.

d'Ambrosio G, del Prete L, Grimaldi C, et al. Pancreaticoduodenectomy for malignancies in children. *J Pediatr Surg*. 2014;49:534-538.

Laje P, Bhatti TR, Adzick NS. Solid pseudopapillary neoplasm of the pancreas in children: a 15-year experience and the identification of a unique immunohistochemical marker. *J Pediatr Surg*. 2013;48:2054-2060.

Shorter NA, Glick RD, Klimstra DS, et al. Malignant pancreatic tumors in childhood and adolescence: The Memorial Sloan-Kettering experience, 1967 to present. *J Pediatr Surg*. 2002;37:887-892.

Duplications

Aboutalebi A, Jessup CJ, North PE, et al. Histopathology of vascular anomalies. *Facial Plast Surg*. 2012;28:545-553.

Kosir MA, Sonnino RE, Gauderer MWL. Pediatric abdominal lymphangiomas: A plea for early recognition. *J Pediatr Surg*. 1991;26:1309.

Laje P, Flake AW, Adzick NS. Prenatal diagnosis and postnatal resection of intraabdominal enteric duplications. *J Pediatr Surg*. 2010;45:1554-1558.

Ovarian Tumors

Hayes-Jordan A. Surgical management of the incidentally identified ovarian mass. *Semin Pediatr Surg*. 2005;14:106-110.

Papic JC, Finnell SM, Slaven JE, et al. Predictors of ovarian malignancy in children: overcoming clinical barriers of ovarian preservation. *J Pediatr Surg*. 2014;49:144-147, discussion 147-148.

Taskinen S, Fagerholm R, Lohi J, et al. Pediatric ovarian neoplastic tumors: incidence, age at presentation, tumor markers and outcome. *Acta Obstet Gynecol Scand*. 2015;94:425-429.

18

Dysuria

Paula Cody

Dysuria is defined as painful urination and can be related to uncomfortable contraction of the muscles of the bladder or when urine comes into contact with the inflamed genitourinary mucosa. The differential diagnoses for a patient presenting with dysuria are extensive (Table 18.1) and can be due to infectious or noninfectious causes. The cause of dysuria varies based on age of the child or adolescent; therefore, specific elements of the patient history, potential causes, and diagnostic evaluation will vary with age. With every patient, the provider must elicit a history of signs and symptoms outside the genitourinary tract, including fever, weight loss, generalized rash, involvement of other mucosa, and joint pain or swelling. Physical examination for every patient should include temperature, blood pressure, inspection of the genitalia for skin lesions or discharge, abdominal palpation, pelvic examination when indicated, and neurologic examination in children with voiding dysfunction to exclude spinal cord pathology.

NEONATES

Neonates and infants cannot complain of dysuria; however urinary tract infections (UTIs) are prevalent in this age group and a major source of morbidity. In this age group, it is difficult to distinguish between upper UTI (pyelonephritis) and lower UTI (cystitis) based on signs and symptoms alone. Unlike UTIs in older children, neonatal UTIs are more common in male neonates compared to females. In neonates, UTIs are associated with bacteremia and/or congenital abnormalities of the kidney and urinary tract. In term infants, infections tend to be community acquired and present in the 2nd to 3rd week after birth. UTIs can be caused by either hematogenous spread or an ascending infection. In preterm infants, infections are more likely to be hospital acquired.

The symptoms suggestive of a UTI in the neonate are the same as those for **suspected sepsis**; therefore, major presenting symptoms include fever, poor feeding, weight loss, lethargy, and vomiting (see Chapter 39). Neonates may also present with jaundice or abdominal distention. A maternal urinary infection at or near term may increase the risk for neonatal pyelonephritis. A mother whose vaginal culture is positive for group B streptococci or who presents with fever, prolonged rupture of the amniotic membranes (>18 hours), uterine tenderness, or preterm labor is at an increased risk for delivering a premature baby with pyelonephritis as part of the neonatal sepsis syndrome. Family history is also important. There is a high genetic component to the presence of **vesicoureteral reflux (VUR)**; the siblings of children with known VUR also have a significant risk of reflux, with or without infection. Children with a UTI and VUR are at increased risk of pyelonephritis and renal scarring. However, the screening for VUR in an asymptomatic sibling of an index case of VUR is controversial; a voiding cystourethrogram (VCUG) is recommended if there is evidence of renal scarring on ultrasound or if there is a history of UTI in the sibling who has not been tested. Given that the value of identifying and treating VUR is unproven in the absence of a UTI, an observational approach without screening for VUR may be taken for siblings of children with VUR, with the prompt treatment of any acute UTI and subsequent evaluation for VUR.

Physical examination of a neonate suspected of having a UTI should include the palpation of the abdomen to identify obstructive lesions or cystic kidneys. Urine culture should be obtained by suprapubic or bladder catheterization, as sterile bag collection has a high rate of contamination with perineal flora. Because of the associated risk of bacteremia, blood cultures and cerebrospinal fluid (CSF) cultures should be obtained in all neonates in whom UTI is suspected. Initial empirical therapy should be initiated after collection of urine, blood, and CSF cultures. The empirical therapy should provide broad coverage against probable uropathogens, and is initially administered parenterally, as the risk of urosepsis is higher in neonates than in other age groups. Common empirical therapy includes ampicillin in addition to either gentamicin or a 3rd-generation cephalosporin. Therapy is then tailored according to the specific uropathogen identified on culture and the antimicrobial sensitivity.

Ultrasound is the first-line imaging method in neonates after the first UTI. The main purpose of diagnostic imaging is the detection of risk factors, such as anomalies of the kidney and urinary tract or vesicoureteral reflux, as well as any renal damage acquired from the infection. Clinical practice guidelines from the American Academy of Pediatrics do not recommend DMSA (dimercaptosuccinic acid) scans as part of routine evaluation of infants with their first febrile UTI because the findings rarely affect acute clinical management.

CHILDREN 2-24 MONTHS OF AGE

Like neonates, children 2-24 months of age cannot report dysuria. Nonetheless, urinary tract infections (UTIs) are common (see Chapter 39). The main risk factor for febrile infant males is whether or not they are circumcised; other individual risk factors for UTI in males include nonblack race, temperature >39°C, fever for at least 24 hours, and absence of another source of infection. Individual risk factors for UTI in infant females include white race, age less than 12 months,

TABLE 18.1 Causes of Dysuria

Infectious causes	Urinary tract infection (cystitis, pyelonephritis) Urethritis Herpes simplex virus infections Varicella infections Epstein-Barr virus infections Hemorrhagic cystitis (adenovirus) Prostatitis Vaginitis* Renal tuberculosis Urinary schistosomiasis Sexually transmitted infections
Urinary tract abnormalities (congenital and acquired)	Urinary calculi Urethral stricture Meatal stenosis Prostate enlargement Malignancy Urethral diverticulum Bladder diverticulum Idiopathic hypercalciuria Bladder outlet obstruction Urethral prolapse
Genital tract abnormalities	Sexually transmitted infections Vaginitis Prostatitis Endometritis Endometriosis Labial adhesions Phimosis Paraphimosis Balanitis Foreign body
Medications and irritants	Primary irritant dermatitis Chemical irritants (soaps, detergents, bubble baths, feminine hygiene products, spermicides) NSAIDs Anticholinergics (amitriptyline, imipramine, and antihistamines) Anti-infectives (isoniazid, sulfonamides) Chemotherapy-related hemorrhagic cystitis (cyclophosphamide)
Other	Trauma Stevens-Johnson syndrome/toxic epidermal necrolysis Behçet syndrome Inflammatory bowel disease Toxic shock syndrome Reactive arthritis (in conjunction with urethritis, conjunctivitis) Neurologic conditions that impact bladder emptying Pinworms Lichen sclerosus Appendicitis (if inflamed appendix or periappendiceal abscess lies low in iliac fossa) Tumor (bladder, kidney, uterus, vagina) Foreign body (urethral, vaginal) Perianal group A streptococcus

*Vaginitis; chemical, nonspecific bacterial, *Candida albicans*, *Trichomonas vaginalis*, herpes simplex, gonorrhea, group A streptococcus, gram-negative organisms.
NSAIDs, nonsteroidal antiinflammatory drugs.

TABLE 18.2 Sensitivity and Specificity of Components of Urinalysis, Alone and in Combination

Test	Sensitivity (Range) (%)	Specificity (Range) (%)
LE test	83 (67-94)	78 (64-92)
Nitrite test	53 (15-82)	98 (90-100)
LE or nitrite positive	93 (90-100)	72 (58-91)
Microscopy (WBCs)	73 (32-100)	81 (45-98)
Microscopy (bacteria)	81 (16-99)	83 (11-100)
LE, nitrite, or microscopy positive	99.8 (99-100)	70 (60-92)

LE, leukocyte esterase; WBC, white blood cell.
Modified from Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management: Clinical practice guideline. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics*. 2011;128:595-610.

temperature of at least 39°C, fever for at least 2 days, and absence of another source of infection.

The method of collecting urine for testing is dependent on the risk factors of the child. Culture of a urine specimen from a sterile bag attached to the perineal area has a high false-positive rate; this method of urine collection is not suitable for diagnosing UTI. However, a culture of a urine specimen from a sterile bag that shows no growth is strong evidence that UTI is absent; if growth of a single uropathogen is present, it may represent a UTI. Nonetheless, a clinical practice guideline from the American Academy of Pediatrics outlines several recommendations in testing and treatment of UTIs in febrile infants:

- If a febrile infant with no apparent source for fever requires antibacterial therapy, a urine specimen should be obtained via suprapubic aspiration or catheterization for both culture and urinalysis (UA) prior to the initiation of antibacterials.
- If the clinician determines that the patient is at low risk for having a UTI, clinical monitoring without urine testing is acceptable.
- If the febrile infant is not in the low-risk category:
  - Clinician should obtain urine sample for UA and culture through catheterization or suprapubic aspiration.
  - Or clinician can obtain clean-void bagged urine sample. If UA results suggest UTI (Table 18.2), then an additional urine specimen for culture should be obtained via catheterization or suprapubic aspiration.

Diagnosing a UTI in young children requires both a positive UA (for white cells and/or bacteria) and >50,000 CFU/mL of a single urinary pathogen on urine culture from a suprapubic or catheterized urine specimen. The usual choices for empirical antibacterial therapy include a 3rd-generation cephalosporin, amoxicillin plus clavulanic acid, or trimethoprim-sulfamethoxazole. The clinician should base choice of antibacterial on local antimicrobial sensitivity patterns if available and should adjust according to sensitivity results of the isolated uropathogen. Most infants can be treated orally.

The rationale for imaging infants with UTI is to identify abnormalities of the genitourinary tract. Renal ultrasound is the first-line imaging modality to identify anatomic abnormalities. Voiding cystourethrogram (VCUG) to detect vesicoureteral reflux (VUR) should not be performed after the first febrile UTI. It is indicated if the ultrasound reveals hydronephrosis, renal scarring, or other findings that suggest high-grade VUR or obstructive uropathy.

PRESCHOOL CHILDREN

A young child may or may not be able to verbalize dysuria; however, they may show signs of urethral irritation including delayed toilet training (especially during the day), secondary enuresis, dribbling, and frequent squatting. Due to the large variability in the time of achievement of daytime dryness (15 months-4 years), delayed toilet training may be an unreliable sign of dysuria; however, **primary diurnal enuresis** should be evaluated if the child is older than 48 months of age. Nocturnal enuresis is rarely a sign of UTI, but urine cultures should probably be obtained in children who do not stay dry at night by 5 years of age. A more significant symptom in young children is the *acute onset* of daytime enuresis after a period of continence.

UTIs are the most common cause of dysuria in preschool children. It may be difficult to distinguish between pyelonephritis and cystitis in these young children. Both urine and stool withholding have a role in causing UTIs in young children. Constipation is associated with large residual urine volumes after voiding, thus the treatment of constipation leads to a reduction in UTIs. Females are at increased risk of UTI due to the ease at which pathogens can migrate from the gastrointestinal tract to the periurethral area and urethra, and ultimately ascend to the bladder. Improper toileting habits can further increase the risk of UTI. Uncircumcised males, patients with neurogenic bladders (spina bifida), patients with indwelling catheters, and patients with renal or bladder anomalies (e.g., cysts, obstructed hydronephrosis, double collecting systems, ectopic ureter, horseshoe kidney, posterior urethral valves, VUR) are at increased risk for UTI.

Children who are toilet-trained can give a clean-void urine sample. Those that are not toilet-trained can give a urine specimen from a sterile bag attached to the perineal area, although this has a high false-positive rate.

Preschool children may also have irritant urethritis.

SCHOOL-AGED/PREPUBERTAL CHILDREN

Dysuria in school-aged children can be due to infectious and noninfectious causes (Table 18.1). Most children with a UTI present with dysuria, frequency, or fever. It is worthwhile to ask about any urine color change, which suggests the presence of hematuria. The child should be questioned about the frequency, character, and size of his or her bowel movements. **Constipation** may predispose the school-aged child to a UTI; stool softeners, such as mineral oil or fiber, may be indicated. Pyelonephritis can be clinically distinguished from cystitis by presence of systemic features (fever, vomiting) and signs (flank pain, costovertebral angle tenderness).

A careful inspection of the genitalia is important in the diagnosis of the cause of dysuria. Boys may have nonspecific bacterial infection of the glans penis (**balanitis**); uncircumcised boys can have infection of both the glans and the prepuce (**balanoposthitis**). Both of these are usually accompanied by painful swelling and inflammation. Irritants can cause a nonspecific urethritis in males, with dysuria being the main symptom.

Prepubertal females can have dysuria as the presenting symptom of **vaginitis**, along with other symptoms including vaginal discharge. In prepubertal females, the vulvar mucosa is thin and susceptible to inflammation from chemicals and mechanical irritation. Because the labia are not well developed, the vulvar mucosa is not anatomically shielded and is thus vulnerable to irritation. Vaginitis in prepubertal females can be nonspecific, due to irritants (soaps, detergents) or may be due to the presence of a foreign body (Table 18.3). Whereas vulvovaginal candidiasis is common in postpubertal females, the vaginal environment in prepubertal females is not typically conducive to *Candida species* growth, unless she has an immunodeficiency or recent antibacterial use. In the majority of cases, vulvovaginitis in prepubertal females is a mixed, nonspecific bacterial infection secondary to contamination by urine and feces. The responsible bacteria are usually normal flora (Table 18.4). Bloody vaginal discharge in young females may be caused by *Shigella species* or group A streptococcal infections, a foreign body (e.g., toilet paper), neoplasm (such as rhabdomyosarcoma), or trauma. Most cases of prepubertal nonspecific vaginitis can be managed with hygiene; some vulvovaginitis may require a course of antibacterial agents or topical estrogen vaginal cream (Table 18.5).

Several **vulvar skin disorders** can be confused with vulvovaginitis and present with dysuria due to contact of urine with inflamed mucosa. **Lichen sclerosus** manifests as white patches on the glabrous skin that are thinned and atrophic and are easily traumatized with resultant bullae (which may be blood-filled) in the vulvar region. **Seborrheic dermatitis** may manifest with inflammation and secondary infection of the intertriginous areas; the face and scalp may be involved as well. Labial or vulvar agglutination may be noted and can be secondary to previous vulvovaginitis of unestrogenized epithelia.

TABLE 18.3 Causes of Noninfectious Vulvovaginitis and Dysuria

Condition	Historical Cues
Poor hygiene	Infrequent bathing, hand washing, and clothing changes, soiled underwear, toilet independence
Poor perineal aeration	Tight clothing, nylon underwear, tights, leotards; wet bathing suits, hot tubs, obesity
Frictional trauma	Tight clothing, sports, sand from sandbox or beach, obesity, excessive masturbation or sexual abuse
Chemical irritants	Bubble baths, harsh or perfumed soaps or detergents, powders, perfumed and/or dyed toilet paper, ammonia, perfumed and/or dyed sanitary products; douches and feminine hygiene products
Contact dermatitis	Topical creams or ointments
Vaginal foreign bodies	Wiping habits, excessive masturbation or self-exploration, sexual abuse
Parasites, insect bites, infestations	Home environment, pets, sandboxes, travel, camping, exposure to woods or beach
Medications	Topical steroid or hormone creams, antibiotics, chemotherapy
Generalized skin disorders	History of pruritus, chronic skin lesions, prior diagnosis
Anatomic anomalies	Vesicovaginal or rectovaginal fistula, ectopic ureter, spina bifida, cloacal anomalies, urogenital anomalies
Neoplasms	Discharge, bleeding, bulging abdomen, change in bowel or bladder function, premature puberty
Systemic illness (Stevens-Johnson syndrome, Crohn disease, toxic shock syndrome)	Tampon use, systemic evidence of inflammatory bowel disease including rash, oral ulcers, failure to gain weight or height, abdominal pain

Modified from Succato GS, Murray PJ. Pediatric and adolescent gynecology. In: Zitelli BJ, Davis HW. *Atlas of Pediatric Physical Diagnosis.* 5th ed. Philadelphia: Mosby Elsevier; 2007 p. 693-730.

TABLE 18.4 Normal Vaginal Flora

- Aerobic
  - Gram-positive rods
    - Diptheroids
    - Lactobacilli
  - Gram-positive cocci
    - *Staphylococcus aureus*
    - *Staphylococcus epidermidis*
    - *Streptococcus* species
      - α-Hemolytic
      - β-Hemolytic
      - Nonhemolytic
      - Group D
  - Gram-negative rods
    - *Escherichia coli*
    - *Klebsiella* and *Enterobacter* species
    - *Proteus* species
    - *Pseudomonas* species
- Anaerobic species
  - *Bacteroides* species
  - *Clostridium* species
  - *Eubacterium* species
  - *Fusobacterium* species

Modified from Larsen B, Monif GRG. Understanding the bacterial flora of the female genital tract. *Clin Infect Dis.* 2001;32(4):e69-e77.

TABLE 18.5 Treatment of Nonspecific Vulvovaginitis in Young Females

- Toilet Hygiene
  - Urinate with knees apart
  - Wipe in an anterior-to-posterior direction with supervision
  - Scent- and dye-free wipes may be useful
- Clothing
  - Choose white cotton underpants, may need to change underpants midday if urinary dribbling
  - Wear loose-fitting clothing
  - Change out of wet swimsuits immediately
- Bathing
  - Take sitz baths in clear water up to four times a day
  - Wash gently with unperfumed soap
  - Do not use bubble bath or wash hair in bath
  - Rinse perineum with clear water, dry gently with towel
- Management of Inflammation and Pruritus
  - Premarin vaginal cream topically twice daily for 10-14 days
  - Hydroxyzine, 0.5 mg/kg/dose orally 4 times daily as needed
  - Diphenhydramine, 1.25 mg/kg/dose orally 4 times daily as needed

Urethritis caused by herpes simplex virus may occur in both males and females of this age group from autoinoculation from herpes stomatitis; however, presence of genital ulcers should always elicit questioning about sexual activity and/or assault.

Other etiologic factors that may lead to urethritis and resultant dysuria include infection (fungi, pinworms, scabies), irritation (soap, shampoo, detergent, bubble bath), systemic illness (Stevens-Johnson syndrome), and trauma (abuse, play, tight clothing, masturbation).

TABLE 18.6 Approach to Clinical Evaluation of Sexually Transmitted Infections: Sexual History

Age at coitarche
Gender of partners
Date of most recent sexual encounter
Duration of relationship with current partner
Numbers of current, recent (within past 3-6 mo), and lifetime partners
Condom usage (overall consistency)
Contraceptive usage
Vaginal intercourse
Oral intercourse
Anal intercourse
Dyspareunia
Involuntary sexual encounters (abuse, rape)
Partner's sexually transmitted infection symptoms and relevant sexual history (i.e., other sex partners)

ADOLESCENTS

There are many causes for dysuria in an adolescent. A detailed sexual history is mandatory (Table 18.6). Greater than 46% of high school students have engaged in sexual intercourse, with an increase to 64% among 12th graders. Over 5% initiated sexual intercourse before 13 years of age, and 34% had a sexual encounter within the previous 3 months. Adolescents are likely to have multiple sexual partners over relatively short periods of time, fail to recognize the symptoms of sexually transmitted infections (STIs), and use condoms inconsistently. It is critical that the provider perform a thorough history in a nonjudgmental and nonthreatening manner. Interviewing the adolescent in the room alone (i.e., without a parent present) for at least a portion of the visit is the standard of care for all adolescent health care visits. The terms of a confidential visit should be explained to the adolescent and parent; all information disclosed by the adolescent remains confidential unless he or she reveals a risk of rendering harm to himself or herself or others, such as with suicidal or homicidal ideation. Questions about victimization and abuse are part of the sexual history, regardless of age or gender.

Urinary tract infections (UTIs) are much more common in adolescent females than adolescent males. Risk factors for recurrent UTIs in females include frequency of sexual intercourse (higher frequency leads to higher risk), maternal history of recurrent UTI, a new sexual partner in the past year, and spermicide use in the past year. Common pathogens in this age group include *Escherichia coli*, *Proteus* species, *Klebsiella* species, *Staphylococcus saprophyticus*, and enterococcus. Although often recommended by clinicians, no evidence supports the thought that postcoital urination leads to a reduction in the frequency of UTIs.

One of the most common causes of dysuria in adolescent males and females is **sexually transmitted infections (STIs)**. Adolescents represent an age group at high risk for acquisition and transmission of STIs. Although many STIs are asymptomatic and are diagnosed by screening asymptomatic sexually active individuals, STIs can present with dysuria, vaginal discharge, penile discharge, and genital lesions (Table 18.7). The most likely time for this to happen is within 1 month of beginning a relationship with a new sexual partner.

Chlamydial genital infection is the most frequently reported bacterial STI. Infections with *Chlamydia trachomatis* may be asymptomatic or may present with dysuria, discharge, intermenstrual bleeding, or

TABLE 18.7 Diagnostic Characteristics of Genital Lesions

Syndrome	Appearance	Number of Lesions	Pain	Adenopathy	Occurrence in the United States
Herpes	Vesicles and superficial ulcers on erythematous base (1-2 mm)	Multiple	Often	Bilateral; inguinal; firm; movable; tender	Frequent
Syphilis	Papule and superficial or deep ulcer (5-15 mm)	Single	No	Bilateral; inguinal; firm; movable; nontender	Uncommon
Lymphogranuloma venereum	Ulcer (2-10 mm), resolves quickly	Single	Yes	Unilateral; inguinal; fluctuant; may suppurate; tender	Uncommon
Human papillomavirus	Anogenital exophytic warts; may resemble cauliflower or be papular with projections	Single or multiple	No	None	Frequent
Lice or nits	Tiny (≤1 mm) insects or eggs adherent to hair shaft; excoriations	Multiple	No but pruritic	None	Common
Chancroid	Deep, purulent ulcers (2-20 mm)	Multiple	Yes	Unilateral; inguinal; fluctuant; may suppurate; tender	Rare

dyspareunia. *C. trachomatis* has also been associated with Fitz-High–Curtis syndrome (perihepatitis) and reactive arthritis. *C. trachomatis* infection may lead to pelvic inflammatory disease (PID), ectopic pregnancy, and infertility. *C. trachomatis* urogenital infection can be detected in women by testing urine or collecting swab specimens from the endocervix or vagina; in men, the diagnosis can be made through urine or urethral swab. Nucleic acid amplification tests (NAATs) are the most sensitive methods for detecting *C. trachomatis.* Treatment of infection improves symptoms, decreases the risk of sequelae, and prevents sexual transmission of the disease (Table 18.8).

Gonorrhea, caused by *Neisseria gonorrhoeae*, is the second most frequently reported bacterial STI. Infections with *N. gonorrhoeae* may be asymptomatic or may present with dysuria, discharge, intermenstrual bleeding, or dyspareunia. *N. gonorrhoeae* infection may lead to pelvic inflammatory disease (PID); late complications include ectopic pregnancy, and infertility. *N. gonorrhoeae* urogenital infection can be detected in women by testing urine or collecting swab specimens from the endocervix or vagina; in men, the diagnosis can be made through urine or urethral swab. Nucleic acid amplification tests (NAATs) are the most sensitive methods for detecting *N. gonorrhoeae*. Treatment of infection improves symptoms, decreases risk of sequelae, and prevents sexual transmission of the disease (Table 18.8). Treatment of gonorrhea is complicated by the ability of *N. gonorrhoeae* to develop resistance to antibacterials.

Trichomoniasis, caused by *Trichomonas vaginalis*, may be asymptomatic or may present with dysuria, frothy yellow-green vaginal discharge, genital pruritus, or intermenstrual bleeding. Diagnosis of *T. vaginalis* is usually assessed by microscopy of vaginal or urethral secretions; however, there are more sensitive methods of detection, including a specific culture, a nucleic acid probe, and an immunochromatographic capillary flow dipstick. See Table 18.8 for treatment recommendations.

Primary herpes simplex virus (HSV) infection can cause genital ulcers and dysuria, as well as other conditions, including nongenital lesions, cervicitis, urethritis, cystitis, proctitis, and pharyngitis. Systemic complications, such as hepatitis, pneumonia, thrombocytopenia, and monoarticular arthritis may occur. HSV-infected patients can present with a primary infection, which can be asymptomatic; a first clinical episode, which may not necessarily occur during the primary infection; or a recurrent episode. Usually, the first clinical episodes are more painful and prolonged than are subsequent ones. Recurrent episodes occur less frequently with a genital HSV-1 infection and with intervals between episodes becoming longer, as compared to HSV-2. Treatment for initial and recurrent outbreaks of HSV is listed in Table 18.8.

Vaginitis due to various causes can cause dysuria in adolescent females. Vulvovaginal candidiasis, bacterial vaginosis, and trichomoniasis are common causes of vulvovaginitis in adolescents. Other causes are local chemical or allergic irritants, bacterial infections caused by *Streptococcus* or *Staphylococcus* species, trauma, and secondary infections from foreign bodies. Rare causes of vaginitis and subsequent dysuria include ulcerating conditions of the mucous membranes, such as toxic shock syndrome and Stevens-Johnson syndrome. Other noninfectious causes of genital ulcers that can be confused with infection include inflammatory bowel disease and Behçet syndrome. Inflammatory bowel disease usually manifests with intestinal symptoms, deeper ulcers, and a longer duration of ulcerative lesions. Behçet syndrome may manifest with lesions of other mucous membranes as well as ocular, central nervous system, and joint manifestations. If the clinical diagnosis is not definitive, viral culture of the lesions is recommended.

Males with dysuria may also have penile pain or dysuria as a result of phimosis, paraphimosis, balanitis, urethral trauma, epididymitis, or meatal stenosis. **Phimosis** is a scarring or narrowing of the preputial opening and manifests as failure to retract the foreskin. The foreskin is normally difficult to retract in neonates, but by 3 years of age, it is easily retracted. **Paraphimosis**, an emergent cause of dysuria and penile pain, is an incarceration of the prepuce behind the glans. Edema, pain, and swelling are present. Balanitis is an infection of the prepuce caused by *Streptococcus* species, *Candida* species, mixed flora, or *Trichomonas* species; it may be recurrent and warrants circumcision.

Evaluation for dysuria in the adolescent female should include a clean catch (midstream) urine for dipstick, microscopic exam, and culture. The presence of leukocytes on urinalysis may indicate vaginitis due to sexually transmitted infections (*N. gonorrhoeae*, *C. trachomatis*, herpes, *T. vaginalis*). To check for gonorrhea or *Chlamydia*, a first-stream urine or a swab of the vagina or cervix should be obtained. Depending on sexual activity, the pharynx and rectum should also be tested to check for infections in those locations. Any lesions suggestive of HSV should be cultured or tested by PCR. The evaluation of any vaginal discharge includes description of the vaginal discharge, measurement of vaginal pH, saline preparation, performance of a whiff

(See *Nelson Textbook of Pediatrics*, p. 1493.)

TABLE 18.8 Recommended Treatments of Selected Sexually Transmitted Infections

Pathogen	Recommended Regimen
Chlamydia trachomatis	Azithromycin, 1 g orally in a single dose or Doxycycline, 100 mg orally twice a day for 7 days
Neisseria gonorrhoeae	Ceftriaxone, 250 mg intramuscularly in a single dose plus Azithromycin, 1 g orally in a single dose
Trichomonas vaginalis	Metronidazole, 2 g orally in a single dose or Tinidazole, 2 g orally in a single dose
Herpes simplex virus First clinical genital episode	Acyclovir, 400 mg orally 3 times a day for 7-10 days or Acyclovir, 200 mg orally 5 times a day for 7-10 days or Famciclovir, 250 mg orally three times a day for 7-10 days or Valacyclovir, 1 g orally twice a day for 7-10 days
Herpes simplex virus Episodic therapy for recurrent genital episodes	Acyclovir, 400 mg orally 3 times a day for 5 days or Acyclovir, 800 mg three times daily for 2 days or Acyclovir, 800 mg orally twice a day for 5 days or Famciclovir, 125 mg orally twice a day for 5 days or Valacyclovir, 500 mg orally twice a day for 3 days or Valacyclovir, 1 g orally once a day for 5 days

Modified from Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2015. *MMWR*. 2015;64(3):1-135. See full document for alternative treatments and specific treatments in pregnancy and treatment for children <8 years old.

test, and microscopic examination (Table 18.9 and Figs. 18.1, 18.2, and 18.3). Thick, adherent cottage cheese–like discharge is suggestive of candidiasis; other physical examination findings include erythema, edema, and excoriation of the vagina. Thin, homogeneous, gray-white, foul-smelling discharge is suggestive of bacterial vaginosis (BV). Purulent, profuse, irritating, frothy green-yellow discharge often accompanies trichomoniasis. The Amsel criteria for diagnosis and treatment of bacterial vaginosis are listed in Tables 18.10 and 18.11, respectively.

The provider should perform a pelvic examination to exclude **pelvic inflammatory disease (PID)** in all sexually active adolescent females when vaginal discharge and/or pelvic pain are reported (Table 18.12). PID is an acute infection of the upper female genital tract (endometriosis, salpingitis, tuboovarian abscess, pelvic peritonitis). Features that suggest PID (vs lower tract infection) include cervical motion tenderness; uterine or adnexal tenderness; temperature >101°F; cervical mucopurlent discharge or friability; abundant white blood cells on saline prep of vaginal fluid; elevated erythrocyte sedimentation rate and C-reactive protein levels; and a documented cervical infection with *N. gonorrhea* or *C. trachomatis*. Table 18.13 lists differential diagnoses for PID, and Table 18.14 details the recommended treatment regimens for PID. Pregnancy testing is indicated when an adolescent female presents with dysuria or any symptoms of an STI; the test results may influence the treatment plan.

The Centers for Disease Control and Prevention recommend gonorrhea and *Chlamydia* testing of all males who meet

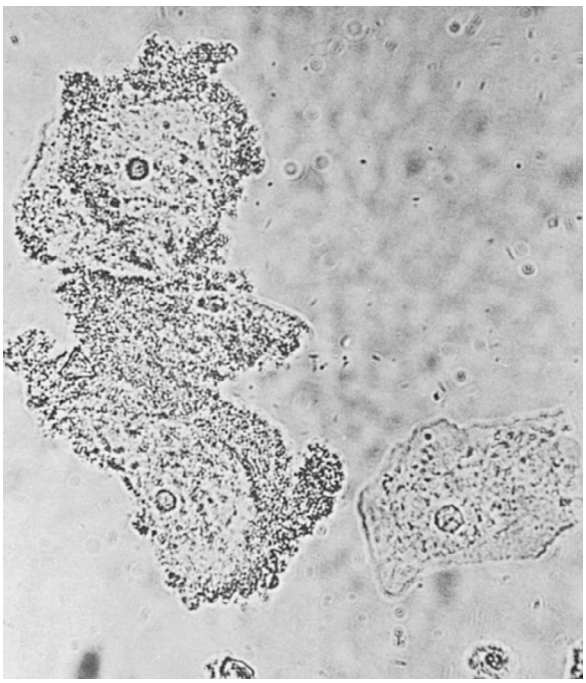


FIGURE 18.1 Bacteria are clinging to the sides of a vaginal epithelial cell ("clue cell"). (From Huffman JW. Genitourinary infections. In: Feigen RD, Cherry JD, eds. *Textbook of Pediatric Infectious Diseases*. 2nd ed. Philadelphia: WB Saunders; 1992:570.)

TABLE 18.9 Differences in Characteristics Between Bacterial Vaginosis, Trichomoniasis, and Vulvovaginal Candidiasis

Clinical Elements		Normal	Bacterial Vaginosis	Trichomoniasis	Vaginal Candidiasis
Symptoms	Vaginal odor	–	+	+/–	–
	Vaginal discharge	Clear-white	Thin, gray, homogeneous	Green-yellow	White, curd like
	Vulvar irritation	–	+/–	+	+
	Dyspareunia	–	–	+	–
Signs	Vulvar erythema	–	–	+/–	+/–
	Bubbles in vaginal fluid	–	+	+/–	–
	Strawberry cervix	–	–	+/–	–
Microscopy	**Saline Wet Mount**				
	Clue cells	–	+	–	–
	Motile protozoa	–	–	+	–
	KOH test				
	Pseudohyphae	–	–	–	+
	Whiff test	–	+	+/–	–
	pH	3.8-4.2	>4.5	>4.5	<4.5

KOH, potassium hydroxide.
Modified from Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2015. *MMWR*. 2015;64(3):1-135.

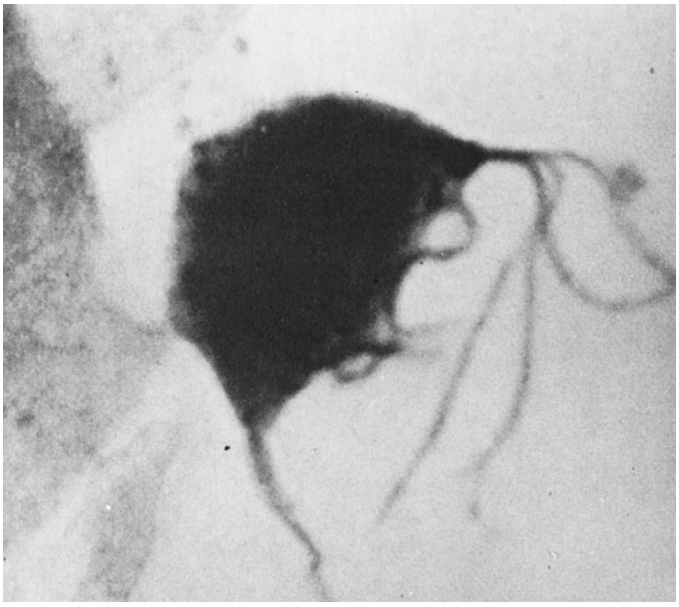


FIGURE 18.2 *Trichomonas vaginalis* identified in wet smears of the vaginal discharge. (From Huffman JW Genitourinary infections. In: Feigen RD, Cherry JD, eds. *Textbook of Pediatric Infectious Diseases*. 2nd ed. Philadelphia: WB Saunders; 1992:568.)

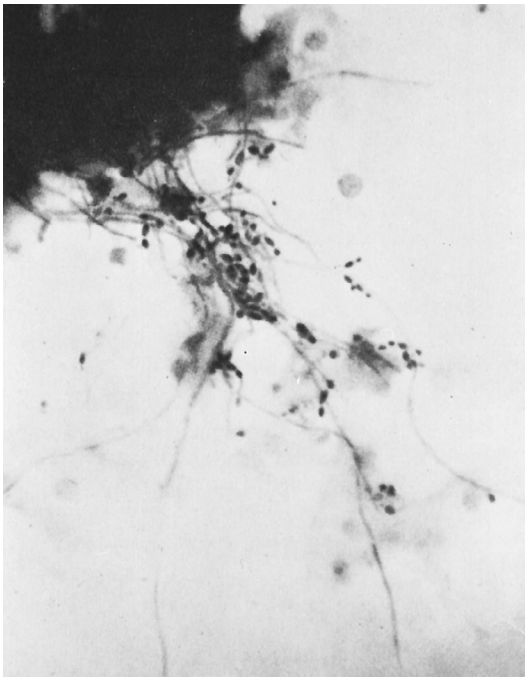


FIGURE 18.3 Hyphae of *Candida albicans* on a wet smear of vaginal discharge. (From Huffman JW. Genitourinary infections. In: Feigen RD, Cherry JD, eds. *Textbook of Pediatric Infectious Diseases*. 2nd ed. Philadelphia, WB Saunders; 1992:564.)

TABLE 18.10 Amsel Criteria for the Diagnosis of Bacterial Vaginosis

Three of the following 4 Amsel criteria are considered necessary to diagnose BV:

1. Vaginal discharge: thin, homogeneous, white, uniformly adherent
2. Vaginal pH >4.5
3. Positive result of whiff test: fishy odor after mixing discharge with 10% KOH
4. >20% clue cells on microscopic examination: bacteria-coated squamous epithelial cells, where both the periphery (cell membrane) and cytoplasm have a granular, irregular, "moth-eaten" appearance

Modified from Amsel R, Totten PA, Spiegel CA, et al. Nonspecific vaginitis. Diagnostic criteria and microbial and epidemiologic associations. *Am J Med*. 1983;74:14-22.
KOH, potassium hydroxide.

TABLE 18.11 Treatment Regimens for Bacterial Vaginosis

Bacterial Vaginosis

Nonpregnant Females

Metronidazole, 500 mg orally twice daily for 7 days
or
Metronidazole gel, 0.75%, 1 full applicator (5 g) intravaginally once a day for 5 days
or
Clindamycin cream, 2%, 1 full applicator (5 g) intravaginally once a day for 7 days

Pregnant Females

Metronidazole, 250 mg orally 3 times daily for 7 days

Modified from Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines 2015. *MMWR*. 2015;64(3):1-135.

TABLE 18.12 Diagnostic Criteria for Pelvic Inflammatory Disease

Minimum Criteria

Uterine or adnexal tenderness (unilateral or bilateral)
or
Cervical motion tenderness

Additional Criteria to Increase Specificity of Minimum Criteria

Abnormal cervical or vaginal mucopurulent discharge
Presence of WBCs on saline microscopy of vaginal secretions
Oral temperature >38.3°C (101°F)
Elevated erythrocyte sedimentation rate or C-reactive protein
Laboratory evidence of *Neisseria gonorrhoeae* or *Chlamydia trachomatis* at cervix

WBCs, white blood cells.
Modified from Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2015. *MMWR*. 2015;64(3):1-135.

TABLE 18.13 Differential Diagnosis for Pelvic Inflammatory Disease

Ectopic pregnancy
Ovarian cyst (with or without ovarian torsion)
Acute appendicitis
Endometriosis
Pyelonephritis
Septic or incomplete abortion
Pelvic thrombophlebitis
Functional pain
Psoas-pelvic muscle abscess
Mesenteric adenitis
Pelvic adhesions
Pelvic bone osteomyelitis
Chronic intestinal disease (e.g., inflammatory bowel disease)

TABLE 18.14 Treatment Regimens for Pelvic Inflammatory Disease

Parenteral Regimens (One of the Following)

Cefotetan, 2 g IV q12h, or cefoxitin, 2 g IV q6h, both plus doxycycline, 100 mg IV or PO q12h *or*
Clindamycin, 900 mg IV q8h, plus gentamicin, loading dose (2 mg/kg body weight) IV or IM, followed by a maintenance dose (1.5 mg/kg) q8h
Parenteral therapy may be discontinued 24 hr after clinical improvement and continue doxycycline, 100 mg PO twice daily, or clindamycin, 450 mg orally 4 times daily for 14 days of total therapy
For tuboovarian abscess, addition of either metronidazole, 500 mg PO twice daily, or clindamycin, 450 mg PO 4 times daily, to oral doxycycline provides better coverage against anaerobes

Outpatient Regimens (One of the Following)

Ceftriaxone, 250 mg IM in a single dose, or cefoxitin, 2 g IM, with probenecid, 1 g PO in a single dose once, or other parenteral 3rd-generation cephalosporin (e.g., ceftizoxime or cefotaxime) **plus** doxycycline, 100 mg PO twice daily for 14 days, with or without metronidazole, 500 mg PO twice daily for 14 days

IM, intramuscularly; IV, intravenously; PO, per os (orally).
Modified from Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2015. *MMWR*. 2015;64(3):1-135.

TABLE 18.15 Treatment Regimens for Epididymitis

One of the following:
- For epididymitis most likely caused by gonococcal or chlamydial infection:
  - Ceftriaxone, 250 mg intramuscularly in a single dose, **plus** doxycycline, 100 mg orally twice daily for 10 days
- For epididymitis most likely caused by enteric organism, or for patients who are allergic to cephalosporins and/or tetracyclines:
  - Ofloxacin, 300 mg orally twice daily for 10 days*
  - Levofloxacin, 500 mg orally once daily for 10 days*

*Fluoroquinolones have not been recommended for persons younger than 18 years because they damage articular cartilage in juvenile animal models. Among children treated with fluoroquinolones, no joint damage attributable to therapy has been observed. Quinolones should not be used to treat possible gonorrhea infections acquired in Asia or the Pacific, including Hawaii, or California.
Modified from Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2015. *MMWR*. 2015;64(3):1-135.

TABLE 18.16 Common Pitfalls in the Correct Diagnosis of Dysuria

Neonates/Infants
- Assume that significant bacteriuria in a bagged urine specimen is a true UTI, and treat before a confirmatory culture is obtained
- Failure to obtain a urine culture in a neonate older than 3 days and miss obstructive uropathy with a secondary infection

Toddlers and School-Aged Children
- Trust a urine culture from a bagged urine specimen
- Accept a laboratory report of "no significant growth" on urine, without knowing that the laboratory reports only >100, 000 CFU/mL as "significant"
- Failure to label a urine as "catheterized specimen," so that the laboratory can plate 0.1 mL as well as 0.01 mL

Adolescents
- Fail to ask about sexual history suggestive of vaginitis, such as a new sexual partner and condom or other birth control device use
- Treat pyuria as a UTI in a sample contaminated with vaginal leukocytes

CFU, colony-forming unit; UTI, urinary tract infection.

TABLE 18.17 Red Flags for Referral to a Pediatric Urologist or Nephrologist After a Urinary Tract Infection

- Dilating VUR (grade III, IV, or V)
- Renal scarring detected on sonography or a DMSA scan obtained >6 mo after the UTI
- Urinary obstruction seen on a sonogram
- Voiding dysfunction (enuresis, frequency, "curtsy" to stop voiding)
- Breakthrough UTI in the child with VUR receiving prophylaxis
- Elevated serum creatinine level
- Hypertension
- Antenatal hydronephrosis that is confirmed after day 3 after birth

DMSA, dimercaptosuccinic acid; UTI, urinary tract infection; VUR, vesicoureteral reflux.

TABLE 18.18 Red Flags and Things Not to Miss: Sexually Transmitted Diseases

Diagnosis of More Than One Sexually Transmitted Infection in the Same Patient
- If patient is diagnosed with syphilis, gonorrhea, or human immunodeficiency virus
- If patient reports engaging in unprotected sex with multiple partners
- If patient is immunocompromised
- If patient has a history of sexually transmitted infections

Abdominal Pain in an Adolescent Girl
- Pelvic inflammatory disease
- Tuboovarian abscess
- Ectopic pregnancy
- Appendicitis
- Ovarian cyst (rupture or torsion)

Fever, Rash, Malaise, Arthralgia
- Disseminated gonococcemia
- Reactive arthritis
- Human immunodeficiency virus infection

Rape

Pregnancy

Treatment of Partners

Asymptomatic Cervicitis

the diagnostic criteria for urethritis. NAATs, the most sensitive gonorrhea and *Chlamydia* diagnostic test, can be performed on a single urine or urethral specimen. Any lesion suspicious for HSV should be cultured. Table 18.8 lists the treatments for selected sexually transmitted infections. Epididymitis, typically presenting as unilateral testicular pain, is most frequently caused by *C. trachomatis* or *N. gonorrhoeae* or a sexually transmitted enteric organisms such as *E. coli* and *Pseudomonas* species. On examination, a hydrocele may be present. Treatment of epididymitis is listed in Table 18.15.

SUMMARY AND RED FLAGS

Dysuria in prepubertal children is usually a symptom of a UTI, but may also be due to other infectious or noninfectious causes of urethritis and vaginitis. The differential diagnosis expands greatly in adolescents, in whom a sexually transmitted infection may be the cause. Table 18.16 demonstrates common pitfalls in the appropriate evaluation of dysuria in children and adolescents. Red flags are noted in Tables 18.17 and 18.18.

Because children younger than 2 years cannot often verbalize a specific complaint of dysuria, the diagnosis of a UTI is more challenging in children this age. Awareness of specific risk factors for UTI

(uncircumcised status in boys, height of fever, and lack of other cause for fever on examination) especially in the first year of life will lead to the evaluation of those at highest risk and avoid unnecessary testing in those at low risk. Combining the results of the UA with an appropriately obtained urine culture allows for expeditious treatment and confirmation of the particular pathogen when the culture results are available.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

American Academy of Pediatrics Subcommittee on Urinary Tract Infection and Steering Committee on Quality Improvement and Management. Urinary Tract Infection. Clinical Practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2-24 months. *Pediatrics*. 2011;128:595-610.

American Urological Association guideline statement. Management and screening of primary vesicoureteral reflux in children: AUA Guideline. 2010. Available from: <https://www.auanet.org/common/pdf/education/clinical-guidance/Vesicoureteral-Reflux-a.pdf>. Accessed 01.08.15.

Bonadio WA. Urine culturing technique in febrile infants. *Pediatr Emerg Care*. 1987;3:75-78.

Centers for Disease Control and Prevention. Youth risk behavior surveillance–United States, 2013. *MMWR*. 2014;63(SS–4):1-168.

Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2015. *MMWR*. 2015;64(3):1-135.

Emamghorashi F, Mahmoodi N, Tagarod Z, et al. Maternal urinary tract infection as a risk factor for neonatal urinary tract infection. *Iran J Kidney Dis*. 2012;6:178-180.

Finnell SM, Carroll AE, Downs SM, et al. Technical report: diagnosis and management of an initial urinary tract infection in febrile infants and young children. *Pediatrics*. 2011;128(3):e749.

Gorelick MH, Shaw KN. Clinical decision rule to identify febrile young girls at risk for urinary tract infection. *Arch Pediatr Adolesc Med*. 2000;154(4):386-390.

Hoberman A, Greenfield SP, Mattoo TK, et al. Antimicrobial prophylaxis for children with vesicoureteral reflux. *N Engl J Med*. 2014;370:2367-2376.

Kanellopoulos TA, Salakos C, Spiliopoulou I, et al. First urinary tract infection in neonates, infants, and young children: a comparative study. *Pediatr Nephrol*. 2006;21:1131-1137.

Kodner CM, Thomas Gupton EK. Recurrent urinary tract infections in women: Diagnosis and management. *Am Fam Physician*. 2010;82:638-643.

Michel RS. Toilet training. *Pediatr Rev*. 1999;20(7):240-245.

19

Proteinuria

Raji Sreedharan

Proteinuria can be detected by various means, and the most common is the dipstick test, a calorimetric assay that spots only albumin and not low-molecular-weight proteins. In addition, alkaline urine and the presence of contrast media in urine can lead to false dipstick positivity. Though 24-hour urine collection is the gold standard to quantify the proteinuria, spot urine protein-to-creatinine ratio can be used for initial confirmation after a positive screen with dipstick or to trend proteinuria (Table 19.1). A ratio below 0.2 protein mg/creatinine mg is considered normal in children older than 2 years of age and a ratio less than 0.5 mg/mg is considered normal in younger children between 6 months and 2 years of age. In timed collection, protein excretion greater than 100 mg/m^2 in 24 hours or 4 mg/m^2/hour is considered abnormal, and over 40 mg/m^2/hr is considered nephrotic range. Qualitative analysis of protein in urine by immunonephelometry helps distinguish glomerular from tubular proteinuria.

Proteinuria in children can be transient, orthostatic, or persistent. Transient and orthostatic proteinuria are benign conditions and require no treatment. Several factors including fever, stress, hypovolemia, exercise, and seizures can lead to transient proteinuria (Table 19.2). **Orthostatic proteinuria** is defined as increased protein in urine only when upright. In this condition, absence of proteinuria when horizontal and resting can be confirmed by documenting absence of protein in a 1st morning void. Split day/night urine collection is the gold standard to diagnose orthostatic proteinuria, which is a common benign cause of proteinuria, especially in adolescents. Persistent proteinuria requires meticulous evaluation to rule out renal pathology.

Evaluation of proteinuria begins with a detailed history and physical examination. Pertinent histories that help distinguish pathologic from benign proteinuria include history of respiratory symptoms concurrent with or preceding the proteinuria, presence of red urine, edema, positive family history of kidney disease, or hearing loss. Findings of edema and hypertension suggest pathologic proteinuria. Repeating urine dipstick in asymptomatic children with a negative history can eliminate unnecessary further testing for transient proteinuria. If still positive, spot urine protein-to-creatinine ratio can help confirm the presence of proteinuria. If confirmed, a 1st morning void protein-to-creatinine ratio can then identify orthostatic proteinuria. Once the benign conditions are ruled out in asymptomatic children, further testing is similar to that of symptomatic children and these children should be referred to nephrologists. This more detailed evaluation begins with 24-hour urine collection where possible, complete urinalysis, and sediment evaluation looking for glomerular or other parenchymal pathology that could be causing the proteinuria (Fig. 19.1). Positive leukocyte esterase, nitrite, and presence of pyuria or bacteriuria suggest a urinary tract infection. If not resolved with treatment of infection, proteinuria will need further evaluation. Low molecular proteins, such as β2-microglobulin, α1-microglobulin, lysozyme, and retinol-binding protein are found in **tubular proteinuria** as is seen in Fanconi syndrome or Dent disease. Red blood cell (RBC) cast is pathognomonic of **glomerulonephritis**. Serum chemistry including creatinine, BUN, electrolytes, albumin, and cholesterol will also help separate proteinuria secondary to glomerulonephritis or nephrotic syndrome. Lupus antibody studies, streptococcal infection, and complement C3 and C4 levels along with viral studies can help delineate the various causes of glomerulonephritis and nephrotic syndrome. Renal ultrasound should be considered to rule out any gross parenchymal etiology for the proteinuria, such as dysplastic kidney and cystic kidney disease. Renal biopsy may be indicated if there is evidence for worsening of proteinuria, hypoalbuminemia, deteriorating renal function, or a poor response to the initial therapy.

Differential diagnoses for proteinuria are extensive, as described in Table 19.2. The initial evaluation of a patient with proteinuria is presented in Table 19.3. Indications for a referral to a pediatric nephrologist are described in Table 19.4. If there is obvious edema with proteinuria, the diagnostic evaluation noted in Table 19.3 advances directly to the 2nd phase and, if necessary, to the 3rd phase.

The combination of proteinuria, hypoalbuminemia, edema, and hyperlipidemia are the defining features of nephrotic syndrome. Nephrotic syndrome may be a result of many primary etiologic factors, with varying renal pathologic processes and long-term consequences. Proteinuria that causes edema is always clinically significant, although not all edema is secondary to proteinuria (Table 19.5). All children with nephrotic syndrome invariably have "nephrotic-range" proteinuria, necessitating detailed evaluation, and most require treatment. In rare cases, a child with asymptomatic proteinuria has nephrotic-range proteinuria. If there is concomitant hypoalbuminemia and hyperlipidemia, the work-up proceeds as if the child presented with nephrotic syndrome, despite the absence of edema. Even without hypoalbuminemia and hyperlipidemia, nephrotic-range proteinuria is less likely to be benign than is less marked asymptomatic proteinuria.

NEPHROTIC SYNDROME IN YOUNG CHILDREN

◆ Differential Diagnosis

Three diseases constitute all cases of isolated nephrotic syndrome: minimal change disease (the most common); focal segmental sclerosis (also called focal glomerular sclerosis); and membranous glomerulopathy. These classifications are based on pathologic findings. Thus these presentations could be primary or secondary due to other causes. In addition, nephrotic syndrome can be present along with glomerulonephritis (GN), such as postinfectious GN, IgA GN, or membranoproliferative GN. Systemic diseases also cause childhood nephrotic syndrome, accounting for 10% of cases. The three foremost considerations include SLE, anaphylactoid purpura (Henoch-Schönlein purpura), and hemolytic uremic syndrome. These diseases have extrarenal manifestations in addition to the proteinuria and must be considered in any child who presents with systemic illness and significant

(See *Nelson Textbook of Pediatrics,* p. 2517.)

(See *Nelson Textbook of Pediatrics,* p. 2571.)

TABLE 19.1 Quantification of Proteinuria in Children

Method	Abnormal Proteinuria	Precautions
Urine dipstick	1+ or more in a concentrated urine specimen (specific gravity ≥1.020)	False positive if urine pH >8.0 or specific gravity >1.025 or tested within 24 hr of a radiocontrast study
Sulfosalicylic acid test	1+ or more	False-positive with iodinated radiocontrast agents
Urine protein/creatinine ratio (U_p/U_{Cr} ratio) in spot urine	>0.02 g/mmol or >0.2 mg/mg in children >2 yr >0.06 g/mmol or >0.6 mg/mg in children 6 mo-2 yr Nephrotic range: >0.2 g/mmol or >2 mg/mg	Protein excretion varies with child's age
Timed urine protein excretion rate	>4 mg/m^2/hr or >150 mg/1.73 m^2/24 hr Nephrotic range: >40 mg/m^2/hr or >3 g/1.73 m^2/24 hr	In an accurately collected 24-hr urine specimen, urine creatinine should be in the range of 0.13-0.20 mmol/kg or 16-24 mg/kg ideal body weight for females, and 0.18-0.23 mmol/kg or 21-27 mg/kg ideal body weight for males

From Yap HK, Lau PYW. Hematuria and proteinuria. In: Geary DF, Schaefer F, eds. *Comprehensive Pediatric Nephrology*. Philadelphia: Elsevier; 2008:185, Table 10.3.

TABLE 19.2 Causes of Proteinuria

Transient Proteinuria
Fever
Exercise
Dehydration
Cold exposure
Congestive heart failure
Seizure
Stress

Orthostatic (Postural) Proteinuria

Glomerular Diseases Characterized by Isolated Proteinuria
Idiopathic (minimal change) nephrotic syndrome
Focal segmental glomerulosclerosis
Mesangial proliferative glomerulonephritis
Membranous nephropathy
Membranoproliferative glomerulonephritis
Amyloidosis
Diabetic nephropathy
Sickle cell nephropathy

Glomerular Diseases with Proteinuria as a Prominent Feature
Acute postinfectious glomerulonephritis (e.g., streptococcal, endocarditis, hepatitis B or C virus, and HIV)
Immunoglobulin A nephropathy
Henoch-Schönlein purpura nephritis
Lupus nephritis
Serum sickness
Alport syndrome
Vasculitic disorders
Reflux nephropathy

Tubular Diseases
Cystinosis
Wilson disease
Lowe syndrome
Dent disease (X-linked recessive nephrolithiasis)
Galactosemia
Tubulointerstitial nephritis
Acute tubular necrosis
Renal dysplasia
Polycystic kidney disease
Reflux nephropathy
Drugs (e.g., penicillamine, lithium, NSAID)
Heavy metals (e.g., lead, gold, mercury)

NSAID, nonsteroidal antiinflammatory drug.
From Pais P, Avner ED. Fixed proteinuria. In: Kliegman RM, Stanton BF, St. Geme JW III, eds. *Nelson Textbook of Pediatrics.* 20th ed. Philadelphia: Elsevier; 2016:2520, Table 526.1.

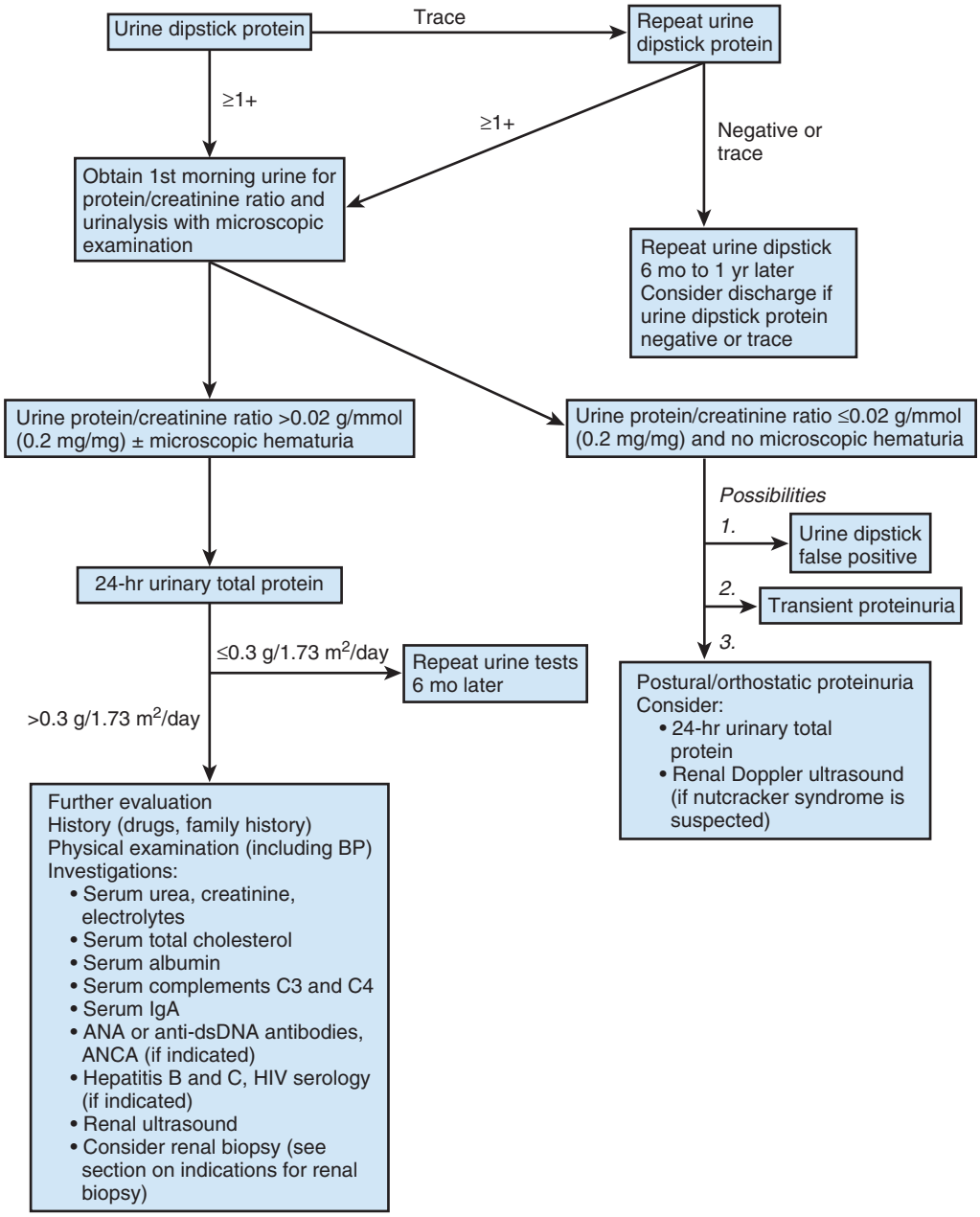


FIGURE 19.1 Algorithm for investigating proteinuria. ANA, antinuclear antibody; ANCA, antinuclear cytoplasmic antibody; anti-dsDNA, anti–double-stranded DNA; BP, blood pressure; IgA, immunoglobulin A. (From Yap HK, Lau PYW. Hematuria and proteinuria. In: Geary DF, Scharfer F, eds. *Comprehensive Pediatric Nephrology*. Philadelphia: Elsevier; 2008:190.)

proteinuria. Hereditary forms of nephrotic syndrome are a genetically heterogeneous group of disorders representing a spectrum of hereditary renal diseases. There are 13 subtypes of hereditary nephrotic syndrome associated with 35 genes. Several of the more common disorders along with other causes of nephrotic syndrome are noted in Tables 19.6 and 19.7.

MINIMAL CHANGE DISEASE

Most cases of nephrotic syndrome in children are caused by minimal change nephrotic syndrome, defined as normal histologic features of the kidney by light microscopy and immune stains. Preschool-aged children constitute the age group in which minimal change nephrotic syndrome is most common. Patients often present with asymptomatic edema, which may manifest as swollen or puffy eyes upon awakening in the morning; increasing abdominal girth (increased waist or belt size) from ascites; pedal or leg edema, which causes difficulty in putting on their regular-sized shoes, especially after being upright during the daytime; or swelling in other sites, such as the scrotum, penis, vulva, and scalp. Tense edema or ascites is occasionally painful.

Minimal change nephrotic syndrome is slightly more common in boys than in girls. The hallmark of this disease is total clearing of the proteinuria with oral prednisone therapy. A common misconception is that neither hematuria nor hypertension is present in children with minimal change disease. Microscopic hematuria and hypertension are present in up to 20% of children who have minimal change disease. The blood urea nitrogen (BUN) or serum creatinine level may also be elevated in up to 30% of the cases, usually from prerenal causes. Serum complement studies, specifically C3, are invariably normal. Older age, hematuria, hypertension, and azotemia may occur with minimal change nephrotic syndrome, but the combination suggests another disease.

◆ Diagnosis

Studies that would help confirm that a patient with nephrotic syndrome has minimal change disease include urinalysis, serum chemistry

TABLE 19.3 Work-up of a Child with Proteinuria

Pediatrician's Work-up: Phase I
Early morning urinalysis to include examination of the sediment
Ambulatory and recumbent urinalyses for dipstick protein testing

Pediatrician's Work-up: Phase II
Blood electrolytes, BUN, creatinine, serum proteins, cholesterol
ASLO titer, C3 complement, ANA
Timed 12-hr urine collections, recumbent and ambulatory
Renal ultrasonography, IVP, voiding cystourethrography

Pediatric Nephrologist's Work-up: Phase III
Renal biopsy
Management of established renal disease

ANA, antinuclear antibody; ASLO, antistreptolysin O; BUN, blood urea nitrogen; IVP, intravenous pyelography.
Modified from Norman ME. An office approach to hematuria and proteinuria. *Pediatr Clin North Am.* 1987;34:545-562.

TABLE 19.4 When to Refer the Child with Proteinuria to a Nephrologist

Persistent nonorthostatic proteinuria
A family history of glomerulonephritis, chronic renal failure, or kidney transplantation
Systemic complaints such as fever, arthritis or arthralgias, and rash
Hypertension, edema, cutaneous vasculitis, or purpura
Coexistent hematuria with or without cellular casts in the spun sediment
Elevated blood urea nitrogen (BUN) and creatinine levels or unexplained electrolyte abnormalities
Increased parental anxiety

Modified from Norman ME. An office approach to hematuria and proteinuria. *Pediatr Clin North Am.* 1987;34:545-561, Table 24.9.

TABLE 19.5 Causes of Edema

Kidney Diseases
Acute glomerulonephritis
Nephrotic syndrome
Acute renal failure
Chronic renal failure

Heart Failure

Liver Failure

Nutritional and Gastrointestinal Disorders
Protein-calorie malnutrition
Protein-losing enteropathy
Nutritional edema (especially on refeeding)

Endocrine Disorders
Hypothyroidism
Mineralocorticoid excess

Miscellaneous
Hydrops fetalis
Venocaval obstruction
Capillary leak syndrome (systemic inflammatory response syndrome)
Turner syndrome (lymphedema)
Allergic reaction (periorbital edema)

including BUN, creatinine, albumin, and cholesterol levels, along with complements and lupus antibody titers.

The urinalysis would be expected to show 3+ to 4+ protein, which is correlated with a urine concentration of 300-2000 mg/dL. The urine may also occasionally yield positive results for blood. Microscopic examination of the urine sediment often shows oval fat bodies and/or refractile granular casts, which are seen when there is significant lipiduria. Red blood cells might also be present, but it is unusual to see red blood cell casts. Their presence would suggest a diagnosis of poststreptococcal glomerulonephritis or other causes of nephritis (see Chapter 20).

The complement C3 and C4 levels are normal in minimal change disease and are depressed in some other causes of nephritis (see Chapter 20). The serum cholesterol values are elevated in minimal change nephrotic syndrome and are usually higher than 250 mg/dL; levels in the range of 500-600 mg/dL may occur. The serum albumin concentration is invariably less than 2.5 and often less than 2.0 g/dL. A renal biopsy is not immediately indicated because most patients (>90%) with minimal change disease respond to prednisone, a response that is considered diagnostic.

◆ Treatment

With a presumptive diagnosis of minimal change nephrotic syndrome, it is recommended in the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines that patients be placed on a therapeutic course of prednisone, 60 mg/m^2/day or 2 mg/kg/day, up to a maximum of 60 mg for 4-6 weeks, followed by a dose of 40 mg/m^2 or 1.5 mg/kg (maximum 40 mg) given every other day for another 6 weeks. In most patients, there is total resolution of proteinuria within 10-21 days of initiating therapy. Patients who do not respond to prednisone therapy should be considered candidates for a renal biopsy to guide further therapy.

Total clearing of proteinuria in response to prednisone is an excellent prognostic sign. Very few patients progress to renal failure, although many patients (~80%) who initially respond to prednisone therapy with total clearing of proteinuria may have relapses and require intermittent prednisone therapy for many years. Approximately 18% of patients treated with prednisone for minimal change nephrotic syndrome respond to therapy and never experience a relapse.

Patients with **recurrent nephrotic syndrome** are subgrouped into those who experience frequent and infrequent relapses. A patient with infrequent relapse has fewer than 2 relapses in any 6-month period; a person with frequent relapse has 2 or more relapses within 6 months. Prednisone should be reinitiated at a dose of 60 mg/m^2/day or 2 mg/kg/day until a maximum of 60 mg/day and continued until the urine test results are negative for protein for 3 consecutive days. After that, alternate-day prednisone is given at a dose of 40 mg/m^2 or 1.5 mg/kg (maximum 40 mg) in the morning for another 4 weeks and then discontinued altogether. Relapses are frequent during the influenza virus seasons; any minor upper respiratory infection may trigger a relapse of nephrotic syndrome. Patients who suffer infrequent relapses may be treated with prednisone alone.

Patients with frequently relapsing nephrotic syndrome may be steroid dependent and require constant daily prednisone therapy to maintain a remission. Because constant daily prednisone has significant untoward side effects (growth failure, cushingoid facies, osteoporosis, cataracts, opportunistic infections, hypertension, and glucose intolerance), other therapies need to be considered. A renal biopsy is recommended prior to initiating alternative agents to confirm the

TABLE 19.6 Causes of Childhood Nephrotic Syndrome

Idiopathic Nephrotic Syndrome
Minimal change disease
Focal segmental glomerulosclerosis
Membranous nephropathy
Glomerulonephritis associated with nephrotic syndrome–membranoproliferative glomerulonephritis, crescentic glomerulonephritis, immunoglobulin A nephropathy

Genetic Disorders Associated with Proteinuria or Nephrotic Syndrome
Over 100 genetic syndromic disorders are associated with proteinuria, the more common disorders are listed below.

Nephrotic Syndrome (Typical)
Finnish-type congenital nephrotic syndrome (absence of nephrin)
Focal segmental glomerulosclerosis (mutations in nephrin, podocin, *MYO1E*, α-actinin-4, TRPC6)
Diffuse mesangial sclerosis (mutations in laminin β_2 chain)
Denys-Drash syndrome (mutations in WT1 transcription factor)
Congenital nephrotic syndrome with lung and skin involvement (integrin α_3 mutation)
Mitochondrial disorders (rare association, steroid resistance, MELAS)

Proteinuria With or Without Nephrotic Syndrome
Nail-patella syndrome (mutation in LMX1B transcription factor)
Alport syndrome (mutation in collagen 4 biosynthesis genes)

Multisystem Syndromes With or Without Nephrotic Syndrome
Galloway-Mowat syndrome
Charcot-Marie-Tooth disease
Jeune syndrome
Cockayne syndrome
Bardet Biedl syndrome

Metabolic Disorders With or Without Nephrotic Syndrome
Alagille syndrome
α_1-Antitrypsin deficiency
Fabry disease
Glutaric acidemia
Glycogen storage disease
Hurler syndrome
Partial lipodystrophy
Mitochondrial cytopathies
Sickle cell disease

Secondary Causes of Nephrotic Syndrome

Infections
Endocarditis
Hepatitis B, C
HIV-1
Infectious mononucleosis
Malaria
Syphilis (congenital and secondary)
Toxoplasmosis
Schistosomiasis
Filariasis

Drugs
Captopril
Penicillamine
Gold
Nonsteroidal antiinflammatory drugs
Pamidronate
Interferon
Mercury
Heroin
Lithium

Immunologic or Allergic Disorders
Vasculitis syndromes
Castleman disease
Kimura disease
Bee sting
Food allergens
Serum sickness

Associated with Malignant Disease
Lymphoma
Leukemia
Solid tumors

Glomerular Hyperfiltration
Oligomeganephronia
Morbid obesity
Adaptation to nephron reduction

Modified from Eddy AA, Symons JM. Nephrotic syndrome in childhood. *Lancet*. 2003;362:629-638; From Pais P, Avner ED. Fixed proteinuria. In: Kliegman RM, Stanton BF, St. Geme JW III, eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:2522, Table 527.1.

diagnosis of minimal change nephrotic syndrome. Treatment strategies with corticosteroid-sparing agents for patients with frequent relapse who develop steroid-related adverse effects include, alkylating agents; cyclophosphamide or chlorambucil. It is not recommended that second courses of alkylating agents be given.

Complications of Nephrotic Syndrome

Even in patients with the frequent relapse variant of minimal change disease, the incidence of renal failure is only 1%. The reported mortality rate remains higher, at approximately 5%.

Infection. The major cause of death in nephrotic syndrome is overwhelming infection, usually secondary to **spontaneous bacterial peritonitis**, which develops in as many as 10% of patients with nephrotic syndrome at some point in the course of illness. Such infection is most frequent in patients who are edematous with significant ascites. Peritoneal fluid interferes with macrophage function, whereas ascitic fluid may dilute local complement or immunoglobulin levels, altering host defense mechanisms in the peritoneum.

The most common pathogen is *Streptococcus pneumoniae*. *Escherichia coli* and *Staphylococcus aureus* are other etiologic agents that may cause spontaneous peritonitis in patients with minimal change disease. With the use of appropriate antibiotics, mortality from peritonitis is ~10%. Any child with nephrotic syndrome in relapse with evidence of ascites needs to be evaluated quickly if either abdominal pain or fever

TABLE 19.7 Causes of Nephrotic Syndrome in Infants Younger Than 1 Year

Secondary Causes
Infections
Syphilis
Cytomegalovirus
Toxoplasmosis
Rubella
Hepatitis B
HIV
Malaria
Drug reactions
Toxins
Mercury
Systemic lupus erythematosus
Syndromes with associated renal disease
Nail-patella syndrome
Lowe syndrome
Nephropathy associated with congenital brain malformation
Denys-Drash syndrome: Wilms tumor
Hemolytic uremic syndrome
Primary Causes
Congenital nephrotic syndrome
Diffuse mesangial sclerosis
Minimal change disease
Focal segmental sclerosis
Membranous nephropathy

From Kliegman RM, Greenbaum LA, Lye PS. *Practical strategies in pediatric diagnosis and therapy*. 2nd ed. Philadelphia: Saunders; 2004:418.

develops. A blood specimen and paracentesis (e.g., Gram stain, culture, neutrophil count, measurement of glucose and protein levels) should be obtained, and the patient should be started on intravenous cefotaxime (or ceftriaxone) and an aminoglycoside without further delay.

Thrombosis. A second serious complication of nephrotic syndrome is spontaneous thrombosis, pulmonary embolus, or both. The blood of patients with nephrotic syndrome is hypercoagulable, and there is an increased incidence of thrombotic phenomena in these children. Children can have arterial thrombosis, as well as venous thrombosis with resultant pulmonary emboli. The renal vein and dural sinus veins are other possible sites of thrombosis. Use of injectable and oral antithrombolytic agents, in addition to heparin, have allowed for more effective treatment of thrombotic complications.

Hyperlipidemia. Hyperlipidemia is treated by some authorities with statins to lower the serum cholesterol levels and theoretically reduce vascular pathologic processes.

OTHER FORMS OF NEPHROTIC SYNDROME

Focal Segmental Sclerosis

Diagnosis

Clinical criteria do not always allow clinicians to differentiate minimal change disease from focal segmental sclerosis before completion of a course of prednisone therapy. Inability to clear proteinuria completely during prednisone therapy may be the first indication of focal segmental sclerosis. Patients who respond to prednisone initially with clearing of proteinuria but do not respond to a subsequent course of steroids should also be considered to have focal segmental sclerosis. Such patients represent about 7% of those who have an initial response to prednisone therapy. A patient who does not respond to prednisone with total clearing of proteinuria should undergo renal biopsy.

Focal segmental sclerosis may be primary (idiopathic) or secondary to severe obesity, reflux nephropathy, sickle cell nephropathy, reduced renal mass (single kidney), opiate or analgesic abuse, chronic bacteremia (endocarditis), renal transplant rejection, or nephropathy resulting from human immunodeficiency virus infection. Genetic variants in several genes result in focal segmental glomerulosclerosis. The genetic basis of these hereditary focal segmental glomerulosclerotic disorders is genetically heterogeneous. Nine hereditary subtypes have been described. *FSGS1 : ACTN4; FSGS2 : TRPC6; FSGS3 : CD2AP; FSGS4 : APOL1; FSGS5 : INF2; FSGS6 : MYO1E; FSGS7 : PAX2; FSGS8 : ANLN; FSGS9 : CRB2.* Many of these genes code for proteins which are involved in the structure and function of the podocyte foot process.

Treatment

Results of treatment of focal segmental sclerosis have been poor. Patients have severe and unremitting proteinuria despite treatment with prednisone, chlorambucil, or cyclophosphamide. The long-term outcome has been poor; 33% are in renal failure ~10 years after diagnosis, and nearly 100% are in renal failure 20 years after diagnosis. The incidence of focal segmental sclerosis appears to be increasing, particularly in the African American population, possibly related to obesity and genetic predisposition.

Patients with focal segmental sclerosis present 2 difficult problems. First, renal function may be maintained reasonably well for years, but massive proteinuria persists. Hence, patients are often edematous for months or years, and stigmata of protein malnutrition may develop as a result of large protein losses. Symptomatic therapy with a low-sodium diet and judicious use of diuretics is sometimes effective. Dietary manipulation of protein intake is ineffective; increasing dietary protein intake is accompanied by a concomitant increase in urinary protein excretion. There is no evidence that protein restriction either modifies serum proteins or prevents progression to renal insufficiency.

The second problem occurs when affected patients progress to end-stage renal failure. Recurrence of the disease in transplanted kidneys occurs in 25-30% of recipients. Therefore, many patients undergo a long period of dialysis before receiving a kidney transplant in an effort to diminish the frequency of recurrent disease.

Some patients respond to calcineurin inhibitors, cyclosporine, or tacrolimus, with total clearing of their proteinuria. There may be no progression to renal insufficiency. It is unknown what percentage of patients with focal segmental sclerosis respond to cyclosporine; it is estimated that 25-60% have an initial response.

Membranous Nephropathy

Membranous nephropathy is a pathologic diagnosis made following renal biopsy and may be primary or secondary to other diseases (e.g., hepatitis, systemic lupus erythematosus [SLE] or malignancy) or toxins and drugs such as nonsteroidal antiinflammatory, gold, mercury, bismuth, silver, D-penicillamine, trimethadione, probenecid, and captopril. All the secondary causes must be considered and should be addressed and treated before the condition is considered primary. Antibodies against the phospholipase A_2 receptor (PLA_2R) in the serum or a renal biopsy by immune staining have been identified in 70% of patients with primary or idiopathic membranous nephropathy. Circulating antibodies against thrombospondin type-1 domain-containing 7A (THSD7A) are found in another 5-10% of the remaining patients with primary membranous nephropathy. The changes in

(See *Nelson Textbook of Pediatrics,* p. 2502.)

the antibody titers correspond to remission or relapse of proteinuria and can be used to monitor the disease.

Treatment

Addressing the triggers of secondary membranous nephropathy in itself may result in resolution of proteinuria in the majority of cases. Membranous nephropathy secondary to SLE is more difficult to treat. In addition, the increased incidence of spontaneous resolution of the proteinuria makes selecting the patients who should be treated very complicated. Close monitoring of primary membranous nephropathy to determine the need for treatment is recommended for 6 months prior to initiating treatment. Sodium restriction, diuretics, and angiotensin-converting enzyme (ACE) inhibitors can be used for control of proteinuria and symptoms. In patients with no decrease of proteinuria, or with severe, life-threatening symptoms related to the nephrotic syndrome, immunosuppression with steroids and cyclophosphamide can be tried.

NEPHROTIC SYNDROME IN INFANTS YOUNGER THAN 1 YEAR

Nephrotic syndrome that manifests very early in life is a much more serious entity, and the prognosis is guarded (see Table 19.7). The outlook is poorest in younger infants (<6 months of age) and improves as the age at presentation approaches 1 year. Minimal change disease is rarely seen in infants younger than 6 months of age. It is more common in infants who present at 6-8 months. By 1 year, it is the most common cause of nephrotic syndrome.

The conditions that result in nephrotic syndrome in infants differ markedly from those seen in older children. Secondary causes are more prominent and need to be considered, particularly in newborns or very young infants. It is especially important to test for syphilis because the early institution of penicillin therapy may lead to the resolution of the renal disease and may mitigate the involvement of other organ systems as well. Congenital toxoplasmosis is also treatable with the combination of steroids and pyrimethamine–sulfadiazine–folinic acid. Other congenital infections offer less opportunity for treatment to influence the outcome; extrarenal manifestations of these infections are much more serious than kidney disease.

Primary renal disease causing nephrotic syndrome in early infancy is most often caused by either congenital nephrotic syndrome or diffuse mesangial sclerosis (Table 19.8). In both diseases, the prognosis for survival is poor unless aggressive supportive therapy and kidney transplantation are undertaken.

Congenital Nephrotic Syndrome

Congenital nephrotic syndrome is an autosomal recessive disorder resulting from mutations in the gene encoding the protein, nephrin (see Table 19.8). Infants with congenital nephrotic syndrome are often premature, with a low birthweight, placentomegaly, increased amniotic fluid α-fetoprotein levels, and hypogammaglobinemia (decreased immunoglobulin G levels).

Ascites and edema, caused by massive proteinuria, are usually present in affected infants during the first few weeks after birth. Patients do not respond to steroids or cytotoxic therapy. Infections and thrombosis are the two major complications; they cause considerable morbidity and mortality. Because of the massive proteinuria, patients fail to thrive; they require nasogastric feeding with a high-calorie, high-protein formula. Nephrectomy and peritoneal dialysis are often necessary to control protein losses and allow for adequate growth and control of uremia so that the infant can reach a size and nutritional state sufficient for renal transplantation.

Diffuse Mesangial Sclerosis

Diffuse mesangial sclerosis is the other diagnostic entity seen in infants (see Table 19.8). This disease is similar to congenital nephrotic syndrome, but it often results in less severe protein losses. Patients are often full term and of a normal birthweight. The amniotic fluid α-fetoprotein is normal, and the onset of edema (1 week-33 months) is later than in congenital nephrotic syndrome (birth-3 months). The patients have hypertension, hematuria, and renal insufficiency at presentation. When diffuse mesangial sclerosis is seen in association with a female phenotype, chromosome typing is recommended to look for patients with Drash syndrome (XY gonadal dysgenesis, nephropathy, and Wilms tumor). When this syndrome is present, bilateral nephrectomy and gonadectomy are recommended because the potential for malignancy is very high.

Treatment is similar to patients with congenital nephrotic syndrome and eventually requires renal transplantation. The major goal is to help these infants achieve the growth and good nutrition necessary for successful renal transplantation. Nephrotic syndrome occasionally occurs after transplantation for congenital nephrotic syndrome, probably secondarily to an autoimmune reaction to nephrin.

ASYMPTOMATIC PROTEINURIA DISORDERS

Many patients have proteinuria, but there is no edema, the blood pressure is normal, and serum protein levels are normal. The extent of the work-up must be tailored to the seriousness of the problem. Whether an evaluation should be performed depends on whether the proteinuria is both persistent and nonorthostatic (see Fig. 19.2). For a **child younger than 7 or 8 years of age** who has persistent proteinuria, normal total protein and serum albumin levels, normal complement, and no other signs of renal disease, there are two options.

One option is to observe the patient carefully with repeated urinalyses every 3-6 months and to counsel the parents with regard to swelling and/or ascites, which may develop in association with influenza or an upper respiratory infection. If there is evidence of overt nephrotic syndrome with edema, a decrease in serum albumin and an increase in serum cholesterol, a trial of daily prednisone therapy is indicated. It is good practice to give the pneumococcal vaccine to patients who have persistent proteinuria but no evidence of edema or nephrotic syndrome, because of the risk of pneumococcal peritonitis if nephrotic syndrome develops. The other option involves instituting prednisone therapy to document that proteinuria has disappeared; this confirms the suspicion that the patient has steroid-responsive nephrotic syndrome. The rationale for withholding prednisone unless symptoms develop is that the natural history of minimal change disease is to remit; this may occur with or without prednisone administration. If the patient has a more serious lesion, symptoms will develop, at which time evaluation and therapy may be undertaken.

In a **patient older than 8 or 9 years**, once the presence of persistent and nonorthostatic proteinuria is established, the next step is to quantify the amount of protein in a 24-hour specimen. If urinary protein excretion is greater than 8 mg/kg/day, a renal biopsy may be considered. Alternatively, these patients can also be treated with steroids and the response assessed. If proteinuria does not clear after 6-8 weeks of therapy, renal biopsy is then indicated. The choice of 8 mg/kg/day of proteinuria is arbitrary; the International Study of Kidney Disease in Children (ISKDC) definition of proteinuria is 8 mg/m^2/hour, and nephrotic syndrome is defined as 40 mg/m^2/hour. Hence, for an average 8-year-old patient who weighs 30 kg and is 1 m^2 tall, proteinuria by these definitions is a level of 96 mg/day, and nephrotic syndrome is at a level of 960 mg/day. Renal biopsy can be considered at a

TABLE 19.8 Nephrotic Syndrome in Children Caused by Genetic Disorders of Podocytes

Gene	Name	Location	Inheritance	Renal Disease
NPHN	NEPHRIN	19q13.12	AR	FINNISH CONGENITAL NEPHROSIS
PDCN	PODOCIN	1q25.2	AR	NEPHROTIC SYNDROME, STEROID-RESISTANT
PLCE1	PHOSPHOLIPASE C, EPSILON-1	10q23.33	AR	NEPHROTIC SYNDROME, EARLY-ONSET, TYPE 3
WT1	Wilms tumor supressor gene	11p13	AD	NEPHROTIC SYNDROME, TYPE 4 / Denys-Drash with diffuse mesangial sclerosis / Frasier syndrome
LAMB2	LAMININ, BETA-2	3p21.31	AR	NEPHROTIC SYNDROME, TYPE 5, WITH OR WITHOUT OCULAR ABNORMALITIES
PTPRO	GLOMERULAR EPITHELIAL PROTEIN 1	12p12.3	AR	NEPHROTIC SYNDROME, TYPE 6
DGKE	DIACYLGLYCEROL KINASE, EPSILON	17q22	AR	NEPHROTIC SYNDROME, TYPE 7, WITH MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS
ARHGDIA	RHO GDP-DISSOCIATION INHIBITOR ALPHA	17q25.3	AR	NEPHROTIC SYNDROME, TYPE 8
ADCK4	AARF DOMAIN-CONTAINING KINASE 4	10q13.2	AR	NEPHROTIC SYNDROME, TYPE 9
EMP2	EPITHELIAL MEMBRANE PROTEIN 2	16p13.3	AR	NEPHROTIC SYNDROME, TYPE 10
NUP107	NUCLEOPORIN KD107	12q15	AR	NEPHROTIC SYNDROME, TYPE 11
NUP93	NUCLEOPORIN, 93-KD	16q13	AR	NEPHROTIC SYNDROME, TYPE 12
NUP205	NUCLEOPORIN	7q33	AR	NEPHROTIC SYNDROME, TYPE 13
LMX1B	LIM-homeodomain protein	9q34	AD	Nail-Patella Syndrome
SMARCAL1	SW1/SNF2-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a-like 1	2q35	AR	Schimke immunoosseous dysplasia with FSGS*

*Podocyte expression of *SMARCAL1* is presumptive but not yet established. Mutations in another protein, CD2-AP or NEPH1 (a novel protein structurally related to nephrin), is the cause of congenital nephrotic syndrome in mice. A mutational variant in the *CD2AP* gene has been identified in some patients with steroid-resistant nephrotic syndrome.
AD, autosomal dominant; AR, autosomal recessive; FSGS, focal segmental glomerulosclerosis.
Modified from Eddy AA, Symons JM. Nephrotic syndrome in childhood. *Lancet.* 2003;362:629-638.

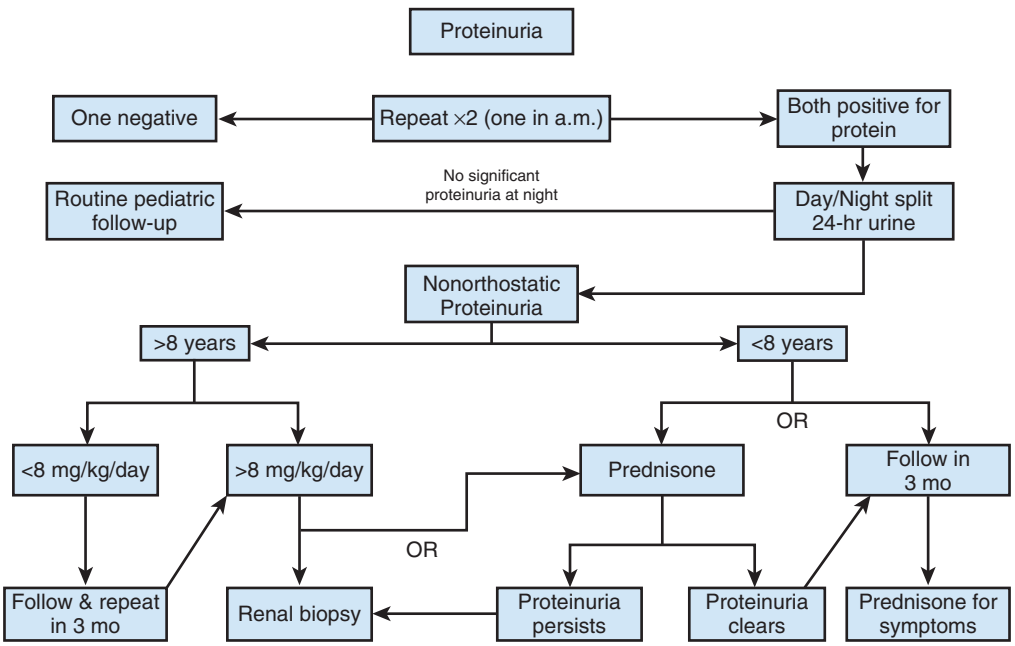


FIGURE 19.2 Algorithm for age-based management of proteinuria.

level of 240 mg/day of proteinuria. This guideline helps avoid a biopsy for the patient with minimal proteinuria but does not require full-blown nephrotic syndrome to develop before a definitive work-up is initiated. Because the patient has isolated proteinuria, membranoproliferative glomerulonephritis (MPGN) or SLE is an unlikely possibility. However, the incidence of focal segmental sclerosis is much higher in adolescents than in younger children. With the possibility of treatment with cyclosporine and/or ACE inhibitors preventing future renal failure, aggressive evaluation is warranted to identify patients who might benefit from these therapies.

Low molecular protein, such as β2-microblobulin, α1-microglobulin, lysozyme, and retinol-binding protein can be seen in urine in tubular disorders, such as Fanconi syndrome or Dent disease. If associated with acidosis, hypokalemia, and hypophosphatemia, Fanconi syndrome should be considered. In males, if proteinuria is associated with hypercalciuria and nephrocalcinosis, Dent disease, an X-linked proximal tubulopathy that eventually leads to end-stage renal disease, should be considered, and the urine should be tested for β2-microblobulin. Gene testing can confirm the diagnosis.

The presence of protein in the urine increases the risk of renal insufficiency, regardless of its cause. This has led to therapies that reduce proteinuria, thereby decreasing the risk of a progressive loss of renal function. The traffic of protein across the glomerular capillary membrane appears to stimulate a cascade of inflammatory events that cause interstitial fibrosis. ACE inhibitors result in efferent arteriolar vasodilatation, leading to a decrease in intraglomerular pressure, which in turn leads to a decreased transport of protein across the glomerular filter. Patients who are treated with ACE inhibitors are less likely to increase their level of proteinuria and are less likely to lose their renal function than are patients who are not treated with these agents. This was first apparent in the treatment of diabetic nephropathy, but there is evidence that ACE inhibitors offer advantages to patients with other nephropathies as well. Angiotensin II blockers offer another avenue for accomplishing a decrease in intraglomerular pressures, and these also decrease proteinuria when used alone or in conjunction with an ACE inhibitor. ACE inhibitors and angiotensin II blockers may be useful for patients with proteinuria either as a 1st step or as adjunctive therapy for those who fail to respond to other medications.

SUMMARY AND RED FLAGS

Asymptomatic proteinuria may be associated with nonspecific febrile benign illnesses, postural mechanisms, and glomerular or tubular dysfunction. Significant proteinuria with edema suggests nephrotic syndrome, which in most children suggests minimal change nephrotic syndrome. An age younger than 1 year or older than 10 years plus significant hematuria, azotemia, and hypertension are red flags that suggests a cause of nephrosis other than the more benign minimal change disease. Additional red flags include a poor response to prednisone therapy and signs of multiple organ system involvement by a primary systemic disease, such as SLE. Fever and abdominal pain in a patient with nephrotic syndrome should suggest spontaneous primary bacterial peritonitis.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline on Glomerulonephritis (GN), Chapters 3 and 4.

Bergstein JM. A practical approach to proteinuria. *Pediatr Nephrol*. 1999;13:697-700.

Bonilla-Felix M, Parra C, Dajani T, et al. Changing patterns in the histopathology of idiopathic nephrotic syndrome in children. *Kidney Int*. 1999;55:1885-1890.

Chesney RW. The idiopathic nephrotic syndrome. *Curr Opin Pediatr*. 1999;11:158-161.

Durkan A, Hodson E, Willis N, et al. Non-corticosteroid treatment for nephrotic syndrome in children. *Cochrane Database Syst Rev*. 2001;(4):CD002290.

Gorensek MJ, Lebel MH, Nelson JD. Peritonitis in children with nephrotic syndrome. *Pediatrics*. 1988;81:849.

Greenstein SM, Delrio M, Ong E, et al. Plasmapheresis treatment for recurrent focal sclerosis in pediatric renal allografts. *Pediatr Nephrol*. 2000;14:1061-1065.

Hodson EM, Knight JF, Willis NS, et al. Corticosteroid therapy for nephrotic syndrome in children. *Cochrane Database Syst Rev*. 2001;(1):CD001533.

Hogg RJ, Portman RJ, Milliner D, et al. Evaluation and management of proteinuria and nephrotic syndrome in children: Recommendations from a pediatric nephrology panel established at the National Kidney Foundation Conference on Proteinuria, Albuminuria, Risk, Assessment, Detection, and Elimination (PARADE). *Pediatrics*. 2000;105:1242-1249.

Homberg C, Jalanko H, Tryggvason K, et al. Congenital nephrotic syndrome. In: Barratt TM, Avner ED, Harmon WE, eds. *Pediatric Nephrology*. Baltimore: Lippincott Williams & Wilkins; 1999:765-777.

Korbet SM. Clinical picture and outcome of primary focal segmental glomerulosclerosis. *Nephrol Dial Transplant*. 1999;14:68-73.

Leung AK, Robson WL. Evaluating the child with proteinuria. *J R Soc Health*. 2000;120:16-22.

Lin CY, Sheng CC, Chen CH, et al. The prevalence of heavy proteinuria and progression risk factors in children undergoing urinary screening. *Pediatr Nephrol*. 2000;14:953-959.

McBryde KD, Kershaw DB, Smoyer WE. Pediatric steroid-resistant nephrotic syndrome. *Curr Probl Pediatr Adolesc Health Care*. 2001;31:280-307.

Nephrotic syndrome in children: Prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. A report of the International Study of Kidney Disease in Children. *Kidney Int*. 1978;13:159-165.

The primary nephrotic syndrome in children: Identification of patients with minimal change nephrotic syndrome from initial response to prednisone. A report of the International Study of Kidney Disease in Children. *J Pediatr*. 1981;98:561-564.

Remuzzi G, Ruggenenti P, Benigni A. Understanding the nature of renal disease progression. Perspective in Clinical Nephrology. *Kidney Int*. 1997;51:2-15.

Ronco P, Debiec H. Pathophysiological advances in membranous nephropathy: time for a shift in patient's care. *Lancet*. 2015;385:1983-1992.

Rood I, Deegens J, Wetzels J. Genetic causes of focal segmental glomerulosclerosis: implications for clinical practice. *Nephrol Dial Transplant*. 2012;27:882-890.

Roth KS, Amaker BH, Chan JC. Nephrotic syndrome: Pathogenesis and management. *Pediatr Rev*. 2002;23:237-248.

Ruggenenti P, Perna A, Gherardi G, et al. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet*. 1999;53:359-364.

Rytand DA, Spreiter S. Prognosis in postural (orthostatic) proteinuria. *N Engl J Med*. 1981;305:618.

Trompeter RS, Lloyd BW, Hicko J, et al. Long-term outcome for children with minimal change nephrotic syndrome. *Lancet*. 1985;1:368.

Vehaskari VM, Rapola J. Isolated proteinuria: Analysis of a school-age population. *J Pediatr*. 1982;101:661.

Yashikawa N, Kitagawa K, Ohta K, et al. Asymptomatic constant isolated proteinuria in children. *J Pediatr*. 1991;119:375.

20

Hematuria

Scott K. Van Why and Cynthia G. Pan

Hematuria is a common issue faced by primary physicians who care for children. While it can cause great anxiety in the patient and family when it presents as gross hematuria, rarely does hematuria alone herald a serious illness during childhood. Indeed, despite thorough evaluation, no cause can be found in a large percentage of children who have hematuria. Nearly 40% of children who present with gross hematuria and 80% of patients with persistent, isolated microscopic hematuria have no identifiable cause despite a thorough investigation. This raises the question of how much investigation should be performed on a child who presents with hematuria, particularly if it is isolated microscopic hematuria because the evaluation can be costly and at times invasive.

How extensive an evaluation is appropriate depends much on the context. Those children who present with gross hematuria or microscopic hematuria with associated signs or symptoms deserve a thorough evaluation. These two groups contain those more likely to have an identifiable cause and include the subset that has an acute or potentially serious illness that can progress to significant morbidity or sequelae if not identified and treated. Associated symptoms and signs that indicate the need for prompt evaluation include other urinary or systemic symptoms that led to testing the urine for blood, and findings of hypertension, edema, poor growth, fever, or other systemic signs at presentation.

The more difficult question is how much testing is required of an apparently healthy child discovered to have isolated microscopic hematuria on routine screening urinalysis. Thorough testing of such a child with no symptoms, a normal physical examination, and no significant family history of kidney disease rarely identifies a cause of hematuria. Therefore, the utility of performing a screening urinalysis in children, with the potential attendant costly and usually uninformative additional investigation, has long been questioned. The American Academy of Pediatrics does not recommend screening urinalysis for early school-aged children. It is reasonable to screen children who have a significant family history of kidney disease, particularly if there is a family history of hereditary nephritis.

GROSS HEMATURIA

Gross hematuria, defined as blood in the urine visible to the naked eye, is a dramatic symptom that is usually brought to medical attention, unless an older child with the symptom is too frightened to bring it to the attention of the parents. Carefully defining the appearance of the urine can be the first and a major clue to the origin of the blood. Hematuria emanating from a nonglomerular, lower urinary tract source can present as frankly bloody urine varying in color from dark red, cherry, or pink-tinged urine. On occasion, lower tract hematuria can result in passing blood clots. Seeing blood in the urine only on initiation or at termination of voiding is an additional clue that the source is from the lower tract. Blood seen at the urethral meatus or only on initiation of voiding suggests a urethral source. In contrast, hematuria originating from a glomerular source more often presents with description of other color changes in the urine, such as brown-, cola-, tea-, or on occasion, even green-colored urine.

The first step when presented with this symptom is to perform a urinalysis. If no hemoglobin is found on macroscopic urinalysis, then causes of urine discoloration other than hematuria need to be considered (Table 20.1). One fairly common presentation that can be particularly frightening to a parent is finding a pink or red-tinged wet diaper, thought to be blood in the urine. This most often is from a simple benign entity commonly called **red diaper syndrome**, caused by precipitation of urate crystals in the diaper. A macroscopic urinalysis negative for heme indicates this to be the most likely cause, and in an otherwise healthy infant, no further investigation is warranted.

If red blood cells are found in the urine of a child with a history suggestive of gross hematuria, then evaluation for potential causes is needed (Tables 20.2 and 20.3 and Fig. 20.1). The first step is a thorough history and physical examination.

◆ History

Development of **pain** with the onset of hematuria usually indicates a lower urinary tract source. Irritative symptoms, such as dysuria, urgency, or frequency can be seen in bleeding from the bladder from a variety of causes. Although not a typical feature of urinary tract infection (UTI), the most common identifiable cause of gross hematuria is a UTI, and is usually accompanied by significant dysuria or abdominal pain, and sometimes fever. Severe and episodic or colicky flank or abdominal pain should raise suspicion for urolithiasis, which may have accompanying dysuria as the stone is being passed. Urinary tract obstruction, such as posterior urethral valves in boys or ureteropelvic junction obstruction in either sex, may remain occult until infection or trauma causes hematuria. In the former, the only preceding symptoms may be a boy who voids only infrequently, commonly strains to void, or has ongoing urinary incontinence beyond the toddler years. Bleeding from renal tumors is an uncommon cause of gross hematuria in children, but should be considered particularly in the setting of associated abdominal pain, a palpable mass, or passing of blood clots.

Gross hematuria due to glomerular disease is rarely accompanied by significant pain, though some may report mild abdominal pain or flank discomfort. An exception is Henoch-Schönlein purpura, a common pediatric systemic vasculitis, which can have variable, including severe, gastrointestinal disease. Clues to underlying glomerular disease may be a recent history of pharyngitis, streptococcal skin infection, or other febrile illnesses, indicating possible acute postinfectious glomerulonephritis. Patients with glomerulonephritis or renal insufficiency may report shortness of breath, edema, or weight gain from fluid retention. They may also have a headache or visual changes secondary to severe hypertension. Abdominal pain, diarrhea, hematochezia, rash, and arthralgias are symptoms indicative of a systemic vasculitis, such as Henoch-Schönlein purpura (HSP).

(See *Nelson Textbook of Pediatrics,* p. 2494.)

Recurrent, painless gross hematuria is often seen in young patients with IgA nephropathy in association with concurrent respiratory illness. Recurrent fever, weight loss, alopecia, mouth ulcers, chest pain, fatigue, and arthritis suggest systemic lupus erythematosis. Hemoptysis or cough is seen in pulmonary-renal syndromes caused by antineutrophil cytoplasmic antibody (ANCA) associated disease, and on occasion in lupus and HSP.

The patient's **medical history** may be most informative. Stressed neonates from birth asphyxia, infection, or volume depletion can develop renal vein thrombus that presents as gross hematuria. Patients with African ancestry should be queried for personal or family history of sickle cell hemoglobinopathy, since gross hematuria from renal papillary necrosis can occur in those with sickle cell disease as well as in children with simple sickle cell trait. Medication history can uncover a cause of gross hematuria from drug-induced interstitial nephritis, seen with several antibiotics, anticonvulsants, or nonsteroidal antiinflammatory drugs, the latter of which can also cause papillary necrosis. Cyclophosphamide can cause a severe hemorrhagic cystitis, which usually has concomitant prominent bladder symptoms.

A history of frequent or severe bleeding from other sites, such as heavy menses, prolonged nosebleeds, hemarthroses, or significant bleeding associated with surgical procedures suggests an undiagnosed bleeding disorder. Exposure history to tuberculosis should be obtained, as well as a travel history, as parasitic infections such as schistosomiasis of the bladder, uncommon in Western societies, is common in other parts of the world. Questions specific to other potential sources of blood in the urine include those directed at foreign body from self-instrumentation of the urethra, trauma, sexual abuse, and menstruation. Extreme sports activities such as running a marathon or long distance cycling can cause gross hematuria.

Review of the **family history** is important to uncover hereditary nephritis, hereditary cystic kidney disease, or potential benign familial hematuria. A family history of kidney disease leading to end-stage renal failure, especially if in men in multiple generations and if not clearly due to diabetes mellitus, would suggest Alport syndrome, the most common cause of hereditary nephritis. **Alport syndrome** is an X-linked recessive disorder that may cause gross hematuria in childhood although more often it is microscopic. When gross hematuria occurs in Alport syndrome, it is often triggered by any infectious process such as a common cold. The gross hematuria then subsequently clears, but microscopic hematuria is a persistent finding. The early clinical features of hereditary nephritis can be exactly the same as benign familial hematuria, but then evolve to develop other features. Early in the course of the disease, there is no associated proteinuria, but that feature develops later, often in childhood as the nephritis progresses. Hearing loss is a common but variable feature of Alport syndrome that tends to run in affected families. Female family members who are carriers usually have persistent and isolated hematuria that does not progress, but on occasion may develop progressive nephritis.

TABLE 20.1 Urine Discoloration from Sources Other Than Hematuria

Pink, Red, Cola-Colored, Burgundy	
Disease Associated	
Hemoglobinuria*	Porphyrinuria
Myoglobinuria*	
Associated with Drug or Food Ingestion	
Aminopyrine	Nitrofurantoin
Anthocyanin	Phenazopyridine
Azo dyes	Phenolphthalein
Beets	Pyridium
Blackberries	Red food coloring
Chloroquine	Rifampin
Deferoxamine mesylate	Rhodamine B
Iron sorbitol	Rhubarb
Methyldopa	Sulfasalazine
	Urates
Dark Brown, Black	
Disease Associated	
Alkaptonuria	Methemoglobinemia
Homogentisic aciduria	Tyrosinosis
Melanin	Bile pigments
Associated with Food or Drug Ingestion:	
Alanine	Resorcinol
Cascara	Thymol

*Heme tests positive.

TABLE 20.2 Laboratory Testing in Suspected Glomerulonephritis*

Symptoms	Suspected Glomerulonephritis	Laboratory
History of preceding pharyngitis, URI, or impetigo	Acute postinfectious GN	C3, C4 complement (low C3, normal C4)
Arthralgia, purpura, pedal edema, abdominal pain, hematochezia	Henoch-Schönlein purpura	Skin biopsy
Arthritis, rash, fever, oral ulcers, weight loss, alopecia, weakness, central nervous system symptoms, other systemic symptoms	Systemic lupus erythematosus	C3, C4 (both low) ANA, anti-ds DNA (both high)
Family history of renal failure, hearing loss, hematuria	Familial nephritis–Alport syndrome	Audiogram, slit lamp exam, genetic testing
Recurrent, painless gross hematuria	IgA nephropathy	None (kidney biopsy)
Hemoptysis, cough, fevers	Goodpasture syndrome	anti-GBM Ab
Rash, sinus disease, hemoptysis, systemic symptoms	ANCA-associated vasculitis	ANCA

*All patients: serum creatinine, electrolytes, complete blood count, random urine protein:creatinine ratio, 24-hr urine collection for protein.
Ab, antibody; GN, glomerulonephritis; URI, upper respiratory infection; ANA, antinuclear antibody; anti-ds (native) DNA, anti-double stranded DNA antibody; anti-GBM, anti-glomerular basement antibody; ANCA, antineutrophil cytoplasmic antibody.

TABLE 20.3 Causes of Gross Hematuria in Children

Glomerular

Primary

Acute postinfectious glomerulonephritis
IgA nephropathy*
Mesangial proliferative glomerulonephritis
Membranoproliferative glomerulonephritis
Familial nephritis (Alport syndrome)
Benign familial hematuria - thin basement membrane disease
Rapidly progressive glomerulonephritis

Systemic

Henoch-Schönlein purpura
Systemic lupus erythematosus
Hemolytic uremic syndrome
ANCA-associated vasculitis
Goodpasture disease (rare in childhood)
Bacterial endocarditis

Interstitial Disease

Pyelonephritis
Acute interstitial nephritis
Polycystic kidney disease (autosomal dominant)

Vascular

Trauma
Sickle cell disease and trait
Renal artery/vein thrombosis
Arteriovenous malformation
Nutcracker syndrome
Sports- and exercise-induced hematuria
Hemangioma/hamartoma

Neoplastic

Wilms tumor
Renal cell carcinoma
Uroepithelial tumors
Rhabdoid tumors
Congenital mesoblastic nephroma
Angiomyolipoma

Urinary Tract

Cystitis
- Bacterial
- Viral (adenovirus)
- Parasitic (schistosomiasis)
- Tuberculosis
- Cyclophosphamide

Urethritis
Urolithiasis
Idiopathic hypercalciuria without urolithiasis
Trauma
Hydronephrosis, severe
Foreign body

Bleeding Disorders

Hemophilia A or B
Platelet disorder
Thrombocytopenia
Coagulopathy, congenital or acquired

*Common cause of asymptomatic gross hematuria.

Benign familial hematuria and familial thin basement membrane nephropathy are also responsible for both microhematuria and gross hematuria. The primary difference in family history that separates benign familial hematuria from progressive hereditary nephritis is that members of sequential generations of the family with benign familial hematuria, either male or female, have persistent isolated hematuria that never progresses to significant renal disease. The genetics of benign familial hematuria due to thin basement membrane nephropathy has been defined and includes mutations that are identical to those seen in some patients with *autosomal* recessive forms of progressive hereditary nephritis. Patients with thin basement membrane nephropathy, or benign familial hematuria, may be carriers of genes that cause autosomal recessive Alport syndrome.

Patients with **autosomal dominant polycystic kidney disease (ADPKD)** may present initially with gross hematuria from spontaneous bleeding into the macrocysts. Because the course of ADPKD can vary widely from one generation to the next, with some members having very mild disease with minimal clinical features until late adulthood, the family history of the disease may not be apparent on presentation. Early onset of hypertension, during youth or young adulthood in a parent of an affected child, may be the only clue to a family member being affected by ADPKD.

Gross hematuria is a presenting complaint in 15% of children with **urolithiasis**. Kidney stone disease can be familial and in some cases related to specific genes, as in X-linked recessive nephrolithiasis (Dent disease) or primary hyperoxaluria. Therefore, family history of early-onset nephrolithiasis, especially in siblings, should be sought in children presenting with gross hematuria and symptoms or imaging that indicate kidney stone disease as the cause. A family history of a bleeding disorder such as hemophilia or platelet disorders should be sought.

◆ Physical Examination

The initial focus of the physical examination should be for evidence of systemic disease for which the hematuria is one manifestation, and for potential sequelae of renal disease. Accurate measurement and attention to blood pressure, recognizing age differences in blood pressure, is critical. **Hypertension** may be the sole feature on physical examination that indicates underlying acute glomerulonephritis, or chronic kidney disease from several causes. The finding of **edema** in this context is highly suggestive of underlying renal parenchymal disease, either acute or chronic, with likely accompanying renal insufficiency. **Poor growth** or failure to thrive may indicate chronic renal disease. Pallor, fever, rashes, or musculoskeletal findings suggest systemic vasculitis with renal involvement from diseases such as HSP, SLE, or less often, ANCA-associated disease. Examination of the abdomen may reveal abdominal or flank masses that could be tumors, cystic kidneys, or urinary obstruction. The most common renal tumor in childhood, typically seen in young children (ages 1-4 years), is Wilms tumor, though other types occur. Hydronephrosis or enlarged cystic kidneys may be palpable. Suprapubic tenderness may indicate bladder infection, stone, or other less common causes of bladder pathology as the source of blood. The genitalia may need to be inspected for blood at the urethral meatus that suggests a urethral source, tears or lacerations due to abuse or accidents such as from straddle injuries, or to look for a foreign body.

◆ Evaluation

Laboratory Tests

Macroscopic and microscopic examination of the urine is the first essential step in laboratory evaluation. If no heme is found on macroscopic examination, then other causes of urine discoloration need to be considered (see Table 20.1 and Fig. 20.1). If the urine is heme

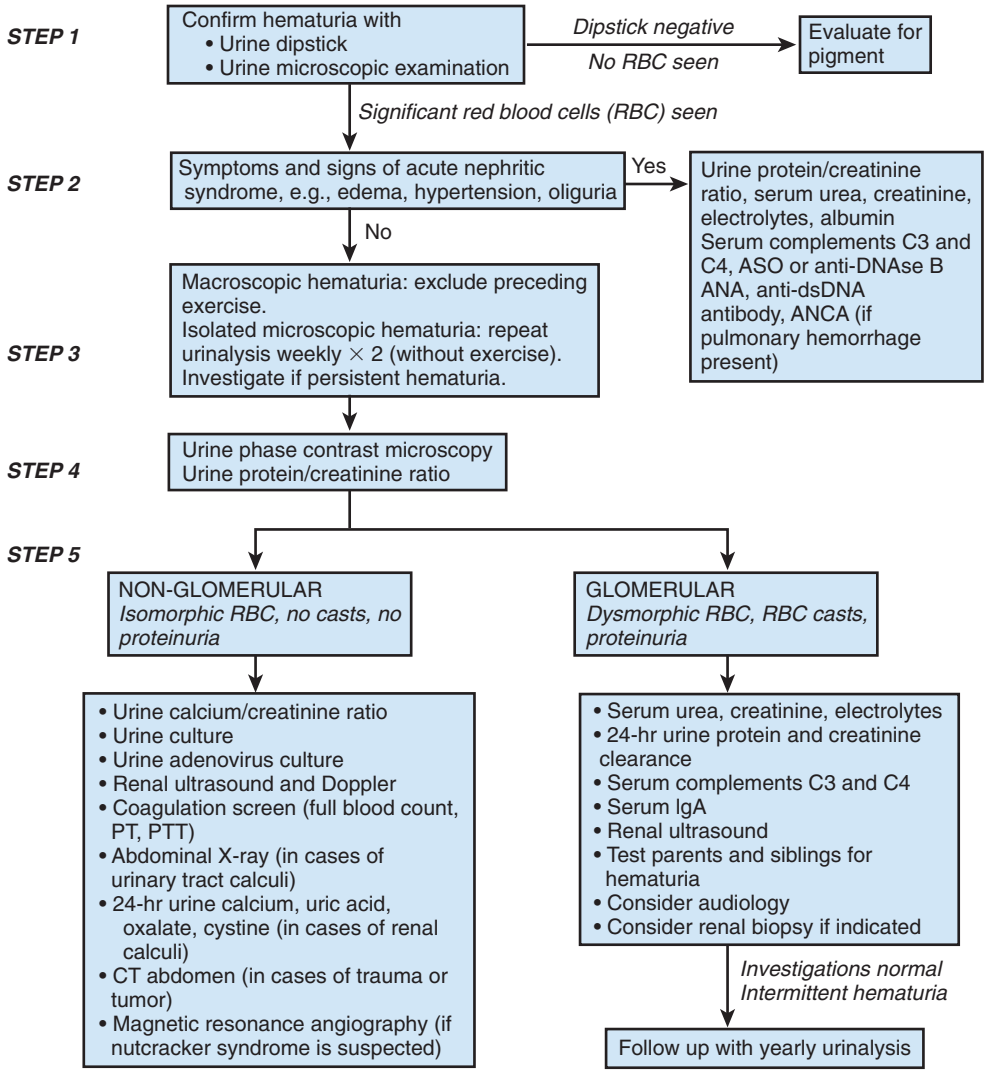


FIGURE 20.1 Algorithm for investigating hematuria. ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; ASOT, antistreptolysin titer; CT, computed tomography; IgA, immunoglobulin A; PT, prothrombin time; PTT, partial thromboplastin time. (From Yap HK, Lau PYW. Hematuria and proteinuria. In: Geary DF, Schaefer F, eds. *Comprehensive Pediatric Nephrology*. Philadelphia: Elsevier; 2008:183.)

positive on macroscopic examination, but no red cells are found on microscopic examination of the urine sediment, then myoglobinuria or hemoglobinuria need to be considered as the possible source, since **rhabdomyolysis** and **acute hemolysis** are both potential life-threatening diseases that require immediate attention. If urine is heme positive but no red cells are seen, and there is no evidence for rhabdomyolysis or acute hemolytic disease, then other reasons for the findings need to be considered. Urine test strips can on occasion be falsely positive for blood if the urine is infected with peroxidase-producing bacteria. More likely is that red cells were present but lysed in urine that either was very dilute or was held for an extended time before microscopic examination was performed. Finding red cell casts in a resuspended pellet of spun urine (centrifuged 3-5 minutes at 1500-2000 rpm) under high-power field is a clear indication that the source of hematuria is glomerular. While the specificity of this finding in localizing the source to the glomerulus is high, the sensitivity of finding red cell casts in the hands of clinical labs is low. When red cell casts have been found in the urine sediment by experienced nephrologists, clinical laboratory reports of finding RBC casts in the urine of the same patients is very low. Unless the urine is thoroughly examined by an experienced clinician, the lack of RBC casts in a lab report does not lower the chance the patient might have a glomerular source of the hematuria. Another finding on microscopic examination of the urine sediment that suggests a glomerular source is the presence of a significant number of dysmorphic red cells (see Fig. 20.1). This finding requires careful inspection of erythrocyte morphology and is best done with a phase-contrast microscope. Clinical labs do not report the number of dysmorphic red cells present, in part because differentiating dysmorphic RBCs from simple crenated RBCs (a result of osmotic shrinkage of RBCs) takes an experienced eye. Keeping these caveats in mind, if an experienced clinician finds RBC casts or a significant number of dysmorphic RBCs in a patient with hematuria, subsequent testing can be focused on identifying potential glomerular causes of hematuria, avoiding unnecessary, costly, or potentially invasive imaging procedures.

An additional feature of urinalysis that may help guide to the source of the red cells include the presence of proteinuria. Gross hematuria from lower tract bleeding can result in urine positive for protein, particularly if any lysis of urinary red cells occurs, but usually is <2+ proteinuria by dipstick reading. *Anything greater than 2+ proteinuria should raise suspicion of glomerular disease, especially if the hematuria is only microscopic.* Bacteria and significant pyuria

suggest pyelonephritis or cystitis, but pyuria can also be a feature of acute suppurative glomerulonephritis. Quantification of the gross hematuria using a "urocrit," with a result >1% can indicate lower tract bleeding.

All patients with suspected glomerulonephritis or suspected chronic kidney disease should have prompt assessment of their renal function with a serum creatinine, and a complete blood count. Serologic studies for immune-mediated glomerulonephritis should be performed including complement levels (C3, C4), antinuclear antibody, and anti–double-stranded DNA antibody. Antineutrophil cytoplasmic antibody titers (ANCA) and anti–glomerular basement membrane antibody titers should also be obtained if vasculitis or pulmonary renal syndromes are suspected (see Table 20.2 and Fig. 20.1).

The diagnosis of most cases of postinfectious glomerulonephritis (GN) can be made clinically. The diagnosis of HSP is also made clinically, but skin biopsy of purpuric lesions demonstrating vasculitis with predominantly IgA deposits can be supportive evidence. A kidney biopsy is often needed to define other forms of glomerulonephritis, especially primary, idiopathic glomerulopathies. In addition, even if the diagnosis of vasculitis is made on clinical and serologic criteria, staging of the severity of renal disease with renal pathology, such as in SLE, HSP, or ANCA-positive disease, is important for guiding therapy. High levels of proteinuria are often an indication to obtain a kidney biopsy to provide a diagnosis or stage the severity of the lesion in several forms of glomerulonephritis. The degree of proteinuria can be assessed with a 24-hour urine collection, or with a spot urine protein : creatinine ratio (see Chapter 19).

A urine culture is indicated in patients with any bladder symptoms, fever, flank pain, or abdominal pain. Gross hematuria can also be seen with nonbacterial infections such as tuberculosis, adenovirus, or schistosomiasis. In immunocompromised patients, BK polyoma virus can cause prominent cystitis.

Idiopathic hypercalciuria can be a cause of gross hematuria. It is characterized by excessive urinary calcium excretion in the absence of hypercalcemia or other known causes of hypercalciuria (Table 20.4). The hematuria is thought to be secondary to calcium oxalate and phosphate crystals adhering to urothelium. The risk of developing kidney stones is not known. Although often asymptomatic, hypercalciuria is also implicated in causing urinary symptoms including abdominal and flank pain. Therefore, in a patient who has any such symptom concomitant with gross hematuria, especially if UTI and anatomic causes of hematuria are ruled out, urinary calcium should be measured.

Hypercalciuria is defined by a 24-hour urine for calcium excretion >4 mg/kg/day. A spot urine calcium : creatinine ratio of >0.22 is considered abnormal in the older child and adolescent, but normal values may be significantly higher in younger children, especially those less than 7 years of age.

Imaging and Cystoscopy

Renal imaging with noninvasive ultrasonography is recommended in all cases of gross hematuria, unless strong evidence for glomerulonephritis is found on clinical grounds as detailed earlier. Ultrasound is excellent in children to investigate potential urologic and congenital abnormalities, as well as certain genetic diseases including polycystic kidney disease and those causing nephrocalcinosis, such as Dent disease. The ultrasound should include imaging of the bladder, which can identify rare bladder tumors, as well as find evidence of obstructive urologic disease. Ultrasound can also provide some evidence for renal parenchymal disease. Enlarged, echogenic kidneys with poor corticomedullary differentiation may be seen in significant glomerular or interstitial nephritis. Nephrolithiasis or calcinosis may be found on ultrasound, as well as hydronephrosis secondary to urinary obstruction from lower tract kidney stones. Urolithiasis may be missed on ultrasound; if the history and examination are highly suggestive of a stone as the source of the hematuria, a CT scan is then necessary.

Computed tomography (CT) imaging is most useful to identify kidney stones (using the helical technique) and is the primary indication to perform this study. CT also provides detailed images of the bladder, pelvis, and retroperitoneum when looking for masses. Angiogram of the kidney may be necessary to identify an arteriovenous malformation of the kidney.

Cystograms generally have no major role in the evaluation of gross hematuria unless there is ultrasound evidence of bladder outlet obstruction from unrecognized urethral valves, or an unusual mass such as a urothelial tumor, rhabdomyosarcoma, or fibromatous polyp. Cystoscopy is rarely indicated in the usual evaluation of hematuria in children. However, if passing blood clots is part of the presentation, or if renal and bladder ultrasound shows a bladder mass or an obstructive lesion, cystoscopy may then be definitive in diagnosing bladder and ureteral sources of bleeding and provides an opportunity to obtain tissue for diagnosis. Cystoscopy may also be helpful to look for unilateral bleeding from one ureter, which can be seen with renal papillary necrosis, or more uncommon lesions such as vascular malformations of the bladder or ureter, all of which can be difficult to define by radiologic methods.

TABLE 20.4 Causes of Hypercalciuria

Physiologic Stimuli to Calcium Excretion
Sodium excretion
Acidosis
Hypophosphatemia

Increased Filtered Load
Hypercalcemia (hyperparathyroidism, dietary, vitamin D excess)
Excess calcium administration

Impaired Renal Tubular Reabsorption of Calcium
Loop diuretics
Selective tubular defects
Bartter syndrome
Hereditary hypophosphatemic rickets with hypercalciuria
Syndrome of hypercalciuria, normocalcemia, growth retardation, polyuria, and proteinuria (Dent disease)
Renal tubular acidosis
Fanconi syndrome

Idiopathic Hypercalciuria
Absorptive
Renal leak

Hypercalciuria of Unknown Cause
Medullary sponge kidney
Diabetes mellitus
Syndrome associated with total parenteral nutrition

From Milliner DS, Stickler GB. Hypercalcemia, hypercalciuria, and renal disease. In: Edelmann CM, ed. *Pediatric Kidney Disease*. 2nd ed. Boston: Little, Brown; 1992:1661-1687.

MICROSCOPIC HEMATURIA

While thorough evaluation of gross hematuria is always warranted, how far to proceed with the evaluation of microscopic hematuria can

be a difficult question. Much depends on the context in which the microscopic hematuria was identified. Thorough evaluation of microscopic hematuria identified on a screening urinalysis at a well-child visit rarely reveals an etiology. One exception is when there is a **family history** of renal disease known or suggestive to be from hereditary nephritis. In that context, particularly if in a pattern indicative of Alport disease where there can be associated hearing loss, performing a screening urinalysis to determine whether a child may be affected is reasonable. The lack of any hematuria in an older child effectively rules out that child having hereditary nephritis. If microscopic hematuria is found, additional noninvasive study can help define whether a child has Alport disease, including audiometry to evaluate for subclinical high frequency hearing deficit and examination by an ophthalmologist who can identify retinal or lens abnormalities that are characteristic of Alport disease. If no hearing or ophthalmologic abnormalities are found, and if proteinuria accompanies microscopic hematuria in a child from a family affected by hereditary nephritis, further investigation may include collagen IV gene sequencing or kidney biopsy.

When microscopic hematuria is found on urinalysis performed because of symptoms or signs, further evaluation is then indicated. If the presentation was with urinary symptoms or abdominal or flank pain, urine culture and imaging of the urinary tract, first with ultrasound to include the bladder, is the first step. If those tests are not revealing, and particularly if abdominal or flank pain is colicky, abdominal CT scan with kidney stone protocol is then indicated. If imaging studies are normal and urine culture is negative, evaluation for idiopathic hypercalciuria may then be pursued.

Abnormalities on physical examination that led to a urinalysis being performed should drive further evaluation for underlying intrinsic kidney disease. Specifically, if hypertension, edema, or failure to thrive triggered the urinalysis, blood tests to assess kidney function and complete blood count should be performed. If acute glomerulonephritis is suspected because of prodromal illness, hypertension, or edema, blood complement C3 and C4 levels should also be measured. If other symptoms or signs suggest possible systemic vasculitis, testing for lupus or ANCA-associated disease should then be considered. If the patient has had poor growth suggesting a chronic process, or supportive evidence for acute nephritis is lacking, renal ultrasound may identify small kidneys indicating a chronic nephropathy, obstructive nephropathy, or cystic kidney disease as the etiology.

MORE COMMON CAUSES OF HEMATURIA

Postinfectious Glomerulonephritis

Gross hematuria appearing 5 days to 4 weeks after a febrile illness suggests a diagnosis of acute postinfectious glomerulonephritis (PIGN), the most common form of acute nephritis in childhood. The typical child with PIGN is school age. The classical findings are hematuria, oliguria, edema, some level of renal insufficiency, and hypertension. It is not uncommon for PIGN to be asymptomatic, and hypertension may not be a feature at initial presentation. The child with suspected PIGN requires close follow-up including monitoring for the development of hypertension, since severe symptomatic hypertension is a common sequela of acute PIGN.

PIGN is a self-limited disease that in the vast majority of cases resolves without the development of chronic kidney disease or established hypertension. Microscopic hematuria is present in virtually all cases; gross hematuria is present in about 30%. The urine is commonly described as smoky or tea- or cola-colored. The gross hematuria usually disappears in 3-5 days; proteinuria disappears in several weeks, and microscopic hematuria resolves in months to 1 year. Group A streptococcal (GAS) infection is the most well-defined cause, described in up to 80% of patients with PIGN, with the triggering infection being either pharyngeal or impetiginous. Other infectious agents have also been implicated in causing PIGN, including several other bacteria and viruses.

The criteria for diagnosis of PIGN relies on defining the clinical picture, supported by finding glomerular hematuria (red cell casts or many dysmorphic RBCs) in the urine sediment by an experienced examiner, and a simple serologic pattern. Practitioners will commonly perform serologic testing for streptococcal infection, an old habit that is not typically informative. Serology positive for anti-streptococcal antibodies at presentation is neither necessary nor sufficient to confirm, nor does the absence of such antibodies rule out, the diagnosis of PIGN. Evidence of recent streptococcal infection can be helpful, and may be provided by positive culture for GAS in the correct time frame preceding onset of nephritis. Most important is testing C3 serum complement level at presentation. In nearly all cases of PIGN, C3 level is low at presentation, then returns to normal by 6-12 weeks after presentation, as the nephritis spontaneously resolves. If the serum C3 level does not return to normal, other causes of nephritis need to be considered, including lupus nephritis, membranoproliferative glomerulonephritis (MPGN), or C3 nephropathy. The complement pattern in active lupus nephritis often is a low C4 along with the low C3 level. In MPGN or C3 nephropathy, C4 is usually normal with persistently low C3. If C3 level is normal at presentation of glomerulonephritis, other etiologies need to be considered, including several idiopathic forms that may only be diagnosed by kidney biopsy (see Tables 20.2 and 20.3).

Therapy for postinfectious GN is symptomatic, with particular attention to hypertension. Early treatment of the streptococcal infection does not prevent development of nephritis. The acute complications from PIGN are principally from hypertension and may include seizures, hypertensive encephalopathy, and heart failure. The prognosis of PIGN is excellent. Mortality is low at ~0.5%. While some level of renal insufficiency is typical, fulminant renal failure is uncommon. Complete recovery occurs in over 95% of patients, with an occasional patient developing rapidly progressive, crescentic GN or indolent chronic GN that progresses to end-stage kidney disease. Recurrent hematuria and proteinuria can occur in patients who have a nonspecific upper respiratory tract illness within several months following the episode of PIGN, but it is unusual for the other features of acute nephritis (hypertension and renal insufficiency) to recur.

Immunoglobulin A (IgA) Nephropathy

Recurrent episodes of painless, gross hematuria are a common presentation of childhood IgA nephropathy. This form of glomerulonephritis is common in both children and adults, with the mean age of presentation in children being 9-10 years. Episodes of gross hematuria are triggered by upper respiratory illnesses, but in contrast to postinfectious GN where the illness precedes onset of hematuria, in IgA nephropathy the illness is concurrent with onset of gross hematuria. Serum complement is normal. Serum IgA levels have been found to be elevated in only 8-16% of affected children, so are not helpful in the diagnosis. Confirmation of the diagnosis is possible only by renal biopsy demonstrating immune deposits of primarily IgA in glomeruli, principally in the mesangium. A wide range of histologic glomerulopathy can be found in IgA nephropathy, ranging from mild mesangial proliferation to crescentic, rapidly progressive GN. Most cases of IgA nephropathy have a benign pattern, with recurrent episodes of gross hematuria during illnesses, followed by complete resolution of gross hematuria within days. Between episodes, the urine may be free of blood or may show persistent microscopic hematuria but lack of proteinuria. This benign pattern commonly does not progress nor require

(See *Nelson Textbook of Pediatrics,* Fig. 511-3.)

treatment. However, the disease is quite variable between patients, with some developing acute nephritic symptoms, acute renal failure, nephrotic syndrome, or progression to end-stage kidney disease in up to 10% of affected children. No specific therapy exists for IgA nephropathy, but an extended course of steroid therapy can be beneficial for patients with more severe forms of IgA nephropathy, including those with acute nephritic syndrome or nephrotic-range proteinuria.

Hereditary Nephritis

A family history of renal disease with progression to renal failure, restricted to male members of the family on the maternal side, suggests a diagnosis of Alport syndrome, an X-linked recessive nephropathy. Affected patients uniformly have some level of hematuria beginning at an early age, even in infancy. The majority of affected children develop hematuria in the school-age years. Initially the hematuria is an isolated finding, but as the disease progresses proteinuria develops. Often there is accompanying development of progressive deafness. Female members of the family who carry the gene usually have isolated microscopic and sometimes periodic macroscopic hematuria that does not progress to the other features of the syndrome. However, occasionally such individuals can develop progressive disease similar to male family members. The disease is caused by a mutation in a gene on the X chromosome that codes for a chain of collagen found in normal glomerular basement membranes; gene testing can help confirm the diagnosis. Renal biopsy provides a definitive diagnosis, which shows characteristic electron microscopic appearance of attenuation, disruption, and lamellation of the glomerular basement membrane. However, these findings may not occur until a later age when the nephropathy has progressed. Early findings may simply be thin glomerular basement membranes, which can be confused with the more benign entity, thin basement membrane nephropathy. No specific therapy exists, but treatment with an angiotensin-converting enzyme (ACE) inhibitor early in the course of the disease after proteinuria develops can slow the progression of the nephropathy.

There is also an autosomal recessive variant of hereditary nephritis that has been associated with mutations in genes that code for other chains of collagen found in the glomerular basement membrane. Progression of the nephropathy is similar to that of patients with the classical form of Alport disease. Individuals who carry a mutation in only one of these autosomal recessive genes may have simple, benign, thin basement membrane nephropathy that does not progress.

Some patients with a more common form of familial hematuria demonstrate persistent microscopic and recurrent gross hematuria *without* development of significant proteinuria or deterioration of renal function. This is called **benign familial hematuria**. Evidence of this cause of hematuria can be obtained when urinalyses are performed on other family members, finding isolated microscopic hematuria in other members of the family. Renal biopsy demonstrates normal light and immunofluorescent microscopic findings. Electron micrographs show uniformly thin basement membranes leading to it being termed "thin membrane nephropathy." It appears to be an autosomal dominant disorder; some such families have been reported to be carriers of mutations of collagen genes that are associated with autosomal recessive hereditary nephritis. This raises the possibility that benign familial hematuria is the hypomorphic state of progressive hereditary nephritis.

Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD) is a common disorder that mainly affects adults, but development of cysts may well begin in childhood, and in rare cases renal cysts may be present at birth. Usually the cysts are asymptomatic in childhood unless there is early and substantial cystic disease. Gross hematuria may be the first manifestation of this disorder and occurs in 50% of patients. It may occur spontaneously or be brought on by minimal trauma. The usual manifestations of the disease in adults (hematuria, hypertension, abdominal mass, and uremia) are seldom seen in children. Furthermore, adults tend to have associated problems not commonly seen in affected children, including acute and chronic pain (60%), urinary tract infection, and nephrolithiasis (20%). With the widespread use of ultrasonography and CT for routine evaluation of acute abdominal pain, it is more common to detect early evidence of the disease as an incidental finding, sometimes presenting as a single renal cyst during childhood. Diagnosis requires finding multiple bilateral renal cysts. Because the primary gene that causes ADPKD lies near the gene that causes tuberous sclerosis, the two diseases occasionally coexist as a contiguous gene deletion syndrome. Renal involvement in patients with tuberous sclerosis may be isolated to renal angiomyolipomas or may also manifest PKD as well, either of which can be a source of gross hematuria.

In contrast to ADPKD, **autosomal recessive polycystic kidney disease (ARPKD)** typically has early onset and evidence of renal disease is often found on prenatal ultrasound. If not discovered in the perinatal period, it may present later in infancy or early childhood as an abdominal mass with hypertension. Typically, the kidneys are significantly enlarged and have a cystic appearance different from ADPKD. However, it is not always possible to distinguish early-onset ADPKD from ARPKD on radiologic grounds.

Nephrolithiasis can occur at any age and may cause the symptoms of renal colic, manifested as intense, episodic flank pain that often radiates to the groin. In young infants, nephrolithiasis and thus renal colic is rare, and may manifest as generalized irritability or abdominal pain. Gross hematuria has been reported in ~25% of patients with nephrolithiasis. The physical examination may be unrevealing; the urinalysis may contain crystals in addition to red blood cells. A high-resolution CT scan is the best study to confirm the presence of a stone. Children with nephrolithiasis should have an evaluation for a metabolic cause of their kidney stones. This begins with a 24-hour urine collection for calcium, urate, citrate, oxalate, cystine, and creatinine. The determination of creatinine excretion is important to ensure that an adequate collection has been obtained (a minimum of 10-15 mg/kg/24 hr, depending on age and body habitus of the child). If an abnormality is found, specific therapy may prevent or delay subsequent complications, which can include frequently recurring stones and acute or chronic renal failure.

Hypercalciuria (defined as urinary calcium levels above 4 mg/kg/day) is the most common metabolic abnormality found in children with nephrolithiasis. Furthermore, hypercalciuria without an overt stone can manifest as gross hematuria with abdominal or flank pain. Hypercalciuria can be idiopathic or secondary to another disease, such as renal tubular acidosis. Therapy depends on the cause of the hypercalciuria or the specific type of stone.

Urinary tract infection is the most common identifiable cause of gross hematuria, with as many as 25% of children presenting with gross hematuria having a documented symptomatic urinary tract infection. Urine culture is essential for a diagnosis of urinary tract infection, and should be performed in all children with gross hematuria, especially if any urinary symptoms accompany.

UNCOMMON CAUSES OF HEMATURIA IN CHILDHOOD

Coagulation abnormalities and hemoglobinopathies are rarely found in patients with gross hematuria. **Sickle cell disease** is the most likely

(See *Nelson Textbook of Pediatrics,* p. 2497.)

(See *Nelson Textbook of Pediatrics,* p. 2515.)

(See *Nelson Textbook of Pediatrics,* p. 1065.)

cause in this category, and gross hematuria is one of the few manifestations of the carrier state that may develop in those with sickle cell trait. A combination of low oxygen tension, reduced blood flow, low pH, and high osmolality in the renal medulla makes a hostile environment that induces sickling and sludging of erythrocytes there. This results in areas of infarction and hemorrhage and can progress to renal papillary necrosis. While the gross hematuria often is asymptomatic, if papillary necrosis ensues or hemorrhage from the renal medulla is substantial with passage of clots, acquired ureteral obstruction can cause significant associated flank or abdominal pain. Therapy is hydration and rest.

Renal vascular thrombosis, particularly renal vein thrombosis, may present with isolated gross hematuria. Two groups of children are at highest risk for this problem. The first group is sick neonates. Renal vascular thrombosis in this group can originate from events associated with perinatal stress that cause hypotension and decreased perfusion to the kidney, umbilical vascular catheters, trauma, hypercoagulable states, dehydration, or disseminated intravascular coagulation. Infants of diabetic mothers are more prone to renal vein thrombosis, possibly because of polycythemia or other associated perinatal stress. The thrombosis in the neonate can be in the renal artery but most often is in the renal vein. Along with gross hematuria, accompanying clinical features may include a palpable enlarged kidney on the affected side, hypertension, and thrombocytopenia. The second group of children who are susceptible to renal vascular thrombosis are those with **nephrotic syndrome**, with the well described associated hypercoagulable state (see Chapter 19). The diagnosis of renal vein thrombosis can be suspected from the patient's history and can be confirmed with a Doppler flow study of the renal vasculature. Several treatment approaches have been advocated. In many cases, careful attention to hydration and hemodynamic status in the neonate, and administration of albumin in the patient with nephrotic syndrome stabilizes the patient with no further progression of the thrombus. With large thrombi that propagate to the vena cava or affect both kidneys, anticoagulation is considered. Renal vein thrombi, even with isolated supportive care, often resolve without late renal sequelae. However, late sequelae of hypertension and renal atrophy can occur. The less common renal artery thrombi more often result in significant renal injury and atrophy.

Renal and bladder **tumors** are rare causes of gross hematuria in children. Wilms tumor, the most common pediatric renal malignancy, usually manifests as a flank or abdominal mass, but on occasion can present with gross hematuria. Renal carcinoma is exceedingly rare in childhood, but can occur in older children and also may present as gross hematuria. Each of these tumors can be readily detected radiographically through ultrasonography or computed tomography, which is why imaging of the urinary tract to include the bladder is an important part of the evaluation of all children with gross hematuria unless the source of the blood has clearly been defined to be of glomerular origin.

Cyclophosphamide treatment can cause **hemorrhagic cystitis**, which can have accompanying severe bladder symptoms and hemorrhage. This results from prolonged contact of the toxic metabolites of cyclophosphamide with the bladder epithelium. Prevention is primarily with increased hydration to ensure high urine flow, and the use of mesna in patients receiving high-dose cyclophosphamide, a drug that prevents bladder mucosa toxicity from the metabolites.

High intensity or long-duration **physical exertion** can cause gross hematuria. Its pathophysiology is not known, but several mechanisms proposed include bladder or kidney trauma, hemolysis, dehydration, peroxidation of red cells, and renal ischemia.

Bleeding from **arteriovenous malformations** of the kidney, ureter, or bladder can manifest as asymptomatic gross hematuria, which often appears bright red. The blood can be localized to the bladder, one kidney, or ureter with cystoscopy. Endoscopic laser treatment can eliminate the source of bleeding. When bleeding from a vascular malformation is severe and not amenable to laser treatment, an angiograph and surgery are considered.

Nutcracker syndrome occurs when the left renal vein is compressed between the superior mesenteric artery and aorta, causing a rise in pressure and development of collateral veins with varicosities in the renal pelvis, ureter, and gonadal vein. It presents with left flank pain, hematuria, and occasionally a varicocele in males. Diagnosis can be difficult, but Doppler studies of the left renal vein, magnetic resonance angiography, and computed tomography may identify this entity.

Symptoms of urethritis with gross hematuria and a negative urine culture in boys suggest urethrorrhagia. The most common complaint is blood-stained underwear. Ultrasound including the bladder should be performed to rule out other lesions discussed earlier. Cystoscopy does not show a treatable lesion and may be contraindicated because of the possibility of producing a stricture. Low-dose, long-term antibiotic treatment may help in some cases. The condition appears to be benign and self-limited, so reassurance is the best approach.

Infections that are unusual in Western societies, but more common in other parts of the world can present with gross hematuria. *Schistosoma haematobium* causes bladder lesions, containing eggs and a surrounding granuloma, that may hemorrhage. Urinary symptoms of suprapubic pain, dysuria, or urgency are common. Chronic inflammation of the ureters may result in urinary obstruction. Diagnosis is made by biopsy of lesions found in the liver, rectum, or bladder, or by the detection of characteristic eggs in feces or urine.

Mycobacterium tuberculosis infection can involve the kidneys, resulting in formation of tuberculomas that may cavitate, rupture, and disseminate the bacterium throughout the urinary tract. Tuberculosis of the genitourinary tract most often occurs in young adults and is characterized by tubercles at the ureteral orifices.

Adenovirus is a common respiratory infection in children, which can cause a hemorrhagic cystitis. This complication occurs most often in immunocompromised patients, but on occasion can also affect normal, healthy children.

RED FLAGS

Blood visible in the urine commonly raises great concern in a child and the parents, and sometimes in the physician, but rarely heralds a serious disease. Parents frequently are concerned that hematuria is a manifestation of a malignancy, so this should be addressed initially with reassurance that it is very rare for the cause of hematuria in a child to be a tumor. The history of recent or current illness and the family history, as well as associated signs or symptoms, can usually direct the appropriate evaluation. The focus of testing initially should be on confirming the presence of hematuria, ruling out urinary infection with culture, assessing renal function with blood tests, and

exploring urinary tract anatomy with ultrasound. Invasive studies, such as cystoscopy or renal biopsy, are rarely indicated.

Features of the evaluation that require prompt attention include absence of red blood cells in the urine (which raises the concern for possible hemoglobinuria or myoglobinuria), hypertension, azotemia, pain, or a palpable mass. The presence of significant proteinuria suggests glomerular disease, which would require further evaluation by a nephrologist for consideration of renal biopsy.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Allen CW, Alexander SI. Adenovirus associated haematuria. *Arch Dis Child*. 2005;90:305-306.

Bergstein J, Leiser J, Andreoli S. The clinical significance of asymptomatic gross and microscopic hematuria in children. *Arch Pediatr Adolesc Med*. 2005;159:353-355.

DeFoor W, Minevich E, Sheldon C. Unusual bladder masses in children. *Urology*. 2002;60:911vii-911x.

Edvardsson VO, Goldfarb DS, Lieske JC, et al. Hereditary causes of kidney stones and chronic kidney disease. *Pediatr Nephrol*. 2013;28:1923-1942.

Feld LG, Meyers KEC, Kaplan MB, et al. Limited evaluation of microscopic hematuria in pediatrics. *Pediatrics*. 1998;102(4):1-5.

Fernandes ET, Manivel JC, Reinberg Y. Hematuria in a newborn infant caused by bladder hemangioma. *Urology*. 1996;47:412-415.

Fine SW, Humphrey PA, Dehner LP, et al. Urothelial neoplasms in patients 20 years or younger; a clinicopathological analysis using the World Health Organization 2004 bladder consensus classification. *J Urol*. 2005;174:1976-1980.

Franc-Guimond J, Houle AM, Barrieras D. The proteus syndrome associated with life threatening hematuria. *J Urol*. 2003;170:2418-2419.

Glassock RJ. Hematuria and proteinuria. In: Greenberg A, Cheung AK, Coffman TM, et al., eds. *Primer on Kidney Diseases*. 4th ed. *(National Kidney Foundation)*. Philadelphia: Elsevier Saunders; 2005:36-46.

Glick RD, Hicks MJ, Nuchtern JG, et al. Renal tumors in infants less than 6 months of age. *J Pediatr Surg*. 2004;39:522-525.

Hoekelman RA. Is screening urinalysis worthwhile in asymptomatic pediatric patients? *Pediatr Ann*. 1994;23:459-460.

Houser M. Assessment of proteinuria using random urine samples. *J Pediatr*. 1984;104:845-848.

Ingelfinger JR, Davis AE, Grupe WE. Frequency and etiology of gross hematuria in a general pediatric setting. *Pediatrics*. 1977;59:557-561.

Jones GR, Newhouse I. Sport-related hematuria: a review. *Clin J Sport Med*. 1997;7:119-125.

Kaplan RE, Spring JE, Feld LG. Screening dipstick urinalysis: a time to change. *Pediatrics*. 1997;100:919-921.

Lischer GH, Sweat SD. 16-year-old boy with gross hematuria. *Mayo Clin Proc*. 2002;77:475-478.

Matos V, van Melle G, Boulat O, et al. Urinary phosphate/creatinine, calcium/creatinine, and magnesium/creatinine ratios in a healthy pediatric population. *J Pediatr*. 1997;131:252-257.

Pahari A, Walters S, Levin M. Infectious diseases of the kidney. In: Avner E, Harmon W, Niaudet P, eds. *Pediatric Nephrology*. 5th ed. Philadelphia: Lippincott, Williams & Williams; 2004:955-986.

Parekh DJ, Pope JC, Adams MC, et al. The association of an increased urinary calcium-to-creatinine ratio, and asymptomatic gross and microscopic hematuria in children. *J Urol*. 2002;167:272-274.

Rana K, Wang YY, Powell H, et al. Persistent familial hematuria in children and the locus for thin basement membrane nephropathy. *Pediatr Nephrol*. 2005;20:1729-1737.

Rasoulpour M, Banco L, Laut JM, et al. Inability of community-based laboratories to identify pathological casts in urine samples. *Arch Pediatr Adolesc Med*. 1996;150:1201-1204.

Shin J, Park JM, Lee SM, et al. Factors affecting spontaneous resolution of hematuria in childhood nutcracker syndrome. *Pediatr Nephrol*. 2005;20:609-613.

Sternberg K, Greenfield SP, Williot P, et al. Pediatric stone disease: an evolving experience. *J Urol*. 2005;174:1711-1714.

Travis LB, Brouhard BH, Kalia A. An approach to the child with hematuria. In: Cornfeld D, Silverman B, eds. *Dialogues in Pediatrics Management*. East Norwalk: CT, Appleton-Century-Crofts; 1985.

Zigman A, Yazbeck S, Emil S, et al. Renal vein thrombosis; a 10-year review. *J Pediatr Surg*. 2000;35:1540-1542.

21

Acute and Chronic Scrotal Swelling

John V. Kryger

The most serious causes of acute scrotal swelling are testicular torsion and incarcerated inguinal hernia, both of which necessitate immediate surgical correction. Consequently, a prompt, careful approach to a painful or inflamed scrotum is essential. The differential diagnosis of scrotal swelling is extensive and varies depending on the age of the patient (Tables 21.1 and 21.2). The most common causes include testicular torsion, torsion of the appendix testis, and epididymitis.

SCROTAL AND INGUINAL ANATOMY

Inguinal Region

The inguinal canal runs obliquely between the external and internal inguinal rings. The anterior wall of the canal is formed by the external oblique aponeurosis; the posterior wall is formed by the inguinal ligament and conjoined tendon. The oblique direction of the inguinal canal allows for the posterior and anterior walls to coapt with increases in intraabdominal pressure.

Testis Descent

The testes develop in the lumbar region of the abdominal cavity between the peritoneum and the transversalis fascia at approximately 7 weeks of gestation. By the 8th week of gestation, the gubernaculum extends from the caudal end of the epididymis through the inguinal canal to insert on the internal wall of the scrotum. The processus vaginalis, a finger-like outpouching of the peritoneum, extends adjacent to the gubernaculum to form the inguinal canal. As the processus vaginalis descends into the scrotum, it carries extensions of the abdominal wall layers.

The testis normally descends through the inguinal canal into the scrotum before birth. As the testis and spermatic cord descend through the inguinal canal, they are covered by the three concentric layers of the anterior abdominal fascia (Fig. 21.1). When the testis reaches the scrotum, the testis and surrounding layers of fascia and tunica vaginalis fuse to the dartos of the scrotum. The processus vaginalis is initially patent, leaving a connection between the scrotum and the peritoneal cavity. Normally, the processus vaginalis obliterates, leaving a residual tunica vaginalis surrounding the testis. Typically, the tunica vaginalis contains 1-2 mL of clear fluid.

Scrotum

The scrotum has 2 separate compartments, each containing a testis, epididymis, and distal spermatic cord. It comprises multiple layers that are continuous with the superficial layers of the anterior abdominal wall. The external location of the scrotum results in the temperature of the testes being 2-3°F below the core body temperature, which allows for normal spermatogenesis.

Testis

The testes are the male reproductive organs and are suspended in the tunica vaginalis of the scrotum by the spermatic cords. The epididymis, attached to the testis posteriorly, consists of the caput (upper pole), corpus (body), and cauda (tail) (Fig. 21.2). The vas deferens can be palpated as a narrow, firm, tubular structure in the spermatic cord. The epididymis is responsible for sperm maturation and storage. Each testis relies on 3 arteries for its blood supply: the testicular artery, the cremasteric artery, and the deferential artery. Each enters the scrotum through the spermatic cord. The testicle receives both sympathetic and parasympathetic innervation. These autonomic nerves carry impulses that, with testicular stimulation, produce symptoms of deep visceral pain and nausea.

DIAGNOSTIC STRATEGIES

◆ History

In evaluating acute or chronic scrotal swelling, the following historical elements should be established:

1. **Onset of pain**: Testicular torsion has a very sudden onset and can be precipitated by activity or can occur at rest or during sleep. Epididymitis or torsion of the appendix testis or other testicular appendage often has a more insidious onset over the course of days, with progressive pain and swelling.
2. **Duration of pain**: Episodic pain lasting seconds and abating is rarely pathologic, whereas severe pain, persistent pain, or episodes lasting more than 1 hour raise concern.
3. **Associated/radiation of pain**: If there is radiation of pain from the flank, then renal or ureteral pathologic processes, such as an obstructing ureteral calculus, should be considered. Inguinal discomfort may suggest hernia or other inguinal pathology.

Although sometimes nonspecific, associated manifestations are also important:

1. **General systemic**: Fever, chills, or rigors suggest an infectious cause.
2. **Abdominal signs/symptoms**: Nausea, vomiting, and abdominal or inguinal pain are common but nonspecific. They may indicate an intestinal process.
3. **Urologic signs/symptoms**: Dysuria, urinary frequency, hematuria, or penile discharge suggests an infectious process such as urinary tract infection, urethritis, or epididymitis.
4. **Unusual rashes**: Henoch-Schönlein purpura may result in vasculitis of the spermatic cord with associated scrotal pain and swelling.

In addition, a thorough medical history is imperative and should include the following:

1. History of urinary tract infections or renal calculi.
2. Prior sexual activity, which would raise the possibility of a sexually transmitted infection.
3. History of any surgical procedures on the groin, scrotum, or abdomen. Often an orchiopexy performed for an undescended testis places the testis in a dartos pouch, which would make testicular torsion unlikely in the future.

(See *Nelson Textbook of Pediatrics,* p. 2593.)

(See *Nelson Textbook of Pediatrics,* p. 2592.)

4. History of any previous episodes of testicular pain. Previous episodes of intermittent or severe pain in the same testis may be secondary to intermittent torsion of the testis.
5. Lower urinary tract pathologic processes, such as posterior urethral valves, neuropathic bladder, or urethral stricture (e.g., after trauma or hypospadias repair) may predispose to urinary tract infection, which could cause bacterial epididymitis.

TABLE 21.1 Differential Diagnosis of Scrotal Masses in Young and Adolescent Males

Painful	Painless*
Testicular torsion	Hydrocele
Torsion of testicular appendage (less common after adolescence)	Inguinal hernia (reducible)
Epididymoorchitis	Varicocele
Trauma: testicular rupture, hematocele	Spermatocele (postpubertal males)
Inguinal hernia (incarcerated)	Testicular tumor
Mumps orchitis	Paratesticular tumor
	Idiopathic scrotal edema
	Henoch-Schönlein purpura

*Occasionally associated with discomfort.

◆ Physical Examination

Examination of the scrotal contents should be performed in any male patient presenting with abdominal, inguinal, or scrotal pain. Essential components include inspection, palpation, and transillumination of any masses.

Pubertal development. In prepubertal males, torsion of the appendix testis is more common than testicular torsion (Table 21.3). Conversely, in the postpubertal male, testicular torsion and epididymitis (if the patient is sexually active) are more common.

Scars in the inguinal region. Scars may imply previous surgery for hernia, hydrocele, undescended testis, or varicocele.

Scrotal skin changes and fixation. Erythema suggests an underlying inflammatory process but is nonspecific. Duskiness or fixation of the skin over the testis is suggestive of testicular necrosis.

TABLE 21.2 Differential Diagnosis of Scrotal Swelling in Newborns

Hydrocele	Scrotal hematoma
Inguinal hernia (reducible)	Testicular tumor
Inguinal hernia (incarcerated)*	Meconium peritonitis
Testicular torsion*	Epididymitis*

*May be associated with scrotal inflammation.

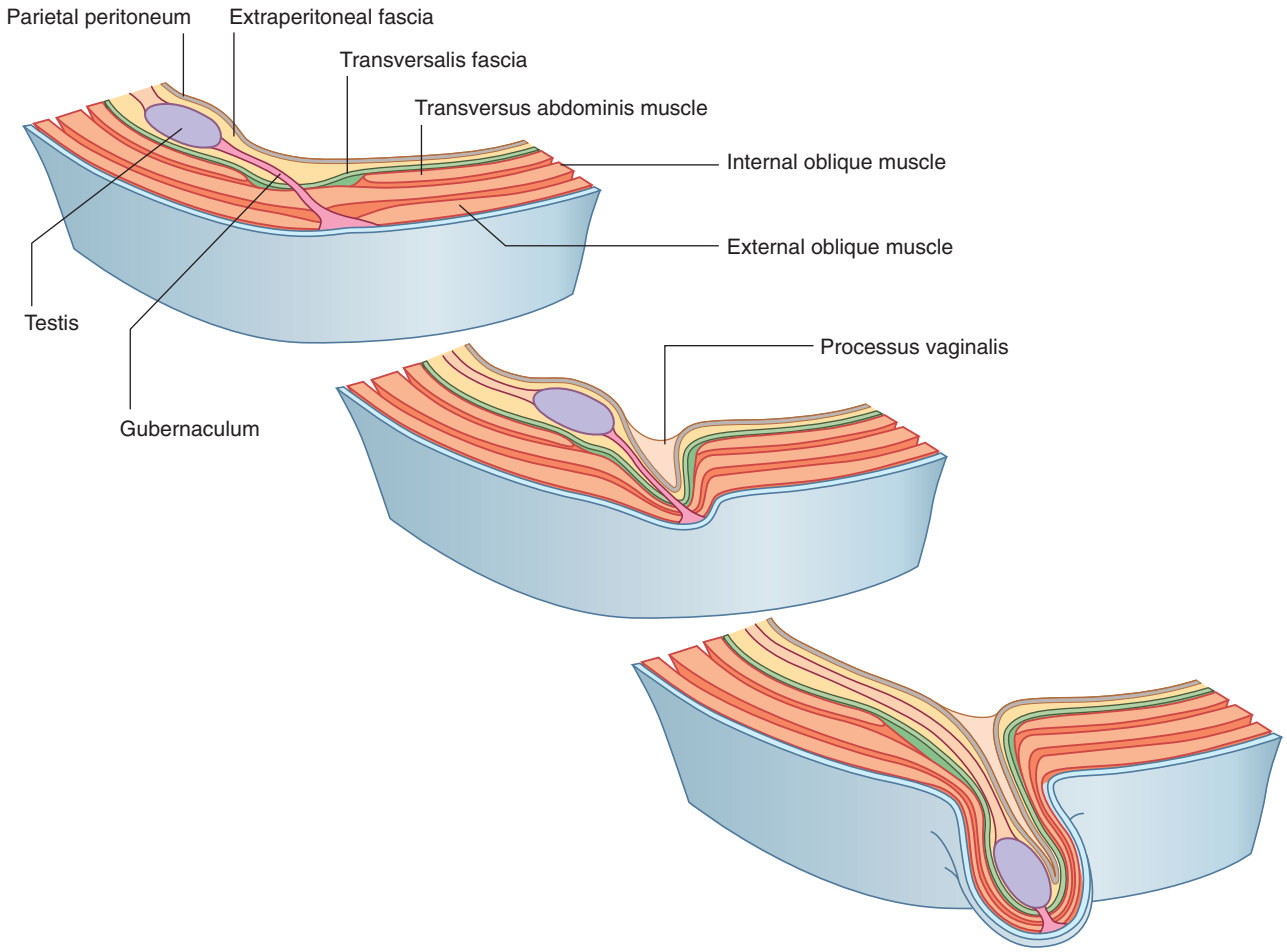


FIGURE 21.1 Descent of the testis from week 7 (postfertilization) to birth. As the testis and spermatic cord descend through the inguinal canal, they are covered by the three concentric layers of the anterior abdominal fascia. (From Drake RL, Vogl AW, Mitchell AWM, eds. *Gray's Anatomy for Students.* 3rd ed. Philadelphia: Churchill Livingstone; 2015:253-420.)

Testis position within the scrotum. A testis positioned high in the scrotum is suggestive of testicular torsion. The spermatic cord shortens as it twists. The affected testis should be compared with the contralateral testis with respect to size, consistency, and tenderness. Accurate localization of pain to the testis, epididymis, or both is important.

Cremasteric reflex. Stimulated by gently scratching the ipsilateral medial thigh, reflexive cremaster muscle contraction causes the scrotum to retract. The presence of a symmetric cremasteric reflex makes testicular torsion less likely. An absent cremasteric reflex is nonspecific. Sometimes with anxiety, the testis of a child will retract high into the inguinal canal. An important maneuver to relax the cremaster muscle is to examine the patient in a seated position with the legs crossed.

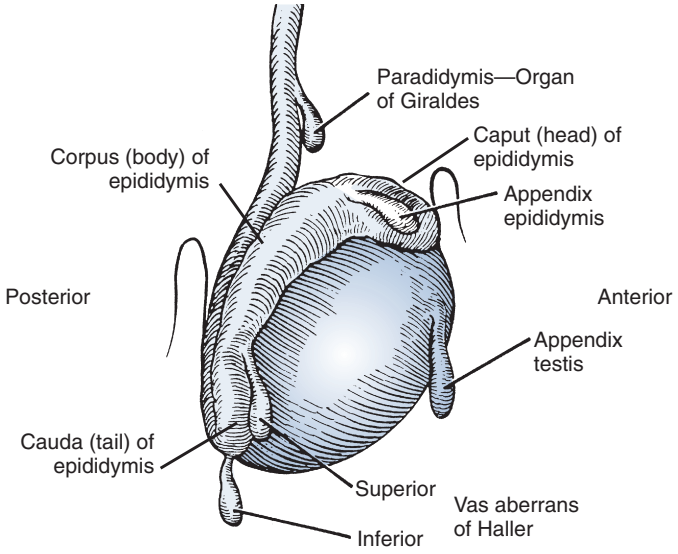


FIGURE 21.2 Lateral view of the testis showing the posterior location of epididymis and appendix testes. The appendix testis is present in almost all males, the appendix epididymis is present in approximately 50% of males, and the other appendages are rarely present. (From Kelalis PP, King LR, Belman AB, eds. *Clinical Pediatric Urology*. 2nd ed. Philadelphia: WB Saunders; 1985.)

◆ Laboratory Data

Basic laboratory evaluation of acute and chronic testicular swelling includes urinalysis, urine culture, and tests for *Chlamydia* and gonorrhea if the patient is sexually active (see Chapter 18).

◆ Imaging Studies

Imaging studies are often helpful in determining the cause of acute and chronic testicular or scrotal swelling. They should not be substituted for a thorough history and careful physical examination performed by a surgical specialist. The conditions necessitating immediate surgical treatment include testicular torsion, incarcerated inguinal hernia, and testicular rupture secondary to trauma; testicular tumor mandates urgent surgical attention. If the history and physical examination strongly support the diagnosis of testicular torsion, then prompt surgical exploration is recommended, without confirmation by an imaging study. If the history or physical findings are equivocal for testicular torsion, or if an alternate diagnosis requires investigation, **color Doppler ultrasonography** should be obtained. Sonography provides a relatively accurate image of the testis and epididymis, and color Doppler imaging assesses blood flow. It is performed by examining the uninvolved testis first and adjusting the color flow settings to detect normal flow. The affected testis is then examined for decreased or absent flow in comparison with the normal testis. Color flow Doppler imaging distinguishes between the increased collateral blood flow within the scrotal skin and the decreased blood flow to the testis in patients with testicular torsion. The sensitivity of Doppler ultrasonography for detecting testicular torsion ranges from 69-100%, and specificity ranges from 77-100%. Sonography can also help determine if a scrotal hematoma represents a testicular rupture. Color flow Doppler imaging accurately demonstrates increased flow resulting from torsion of the appendix testis or epididymitis, but is usually unable to distinguish these 2 entities. It also cannot distinguish viral from bacterial epididymitis. If a tumor is present, sonography can demonstrate whether the mass arises from the testis or paratesticular structures. It can also distinguish the presence of hydrocele, cyst, tumor, or varicocele. The test is quick, easy to perform, and noninvasive. There are several important limitations of color Doppler imaging:

TABLE 21.3 Differentiation of Acute Painful Scrotal Swelling in Childhood

	Testicular Torsion	Epididymoorchitis	Torsion of the Appendix Testis
Age	Usually perinatal and 12–18 yr, but any age possible	Usually adolescence, but any age possible	2–12 yr
Symptoms and signs	Abrupt onset; may have previous similar episodes	Gradual onset	Gradual onset
Pain	Localized to the testis and may radiate to groin and lower abdomen	Localization to epididymis; may involve entire testis after 24 hr	Localization to upper pole of testis; may involve entire testis after 24 hr
Fever	Rare	Common	Rare
Vomiting	Common	Rare	Rare
Dysuria	Rare	Common	Rare
Physical examination	Testis may be high riding, swollen, exquisitely tender; scrotal erythema may be present; cremasteric reflex absent	Testis and epididymis are firm, tender, swollen; scrotal erythema may be present; cremasteric reflex present	Testis is normal or enlarged; firm mass may be seen or felt at upper pole, distinct from epididymis; scrotal erythema may be present; cremasteric reflex present
Pyuria, urinary infection	Rare	Possible, particularly in bacterial epididymitis	Rare
Blood flow (color Doppler study)	Diminished or absent	Increased	Normal or increased

1. If the duration of torsion is brief and if the torsional rotation is incomplete, there may be venous congestion without impairment of arterial blood flow; color Doppler imaging may demonstrate normal or decreased blood flow.
2. In the prepubertal testis, blood flow may be difficult to demonstrate, even when the testes are normal, and absence of flow may be misinterpreted for testicular torsion.
3. The color Doppler aspect of the study is user dependent.

DIFFERENTIAL DIAGNOSIS

(Table 21.4; see also Table 21.3)

Testicular Torsion

Testicular torsion is a surgical emergency because of the risk of ischemic damage to the testis. The likelihood of testicular survival depends on the duration and severity of torsion. Consequently, testicular survival depends on accurate diagnosis and timely emergency management.

The incidence of spermatic cord torsion is 1 in 4000 among male patients younger than 25 years. The peak ages for testicular torsion are in the neonatal period, as well as from the ages of 12-18 years. The pathogenesis of torsion and the presentation in these two age groups are different.

In testicular torsion, the testis and spermatic cord rotate or twist within the tunica vaginalis (termed "intravaginal" torsion), resulting in obstruction of venous drainage, followed by compromise of arterial flow and subsequent infarction (Fig. 21.3). In many instances of

TABLE 21.4 Causes of Acute Scrotal Pain

Common
- Testicular torsion
- Torsion of testicular appendage
- Epididymitis (gonorrheal and/or chlamydial infection in sexually active adolescents)*
- Trauma*
- Scrotal edema (Henoch-Schönlein purpura)
- Pain referred to scrotum (nephrolithiasis, ureteropelvic junction obstruction, appendicitis, spinal cord tumor, IgA nephropathy)

Less Common
- Orchitis (mumps, varicella, coxsackievirus, dengue)*
- Abscess
- Infarction
- Malignancy: primary testicular neoplasm (e.g., seminoma), germ cell (usually painless mass)
- Leukemia: primary or relapse (usually painless swelling)*

Uncommon
- Granulomatous orchitis*
- Drug-induced epididymitis (amiodarone)*
- Behçet disease
- Sarcoidosis
- Polyarteritis nodosa*
- Epididymitis (tuberculosis, brucellosis, actinomycosis, leprosy, *Salmonella* infection, fungal infection, parasitic infestation, *Nocardia* infection)
- Orchitis (rickettsial, *Nocardia* infections, toxoplasmosis, cytomegalovirus)
- Testicular pyocele
- Fournier gangrene

*Bilateral involvement possible.

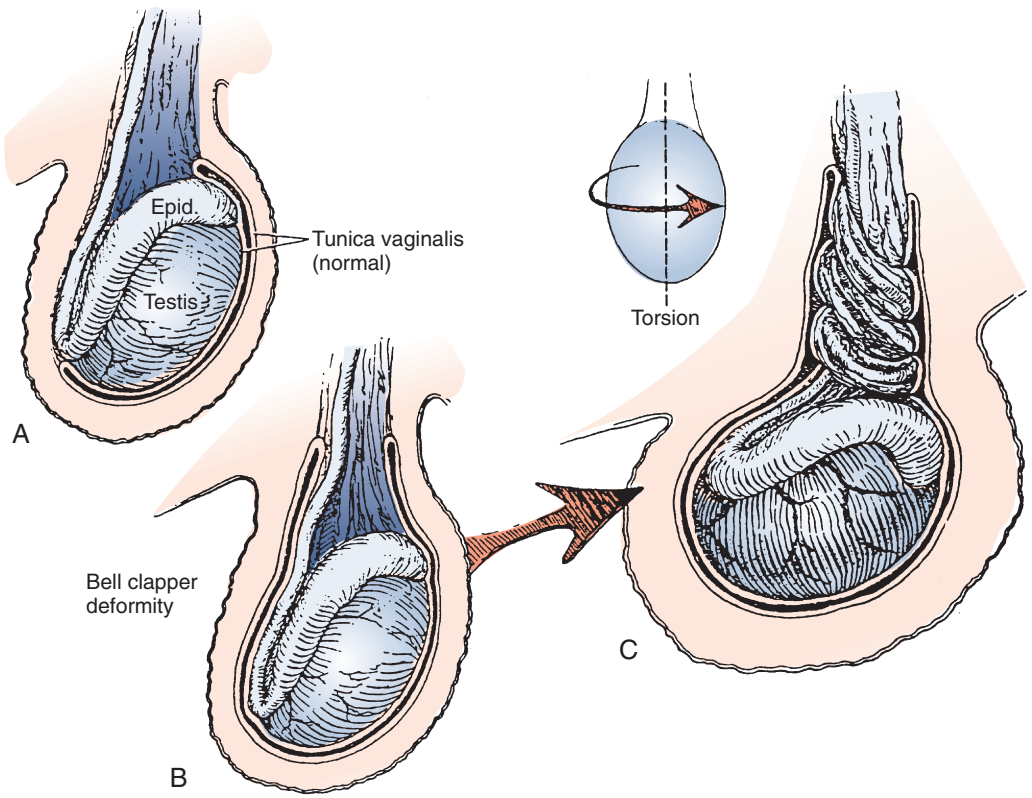


FIGURE 21.3 *A* to *C*, Mechanism of testicular torsion associated with the bell clapper deformity. Epid, epididymis. (From Fleisher GR, Ludwig S. *Textbook of Pediatric Emergency Medicine.* 3rd ed. Baltimore: Williams & Wilkins; 1993.)

(See *Nelson Textbook of Pediatrics,* p. 2595.)

torsion occurring beyond the neonatal period, a preexisting anatomic abnormality termed the **bell clapper deformity** increases the likelihood of the testis rotating on the spermatic cord. The "bell clapper" refers to a redundant tunica vaginalis that inserts higher along the spermatic cord, allowing the testis to rotate freely within, and lie more transversely in the scrotum (Fig. 21.4). The deformity is common, present unilaterally in 17% and bilaterally in 40% of males.

The likelihood of irreversible testicular damage depends on the severity and duration of torsion. If the torsion results in complete ischemia, the testis may become necrotic within 6-12 hours; however, if testicular torsion is incomplete, there may be continued arterial perfusion for 24-48 hours. Because the viability of the testis cannot reliably be gauged based on the perceived duration of torsion, immediate surgical exploration should always be considered.

Patients with testicular torsion typically experience the sudden onset of severe testicular pain and swelling. The event is often incorrectly attributed to minor trauma or exercise, but pain may also occur independent of activity or suddenly awaken the patient from sleep. The pain is usually localized to the affected hemiscrotum, and patients may also report inguinal or abdominal pain. Associated symptoms may include nausea and vomiting. Up to half of patients describe previous episodes of severe scrotal pain that resolved spontaneously. Dysuria and other voiding symptoms are absent.

On examination, the scrotum is erythematous and edematous and the testis is enlarged and extremely tender. If the patient has been experiencing severe pain for more than 24 hours, there may be too much inflammation to delineate the scrotal contents. The cremasteric reflex is usually always absent, although this is not a perfectly reliable sign. The testis may be high in the scrotum with a transverse lie. Urinalysis results are negative. If testicular torsion has been present for more than 48 hours, the scrotum is typically severely enlarged, erythematous, and edematous, and the testis is an enlarged and indurated mass. Color Doppler imaging typically reveals hyperemia in the scrotal wall and absent testicular blood flow.

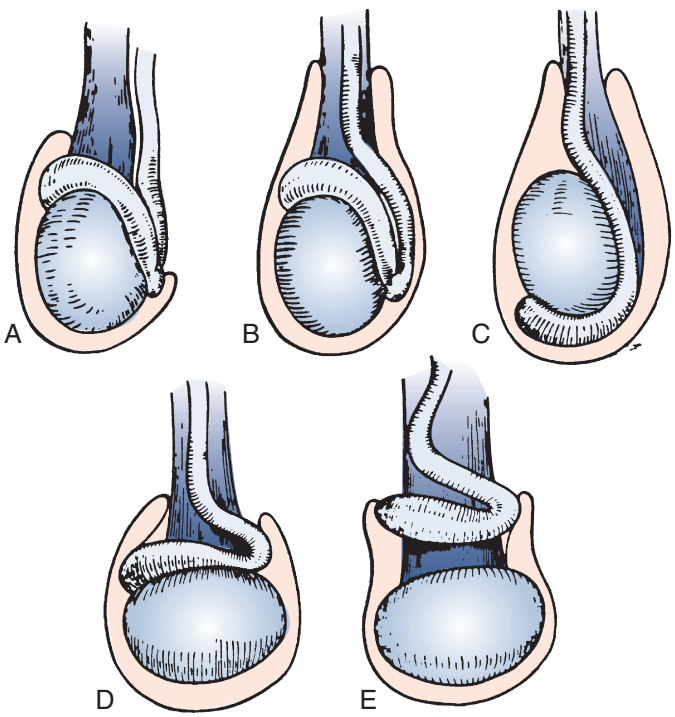


FIGURE 21.4 Anomalies of suspension associated with intravaginal testicular torsion. *A,* Normal. *B,* Envelopment by the tunica vaginalis. *C,* Inversion of the epididymis. *D and E,* Horizontal lie. Bell clapper deformity is shown in *B* through *E.* (From Kelalis PP, King LR, Belman AB, eds. *Clinical Pediatric Urology.* 2nd ed. Philadelphia: WB Saunders; 1985.)

In most cases, the diagnosis of testicular torsion can be made from the history and physical examination. If torsion is the likely diagnosis, scrotal exploration should proceed immediately and should not be delayed awaiting confirmatory imaging. If the diagnosis is uncertain, imaging should be obtained. Color Doppler ultrasonography typically demonstrates absent blood flow.

Some patients present with a history of severe testicular pain that resolved in the emergency room or on the way to the hospital. In these cases, **intermittent torsion** should be suspected. While immediate scrotal orchiopexy is not mandated under these circumstances, surgical fixation should still be considered, as the recurrence rate is high. Furthermore, some patients may fail to seek prompt medical evaluation in the event of recurrence because of fear of surgery or wishful thinking that the torsion will spontaneously resolve again.

Surgical management of testicular torsion consists of exploration, detorsion, and evaluation of testicular viability. An infarcted testicle is removed. If the testis is viable, orchiopexy is performed, in which the viable testis is fixed to the dartos layer of the scrotal wall with nonabsorbable sutures. Contralateral scrotal orchiopexy is also performed given the significant risk of contralateral torsion. If torsion is detected and treated within 4 hours of the onset of symptoms, the salvage rate approaches 100%; at 8-12 hours, it falls to 20%; and after 24 hours, infarction is likely.

Testicular torsion also occurs in the fetus and neonate. In these cases, torsion results from incomplete attachment of the gubernaculum and tunica vaginalis to the scrotal wall. The entire testis, epididymis, and tunica vaginalis twist in a process termed **extravaginal testicular torsion**. If torsion occurs prenatally, the testis is typically large and firm. The ipsilateral hemiscrotum may be ecchymotic if torsion occurred shortly prior to birth; although if torsion occurred more remotely, ecchymoses may have resolved by the time of delivery. Prenatal torsion always results in a nonviable testis. Postnatal extravaginal testicular torsion can occur up to 46 weeks corrected gestational age. Affected neonates typically have sudden onset of irritability with progressive enlargement of the testis, with associated scrotal erythema. Color Doppler ultrasonography in the neonate is fairly reliable in distinguishing testicular torsion from scrotal hematoma and testicular tumor. Although testicular salvage in neonates with in utero torsion is highly unlikely, urgent exploration is recommended to confirm the diagnosis and to perform a contralateral scrotal orchiopexy to protect the solitary remaining testis, which is also at risk for torsion. If there is a possibility that torsion occurred after birth, there is a chance of saving the testis, and immediate exploration is warranted.

TORSION OF THE APPENDIX TESTIS

The appendix testis, a vestigial remnant of the müllerian duct system, is attached to the upper pole of the testis and is present in approximately 90% of males. The appendix epididymis, a remnant of the wolffian ducts, is present in about 10% of males. When these appendages are long and pedunculated, they have a tendency to twist at their base, resulting in ischemia and eventual infarction. This type of torsion is most common between 2 and 12 years of age and is uncommon in adolescents. Torsion of the appendix testis results in progressive pain and inflammation of the epididymis and scrotum.

The onset of pain and swelling is typically gradual. Affected males often adopt a wide-based gait but otherwise appear comfortable. Constitutional symptoms are usually less severe than with testicular torsion,

but may include nausea, vomiting, and pain referred to the lower abdomen. Physical examination reveals an erythematous and edematous scrotum. Palpation of the testis may reveal a 3- to 5-mm tender indurated mass on the upper pole. The torsed appendix testis may be visible through the scrotal skin; this finding is termed the **blue dot sign** and is present in approximately 20% of cases. As the duration of torsion increases, differentiation from testicular torsion becomes increasingly difficult as reactive inflammation of the testis and epididymis worsen. A clinical diagnosis of torsion of the appendix testis should not be made unless the appendix testis is palpated or visualized.

The natural history of torsion of the appendix testis is for the inflammation to resolve gradually after infarction of the appendage. In general, the process is complete within 10 days from the onset of symptoms. Scrotal exploration and excision of the torsed appendage is unnecessary unless there is uncertainty regarding the diagnosis and testicular torsion is possible. If the diagnosis of torsion of the appendix testis is highly likely, color Doppler ultrasonography is optional for confirmation. Management includes strict rest for 2-3 days and nonsteroidal antiinflammatory medications to reduce inflammation and pain. Vigorous activity such as sports should be restricted for at least 7 days, as activity may worsen and prolong pain and swelling. The patient should be instructed to seek prompt medical evaluation if pain does worsen, as such worsening may be indicative of testicular torsion.

EPIDIDYMITIS, EPIDIDYMOORCHITIS, AND ORCHITIS

The inflammation of **epididymitis** may be caused by an infectious process, or may be secondary to trauma, torsion of the appendix testis, or sterile reflux of urine down the vas deferens. Pain and swelling are typically insidious in onset. Patients may have associated dysuria, urgency, frequency, and urethral discharge, and some may report transient episodes of inguinal pain that preceded the onset of testicular symptoms and that were secondary to spermatic cord inflammation. The epididymis is tender, enlarged, indurated, and situated posterior to the testis; in **epididymoorchitis**, inflammation progresses to involve the testis, which also becomes enlarged and tender. A reactive hydrocele may be present, obscuring testicular examination. The cremasteric reflex is typically preserved. Isolated **orchitis** is less common, particularly in prepubertal males, though it may be seen in postpubertal males with mumps virus infection.

Bacterial epididymitis usually results from urethral infection passing retrograde through the vas deferens to the epididymis (Fig. 21.5). In prepubertal males, bacterial epididymitis is most frequently secondary to a structural abnormality of the lower genitourinary tract, such as ectopic ureter, ectopic vas deferens, or urethral stricture, or may be secondary to dysfunctional voiding. Urinalysis typically demonstrates pyuria, bacteriuria, or both, and bacterial culture of the urine may isolate the causative organism, usually a gram-negative coliform. Given the association with underlying urogenital abnormalities, further evaluation should include renal ultrasonography and voiding cystourethrography. In postpubertal males without underlying genitourinary abnormalities, bacterial epididymitis is most frequently caused by sexually transmitted infection, typically *Chlamydia trachomatis*, although *Neisseria gonorrhoeae* and *Ureaplasma urealyticum* may be causative as well. Additional causes of bacterial epididymitis include extension of urinary tract infection or infection with *Mycoplasma pneumoniae* or mycobacteria. Urinalysis and bacterial culture of the urine should be obtained, as should nucleic acid amplification tests for *C. trachomatis* and *N. gonorrhoeae* from urine or urethral swab specimens (see Chapter 18). Patients whose epididymitis is related to a sexually transmitted infection should further be tested for syphilis and human immunodeficiency virus.

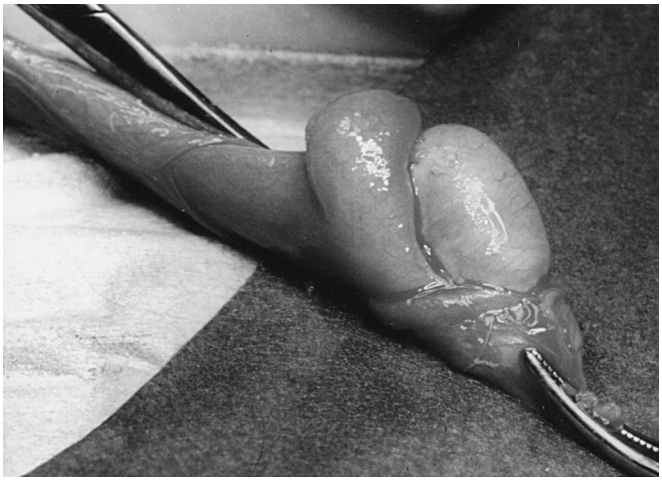


FIGURE 21.5 Epididymitis in a 6-year-old male. Note the reactive orchitis as well as the significant enlargement of the epididymis.

Viral epididymitis may be difficult to distinguish from noninfectious inflammatory causes of epididymitis. Enteroviruses and adenoviruses are typically implicated, either as a primary infection or as a postinfectious sequela. The inflammation of **orchitis** most commonly represents an extension of epididymitis; however, isolated orchitis may be seen in males with **mumps infection**. This manifestation is rare in prepubertal males, though may complicate infection in up to 35% of postpubertal males. The onset of orchitis usually occurs within 1 week of the onset of mumps parotitis and is more frequently unilateral. Diagnosis may be clinical, although given the markedly decreased incidence of mumps following the introduction of an effective vaccine and the possibility of alternate infectious etiologies, confirmatory testing may be obtained. Patients with parotitis may provide buccal swabs or saliva samples for nucleic acid amplification testing. Mumps-specific IgM antibody testing or acute and convalescent serum IgG antibody titer quantification may confirm the diagnosis. Up to a third of patients with mumps orchitis develop testicular atrophy and subfertility, although true infertility is rare, even with bilateral testicular involvement.

Noninfectious etiologies of epididymitis include torsion of the appendix testis, trauma, and medication exposure, particularly to amiodarone. Scrotal ultrasonography shows epididymal swelling and hyperemia consistent with epididymitis. Urinalysis and urine culture reveal no evidence of bacterial urinary tract infection.

TRAUMA AND HEMATOCELE

Blunt scrotal trauma can result in a spectrum of injuries ranging from testicular contusion to testicular rupture (Fig. 21.6). Testicular injuries usually result from a fall, kick, or direct blow from a blunt object that compresses the testis up against the pubic bone. A detailed history of the nature of the injury aids in recognizing the likelihood of serious testicular injury. With disruption of the tunica albuginea (capsule) of the testis, there is such significant painful scrotal swelling that the testis cannot be palpated. Often there is associated erythema or ecchymosis of the scrotal wall. In cases of suspected testicular injury, other diagnoses such as torsion and epididymitis should be considered. Scrotal ultrasonography should be performed to assess the integrity of the testis and to assess for torsion. Urinalysis should be performed to assess for bacterial epididymitis.

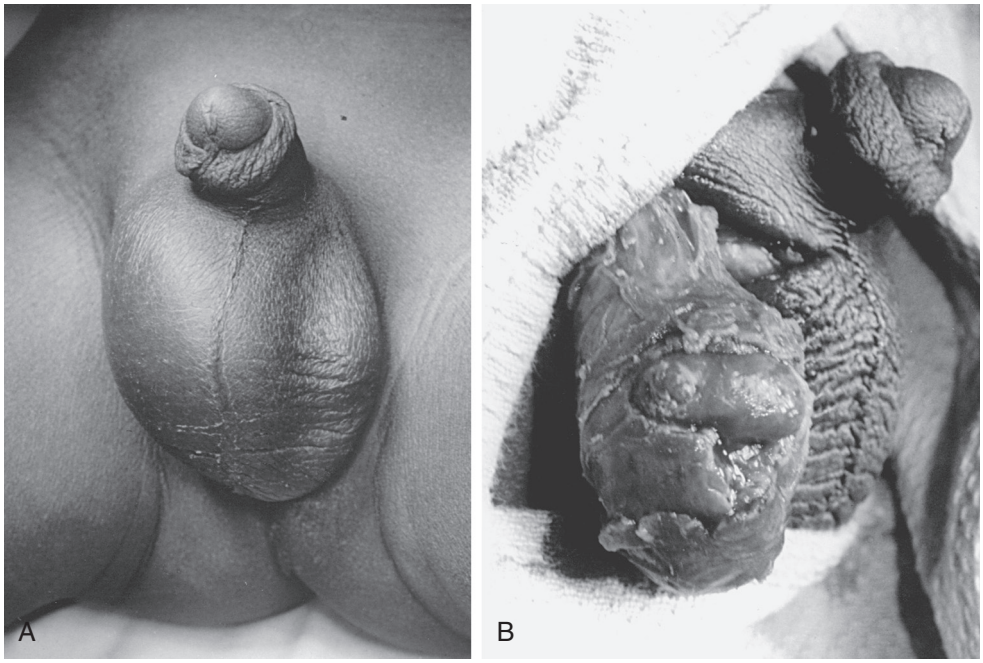


FIGURE 21.6 *A,* Appearance in an 8-year-old male kicked in the scrotum while performing karate with his brother. Note right scrotal swelling. An ultrasound study showed scrotal hematoma and a ruptured testis. *B,* Scrotal exploration shows a nonviable testis. Orchiectomy was performed.

VARICOCELE

A **varicocele** is an abnormal dilation of the veins of the pampiniform plexus in the scrotum. Varicoceles are rare under 10 years of age; however, approximately 10% of adolescent males and 15% of adult males have a varicocele. The increased prevalence among adolescents and adults is secondary to the increased testicular blood flow that occurs with puberty. More than 95% of varicoceles are left-sided, likely secondary to the higher venous pressure of the left internal spermatic vein and the absence of a venous valve at the insertion of the left internal spermatic vein into the renal vein. If a varicocele is detected on the right side or in a male younger than 10 years old, abdominal ultrasonography is indicated to ascertain whether an abdominal tumor is present.

A varicocele manifests as a painless, paratesticular mass often described as a "bag of worms." On occasion, patients describe a chronic, dull ache in or adjacent to the testis. Physical examination in both the supine and the upright positions, with and without the Valsalva maneuver, facilitates the diagnosis. Typically, the varicocele is decompressed while supine and is more prominent when standing. Measuring the volume of both testicles is important to document size discrepancies, as approximately one third of affected males have associated volume loss. Calipers, an orchiometer, or ultrasonography may be used.

Appropriate and timely diagnosis is essential, as an untreated varicocele may lead to degeneration of germinal centers, interstitial fibrosis, and impaired spermatogenesis and testosterone production. Up to 15% of adult males with a varicocele are infertile. The goal in treatment of a varicocele is preservation and restoration of spermatogenesis. Because the majority of testicular volume is composed of seminiferous tubules, if the left testis is significantly smaller than the right, the clinician may presume that the varicocele has affected testicular growth. Typically, after varicocelectomy in an adolescent, the testis shows catch-up growth. Surgical management does not guarantee paternity as an adult.

INGUINAL HERNIA

Hernias and hydroceles result from incomplete obliteration of the processus vaginalis. Indirect inguinal hernias result from a patent processus vaginalis that allows bowel or omentum to pass through the internal inguinal ring (Fig. 21.7). Patients usually present with inguinal swelling, scrotal swelling, or both. While swelling should reduce with gentle pressure, a hernia that cannot be reduced is called an **incarcerated hernia** and is a surgical emergency, as the vascular supply of the herniated bowel may become compromised. Physical signs of incarceration include inguinal or scrotal erythema, pain, signs of bowel obstruction, and inability to reduce the hernia. Infants with an incarcerated hernia have a 10% incidence of ipsilateral testicular infarction secondary to increased pressure on the spermatic cord.

If an incarcerated hernia is suspected, the child is hospitalized and sedated, and manual reduction of the hernia is attempted. Most incarcerated hernias can be reduced successfully and should be repaired promptly. Children with an easily reducible hernia should also undergo herniorrhaphy within a reasonable time to reduce the possibility of incarceration.

HYDROCELE

A **hydrocele** is an accumulation of fluid within the tunica vaginalis. Communicating hydroceles, defined by a patent processus vaginalis, are present in approximately 2% of newborn males, are more common in preterm infants, and tend to persist (see Fig. 21.7). The diameter of the patent processus vaginalis is much smaller than that seen with a hernia, allowing only peritoneal fluid to pass into the scrotum. Typically, affected males have painless scrotal swelling that progresses over the course of the day and resolves while sleeping or otherwise recumbent, as fluid returns to the peritoneal cavity. Noncommunicating hydroceles are characterized by the presence of an unobliterated portion of the processus vaginalis (see Fig. 21.7), and may be acquired following an inflammatory condition within the scrotum, such as

(See *Nelson Textbook of Pediatrics,* p. 2596.)

(See *Nelson Textbook of Pediatrics,* p. 1903.)

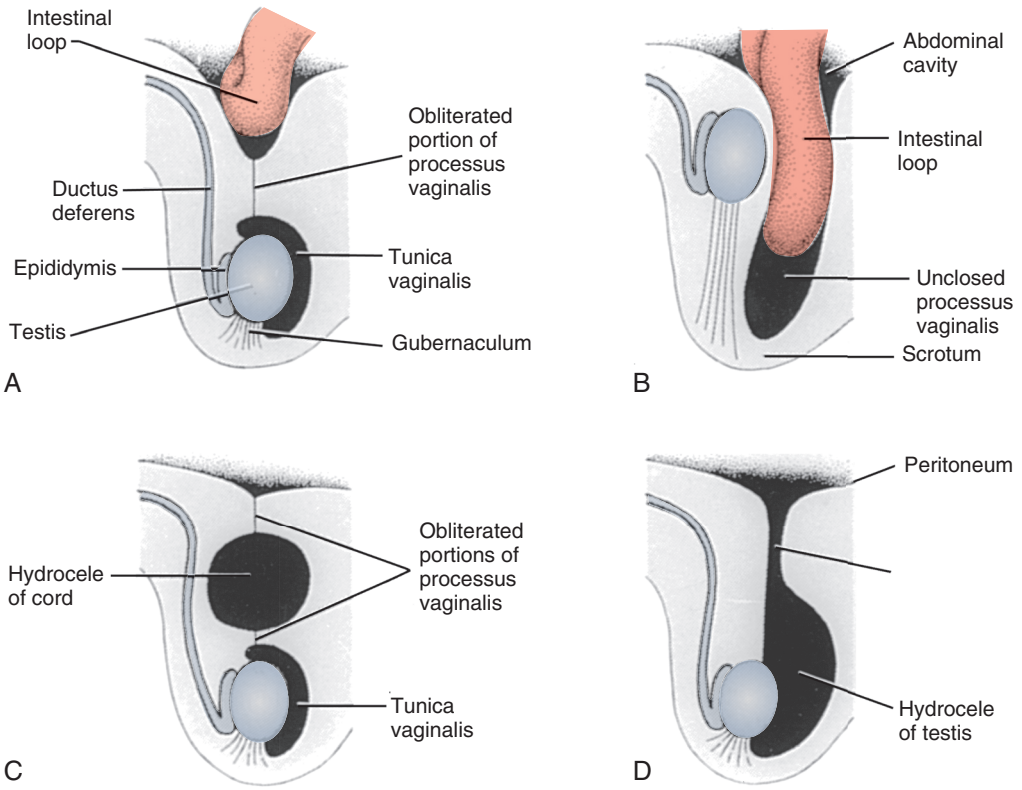


FIGURE 21.7 Diagrams of sagittal sections of the inguinal region. *A,* Incomplete indirect inguinal hernia, resulting from persistence of the proximal processus vaginalis. *B,* Indirect inguinal hernia into the scrotum, resulting from persistence of the entire processus vaginalis. Note the presence of an undescended testicle, which is a commonly associated malformation. *C,* Hydrocele of the cord, derived from an unobliterated portion of the processus vaginalis. *D,* Communicating hydrocele, resulting from peritoneal fluid passing through a patent processus vaginalis. (From Moore KL. *Clinically Oriented Anatomy*. 2nd ed. Baltimore: Williams & Wilkins; 1993:299.)

testicular torsion, torsion of the appendix testis, epididymitis, or testicular tumor.

Physical examination reveals a smooth and nontender scrotal mass that is clear upon transillumination. Because hydroceles can be associated with testicular neoplasms in postpubertal males, testicular examination should be performed. If the size of the hydrocele precludes adequate testicular examination, scrotal ultrasonography is advised. Most communicating hydroceles resolve by 1 year of age and can be managed expectantly; however, large and tense masses may be difficult to distinguish from hernias, and may require ultrasonography. Large hydroceles or hydroceles persisting beyond the age of 2 years rarely regress spontaneously and may predispose to inguinal hernia.

A severe form of the hydrocele is the **abdominoscrotal hydrocele**, in which the hydrocele sac is tense with fluid and extends from the scrotum proximally through the inguinal canal into the abdominal cavity. On examination, these hydroceles are palpable in the inguinal canal, and an abdominal mass is often present. These hydroceles do not resolve and may cause extrinsic testicular compression. Early repair is recommended.

TESTICULAR TUMORS

Although testicular and paratesticular tumors are uncommon, testicular cancer is the most common solid malignancy in postpubertal males between the ages of 15 and 35 years, with a bimodal age distribution reflecting this age range, and another peak in the 1st 2 years of life. Most testicular cancers are germ cell tumors, representing approximately 95% of testicular cancers, while the remaining 5% are stromal tumors derived from Leydig, Sertoli, and granulosa cells. Risk factors for testicular tumors include a history of cryptorchidism, a prior history of testicular cancer in the contralateral testicle, and a family history of testicular cancer.

Most patients with testicular tumors present with an incidentally noted nontender, hard mass that fails to transilluminate on examination. Pain is uncommon, although some patients may present with pain secondary to hemorrhage or infarction within the mass. Up to 15% of testicular tumors are associated with a noncommunicating hydrocele, prompting affected patients to seek medical evaluation. Stromal tumors may elaborate hormones that can lead to precocious pseudopuberty, gynecomastia, galactorrhea, or other endocrinologic manifestations.

Scrotal ultrasonography should be performed to confirm the finding of a testicular mass and may help delineate the type of testicular tumor. Serum tumor markers, such as α-fetoprotein and β-human chorionic gonadotropin, should be evaluated before surgical intervention. Partial orchiectomy is typically performed for prepubertal testis tumors with negative α-fetoprotein; radical orchiectomy is performed for postpubertal testis tumors and prepubertal testis tumors with elevated α-fetoprotein, given their higher metastatic potential. After radical orchiectomy, abdominal and chest computed tomography is obtained to evaluate the most common sites of metastatic disease, the retroperitoneum and lungs.

Leukemia and lymphoma are the most common secondary malignancies to affect the testis. These tumors can present bilaterally, and,

because the blood-testis barrier protects the intratesticular cells, the testis may be the site of residual tumor in children after chemotherapy. Paratesticular structures can give rise to various benign tumors, such as lipomas, leiomyomas, hemangiomas, and fibromas. Malignant paratesticular tumors are rare; rhabdomyosarcoma is the most common malignant paratesticular tumor.

MECONIUM PERITONITIS

Antenatal peritonitis may result from intestinal perforation. Although the intestinal perforation may heal, the intraabdominal meconium may track down the patent processus vaginalis into the scrotum, resulting in the formation of an inflammatory mass. This condition can manifest as bilateral neonatal hydroceles, which eventually regress into firm, nodular masses involving either or both testicles. Scrotal sonography demonstrates multiple areas of echogenic foci suggestive of calcification. In addition, a plain film of the scrotum shows calcification.

SCROTAL WALL SWELLING

Henoch-Schönlein Purpura

Henoch-Schönlein purpura is a systemic vasculitis of unknown etiology that involves the skin, gastrointestinal tract, joints, and kidneys. Most affected patients are younger than 7 years. Genitourinary manifestations may include glomerulonephritis (see Chapter 20), ureteritis, renal pelvic bleeding, and acute swelling of the scrotum and spermatic cord. Scrotal wall and testicular involvement has been reported in up to a third of affected patients.

Palpable purpura (the characteristic skin finding in Henoch-Schönlein purpura) often begin in the lower extremities and buttock region. Later, the rash may spread to the scrotum; on occasion, the rash may begin on the scrotum. If scrotal swelling and pain precede the development of the characteristic rash, the presentation may be difficult to distinguish from testicular torsion. However, as these conditions may coexist, if there is any uncertainty regarding the diagnosis, color Doppler ultrasonography should be performed.

Acute Idiopathic Scrotal Wall Edema

Acute idiopathic scrotal wall edema is an uncommon entity that accounts for up to 5% of acute scrotal swelling. The average patient is between 4 and 7 years of age and typically presents with the sudden onset of unilateral or bilateral scrotal wall edema and mild tenderness. The overlying skin is erythematous, and the edema may extend anteriorly onto the abdominal wall or posteriorly into the perineum. The testicles are easily palpable, normal in size, and nontender. The origin of this syndrome is unknown, but allergic causes have been implicated. Most cases spontaneously resolve within 48-72 hours.

Idiopathic Fat Necrosis

Idiopathic fat necrosis is an uncommon cause of acute painful swelling of the scrotum, secondary to necrosis of the intrascrotal fat that is present in prepubertal males. Examination of the underlying testis may be hampered by inflammation within the scrotal wall. The etiology is unknown but may be related to trauma with physical activity. Ultrasonography demonstrates hyperechoic intrascrotal masses with posterior shadowing and a hyperechoic striated scrotal wall with normal-appearing testes and epididymi. Treatment is supportive.

Fournier Gangrene

Fournier gangrene of the scrotum usually affects adults, but rarely can afflict infants and children. In children, it occurs primarily as a result of genital insect bites, as a complication of circumcision, or from extension of perianal skin abscesses. Other predisposing factors include diabetes mellitus, trauma, instrumentation, urethral stricture, and inguinal or perineal surgery. Symptoms of this life-threatening infection include acute scrotal swelling with tenderness, erythema, skin necrosis, and systemic manifestations of fever, chills, and septicemia. The most common organisms identified include *Staphylococcus aureus*, *Bacteroides fragilis*, *Escherichia coli*, *Clostridium perfringens*, and streptococcal species. Despite aggressive treatment, mortality rates approach 50%.

REFERRED PAIN

Pain in the scrotum without inflammatory signs or abnormalities on physical examination may be referred pain. Sensory innervation to the scrotum includes the genitofemoral and ilioinguinal nerves. Most common causes include distal ureteral stones and constipation.

RED FLAGS

- Testicular torsion is a surgical emergency and acute scrotal pain should be evaluated promptly. Physical examination findings suggesting testicular torsion include marked tenderness, high-riding testis, and absent cremasteric reflex.
- Partial or intermittent torsion can present with persistent arterial blood flow on ultrasonography.
- A varicocele before puberty or on the right side is a red flag; abdominal ultrasonography is indicated.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Testicular Torsion

Baker LA, Sigman D, Mathews RI, et al. An analysis of clinical outcomes using color Doppler testicular ultrasound for testicular torsion. *Pediatrics*. 2000;105:604.

Barada JH, Weingarten JL, Cromie WJ. Testicular salvage and age-related delay in the presentation of testicular torsion. *J Urol*. 1989;142:746.

Barthold JS. Abnormalities of the testis and scrotum and their surgical management. In: McDougal WS, Kavoussi LR, Novick AC, et al., eds. *Campbell-Walsh Urology*. 10th ed. Philadelphia: WB Saunders; 2012:642-645.

Chapman RH, Walton AJ. Torsion of the testis and its appendages. *Br Med J*. 1972;5793:164.

Cornel EB, Karthaus HF. Manual detorsion of the twisted spermatic cord. *BJU Int*. 1999;83:672.

Cuckow PM, Frank JD. Torsion of the testis. *BJU Int*. 2000;86:349.

Eaton S, Cendron MA, Estrada CR, et al. Intermittent testicular torsion: diagnostic features and management outcomes. *J Urol*. 2005;174:1532H.

Joo JM, Yang SH, Kang TW, et al. Acute epididymitis in children: the role of the urine test. *Korean J Urol*. 2013;54(2):135-138.

Karmazyn B, Steinberg R, Kornreich L, et al. Clinical and sonographic criteria of acute scrotum in children: a retrospective study of 172 boys. *Pediatr Radiol*. 2005;35:302.

Lam WW, Yap TL, Jacobsen AS, et al. Colour Doppler ultrasonography replacing surgical exploration for acute scrotum: myth or reality? *Pediatr Radiol*. 2004;35:597.

Munden MM, Williams JL, Zhang W, et al. Intermittent testicular torsion in the pediatric patient: sonographic indicators of a difficult diagnosis. *AJR Am J Roentgenol*. 2013;201:912.

Nelson CP, Williams JF, Bloom DA. The cremasteric reflex: a useful but imperfect sign in testicular torsion. *J Pediatr Surg*. 2003;38:1248.

Pinto KJ, Noe HN, Jerkins GR. Neonatal testicular torsion. *J Urol*. 1997;158:1196.

Sessions AE, Rabinowitz R, Hulbert WC, et al. Testicular torsion: direction, degree, duration and disinformation. *J Urol*. 2003;82:899.

Van Glabeke E, Philippe-Chomette P, Gall O, et al. Spermatic cord torsion in the newborn: Role of surgical exploration. *Arch Pediatr*. 2000;7:1072.

Yazbeck S, Patriquin HB. Accuracy of Doppler sonography in the evaluation of acute conditions of the scrotum in children. *J Pediatr Surg*. 1994;29:1270.

Torsion of the Appendix Testis

Boettcher M, Bergholz R, Krebs TF, et al. Differentiation of epididymitis and appendix testis torosion by clinical and ultrasound signs in children. *Urology*. 2013;82:899.

Epididymoorchitis

American Academy of Pediatrics. Mumps. In: Kimberlin DW, Brady MT, Jackson MA, et al., eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. Elk Grove Village, IL: American Academy of Pediatrics; 2015:564-568.

Beard CM, Benson RC, Kelalis PP, et al. The incidence and outcome of mumps orchitis in Rochester, Minnesota, 1935 to 1974. *Mayo Clin Proc*. 1977;52:3.

Bukowski TP, Lewis AG, Reeves D, et al. Epididymitis in older boys: Dysfunctional voiding as an etiology. *J Urol*. 1995;154:762.

Gnann J. Chapter 369: Mumps. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 25th ed. Philadelphia: Elsevier: 2016:2206-2208.

Merlini E, Rotundi F, Seymandi PL, et al. Acute epididymitis and urinary tract anomalies in children. *Scand J Urol Nephrol*. 1998;32:273.

Nikolaou M, Ikonomidis I, Lekakis I, et al. Amiodarone-induced epididymitis: a case report and review of the literature. *Int J Cardiol*. 2007;121(1):e15-e16.

Santillanes G, Gausche-Hill M, Lewis RJ. Are antibiotics necessary for pediatric epididymitis? *Pediatr Emerg Care*. 2011;27:174.

Siegel A, Snyder H, Duckett JW. Epididymitis in infants and boys: Underlying urogenital anomalies and efficacy of imaging modalities. *J Urol*. 1987;138:1100.

Somekh E, Gorenstein A, Serour F. Acute epididymitis in boys: evidence of a post-infectious etiology. *J Urol*. 2004;171:391.

Trauma

Buckley JC, McAninch JW. Use of ultrasonography for the diagnosis of testicular injuries in blunt scrotal trauma. *J Urol*. 2006;175(1):175-178.

Cubillos J, Reda EF, Gitlin J, et al. A conservative approach to testicular rupture in adolescent boys. *J Urol*. 2010;184(4):1733-1738.

Lee SH, Bak CW, Choi MH, et al. Trauma to male genital organs: a 10-year review of 156 patients, including 118 treated by surgery. *BJU Int*. 2008;101(2):211-215.

Wan J, Corvino TF, Greenfield SP, et al. Kidney and testicle injuries in team and individual sports: data from the National Pediatric Trauma Registry. *J Urol*. 2003;170(4 Pt 2):1528-1531, discussion 1531-1532.

Varicocele

Bogaert G, Orye C, De Win G. Pubertal screening and treatment for varicocele do not improve chance of paternity as adult. *J Urol*. 2013;189(6):2298-2303.

Chen SS, Chen LK. Risk factors for progressive deterioration of semen quality in patients with varicocele. *Urology*. 2012;79(1):128-132.

Diamond DA, Paltiel HJ, DiCanzio J, et al. Comparative assessment of pediatric testicular volume: Orchidometer versus ultrasound. *J Urol*. 2000;164:1111.

Diamond DA, Zurakowski D, Atala A, et al. Is adolescent varicocele a progressive disease process? *J Urol*. 2004;172(4 Pt 2):1746-1748, discussion 1748.

Kass EJ, Stork BR, Steinert BW. Varicocele in adolescence induces left and right testicular volume loss. *BJU Int*. 2001;87:499.

Sayfan J, Siplovich L, Koltun L, et al. Varicocele treatment in pubertal boys prevents testicular growth arrest. *J Urol*. 1997;157:1456.

Thomas JC, Elder JS. Testicular growth arrest and adolescent varicocele: Does varicocele size make a difference? *J Urol*. 2002;168:1689.

Vasavada S, Ross J, Nasrallah P, et al. Prepubertal varicoceles. *Urology*. 1997;50:774.

Testicular Tumors

Agarwal PK, Palmer JS. Testicular and paratesticular neoplasms in prepubertal males. *J Urol*. 2006;176(3):875-881.

Pohl HG, Shukla AR, Metcalf PD, et al. Prepubertal testis tumors: actual prevalence rate of histological types. *J Urol*. 2004;172(6 Pt 1):2370-2372.

Ross JH. Prepubertal testicular tumors. *Urology*. 2009;74(1):94-99.

Ross JH, Kay R. Prepubertal testis tumors. *Rev Urol*. 2004;6(1):11-18.

Ross J, Kay R, Elder J. Testis sparing surgery for pediatric epidermoid cysts of the testis. *J Urol*. 1993;149:353.

Rushton HG, Belman AB, Sesterhenn I, et al. Testicular sparing surgery for prepubertal teratoma of the testis. *J Urol*. 1990;144:726.

Stevenson SM, Lowrance WT. Epidemiology and diagnosis of testis cancer. *Urol Clin North Am*. 2015;42(3):269-275.

Thomas JC, Ross JH, Kay R. Stromal testis tumors in children: a report from the Prepubertal Testis Tumor Registry. *J Urol*. 2001;166(6):2338-2340.

Other Diagnoses

Anzai AK. Fournier's gangrene: A urologic emergency. *Am Fam Physician*. 1995;52:1821.

Corman JM, Moody JA, Aronson WJ. Fournier's gangrene in a modern surgical setting: Improved survival with aggressive management. *BJU Int*. 1999;84:85-88.

Dayanir YO, Akdilli A, Karaman CZ, et al. Epididymoorchitis mimicking testicular torsion in Henoch-Schönlein purpura. *Eur Radiol*. 2001; 11:2267.

Harkness G, Meikle G, Craw S, et al. Ultrasound appearance of scrotal fat necrosis in prepubertal boys. *Pediatr Radiol*. 2007;37(4):370-373.

Ioannides AS, Turnock R. An audit of the management of the acute scrotum in children with Henoch-Schönlein purpura. *J R Coll Surg Edinb*. 2001;46:98.

Kaplan GW. Acute idiopathic scrotal edema. *J Pediatr Surg*. 1977;12:647.

Yeh ML, Chang CJ, Mu SC. Neonatal idiopathic scrotal hemorrhage: Patient reports. *Clin Pediatr (Phila)*. 2000;39:493.

Diagnostic Strategies

Hawtrey CE. Assessment of acute scrotal symptoms and findings. A clinician's dilemma. *Urol Clin North Am*. 1998;25:715.

Kadish HA, Bolte RG. A retrospective review of pediatric patients with epididymitis, testicular torsion, and torsion of testicular appendages. *Pediatrics*. 1998;102:73.

Kass EJ, Lundak B. The acute scrotum. *Pediatr Clin North Am*. 1997;44:1251.

Lewis AG, Bukowski TP, Jarvis PD, et al. Evaluation of acute scrotum in the emergency department. *J Pediatr Surg*. 1995;30:277.

Marcozzi D, Suner S. The nontraumatic acute scrotum. *Emerg Med Clin North Am*. 2000;19:547.

Imaging

Allen TD, Elder JS. Shortcomings of color Doppler sonography in the diagnosis of testicular torsion. *J Urol*. 1995;154:1508.

Baker LA, Sigman D, Mathews RI, et al. An analysis of clinical outcomes using color Doppler testicular ultrasound for testicular torsion. *Pediatrics*. 2000;105:604.

Dogra VS, Sessions A, Mevorach RA, et al. Reversal of diastolic plateau in partial testicular torsion. *J Clin Ultrasound*. 2001;29:105.

Kravchick S, Cytron S, Leibovici O, et al. Color Doppler sonography: Its real role in the evaluation of children with highly suspected testicular torsion. *Eur Radiol*. 2001;11:1000.

Weber DM, Rosslein R, Fliegel C. Color Doppler sonography in the diagnosis of acute scrotum in boys. *Eur J Pediatr Surg*. 2000;10:235.

22

Menstrual Problems and Vaginal Bleeding

Jessica Francis and Seema Menon

PREPUBERTAL VAGINAL BLEEDING

The source of abnormal bleeding during childhood is much more likely to be the vulva or vagina rather than the uterus. There are unique characteristics making history and physical examination effective in narrowing the diagnostic possibilities as seen in Table 22.1. Collecting information regarding recent trauma, medication exposure, rashes or irritation of the external genitalia, abdominal pain, chronic cough, constipation, and malodorous discharge are essential in making a diagnosis efficiently. A sensitive assessment regarding the possibility of sexual assault should be made, and an age-appropriate physical examination should be conducted noting the presence or absence of other pubertal signs, abnormalities of the vulva or urethra, vaginal discharge, and abdominal or vaginal masses.

Vaginal bleeding presenting within the first several days of life is most commonly due to estrogen withdrawal. Maternal estrogen enters fetal circulation stimulating growth of the endometrium. External genitalia examination typically reveals estrogenization, with thickened vulvar mucosa and leucorrhea. Several days after delivery, serum estrogen levels fall significantly, leading to a reduction of blood supply to the endometrium and the lining sheds as ischemia develops. If vaginal bleeding occurs within the 1st few days of life with a normal physical examination, a work-up is not needed provided the bleeding spontaneously resolves.

The presence of a **vaginal foreign body** is another common cause of vaginal bleeding in early childhood. This bleeding is often described as persistent, light in quantity, brown colored, and malodorous. The physical examination is unremarkable other than detection of a vaginal malodor. The most common foreign body in the vagina is toilet paper, although many other solid objects have been reported. Depending on the age and cooperation of the patient, lateral and downward traction of the labia majora may allow direct visualization of the foreign body. Toilet paper can be retrieved in the office by gently irrigating the vagina with water using a small, flexible pediatric feeding tube. In cases where the patient is not able to cooperate, a vaginoscopy under sedation should be performed. One technique is to place an 8 French Foley catheter in the vagina. A 5-mm laparoscope is simultaneously placed in the vagina. Saline is then flushed into the vagina using the Foley catheter while the labia majora are manually held together. The vagina is then distended allowing for complete visualization of the vaginal cavity including the cervix and any foreign body present. Simply removing the foreign body will adequately treat the symptoms; no antibiotic therapy is needed. A vaginal foreign body should not automatically trigger a full sexual assault evaluation; this investigation should be conducted if there is indication by history, or if suspicious scarring of the posterior fourchette is noted.

Prepubertal **vaginal infection** may present with bleeding and discharge, but unlike foreign body, the bleeding is typically red in color and nonmalodorous. Vaginal infection is also associated with complaints of external genital irritation. Mucosal erythema on physical examination is notable, particularly when the pathogen is group A β-hemolytic streptococcus. The diagnosis is confirmed with culture of the vaginal canal. A specimen for culture can be collected using the gentle irrigation technique described previously if vaginal swab placement is not possible. In addition to group A β-hemolytic streptococcus, other pathogens that are commonly identified include *Haemophilus influenzae*, *Escherichia coli*, *Shigella,* and *Salmonella* species with the latter 2 being particularly associated with vaginal bleeding. Notably, *Candida* infections of the vagina are uncommon in this population. A recent history of an upper respiratory infection should raise suspicion of this diagnosis as the majority of vaginal infections arise from autoinoculation.

Vulvar dermatoses can also present with vaginal bleeding and significant irritation or pain of the external genitalia. In this case, the bleeding is minimal, typically related to trauma from scratching. While vulvar dermatosis in the prepubertal population is relatively uncommon, **lichen sclerosus** and **psoriasis** are the most commonly described conditions. Suspicion for either condition should be raised if extragenital skin findings are noted, or if a positive family history is elicited. The typical appearance of lichen sclerosus is white parchment paper-like appearance in an hourglass distribution. Obliteration of the labia minora and clitoris can occur with long-standing disease. The treatment involves short courses of high-potency topical steroids and usually resolves as serum estrogen levels rise with maturation. Psoriasis typically appears as an erythematous plaque or papule marked by fissures, erosions, or scales. Treatment includes topical steroids, fluorinated ointments, and emollients. In both cases, biopsy is needed to confirm the diagnosis; however, if clinical suspicion is high and symptoms are severe, empiric treatment prior to biopsy is reasonable. Other vulvar lesions that can produce bleeding include hemangiomas and genital warts.

Urethral prolapse is another cause of prepubertal vaginal bleeding associated with a classic physical examination finding. The only complaint is bleeding; there is no coexisting pain or irritation. The limited estrogen levels in childhood leave the urethra vulnerable to prolapse, especially in the setting of frequent valsalva maneuvers from chronic cough or constipation. On physical examination, the urethra appears prominent, erythematous, and tubular "doughnut shaped," protruding well beyond the urethral meatus. Topical estrogen therapy for 1-2 weeks is typically effective in resolving this condition. Rarely, urethral necrosis can occur in which conservative therapy with estradiol can still be effective; however, surgical resection may be needed.

While the vast majority of lesions of the external genitalia causing prepubertal bleeding are benign, malignancy has been reported. **Sarcoma botryoides**, a variant of rhabdomyosarcoma, is the most common vaginal tumor in childhood. The classic description of this tumor is a protruding vaginal mass with grapelike vesicles. Other malignant tumors of the lower genital tract that have been reported include mesencymal tumors, neural ectodermal tumors in the Ewing family, and mixed müllerian tumors. Any abnormal-appearing vaginal

(See *Nelson Textbook of Pediatrics,* p. 2613.)

TABLE 22.1 Causes of Prepubertal Bleeding

	Pain or Irritation	Associated Characteristics	Family History
Estrogen withdrawal	No	Within 1st wk of life	No
Foreign body	No	Malodorous	No
Vaginal infection	Yes	Recent upper respiratory infection	No
Vulvar dermatoses	Yes	Vulvar discoloration or lesion Extragenital skin findings	Yes
Urethral prolapse	No	Chronic cough or constipation Red, beefy, protuberant urethra	No
Straddle injury	Yes	Provoking injury Visible laceration	No
Precocious puberty	No	Cyclic pattern of bleeding Secondary sexual characteristics present	Yes
Vaginal malignancy	Possible	Visible mass	No

TABLE 22.2 Comparison of GnRH-Dependent and GnRH-Independent Precocious Puberty

	GnRH-Dependent Precocious Puberty	GnRH-Independent Precocious Puberty
Prevalence	More common	Less common
Family history of early puberty	Positive	Negative
Unique characteristics	History or symptoms of CNS lesions, tumors, or infections	Symptoms of hypothyroidism, café-au-lait lesions, known Peutz-Jeghers syndrome
GnRH stimulation test	Positive	Negative

CNS, central nervous system; GnRH, gonadotropin-releasing hormone.

mass should raise concern for malignancy and should prompt a referral to an appropriate specialist for evaluation.

Bleeding secondary to a **perineal injury** presents acutely with pain and is associated with a clear provoking event unlike the other causes of childhood vaginal bleeding. Straddle injuries are the most common childhood injury to the genitalia and can lead to a bleeding laceration. This injury is caused by a nonpenetrating blunt force to the perineum when the legs are apart. Classic activities associated with straddle injuries include bike riding, playing on a seesaw, and gymnastics. An examination must be done to determine whether the laceration requires primary closure with suture. Conscious sedation or examination under anesthesia is appropriate for straddle injury evaluations as pain may prohibit a thorough evaluation. If the history does not substantiate the injury, a sensitive interview should be conducted prior to the examination. Co-examination with the sexual assault team is important should there be any suspicion.

Prepubertal vaginal bleeding presenting with breast development and growth acceleration should raise concern for **precocious puberty**. Pubertal changes before age 8 is precocious, and important historical cues that are helpful in making a diagnosis include symptoms of, or known existing central nervous system (CNS) abnormalities, symptoms of hypothyroidism, family history of early puberty, Peutz-Jeghers syndrome or neurofibromatosis, type 1. Height, Tanner staging of the breast and pubic hair, and external genital changes consistent with estrogen exposure, such as elongation of the labia minora and thickening of vulvar mucosa, should be specifically evaluated during physical examination. Café-au-lait spots, presence of an abdominal mass, and thyroid gland abnormalities should also be assessed. Radiographic imaging of the left wrist showing advanced bone age signifies elevated serum estrogen levels and is a good, initial screening test. Laboratory evaluation confirming precocious puberty includes elevated serum estradiol, androgen panel, and gonadotropins.

Early elevated serum estrogen most commonly occurs because of maturation of the hypothalamic-pituitary-ovarian (HPO) axis, termed gonadotropin-releasing hormone (GnRH)–dependent precocious puberty. In this condition, the pathology is simply the early timing of maturation. Administration of a GnRH analog is effective in temporarily stopping anterior pituitary production of gonadotropins, ultimately preventing sex hormone production from the ovary. The purpose of halting early puberty is to avoid age-inappropriate social contact, and to preserve height, which is particularly effective when treating patients 6 years of age or younger. Rarely, GnRH pulsatile release is stimulated by CNS abnormalities such as infection, tumors, hydrocephaly, meningomyelocele, neonatal encephalopathy, or cranial radiation. Type 1 neurofibromatosis and tuberous sclerosis are also associated with GnRH-dependent precocious puberty. Imaging of the CNS should be aggressively pursued if there is suspicion of a CNS lesion, if pubertal progression is rapid, or if the child is under age 6.

GnRH-independent precocious puberty is a much less common cause of precious puberty. In this condition, the hypothalamus is not driving ovarian sex steroid hormone production. Conditions such as malignant granulosa cell tumors of the ovary, benign ovarian cysts, or tumors of the pituitary or adrenal gland are responsible for the elevated serum estrogens. McCune-Albright syndrome, Peutz-Jeghers syndrome, and hypothyroidism are associated with GnRH-independent precocious puberty as well.

GnRH-dependent and -independent precocious puberty are associated with different history and physical examination cues (Table 22.2). A GnRH stimulation test is effective in differentiating these 2 processes. A rise in gonadotropins after exogenous administration of GnRH

TABLE 22.3 Causes of Abnormal Bleeding in Adolescents

	Cycle Length	Intermenstrual Bleeding	Heavy Menses	Unique Characteristics	Family History
Coagulopathy	Prolonged	No	Yes	Bruising Epistaxis Gingival bleeding	Yes
HPO axis immaturity	Variable	No	Variable	None	No
PCOS	Variable	No	Variable	Acne Hirsutism Central obesity	Yes
Endometrial causes	Prolonged	Yes	No	Unprotected sexual activity Vaginal discharge Fever Cervical motion tenderness Uterine tenderness	No
Contraceptive breakthrough	Prolonged	Yes	No	Progesterone-only contraceptive use Improper use of hormonal contraception	No
Adenomyosis	Prolonged	No	Yes	Symmetrically enlarged uterus	Possible
Leiomyoma	Prolonged	No	Yes	Asymmetrically enlarged uterus	Yes
Polyp	Prolonged	Yes	No	None	No

HPO, hypothalamic-pituitary-ovary; PCOS, polycystic ovary syndrome.

suggests that the HPO axis is active, confirming GnRH-depending precocious puberty.

ABNORMAL BLEEDING IN ADOLESCENCE

Establishment of the menstrual cycle is a major hallmark of adolescence. The menstrual cycle serves as a marker of health, so much so, it has been heralded as a "vital sign" during adolescence. Irregular menstrual bleeding may simply be related to the maturation of the complex physiologic process leading to puberty. In other cases, irregular menstrual bleeding may be a symptom of a significant medical condition (Table 22.3). A basic understanding of the menstrual cycle is helpful when trying to understand the many causes of abnormal bleeding.

REVIEW OF THE MENSTRUAL CYCLE

Complex interaction between the hypothalamus, pituitary, ovary, and uterus leads to ovulatory menstrual cycles (Fig. 22.1). The hypothalamus releases pulses of gonadotropin-releasing hormone (GnRH) into a portal system to the pituitary gland. The anterior pituitary is stimulated to release the gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), when exposed to GnRH pulses. LH acts on the theca cells of the ovary leading to androgen production; these hormones are aromatized to estrogens in the granulosa cells of the ovary under the influence of FSH. This drives development of the dominant follicle.

Interaction between the anterior pituitary and ovary is complex in that it is bidirectional. Gonadotropin release is stimulated by GnRH, and modulated by ovarian hormones, both the sex steroid hormones and the peptide hormones, activin and inhibin. In the first half of the cycle, the dominant follicle grows in size leading to increased estradiol production. A positive feedback relationship is seen between the ovary and the anterior pituitary with higher levels of estradiol stimulating gonadotropin release. This ultimately leads to the LH surge, triggering ovulation.

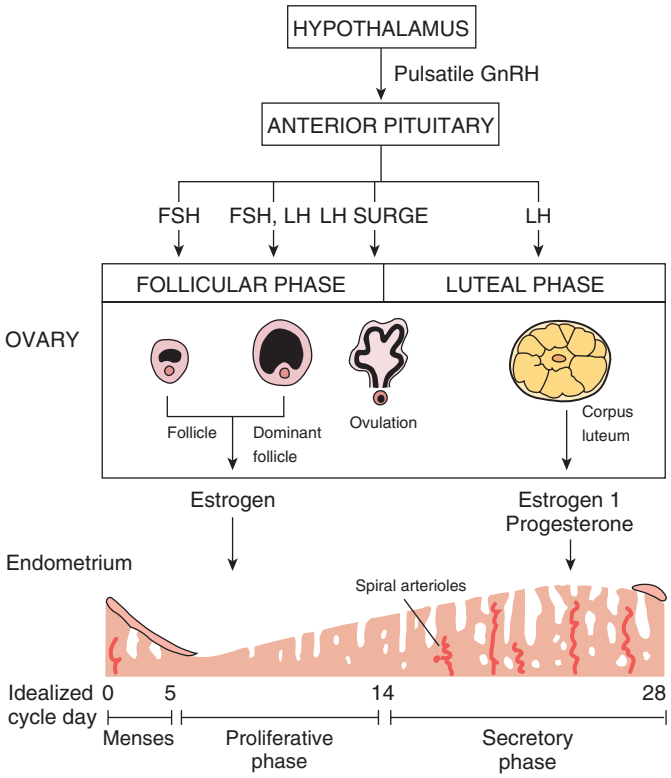


FIGURE 22.1 Hypothalamic-pituitary-ovarian endometrial axis: changes over time. FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

Postovulation, the dominant follicle transforms into a progesterone secreting corpus luteum. During this phase of the cycle, estradiol inhibits gonadotropin release preventing the development of another dominant follicle. The corpus luteum sustains progesterone secretion for 14 days; beyond this point, continued progesterone secretion is

(See *Nelson Textbook of Pediatrics,* p. 963.)

TABLE 22.4 New Classification System for Abnormal Bleeding

PALM	COIEN
Polyp	Coagulopathy
Adenomyosis	Ovulation dysfunction
Leiomyoma	Iatrogenic causes
Malignancy	Endometrial causes
	Not otherwise specified

dependent on β-human chorionic gonadotropin (β-hCG) signaling from a pregnancy. If no pregnancy occurs, the corpus luteum regresses, and progesterone levels drop.

The endometrium is a mucosal surface lining the uterine cavity. Its thickness and composition are under the control of estradiol and progesterone. During the preovulatory estradiol-dominant phase, termed the *proliferative phase,* the endometrium rapidly grows. The endometrial lining undergoes glandular differentiation to optimize implantation during the postovulatory progesterone-dominant phase, termed the *secretory phase*. If no pregnancy occurs, the spiral arterioles supplying the endometrium undergo spasm secondary to waning estradiol and progesterone levels. The endometrium becomes ischemic and sheds, producing menstrual bleeding. The amount of menstrual blood directly correlates with the thickness of the endometrium, the activity of the coagulation cascade directing the clotting of the vessels, and the re-exposure to estrogen with the start of the new cycle. Any abnormality in these processes can lead to an abnormal bleeding pattern.

Normal parameters of the menstrual cycle should be understood to correctly identify abnormal patterns of bleeding. The cycle interval describes the number of days between the first day of 1 period and the 1st day of the next period. A normal cycle *interval* in adolescents is between 21-45 days, with the most common upper limit of 35 days. The cycle *length* describes the number of days menstrual bleeding lasts. A normal cycle length is conventionally described as between 3 and 7 days. The amount of bleeding is much harder to quantify. Greater than 80 mL of menstrual blood loss during a cycle is considered pathologically heavy, with the average blood loss being 30 mL. The clinical impracticality of obtaining this information is obvious; subjective clinical interview is used to determine heavy blood flow.

Information regarding the start of menarche, cycle interval, cycle length, bleeding between menses, and questions detailing the quantity of blood flow are essential in the assessment of abnormal bleeding. The Federation of Gynecology and Obstetrics Menstrual Disorders Group has recommended a classification system to categorize the causes of abnormal uterine bleeding. The acronym PALM-COEIN has been devised to categorize the multiple causes of abnormal uterine bleeding (Table 22.4). The conditions falling under the PALM group describe structural abnormalities and are much less common in the adolescent population than the nonstructural conditions falling under the COEIN group.

PREGNANCY

Pregnancy evaluation is an important early step in the assessment of abnormal bleeding in the adolescent. Bleeding in pregnancy, particularly in the 1st trimester is common and can occur with a normal or abnormal intrauterine pregnancy or an ectopic pregnancy. Pregnancy-associated bleeding can be light or heavy; similarly, it may be painless or associated with uterine cramping. A thorough history is helpful in understanding the heaviness of the current bleeding episode, the date of the last normal menstrual cycle, and assessing sexual and contraceptive activity. Physical examination can be helpful if the patient is beyond the 1st trimester as the uterus may be palpable on abdominal examination. A pelvic examination to assess the size of the uterus is helpful in the 1st trimester, but may not be appropriate for all adolescent patients. If a pregnancy is diagnosed by urine β-hCG testing, the viability of the pregnancy may be determined with ultrasound or serial β-hCG measurements 48 hours apart early in pregnancy. This hormone will increase by at least 53% over a 48-hour time period. β-hCG levels that drop or plateau are typically diagnostic of an abnormal intrauterine or ectopic pregnancy.

COAGULOPATHY

Bleeding dyscrasias, particularly platelet dysfunction, is associated with heavy and prolonged menstrual bleeding. In the adolescent population, menstrual cycles consistently lasting more than 7 days with a gushing sensation, or the need to change pads 8 or more times a day have been associated with a bleeding dyscrasia. Capturing information related to the cycle length, saturation of pads and frequency of change, frequency of menstrual blood leakage onto clothing, and the number of school days or social activities missed are effective in assessing heavy bleeding in the adolescent. Patients who report easy bruising, gingival bleeding, or frequent epistaxis should raise suspicion for a platelet function defect. The American College of Obstetricians and Gynecologists recommends testing adolescent patients for dyscrasia if they have one of the following: menses lasting >7 days with flooding, gushing, or leakage through pads in 2 hours, a history of anemia, a family history of a bleeding disorder, or heavy bleeding after a hemostatic challenge such as tooth extraction, surgery, or child birth. A reasonable basic approach to testing involves evaluating the platelet count, prothrombin time/international normalized ratio and partial thromboplastin time, and von Willebrand disease panel. Hematology referral is advisable in patients with severe, heavy and prolonged bleeding, and for those patients whose bleeding is not controlled with standard hormone therapy. Although not as common as platelet function disorders, coagulation factor deficiencies may present with heavy uterine bleeding during adolescence.

OVULATORY DYSFUNCTION

The complex feedback relationship between estrogen and the anterior pituitary is the last part of the menstrual cycle to mature. Before positive feedback is established, FSH may actually decrease with rising estrogen levels. This stunts dominant follicle development and ovulation does not occur. Without ovulation, the corpus luteum does not develop; consequently, progesterone secretion from the ovary is limited. The endometrial lining is unstable without progesterone influence leading to an abnormal bleeding pattern. This scenario is often termed *immaturity of the HPO axis*. The associated **anovulatory bleeding** pattern can present as frequent, absent, or heavy uterine bleeding. The abnormal bleeding associated with HPO immaturity is typically seen within the first 3 years of menarche, but can persist for 5 years after menarche. While this is the most common cause of irregular bleeding in early adolescence, other causes should be considered because immaturity of the HPO axis is a diagnosis of exclusion.

Polycystic ovary syndrome (**PCOS**) is a complex endocrinopathy that is likely the result of a heterogeneous combination of influences including genetics, the intra- and extrauterine environment, insulin resistance, steroid hormone metabolism, and other metabolic abnormalities. The presenting clinical pattern can include hyperandrogenemia causing hirsutism and acne, infrequent or absent ovulation leading to amenorrhea, oligomenorrhea, and subfertility, polycystic

ovaries on ultrasound, and eventual development of metabolic syndrome (obesity, type 2 diabetes, hypertension). The bleeding pattern most commonly associated with PCOS is infrequent or absent menses, although prolonged and heavy bleeding may occur. Diagnosis of PCOS typically relies on a variable presentation of 3 key features: hyperandrogenism, oligomenorrhea, and polycystic-appearing ovaries. The hormonal changes and physical symptoms associated with PCOS overlap greatly with early adolescence, making the evaluation particularly difficult in this age group. A stricter criterion for diagnosis includes hyperandrogenemia and progressive hirsutism, cycle length of 45 days or more, and polycystic ovaries with a size greater than 10 cm by sonogram. The diagnostic work-up of PCOS also involves the exclusion of mimicking causes such as late-onset congenital adrenal hyperplasia, androgen-secreting tumors, and Cushing disease. Normal early adolescence should also be considered as a mimicking condition. Therefore, considering this diagnosis within the 2 years of menarche should be done with caution, and only in the case of obvious pathology. Given the association of PCOS with future morbidity, these adolescents should be monitored closely and retested if the abnormal bleeding pattern persists.

Thyroid dysfunction can lead to an abnormal uterine bleeding pattern by disrupting ovulation. Similar to PCOS, the bleeding pattern most commonly associated with thyroid dysfunction is absent or infrequent menses, but heavy, prolonged bleeding can develop. In this case, severe hypothyroidism leads to significantly elevated levels of thyroid-stimulating hormone. This hormone, also from the anterior pituitary, has FSH-like activity and stimulates the stromal cells of the ovary to produce high levels of estrogen. The dysregulated production of estrogen leads to a thickened endometrial lining that eventually outgrows its blood supply, leading to ischemia and shedding. Bleeding is heavy and prolonged because this shedding is asynchronous, and the volume of endometrium is high.

Ovulatory dysfunction often presents as absent menses or amenorrhea. The **amenorrhea presentation** has an extremely wide range of diagnostic possibilities, some of which are associated with significant morbidity and even mortality if not recognized. Significant anatomic abnormalities, male karyotype, tumor of the anterior pituitary gland, significant malnutrition, and premature ovarian insufficiency illustrate the complexity of diagnostic possibilities (Table 22.5).

The 1st step in accurate diagnosis is determining when amenorrhea is actually pathologic. A work-up for absent menses should be done for adolescents who show no signs of secondary sexual maturation by age 13, no menses with other sexual characteristics by age 15, or if more than 3 months pass between menstrual cycles. Starting with a thorough history to identify any risk factors such as known renal anomalies, childhood exposure to chemotherapy or radiation, exercise and nutrition imbalance, galactorrhea, or family history of early menopause is important. A physical examination, including assessment of height, body mass index, acne and hirsutism, Tanner staging of breast and pubic hair development, and confirmation of a patent vagina if appropriate can help to further narrow the diagnostic possibilities. Ultrasound evaluation is a reasonable early test if the patient is not amenable to an examination, particularly if there is high risk of an anatomic abnormality. Laboratory assessment should include a pregnancy test, and serum thyroid-stimulating hormone, FSH, and prolactin.

If the thyroid or pregnancy testing is abnormal, the diagnosis is clear. If the prolactin level is elevated and there is no evidence of hypothyroidism, magnetic resonance imaging of the anterior pituitary is warranted. Over 50% of the time, an elevated prolactin level is secondary to an anterior pituitary tumor. Other CNS lesions that irritate the pituitary stalk are also associated with elevated prolactin levels. A thorough medication review should also be conducted in the case of hyperprolactinemia as this is a common side effect of antipsychotic medications that competitively bind to dopamine receptors, effectively

TABLE 22.5 Characteristics of the Causes of Amenorrhea

	FSH	Karyotype	Family History	Classic Unique Findings
Turner syndrome	Elevated	45,X	Fragile X syndrome	Short stature Webbed neck Lymphedema of hands and feet Low neck hairline
XY gonadal dysgenesis	Elevated	46,XY	No	No secondary sexual development
Hypothalamic amenorrhea	Low or normal	46,XX	No	Low body mass index Poor dentition
Imperforate hymen	Normal	46,XX	No	Pain Bulging hymen
PCOS	Normal	46,XX	Yes	Acne Hirsutism Central obesity
Mullerian anomalies	Normal	46,XX	Possible	Normal breast development Absent vagina
AIS	Normal	46,XY	No	Normal breast development Scant or no body hair Absent vagina
Premature ovarian insufficiency	Elevated	46,XX	Yes	Variable presence of secondary sexual characteristics
Kallman syndrome	Low or normal	46,XX	Yes	Inability to smell Absent secondary sexual characteristics

AIS, androgen insensitivity syndrome; PCOS, polycystic ovary syndrome.

lowering dopamine activity leading to an elevation of prolactin secondary to the inhibitory relationship between dopamine and prolactin.

An elevated FSH is associated with complex diagnoses such as premature ovarian insufficiency and gonadal dysgenesis. Immediate karyotype evaluation should be performed with the intent of making an early diagnosis of **Turner syndrome** or **gonadal dysgenesis** involving an XY karyotype. Both of these conditions are associated with significant morbidity if early treatment is not initiated. XY karyotype is associated with malignancy requiring gonadectomy; Turner syndrome is associated with left-sided cardiac abnormalities (bicuspid aortic valve, coarctation of aorta) in 50% of patients. Certainly emotional support, with both individual and family therapy, and referral to a support group should be considered in patients with the elevated FSH, as natural fertility is compromised and to support any gender identity concerns that might be raised.

In many cases of amenorrhea, the hormone evaluation and physical examination will be largely normal. Functional hypothalamic amenorrhea, most likely caused by immaturity of the HPO axis, is a diagnosis of exclusion and presents with either normal or low FSH levels. Identification of excessive stress related to either the social environment or a medical condition, sports or exercise activity not supported with sufficient calories, physical examination findings confirming poor nutrition based on low body mass index percentile, or poor dentition from frequent vomiting are important to identify. Amenorrhea and anosmia is suspicious for Kallmann syndrome, which is associated with GnRH deficiency. In the case of functional hypothalamic amenorrhea, magnetic resonance imaging of the central nervous system should be considered when the history interview does not produce any suspicion for stress or nutrition abnormalities, and particularly when symptoms such as nausea, headaches, and vision changes are present.

ENDOMETRIAL CAUSES

Infection and inflammation of the endometrium can lead to an abnormal uterine bleeding pattern. The bleeding pattern can range from light, intermenstrual bleeding to prolonged menstrual bleeding. Infection of the upper genital tract, pelvic inflammatory disease (PID), is a common diagnosis in adolescents and is directly linked to the high prevalence of gonorrhea and chlamydia infections in this population. Treating gonorrhea and chlamydia infections of the lower genital tract has been shown to reduce the risk of PID, which has clinical implications much more severe than abnormal bleeding. Testing for gonorrhea and chlamydia infections is recommended at least annually in sexually active women 25 years of age or younger, regardless of symptoms. Nucleic acid amplification test (NAAT) is the most sensitive and clinically useful as testing can be done on urine specimens and vaginal swabs as well as endocervical specimens. An infectious source of bleeding should be considered when evaluating a sexually active teenager.

IATROGENIC CAUSES

The most common group of medications that lead to abnormal uterine bleeding prescribed to adolescents is hormonal contraceptives. This bleeding is referred to as **breakthrough bleeding** and is typically described as prolonged or intermenstrual and is rarely heavy. Combination contraceptives (pills, transvaginal ring, and transdermal patch) are designed to provide 21 days of hormones for the purpose of blocking ovulation, and 7 days of placebo triggering the endometrium to shed, leading to a menstrual cycle. If pills are missed, or if the transdermal patch or ring are left in place longer than prescribed, or removed too early, endometrial bleeding will be triggered. In some cases, breakthrough bleeding may occur even if the contraceptive method is being used correctly. Some follicular development has been described particularly with the very low dosage ethinyl estradiol contraceptive pills. While this is not associated with lower contraceptive efficacy, it may be associated with more ovarian cyst development and irregular bleeding. All progestin-only contraceptive methods are particularly troublesome for the breakthrough bleeding side effect. The majority of women using progesterone-only contraception report abnormal bleeding pattern after 1 year of use; however, the longer these methods are used, the more acceptable the bleeding pattern becomes. The actual mechanism causing breakthrough bleeding when using progesterone-only contraception is not clear; endometrial evaluation shows abnormal, enlarged, thin-walled fragile blood vessels. The intrauterine device (IUD), both the progestin-releasing and the nonhormonal device, can be associated with an abnormal bleeding pattern after initial insertion; the abnormal bleeding pattern will improve over time. The majority of hormonal IUD users ultimately experience a decrease in monthly menstrual bleeding, while the majority of nonhormonal IUD users report no change from their preinsertion menstrual pattern after 1 year of use.

Abnormal bleeding in adolescents can be associated with nonhormonal medications as well. Anticoagulation medications can lead to a heavy and prolonged bleeding pattern, especially when supratherapeutic anticoagulation occurs. In some cases, the bleeding associated with anticoagulation is quite heavy and requires acute, aggressive therapy to prevent significant anemia. A strategy to avoid heavy menstrual bleeding from anticoagulation is to start a safe hormonal contraceptive method with the purpose of limiting menses altogether.

NOT YET CLASSIFIED

Persistent abnormal bleeding sometimes requires multiple evaluations over time to identify the cause. In many cases, the initial evaluation, even when complete, may not identify the abnormality. PCOS is a good example of a condition that evolves over time and sometimes requires multiple evaluations to confirm. If the bleeding pattern is causing anemia or significant quality-of-life disruption, treatment should not be withheld simply because a clear diagnosis has not been established.

STRUCTURAL CAUSES: PALM

The structural causes of abnormal bleeding are much less common in the adolescent population. Gynecologic malignancy and hyperplasia in adolescence are rare conditions. In the case of the rare vaginal or cervical malignancy, the abnormal bleeding is typically prolonged or intermenstrual; endometrial malignancies and uterine sarcomas, also exceedingly rare, typically present with heavier bleeding. **Ovarian germ cell** tumors are the most common gynecologic malignancy during adolescence, most commonly presenting in the 15-19 year age group. Abnormal uterine bleeding is not a common presenting symptom of germ cell tumors; however, malignant stromal cell tumors of the ovary, specifically juvenile granulosa cell tumors, classically present with heavy and prolonged uterine bleeding. Ultrasound evaluation should be immediately performed if an adolescent presents with abnormal uterine bleeding and an abdominal mass.

In addition to malignancy, ultrasound evaluation is effective in diagnosing leiomyomas (fibroids) and polyps. Both represent a benign overgrowth of uterine tissue, and, again, are extremely uncommon in the adolescent population. A **leiomyoma** is a smooth muscle tumor of the myometrium that loses growth regulation and often presents with heavy and prolonged uterine bleeding. A **polyp** is typically an

overgrowth of the endometrium or the endocervix and classically presents as intermenstrual bleeding. This structural abnormality is not well reported in the adolescent population. **Adenomyosis** is another abnormality where islands of endometrial tissue are embedded in the myometrium of the uterus. While this condition is rare in the adolescent population, it typically presents with heavy and prolonged bleeding, similar to a leiomyoma. Adenomyosis is also a benign condition, but unlike leiomyoma, the sensitivity of ultrasound diagnosis is low; magnetic resonance imaging is more sensitive and reliable for diagnosis.

CONGENITAL ANOMALIES

Müllerian anomalies are another important structural cause of abnormal bleeding. The müllerian ducts, embryonically called the paramesonephric ducts, appear 37 days post fertilization and undergo a process of invagination, elongation, fusion, and resorption with canalization to become the fallopian tubes, uterus, cervix and upper vagina. Müllerian anomalies result from agenesis, failed resorption, or failed lateral fusion. Absent menstrual bleeding is the most common abnormal bleeding pattern associated with müllerian anomalies, although most anomalies, such as bicornuate, didelphys, and septate uterus do not result in abnormal bleeding. Anomalies presenting with amenorrhea are associated with an absence of the vagina, uterus and/or cervix, or a complete obstruction such as a transverse vaginal septum.

Anomalies involving a transverse vaginal septum are actually quite rare and may present with prolonged irregular bleeding as well as with amenorrhea. If spontaneous perforation of the vaginal septum occurs, a prolonged, irregular bleeding pattern is produced. Similarly, an obstructed hemivagina that spontaneously ruptures leads to a similar bleeding pattern. This müllerian anomaly describes uterine didelphys and bicollis, with a partial vaginal septum obstructing the outflow of one of the müllerian tracts. If an abnormality of the upper genital tract is suspected, magnetic resonance imaging is indicated for confirmation.

A simple external genital examination should always be done during the evaluation of amenorrhea as imperforate hymen, a structural anomaly much more common than müllerian anomalies, is easily diagnosed by inspection. An imperforate hymen is the complete obstruction by the hymenal membrane at the level of the vaginal introitus preventing the passage of menstrual bleeding. Pain is a key complaint. Diagnosis by examination is reliable as the hymenal tissue is often bulging from the pressure resulting from the hematocolpos. In this case, a simple surgical procedure to remove the redundant hymen can be done to achieve normal anatomy.

Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome and androgen insensitivity syndrome (AIS) are 2 other diagnostic possibilities that present with absent vagina and amenorrhea. In both of these conditions, the müllerian structures are absent, and both external genitalia and breast development are consistent with a female phenotype. Karyotype and testosterone level differentiates the 2 disorders, as MRKH individuals are 46,XX with serum testosterone in the female range whereas AIS individuals are 46,XY with testosterone levels in the male range. In AIS, the absent androgen activity leads to female external genitalia development and limited body hair, as well as no wolffian structure development. Peripheral conversion of androgens to estrogens leads to estrogenization, specifically breast development, during puberty. The gonads are at risk for malignancy and removal after achievement of adult height is recommended. After gonadectomy, estrogen replacement is needed until natural age of menopause is reached for optimal health. AIS is significantly less common than MRKH (2-5/100,000 vs 4/1500) and is associated with an X-linked recessive inheritance pattern, whereas MRKH appears to be more sporadic.

TREATMENT

Progestins alone, or in combination with estradiol, are the most effective medical therapy to treat abnormal bleeding in adolescents. Hormones should be considered 1st-line therapy even when managing adolescents with bleeding dyscrasias or structural abnormalities such as adenomyosis or leiomyomas. When given cyclically, especially in the combination contraceptive formulation, bleeding becomes regular and light. If progestin-only therapy is given continuously, menstrual bleeding will theoretically be suppressed, although breakthrough bleeding, as described previously, can occur.

Selecting the best method for abnormal bleeding management should first focus on safety considerations, particularly if an estrogen-containing treatment is selected. Contraindications to estrogen therapy are listed in Table 22.6. After a determination of safety is made, a detailed discussion should be held to determine any potential compliance concerns as improper use of hormone therapy can lead to irregular bleeding and ultimately treatment failure.

Antifibrinolytics, specifically tranexamic acid, are effective nonhormonal medications that can be considered for those adolescents who are not comfortable taking hormonal medications or who have significant contraindications or side effects to hormone therapy. These medications can also be used adjunctively with hormone therapy if bleeding control is suboptimal, but the risk for venous thromboembolism should be discussed with the patient. A platelet transfusion, factor replacement, desmopressin, intravenous immune globulin, or oral corticosteroids may be appropriate adjunctive therapy depending on the etiology. Hormone therapy is effective in controlling bleeding secondary to all of these conditions and should be concurrently administered. In the rare case of a malignancy, polyp, or a resectable partial anatomic blockage, surgical management is required.

If abnormal uterine bleeding is profound, producing significant anemia, hormonal therapy remains the mainstay of medical treatment, but with different dosing regimens (see Table 22.7). Both estrogens and progestins alone or in combination are effective. High-dose progestin therapy leads to endometrial atrophy. High-dose estradiol therapy is effective by inducing endometrial vascular vasospasm, regenerating denuded epithelium, and increasing clotting factors. Both intravenous and oral high-dose estradiol preparations are available and the intravenous route may be preferable in patients who are unable to tolerate

TABLE 22.6 Contraindications to Estrogen Therapy

Poorly controlled hypertension, or coexisting vascular disease
Current/history of ischemic heart disease
Liver dysfunction: severe cirrhosis, adenoma, hepatocellular carcinoma
History of venous thromboembolism/known thrombophilia
Complicated valvular heart disease
Migraine with aura
Active cancer or within 6 mo of treatment
<6 mo since diagnosis of peripartum cardiomyopathy
Diabetes with vascular complication
Major surgery with prolonged immobilization
Moderate to severe impairment of cardiac function
Solid organ transplant complicated by graft failure, rejection, cardiac allograft vasculopathy

TABLE 22.7 Hormone Treatment Regimens for Acute Heavy Bleeding

IV Estrogen	Combination Oral Contraceptives	Oral Progesterone
Conjugated estrogen 25 mg every 4-6 hr	30-50 μg of ethinyl estradiol–containing tablets every 4-8 hr Taper dosage over several days when bleeding subsides	Medroxyprogesterone 20 mg orally bid to tid or norethindrone 5-10 mg orally bid

oral medication secondary to nausea. Regardless of which high-dose hormone regimen is used, once cessation of bleeding has been achieved, transitioning to a progestin-dominant therapy is imperative. If this is not done, sudden stoppage of the high dosage of hormone therapy will lead to withdrawal bleeding. Specific factor replacement, particularly factor VII replacement, may also be effective in controlling profound heavy bleeding, regardless of the cause.

GnRH agonist therapy is another option to acutely control heavy uterine bleeding. The mechanism of action involves decreased expression of GnRH receptors of the anterior pituitary secondary to receptor saturation, which leads to decreasing sex hormone production from the ovaries. This medication should be used with caution as a flare in bleeding may initially occur. Traditional dosing involves an intramuscular injection of either 11.25 mg given at 3-month intervals, or monthly dosing of 3.75 mg. GnRH agonist therapy is limited to 12 months of use secondary to the significant lowering of bone mineral density as a result of decreased circulating ovarian estrogens. Vasomotor symptoms are also a common side effect of decreased estrogens; treatment low-dose progestins or estradiol is typically effective in relieving symptoms.

Management of acute bleeding may require surgical therapy. Placement of a Foley balloon into the endometrium filled with 30 mL of saline is effective by tamponading the bleeding endometrium and reducing the blood supply to the uterus by partially compressing the uterine arteries. The balloon is deflated gradually over 2-3 days while hormone therapy is ongoing. A dilation and curettage is often performed with Foley balloon placement. This procedure leads to endometrial thinning and can be effective in controlling heavy bleeding on its own. Again, hormone therapy should be ongoing. The final 2 surgical options impair fertility and should be reserved as a last resort: uterine artery embolization and hysterectomy. Hysterectomy is the last resort when all other conservative management fails.

MENSTRUAL PAIN IN ADOLESCENTS

Dysmenorrhea, defined as pain during the menstrual cycle, is the most common reason adolescent patients seek gynecologic care. Pain is most commonly in the pelvis secondary to uterine cramping, but can also be reported in the back and upper thighs. Sixty to seventy percent of adolescents report pain during menses, and 15% report significant quality-of-life dysfunction leading to a disruption of normal activities. Dysmenorrhea is associated with ovulatory cycles; therefore, this symptom typically presents in the later adolescent years. Dysmenorrhea, unlike chronic pelvic pain, presents with cyclic pain beginning within 48 hours of the 1st day of the menstrual cycle, and resolves by menstrual cycle day 2 or 3. Primary dysmenorrhea is significantly more common in adolescents. In this condition, high levels of prostaglandin E_2 and $F_{2\alpha}$, produced by the endometrium, cause painful uterine cramping. Secondary dysmenorrhea is the result of an anatomic abnormality causing uterine cramping. About 10% of adolescents with menstrual pain have secondary dysmenorrhea.

If the physical examination is normal, and there are no factors in the medical history raising suspicion for an anatomic abnormality, empirical treatment without laboratory or radiologic evaluation is a reasonable approach. Nonsteroidal antiinflammatory drugs (NSAIDs) are effective therapy as prostaglandin production is directly reduced. This therapy is most effective when started 24-48 hours prior to the onset of pain. Contraceptive agents that block ovulation and limit the growth of the endometrial lining lead to a decreased in prostaglandin production and, therefore, are also effective in treating dysmenorrhea. Although NSAIDs are traditionally considered 1st-line therapy for primary dysmenorrhea, starting a contraceptive agent without an NSAID trial is acceptable given the inherent administration difficulty associated with proper NSAID use. Nontraditional therapies such as vitamin E, magnesium supplementation, acupuncture, transcutaneous electrical nerve stimulation, and dietary supplements are not well studied.

If menses are reported to be painful, and if there is some persistence of pain between cycles, or if empirical therapy for primary dysmenorrhea is unsuccessful after 3-6 months of treatment, a diagnosis of secondary dysmenorrhea should be considered. Uterine leiomyomas, adenomyosis, and outflow tract abnormalities that block the egress of menstrual blood can cause significant pain during menses and discomfort between menstrual cycles. The most common cause of **secondary dysmenorrhea** during adolescence is **endometriosis.** The prevalence of endometriosis in the adolescent population has not been established, but 60% of adult women with endometriosis report symptoms prior to age 20, and 45-70% of adolescents undergoing laparoscopy for pain are found to have endometriosis. Confirmation of endometriosis is challenging as no blood test or imaging study is diagnostic. Laparoscopic surgical evaluation of the pelvis can be helpful, but the lesions are often subtle and heterogeneous in appearance and consequently can be missed. The hormonal therapies effective in treating primary dysmenorrhea are also effective in the treatment of secondary dysmenorrhea, with the exception of outflow tract obstruction abnormalities, which always require surgical management. The levonorgestrel intrauterine device has been particularly effective in controlling symptoms of endometriosis and leiomyomas.

While dysmenorrhea is a common premenstrual symptom, it is a different entity than **premenstrual syndrome** (**PMS**). The basic diagnostic strategy for PMS involves confirming the presence of at least 1 somatic complaint (breast tenderness, abdominal bloating, headache, or swelling of extremities) and 1 affective complaint (depression, angry outbursts, irritability, anxiety, confusion, or social withdrawal) during the 5 days preceding menses for 3 consecutive menstrual cycles. The symptoms must be resolved by the 4th day of the menses, and should not recur until at least 13 days have passed from cycle day 1 of the last menses. For diagnostic purposes, these symptoms should also negatively impact social or school participation.

Premenstrual dysphoric disorder (**PMDD**) is often grouped with PMS but the diagnostic criteria differ. The American Psychiatric Association requires at least 5 of the following symptoms: marked depressed mood, marked anxiety, marked emotional lability, persistent and marked anger, decreased interest in usual activities, difficulty concentrating, lethargy, marked change in appetite, sleep disturbance, loss of control sensation, and physical symptoms of breast tenderness, swelling, headaches, joint pain, muscle pain, bloating, or weight gain. For diagnosis, the symptoms must interfere with activities and relationships, and the symptoms cannot be an exacerbation of a mood or personality disorder. These criteria must be confirmed by daily

prospective ratings over 2 consecutive cycles. The pathophysiology of PMS and PMDD have been linked to the fluctuation of ovarian sex steroid hormones after ovulation. While no difference in hormonal levels have been confirmed in women with PMS/PMDD compared to those that do not have these conditions, there may be a different serotonin activity or γ-aminobutyric receptor activity response to the hormone fluctuations during the luteal phase.

Treatment options include hormonal suppression of ovulation to prevent the luteal phase fluctuation of hormones. Hormonal agents containing the 4th-generation progestin drospirenone have been effective in controlling affective and somatic symptoms. The possible small increased risk of venothromboembolic events associated with this particular progestin preparation warrants a careful risk-benefit analysis. NSAIDS and spironolactone have been shown to be helpful in the alleviation of the physical symptoms. Selective serotonin reuptake inhibitors (SSRIs) have been put forth as a 1st-line treatment option in adult women with severe PMS and PMDD as improvement in both somatic and affective symptoms have been documented. However, the efficacy of these medications in adolescents with PMS/PMDD is unclear, and the association of these medications with increased suicidality has blunted widespread use. Nonpharmacologic therapies that have been utilized include exercise, stress management, cognitive-behavioral therapy, education about the syndrome, supplementation with calcium, magnesium, vitamin B_6, and vitamin E, and chasteberry, ginkgo biloba, and St. John's wort herbal remedies. Data supporting these therapies are promising, but limited for conclusions of efficacy. Red flags include a mass, extragenital bleeding, anemia, a positive family history, and the possibility of an abnormal pregnancy.

SUMMARY AND RED FLAGS

Menstrual concerns and abnormal bleeding are common complaints in childhood and adolescence with a wide range of diagnostic possibilities. At first, the work-up may appear overwhelming. However, a thorough history and physical examination helps to quickly identify the more likely underlying causes, narrowing the laboratory and imaging evaluation that may be needed to efficiently make an accurate diagnoses. Red flags in the evaluation include prolonged bleeding, anemia, or fevers. For the vast majority of adolescents presenting with menstrual concerns, treatment can be initiated with limited evaluation secondary to the likelihood of the underlying cause being a benign, transient process. Abnormal bleeding in childhood typically warrants more of a diagnostic work-up, although most often, the underlying cause is also benign.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

ACOG Committee on Adolescent Health Care. ACOG Committee Opinion No. 349, November 2006. Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. *Obstet Gynecol*. 2006;108:1323-1328.

Adachi T, Sato H, Nakayama S, et al. Primary amenorrhea due to juvenile granulosa-cell tumor of the ovary: A case report. *J Obstet Gynaecol Res*. 2012;38:597-600.

Ahuja S, Hertweck P. Overview of bleeding disorders in adolescent females with menorrhagia. *J Pediatr Adolesc Gynecol*. 2010;23:S15.

American College of Obstetricians and Gynecologists. Medical management of ectopic pregnancy. ACOG Practice Bulletin No. 94. *Obstet Gynecol*. 2008;111:1479-1485.

American College of Obstetricians and Gynecologists. Von Willebrand disease in women. Committee Opinion No. 580. *Obstet Gynecol*. 2013;122:1368-1373.

Amr SS, Tavassoli FA, Hassan AA, et al. Mixed mesodermal tumor of the uterus in a 4-year-old girl. *Int J Gynecol Pathol*. 1986;5:371-378.

Amsterdam ESHRE/ASRM-sponsored 3rd PCOS Consensus Workshop Group. Consensus on women's health aspects of polycystic ovary syndrome (PCOS). *Hum Reprod*. 2012;27(1):14-24.

Andres MP, Podgaec S, Carreiro KB, et al. Endometriosis is an important cause of pelvic pain in adolescence. *Rev Assoc Med Bras*. 2014;60(6):560-564.

Baker VL. Primary ovarian insufficiency in the adolescent. *Curr Opin Obstet Gynecol*. 2013;25:375-381.

Baker WD, Soisson AP, Dodson MK. Endometrial cancer in a 14-year-old girl with Cowden syndrome: a case report. *J Obstet Gynaecol Res*. 2013;39(4):876-878.

Berberoglu M. Precocious puberty and normal variant puberty: definition, etiology, diagnosis and current management. *J Clin Res Ped Endo*. 2009;1(4):164-174.

Braverman PK. Premenstrual syndrome and premenstrual dysphoric disorder. *J Pediatr Adolesc Gynecol*. 2007;20:3-12.

Brosens I, Gordts S, Habiba M, et al. Uterine cystic adenomyosis: a disease of younger women. J Pediatr Adolesc Gynecol. 2015;28:420-426.

Brown J, Friedlander M, Backes FJ, et al. Gynecologic Cancer Intergroup (GCIG) consensus review for ovarian germ cell tumors. *Int J Gynecol Cancer*. 2014;24:S48-S54.

Carmina E, Oberfield SE, Lobo RA. The diagnosis of polycystic ovary syndrome in adolescents. *Am J Obstet Gynecol*. 2010;201(e1–201):e5.

Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines. *MMWR*. 2010;59(RR–12):40-47.

Centers for Disease Control and Prevention (CDC). U. S. medical eligibility criteria for contraceptive use, 2010. *MMWR Recomm Rep*. 2010;59(RR–4):1-86.

Chi C, Pollard D, Tuddenham E, et al. Menorrhagia in adolescents with inherited bleeding disorders. *J Pediatr Adolesc Gynecol*. 2010;23:215.

Claman F, Miller T. Premenstrual syndrome and premenstrual dysphoric disorder in adolescence. *J Pediatr Health Care*. 2006;20(5):329-333.

Cohen-Kettenis PT. Psychosocial and psychosexual aspects of disorders of sex development. *Best Pract Res Clin Endocrinol Metab*. 2010;24:325-334.

Deligeoroglou E, Karountzos V, Creatsas G. Abnormal uterine bleeding and dysfunctional uterine bleeding in pediatric and adolescent gynecology. *Gynecol Endocrinol*. 2013;29(1):74-78.

Dietrich JE. An update on adenomyosis in the adolescent. *Curr Opin Obstet Gynecol*. 2010;22(5):388-392.

Dietrich JE, Millar DM, Quint EH. Non-obstructive mullerian anomalies. *J Pediatr Adolesc Gynecol*. 2014;27:386-395.

Dietrich JE, Miller DM, Quint EH. Obstructive reproductive tract anomalies. *J Pediatr Adolesc Gynecol*. 2014;27:396-402.

Emans SJ, Laufer MR, Goldstein DP. *Pediatric &Adolescent Gynecology*. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2005.

The ESHRE Capri Workshop Group. Endometrial bleeding. *Hum Reprod Update*. 2007;13(5):421-431.

Fothergill DJ. Common menstrual problems in adolescence. *Arch Dis Child Educ Pract Ed*. 2010;95:199-203.

Fuqua JS. Treatment and outcome of precocious puberty: An update. *J Clin Endocrinol Metab*. 2013;98(6):2198-2207.

Gordon CM. Functional hypothalamic amenorrhea. *N Engl J Med*. 2010;363:365-371.

Gray SH. Menstrual disorders. *Pediatr Rev*. 2013;34:6-18.

Gray SH, Emans SJ. Abnormal vaginal bleeding in adolescents. *Pediatr Rev*. 2007;28:175-182.

Gruessner SE, Omwandho COA, Dreyer T, et al. Management of stage I cervical sarcoma botryoides in childhood and adolescence. *Eur J Pediatr*. 2004;163:452-456.

Gupta J, Kai J, Middleton L, et al. Levonorgestrel intrauterine system versus medical therapy for menorrhagia. *N Engl J Med*. 2013;368:128-137.

Hickey M, Higham JM, Fraser I. Progestogens versus estrogens and proestrogens for irregular uterine bleeding associated with anovulation. *Cochrane Database Syst Rev*. 2007;(4):CD001895.

Hillard PJ. Menstruation in adolescents: what's normal, what's not. *Ann NY Acad Sci*. 2008;1135:29-35.

James AH, Kouides PA, Abdul-Kadir R, et al. Evaluation and management of acute menorrhagia in women with and without underlying bleeding disorders: consensus from an international expert panel. *Eur J Obstet Gynecol Reprod Biol*. 2011;158(2):124-134.

Kirsch CH, Goodman M, Esiashvili N. Outcome of female pediatric patients diagnosed with genital tract rhabdomyosarcoma based on analysis of cases registered in SEER database between 1973 and 2006. *Am J Clin Oncol*. 2014;37(1):47-50.

Kondamudi NP, Gupta A, Watkins A, et al. Prepubertal girl with vaginal bleeding. *J Emerg Med*. 2014;46(6):769-771.

Mariani G, Konkle BA, Ingerslev J. Congenital factor VII deficiency: therapy with recombinant activated factor VII – a critical appraisal. *Haemophilia*. 2006;12:19-27.

Matteson K, Rahn DD, Wheeler TL 2nd, et al. Nonsurgical management of heavy menstrual bleeding: a systematic review. *Obstet Gynecol*. 2013;121:632-643.

McCluggage WG, Sumathi VP, Nucci MR, et al. Ewing family of tumours involving the vulva and vagina: report of a series of four cases. *J Clin Pathol*. 2007;60:674-680.

Meirow D, Rabinovici J, Katz D, et al. Prevention of severe menorrhagia in oncology patients with treatment-induced thrombocytopenia by luteinizing hormone-releasing hormone agonist and depo-medroxyprogesterone acetate. *Cancer*. 2006;107:1634-1641.

Mills HL, Abdel-Baki MS, Teruya J, et al. Platelet function defects in adolescent with heavy menstrual bleeding. *Haemophilia*. 2013;20:249-254.

Moroni RM, Vieira CS, Ferriani RA, et al. Presentation and treatment of uterine leiomyoma in adolescence: a systematic review. *BMC Womens Health*. 2015;15:4.

Munro MG, Critchley HOD, Broder MS, et al. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. *Int J Gynecol Obstet*. 2011;113:3-13.

Munro MG, Critchley HOD, Fraser IS. The FIGO classification of causes of abnormal uterine bleeding in the reproductive years. *Fertil Steril*. 2011;95(7):2204-2208.

Ong LY, Hwang WS, Wong A, et al. Perivascular epithelioid cell tumour of the vagina in an 8 year old girl. *J Pediatr Surg*. 2007;42:564-566.

Ott MA, Sucato GS, Committee on Adolescence. Contraception for adolescents. *Pediatrics*. 2014;134:e1257.

Özcan J, Dülger O, Küpelioğlu L, et al. Uterine sarcoma in a 14-year-old girl presenting with uterine rupture. *Gynecol Oncol Rep*. 2014;10:44-46.

Panico A, Lupoli GA, Fonderico F, et al. Multiple ovarian cysts in a young girl with severe hypothyroidism. *Thyroid*. 2007;17(12):1289-1293.

Peacock A, Alvi NS, Mushtaq T. Period problems: disorders of menstruation in adolescents. *Arch Dis Child*. 2012;97:554-560.

Powell J. The approach to chronic pelvic pain in the adolescent. *Obstet Gynecol Clin N Am*. 2014;41:343-355.

Practice Committee of the American Society for Reproductive Medicine. Current evaluation of amenorrhea. *Fertil Steril*. 2008;90(3):s219-s225.

Rapkin AJ, Mikacich JA. Premenstrual syndrome and premenstrual dysphoric disorder in adolescence. *Curr Opin Obstet Gynecol*. 2008;20:455-463.

Rosenfield RL. Adolescent anovulation: maturational mechanisms and implications. *J Clin Endocrinol Metab*. 2013;98:3572-3583.
Sanfilippo J, Erb TE. Evaluation and management of dysmenorrhea on adolescents. *Clin Obstet Gynecol*. 2008;41(2):257-267.
Seravalli V, Linari S, Peruzzi E, et al. Prevalence of hemostatic disorders in adolescents with abnormal uterine bleeding. *J Pediatr Adolesc Gynecol*. 2013;26:285-289.
Smith YR, Berman DR, Quint EH. Premenarchal vaginal discharge: findings of procedures to rule out foreign bodies. *J Pediatr Adolesc Gynecol*. 2002;15(4):227-230.
Speroff L, Fritz MA. *Clinical Gynecologic Endocrinology and Infertility*. Philadelphia: Lippincott Williams & Wilkins; 2005.
Spritzer PM, Motta AB. Adolescent and polycystic ovary syndrome: current concepts on diagnosis and treatment. *Int J Clin Pract*. 2015;69:1236-1246.
Stricker T, Navratil F, Sennhauser FH. Vagina foreign bodies. *J Paeditr Child Health*. 2004;40(4):205-207.
Sugar N, Graham E. Common gynecologic problems in prepubertal girls. *Pediatr Rev*. 2006;27:213-223.
Tong LX, Sun GS, Teng JMC. Pediatric lichen sclerosus: A review of the epidemiology and treatment options. *Pediatr Dermatol*. 2015;32(5):593-599.
Van Eyk N, Allen L, Giesbrecht E, et al. Pediatric vulvovaginal disorders: a diagnostic approach and review of the literature. *J Obstet Gynaecol Can*. 2009;31(9):850-862.
Werner R, Grötsch H, Hiort O. 46,XY disorders of sex development- the undermasculised male with disorders of androgen action. *Best Pract Res Clin Endocrinol Metab*. 2010;24:263-277.
Williams CE, Creighton SM. Menstrual disorders in adolescents: review of current practice. *Horm Res Paediatr*. 2012;78:135-143.
Witchel SF, Oberfield S, Rosenfield RL, et al. The diagnosis of polycystic ovary syndrome during adolescence. *Horm Res Paediatr*. 2015;83:376-389.
Young RH. Ovarian tumors and tumor-like lesions in the first three decades. *Semin Diagn Pathol*. 2014;31:382-426.
Zapata LB, Whiteman MK, Tepper NK, et al. Intrauterine device use among women with fibroids: a systematic review. *Contraception*. 2010;82(1):41-55.

23

Disorders of Sex Development

Patricia A. Donohoue

The term *disorders of sex development (DSD)* replaces the former terms *intersex* and *hermaphroditism* (Table 23.1). The most common presenting symptom of DSD is **atypical (ambiguous) genitalia** at birth. Other presenting signs and symptoms include lack of some or all aspects of pubertal development, postnatal virilization of a phenotypic female, or infertility. The classification of DSD is based on broad categories related to blood sex chromosome composition and gonadal structure. These categories include 46,XX DSD, 46,XY DSD, ovotesticular DSD, and sex chromosome DSD (Table 23.2).

The terms *atypical,* or *ambiguous genitalia,* in a broad sense, refer to any case in which the external genitalia do not appear completely male or completely female. Although there are standards for genital size dimensions, variations in size of these structures do not always constitute ambiguity.

Development of the external genitalia begins with the potential to be either male or female (Fig. 23.1 and Table 23.3). Virilization of a female, the most common form of DSD, results in varying phenotypes (Fig. 23.2) that develop from the basic bipotential genital appearances of the embryo (see Fig. 23.1). Degrees of virilization at birth are often classified using the **Prader stages** (Fig. 23.3).

OVERVIEW OF SEX DIFFERENTIATION

In typical differentiation from the sexually undifferentiated early fetus, the final phenotype of the external and internal genitalia is consistent with a normal sex chromosome complement (either XX or XY). The process of sex differentiation and development follows a consistent timeline (Fig. 23.4). The control of sex development is vast in its complexity and timing. A 46,XX complement of chromosomes as well as genetic factors, including DAX1, the signaling molecule WNT-4, CTNNB1 and R-spondin 1, are among the many factors needed for the development of normal ovaries and müllerian (paramesonephric) ducts (uterus, fallopian tubes, and upper vagina). Development of the male phenotype requires the product of a Y chromosome gene called *SRY* (Sex-determining Region on the Y chromosome), which, in concert with products of other genes such as *SOX9, SF1, WT1, FGF9* and others, directs the undifferentiated gonad to become a testis. SRY acts as a transcriptional regulator to increase cellular proliferation, attract interstitial cells from adjacent mesonephros into the genital ridge, and stimulate testicular Sertoli cell differentiation. Sertoli cells act as an organizer of steroidogenic and germ cell lines and produce antimüllerian hormone (AMH) that causes the female (paramesonephric) duct system to regress. Aberrant genetic recombinations may result in X chromosomes carrying *SRY,* resulting in XX males (46,XX testicular DSD), or Y chromosomes that have lost *SRY,* resulting in XY females (46,XY DSD due to gonadal dysgenesis). Epigenetic causes of abnormal sex differentiation have been shown in plants, invertebrates, and vertebrates and will likely be shown to contribute to human DSD as well.

Antimüllerian hormone (AMH) from the ipsilateral fetal testis causes the müllerian (paramesonephric) ducts to regress. In its absence, they persist as the uterus, fallopian tubes, cervix, and upper vagina. By about 8 weeks of gestation, the Leydig cells of the testis begin to produce testosterone. During this critical period of male differentiation, testosterone secretion is stimulated by placental human chorionic gonadotropin (hCG), which peaks at 8-12 weeks. In the latter half of pregnancy, lower levels of testosterone are maintained by luteinizing hormone (LH) secreted by the fetal pituitary. **Testosterone** produced locally initiates development of the ipsilateral wolffian (mesonephric) duct into the epididymis, vas deferens, and seminal vesicle. Development of the external genitalia also requires **dihydrotestosterone (DHT)**, the more active metabolite of testosterone. DHT is produced largely from circulating testosterone and is necessary for fusion of the genital folds to form the penis and scrotum. DHT is also produced via an alternative biosynthetic pathway from androstanediol, and this pathway must also be intact for normal and complete prenatal virilization to occur. A functional **androgen receptor**, produced by an X-linked gene, is required for testosterone and DHT to produce the androgen effects.

In the XX fetus with normal long and short arms of the X chromosomes, the bipotential gonad develops into an ovary by about the 10th-11th week. This occurs only in the absence of *SRY,* testosterone, and AMH and requires a normal gene in the DSS (Dosage Sensitive Sex reversal) locus of DAX1 (DSS Adrenal hypoplasia congenital region on X, also known as NROB1), the WNT-4 molecule, and R-spondin 1. A female external phenotype will develop even in the absence of fetal gonads. Unlike development of the male external phenotype, which requires androgen production and its action, estrogen is unnecessary for normal female prenatal sex differentiation. This is demonstrated by 46,XX patients who lack estrogen due to a deficiency of aromatase, the enzyme required for conversion of androgen to estrogen. Development of the ovary was once thought to be a passive process in the absence of SRY. Although the morphologic changes in the developing ovary are less marked than in the testis, there are a number of sequentially expressed genes and pathways that are required for complete ovarian development as well as maintenance of ovarian integrity postnatally. One of these genes is R-spondin 1 which, if mutated, can result in testicular or ovotesticular development in 46,XX individuals. Once developed, the ovary requires FAX12 to preserve its differentiation and stability.

Several genes important to the pathoetiology of DSD are listed in Table 23.4.

OVERVIEW OF GONADAL FUNCTION

Testes

Levels of placental hCG peak at 8-12 weeks of gestation and in males hCG stimulates the fetal Leydig cells to secrete testosterone, the main

(See *Nelson Textbook of Pediatrics,* p. 2750.)

TABLE 23.1 Revised Nomenclature

Previous	Currently Accepted
Intersex	Disorders of sex development (DSD)
Male pseudohermaphrodite	46,XY DSD
Undervirilization of an XY male	46,XY DSD
Undermasculinization of an XY male	46,XY DSD
46,XY intersex	46,XY DSD
Female pseudohermaphrodite	46,XX DSD
Overvirilization of an XX female	46,XX DSD
Masculinization of an XX female	46,XX DSD
46,XX intersex	46,XX DSD
True hermaphrodite	Ovotesticular DSD
Gonadal intersex	Ovotesticular DSD
XX male or XX sex reversal	46,XX testicular DSD
XY sex reversal	46,XY complete gonadal dysgenesis

From Lee PA, Houk CP, Ahmed SF, et al. Consensus statement on management of intersex disorders. *Pediatrics*. 2006;118:e488-e500.

hormonal product of the testis. In the classical androgen biosynthetic pathway (Fig. 23.5), testosterone is then converted by the enzyme 5α-reductase to its more potent metabolite, DHT. This early period is critical for virilization of the XY fetus including fusion of the midline to form the scrotum and extension of the urethral meatus to distal penile opening (see Fig. 23.1). Defects in this process lead to various deviations from typical male development. After virilization, fetal levels of testosterone decrease but are maintained at lower levels in the latter half of pregnancy by luteinizing hormone (LH) secreted by the fetal pituitary. This LH-mediated testosterone secretion is required for continued penile growth and to some degree, for testicular descent.

As part of the normal transition from intrauterine to extrauterine life, perhaps related to the sudden withdrawal of maternal and placental hormones, newborns and young infants experience a transient surge of gonadotropins and sex steroids. This is the so-called minipuberty.

In males, LH and testosterone peak at 1-2 months of age and then decline to reach prepubertal levels by 4-6 months of age. Follicle-stimulating hormone (FSH), along with inhibin B, peaks at 3 months and declines to prepubertal levels by 9 and 15 months, respectively. The LH rise is more dominant than that of FSH.

TABLE 23.2 Etiologic Classification of Disorders of Sex Development

46,XX Disorders of Sex Development (DSD)

Androgen Exposure

Fetal/Fetoplacental Source
- Congenital Adrenal Hyperplasia
  - 21-Hydroxylase (CYP21A2) deficiency
  - 11β-Hydroxylase (CYP11B1) deficiency
  - 3β-Hydroxysteroid dehydrogenase II (HSD3B2) deficiency
- Cytochrome P450 oxidoreductase (POR)
- Aromatase (CYP19) deficiency
- Glucocorticoid receptor gene mutation

Maternal Source
- Virilizing ovarian tumor
- Virilizing adrenal tumor
- Androgenic drugs

Disorders of Ovarian Development

XX gonadal dysgenesis
Testicular DSD

Undetermined Origin/Associated with Genitourinary and Gastrointestinal Tract Defects

Cloacal exstrophy
MURCS association
Mayer–Rokitansky–Küster–Hauser syndrome

46,XY DSD

Defects in Testicular Development

WT-1 Defects
- Denys–Drash syndrome
- Fraser syndrome
- WAGR syndrome

Campomelic syndrome and SOX9 mutation
SF1 mutation
Mutation in *SRY*-gene (XY pure gonadal dysgenesis, Swyer syndrome)
XY gonadal agenesis (Embryonic testicular regression syndrome)

Deficiency of Testicular Hormone Production

Leydig cell aplasia/hypoplasia
- Mutation in LH receptor

Congenital adrenal hyperplasia
- Lipoid adrenal hyperplasia (CYP11A1) deficiency; mutation in StAR (steroidogenic acute regulatory protein)
- 3β-Hydroxysteroid dehydrogenase type II (HSD3B2) deficiency
- 17-Hydroxylase/17,20-lyase (CYP17A1) deficiency

17β-Hydroxysteroid dehydrogenase (17β-HSD) or 17-ketosteroid reductase deficiency
Smith-Lemli-Opitz syndrome (defect in conversion of 7-dehydrocholesterol to cholesterol [DHCR7])

Persistent Müllerian Duct Syndrome Due to Antimüllerian Hormone Gene Mutations, or Receptor Defects for Antimüllerian Hormone

Defect in Androgen Action

Dihydrotestosterone (DHT) deficiency
- 5α-Reductase II (SDR5A2) mutations
- 3α-Reductase (AKR1C2/AKR1C4) mutations

Androgen receptor defects
- Complete androgen insensitivity syndrome (CAIS)
- Partial androgen insensitivity syndrome (PAIS)

Undetermined Causes, Including Those Associated with Other Congenital Defects

Ovotesticular DSD
XX
XY
XX/XY chimeras

Sex Chromosome DSD
45,X (Turner syndrome and variants)
47,XXY (Klinefelter syndrome and variants)
45,X/46,XY (mixed gonadal dysgenesis, sometimes a cause of ovotesticular DSD)
46,XX/46,XY (chimeric, sometimes a cause of ovotesticular DSD)

From Lee PA, Houk CP, Ahmed SF, et al. Consensus statement on management of intersex disorders. *Pediatrics*. 2006;118:e48-e500.

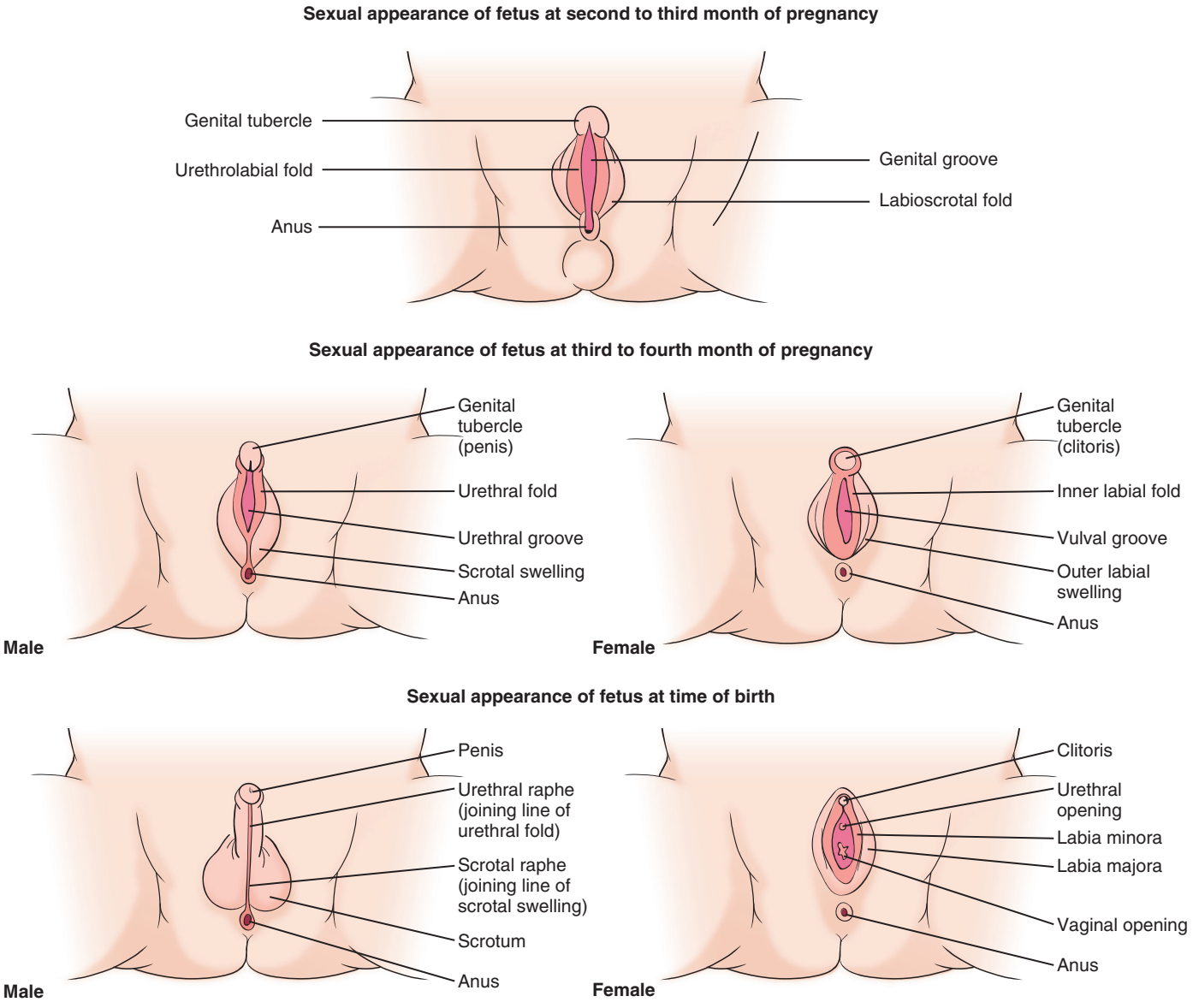


FIGURE 23.1 Schematic illustration of differentiation of normal male and female genitalia during embryogenesis. (From Zitelli BJ, Davis HW. *Atlas of Pediatric Physical Diagnosis*. 4th ed. St Louis: Mosby; 2002:328.)

TABLE 23.3 Embryologic Origins of Female and Male Reproductive Structures

Precursor	Female	Male
Undifferentiated bipotential gonad	Ovary	Testis
Internal ducts		
Wolffian (mesonephric)	Involution	Epididymis, vas deferens, seminal vesicles
Mullerian (paramesonephric)	Fallopian tubes, uterus, cervix, upper vagina	Involution, prostatic utricle
Urogenital sinus	Lower vagina, urethra	Urethra
External genitalia		
Genital tubercle	Clitoris	Penile corpora cavernosa
Labioscrotal folds	Labia majora	Scrotum
Labiourethral folds	Labia minora	Penile urethra

The neonatal surge may be important for postnatal maturation of the gonads, stabilization of male external genitalia, and perhaps also for gender identity and sexual behaviors. The postnatal surge in LH and testosterone is absent or blunted in infants with hypopituitarism, cryptorchidism, and complete androgen insensitivity syndrome (CAIS). The development of nocturnal pulsatile secretion of LH marks the advent of puberty.

Antimüllerian hormone (AMH), inhibin, and activin are members of the transforming growth factor-β (TGF-β) superfamily of growth factors. AMH is the earliest secreted product of the Sertoli cells of the fetal testis. The AMH receptor is expressed in Sertoli cells. In the female it is present in fetal müllerian duct cells, and in granulosa cells (fetal and postnatal). During sex differentiation in males, AMH causes involution of the müllerian ducts. AMH is secreted in males by Sertoli cells during both fetal and postnatal life. In females, it is secreted by ovarian granulosa cells from 36 weeks of gestation to menopause, but at lower levels. The serum concentration of AMH in males is highest at birth, whereas in females it is highest at puberty. After puberty, both sexes have similar serum concentrations of AMH. Its role in postnatal life is not yet fully characterized.

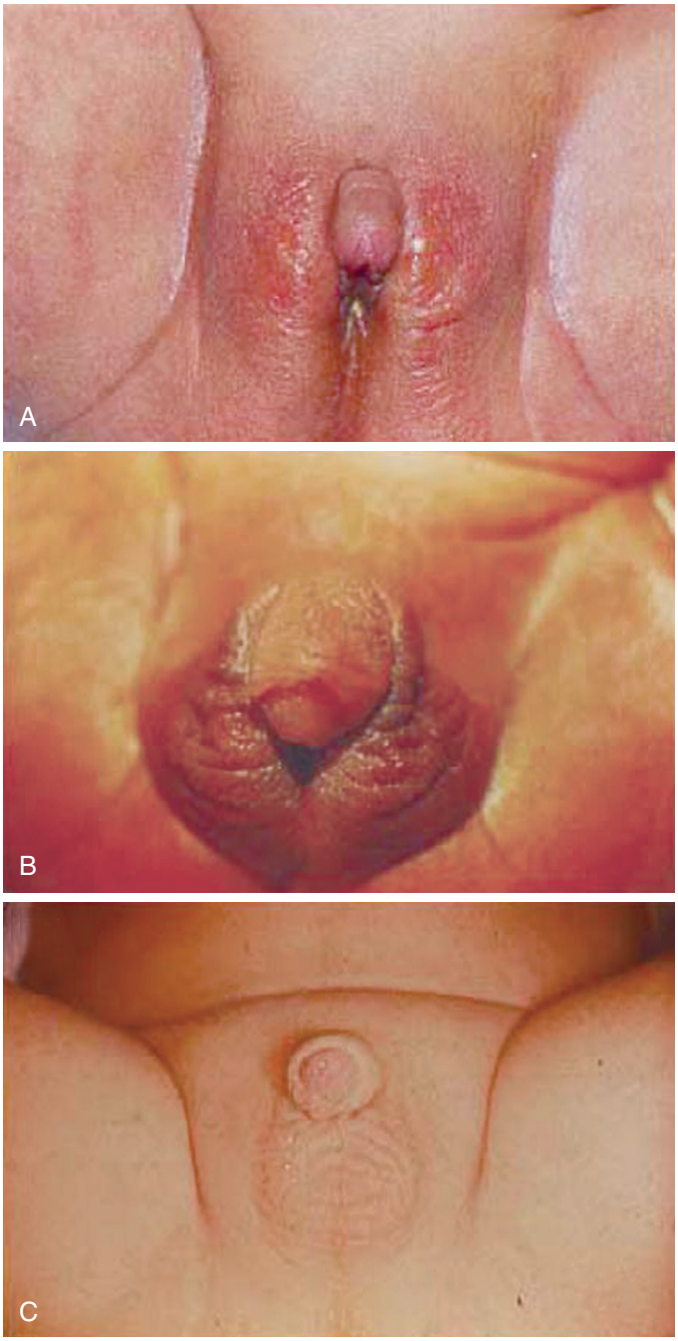


FIGURE 23.2 Examples of atypical genitalia in 46,XX DSD due to CAH (21-OH deficiency) with varying degrees of virilization. *A,* 2-week-old infant; positive newborn screen: abnormal genitalia missed; serum 17-OH progesterone = 30,690 ng/dL; electrolytes: Na = 133 meq/L, K = 7.1 meq/L. *B,* 12-day-old "male with perineal hypospadias and cryptorchidism"; newborn screen: 17-OH progesterone was normal; urology consultant suggested endocrine evaluation; high-dose steroids for respiratory problems on days of life 1-12; day 12: 17-OH progesterone = 169 ng/dL, karyotype 46,XX; day 14: 17-OH progesterone = 37,400 ng/dL. *C,* 3-week-old infant; discharged after circumcision as bilateral cryptorchid male with follow-up appointment in urology clinic; presented near death with salt-losing crisis; karyotype 46,XX. (From Kim MS, Donohoue PA. Adrenal disorders. In: Kappy MS, Allen DB, Geffner ME, eds. *Pediatric Practice Endocrinology*. 2nd ed. New York: McGraw-Hill; 2014.)

Inhibin is another glycoprotein hormone secreted by testicular Sertoli cells and ovarian granulosa and theca cells. Inhibin A consists of an α subunit disulfide linked to the β-A subunit, whereas inhibin B consists of the same α subunit linked to the β-B subunit. Activins are dimers of the B subunits, either homodimers (BA/BA, BB/BB) or heterodimers (BA/BB). Inhibins selectively inhibit, whereas activins stimulate pituitary FSH secretion. Inhibin A is absent in males and is present mostly in the luteal phase in women. Inhibin B is the principal form of inhibin in males, and in females during the follicular phase. *Inhibin B is useful as a marker of Sertoli cell function in males.* FSH stimulates inhibin B secretion in females and males, but only in males is there also evidence for gonadotropin-independent regulation. Levels of inhibin B are currently being studied in children with various forms of gonadal and pubertal disorders. In males with delayed puberty, inhibin B may be a useful screening test to differentiate between constitutional delay of puberty and hypogonadotropic hypogonadism (HH). In HH the serum inhibin B level has been shown to be very low to undetectable.

Like inhibin and activin, follistatin (a single-chain glycosylated protein) is produced by gonads and other tissues such as the hypothalamus, kidney, adrenal gland, and placenta. Follistatin inhibits FSH secretion principally by binding activins, thereby blocking the effects of activins at the level of both the ovary and pituitary.

Many additional peptides act as mediators of the development and function of the testis. They include neurohormones such as growth hormone-releasing hormone, gonadotropin-releasing hormone, corticotropin-releasing hormone, oxytocin, arginine vasopressin, somatostatin, substance P, and neuropeptide Y; growth factors such as insulin-like growth factors (IGFs) and IGF-binding proteins, TGF-β, and fibroblast, platelet-derived, and nerve growth factors; vasoactive peptides; and immune-derived cytokines such as tumor necrosis factor and interleukins IL-1, IL-2, IL-4, and IL-6.

Testicular development is marked by major maturational changes at puberty (see Chapter 42). Clinical patterns of pubertal changes vary widely. In 95% of boys, enlargement of the genitals, which is typically the first sign of puberty, begins between 9.5 and 13.5 years, reaching maturity at 13-17 years. In a minority of normal boys, puberty begins after 15 years of age. In some boys, pubertal development is completed in less than 2 years, but in others it may take longer than 4.5 years. Pubertal development and the adolescent growth spurt occur at an older age in boys than in girls.

The median age of sperm production (spermarche) is 14 years. This event occurs in mid-puberty as judged by pubic hair, testis size, evidence of growth spurt, and testosterone levels. Nighttime levels of FSH are in the adult male range at the time of spermarche; the first conscious ejaculation occurs at about the same time.

Ovaries

In the normal female, the undifferentiated gonad can be identified histologically as an ovary by 10-11 weeks of gestation (see Fig. 23.4), after the upregulation of R-spondin 1. Oocytes are present from the 4th month of gestation and reach a peak of 7 million by 5 months of gestation. For normal maintenance, oocytes need granulosa cells to form primordial follicles. Functional FSH (but not LH) receptors are present in oocytes of primary follicles during follicular development. Two normal X chromosomes are needed for maintenance of oocytes. In contrast to somatic cells, in which only one X chromosome is active, both Xs are active in germ cells. At birth, the ovaries contain about 1 million active follicles, which decrease to 0.5 million by menarche. Thereafter, they decrease at a rate of 1000/mo, and at an even higher rate after the age of 35 years.

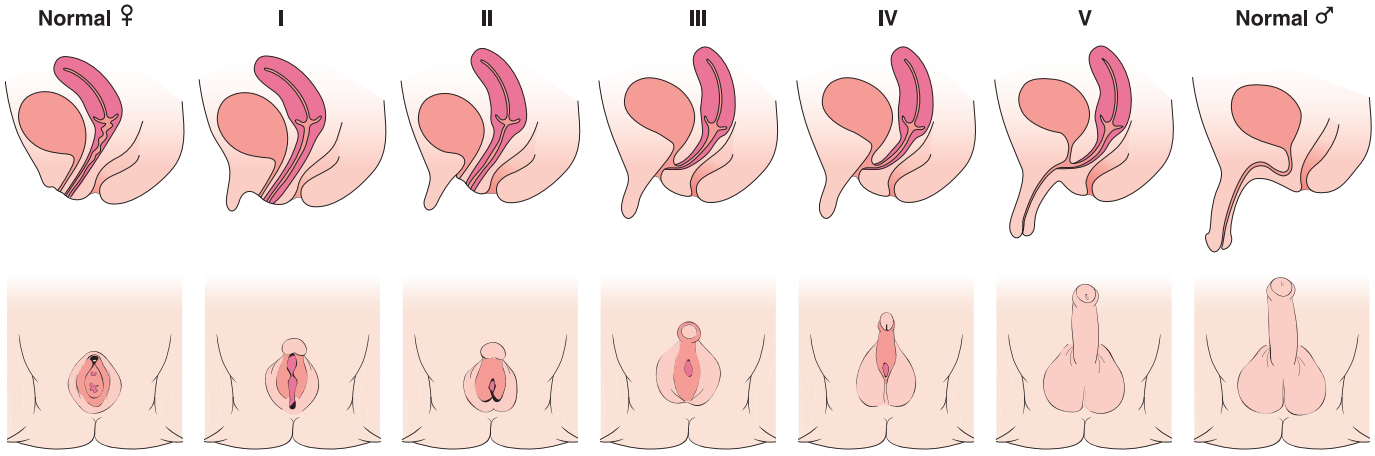


FIGURE 23.3 Method of staging the degree of virilization of the external genitalia of females as proposed by Prader (1958). In type I, the only abnormality is a slight enlargement of the clitoris. In type V, there is a markedly enlarged phallus with a penile urethra. (Redrawn from Prader A. Vollkommen männliche äussere gentialentwicklung und salzverlustsyndrom bei madchen mit kongenitalem adrenogenitalem syndrom. *Helv Paediat Acta.* 1958;13:5.)

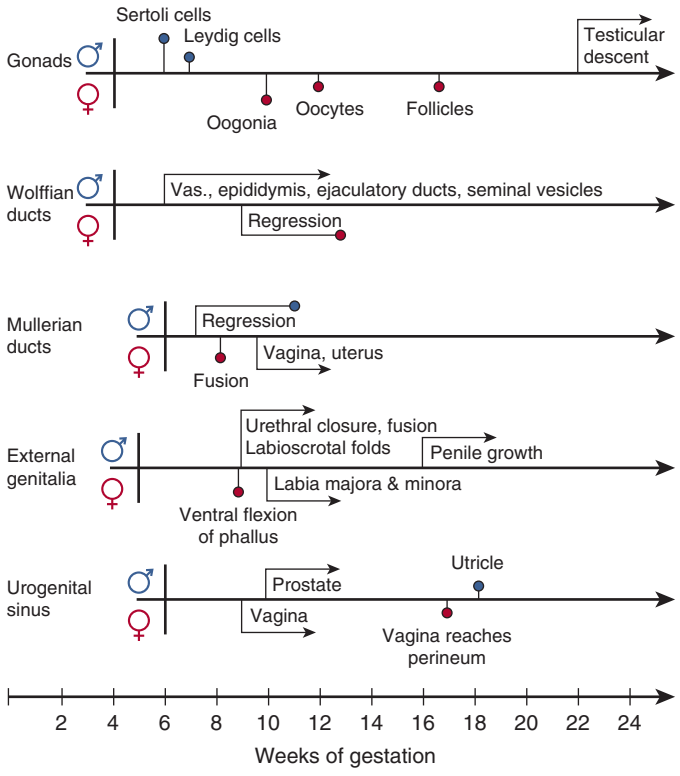


FIGURE 23.4 Timing of Development of External and Internal Genitalia. The *solid dot* shows the age at onset of the various developmental changes. Male differentiation is shown above each line, with female differentiation below. (From White PC, Speiser PW. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Endocr Rev.* 2000;21:245-291.)

The hormones of the fetal ovary are provided mostly by the feto-placental unit. As in males, peak gonadotropin secretion occurs in fetal life and then again at 2-3 months of life, with the lowest levels at about 6 years of age. In contrast to males, the FSH surge predominates over LH in females. FSH peaks around 3-6 months of age, declines by 12 months, but remains detectable for 24 months. Under LH influence, estradiol peaks at 2-6 months of age. The inhibin B response is variable, peaking at between 2-12 months and remaining above prepubertal levels until 24 months. In both infancy and childhood, gonadotropin levels are higher in females than in males.

The most important estrogens produced by the ovary are estradiol-17β (E2) and estrone (E1); estriol is a metabolic product of both, and all 3 estrogens may be found in the urine of mature females. Estrogens arise from androgens produced by the adrenal glands, the ovaries, or the testes (see Fig. 23.5). This conversion explains why in certain types of 46,XY DSD, feminization occurs at puberty. In HSD17B3 deficiency (see later), for example, the enzymatic block results in markedly increased secretion of androstenedione, which is converted in the peripheral tissues to estradiol and estrone. These estrogens, in addition to those directly secreted by the testis, result in breast development. Estradiol produced from testosterone in the complete androgen insensitivity syndrome causes complete feminization in these XY individuals.

Plasma levels of estradiol increase slowly but steadily with advancing sexual maturation and correlate well with clinical progression of pubertal development, skeletal age, and rising levels of FSH. Levels of LH do not rise measurably until secondary sexual characteristics are present. Estrogens, like androgens, inhibit secretion of both LH and FSH (negative feedback). In females, estrogens also provoke the surge of LH secretion that occurs in the mid-menstrual cycle and results in ovulation. The capacity for this positive feedback is another maturational milestone of puberty.

The average age at menarche in Caucasian American girls is about 12.5-13 years, but the range of "normal" is wide, and 1-2% of normal girls have not menstruated by 16 years of age (see Chapter 42). The age at onset of pubertal signs is about 2 years before menarche. This age varies, with some studies suggesting earlier ages than previously thought, especially in the U.S. African-American population. Menarche generally correlates closely with skeletal age. Maturation and closure of the epiphyses is partially estrogen dependent, as demonstrated by a very tall 28-year-old normally-masculinized male with continued growth due to incomplete closure of the epiphyses, who proved to have complete estrogen insensitivity due to an estrogen-receptor defect.

TABLE 23.4 Genes Mutated in Disorders of Sex Development

Gene	Protein	OMIM #	Locus	Inheritance	Gonad	Müllerian Structures	External Genitalia	Associated Features/ Variant Phenotypes
46,XY DSD								
Disorders of Gonadal (Testicular) Development: Single Gene Disorders								
WT1	TF	607102	11p13	AD	Testicular dysgenesis	±	Female or ambiguous	Wilms tumor, renal abnormalities, gonadal tumors (WAGR, Denys-Drash, and Frasier syndromes)
SF1 (NR5A1)	Nuclear receptor TF	184757	9q33	AD/AR	Testicular dysgenesis	±	Female or ambiguous	More severe phenotypes include primary adrenal failure; milder phenotypes have isolated partial gonadal dysgenesis; mothers who carry SF1 mutation have premature ovarian insufficiency
SRY	TF	480000	Yp11.3	Y	Testicular dysgenesis or ovotestis	±	Female or ambiguous	
SOX9	TF	608160	17q24-25	AD	Testicular dysgenesis or ovotestis	±	Female or ambiguous	Campomelic dysplasia (17q24 rearrangements; milder phenotype than point mutations)
DHH	Signaling molecule	605423	12q13.1	AR	Testicular dysgenesis	+	Female	The severe phenotype of 1 patient included minifascicular neuropathy; other patients have isolated gonadal dysgenesis
ATRX	Helicase (?chromatin remodeling)	300032	Xq13.3	X	Testicular dysgenesis	–	Female, ambiguous or male	α-Thalassemia, developmental delay
ARX	TF	300382	Xp21.13	X	Testicular dysgenesis	–	Ambiguous	X-linked lissencephaly, epilepsy, temperature instability
Disorders of Gonadal (Testicular) Development: Chromosomal Changes Involving Key Candidate Genes								
DMRT1	TF	602424	9p24.3	Monosomic deletion	Testicular dysgenesis	±	Female or ambiguous	Developmental delay
DAX1 (NR0B1)	Nuclear receptor TF	300018	Xp21.3	dupXp21	Testicular dysgenesis or ovary	±	Female or ambiguous	
WNT4	Signaling molecule	603490	1p35	dup1p35	Testicular dysgenesis	+	Ambiguous	Developmental delay
Disorders in Hormone Synthesis or Action								
LHGCR	G-protein receptor	152790	2p21	AR	Testis	–	Female, ambiguous or micropenis	Leydig cell hypoplasia
DHCR7	Enzyme	602858	11q12-13	AR	Testis	–	Variable	Smith-Lemli-Opitz syndrome: coarse facies, 2nd-3rd toe syndactyly, failure to thrive, developmental delay, cardiac and visceral abnormalities

Continued

TABLE 23.4 Genes Mutated in Disorders of Sex Development—cont'd

Gene	Protein	OMIM #	Locus	Inheritance	Gonad	Müllerian Structures	External Genitalia	Associated Features/ Variant Phenotypes
StAR	Mitochondrial membrane protein	600617	8p11.2	AR	Testis	–	Female	Congenital lipoid adrenal hyperplasia (primary adrenal failure), pubertal failure
CYP11A1	Enzyme	118485	15q23-24	AR	Testis	–	Female or ambiguous	Congenital adrenal hyperplasia (primary adrenal failure), pubertal failure
HSD3B2	Enzyme	201810	1p13.1	AR	Testis	–	Ambiguous	CAH, primary adrenal failure, partial androgenization due to ↑ DHEA
CYP17	Enzyme	202110	10q24.3	AR	Testis	–	Female ambiguous or micropenis	CAH, hypertension due to ↑ corticosterone and 11-deoxycorticosterone (except in isolated 17,20-lyase deficiency)
POR (P450 oxidoreductase)	CYP enzyme electron donor	124015	7q11.2	AR	Testis	–	Male or ambiguous	Mixed features of 21-hydroxylase deficiency, 17α-hydroxylase/17,20-lyase deficiency and aromatase deficiency; sometimes associated with Antley-Bixler skeletal dysplasia
HSD17B3	Enzyme	605573	9q22	AR	Testis	–	Female or ambiguous	Partial androgenization at puberty, ↑ androstenedione : testosterone ratio
SRD5A2	Enzyme	607306	2p23	AR	Testis	–	Ambiguous or micropenis	Partial androgenization at puberty, ↑ testosterone : DHT ratio
AKR1C4	Enzyme	600451	10p15.1	Unclear	Testis	–	Ambiguous or micropenis	DHT deficiency in patients once thought to have 17,20-lyase deficiency; dose effect with AKR1C2 mutation is possible
AKR1C2	Enzyme	600450	10p15.1	Unclear	Testis	–	Ambiguous or micropenis	DHT deficiency in patients once thought to have 17,20-lyase deficiency; dose effect with AKR1C2 mutation is possible
AMH	Signaling molecule	600957	19p13.3-13.2	AR	Testis	+	Normal male	Persistent müllerian duct syndrome (PMDS); male
AMH receptor	Serine–threonine kinase transmembrane receptor	600956	12q13	AR	Testis	–	Normal male	External genitalia, bilateral cryptorchidism
Androgen receptor	Nuclear receptor TF	313700	Xq12	X	Testis	–	Female, ambiguous, micropenis, or normal male	Phenotypic spectrum from complete androgen insensitivity syndrome (female external genitalia) and partial androgen insensitivity (ambiguous) to normal male genitalia/infertility

TABLE 23.4 Genes Mutated in Disorders of Sex Development—cont'd

Gene	Protein	OMIM #	Locus	Inheritance	Gonad	Müllerian Structures	External Genitalia	Associated Features/ Variant Phenotypes
46,XX DSD								
Disorders of Gonadal (Ovarian) Development								
SRY	TF	480000	Yp11.3	Translocation	Testis or ovotestis	–	Male or ambiguous	
SOX9	TF	608160	17q24	dup17q24	ND	–	Male or ambiguous	
R-spondin 1	TF	610644	1p34.3	AR	Ovotestis	+/–	Male or ambiguous	Palmoplantar hyperkeratosis and certain malignancies
Androgen Excess								
HSD3B2	Enzyme	201810	1p13	AR	Ovary	+	Clitoromegaly	CAH, primary adrenal failure, partial androgenization due to ↑ DHEA
CYP21A2	Enzyme	201910	6p21-23	AR	Ovary	+	Ambiguous	CAH, phenotypic spectrum from severe salt-losing forms associated with adrenal failure to simple virilizing forms with compensated adrenal function, ↑ 17-hydroxyprogesterone
CYP11B1	Enzyme	20210	8q21-22	AR	Ovary	+	Ambiguous	CAH, hypertension due to ↑ 11-deoxycortisol and 11-deoxycorticosterone
POR (P450 oxidoreductase)	CYP enzyme electron donor	124015	7q11.2	AR	Ovary	+	Ambiguous	Mixed features of 21-hydroxylase deficiency, 17α-hydroxylase/17,20-lyase deficiency and aromatase deficiency; associated with Antley-Bixler skeletal dysplasia
CYP19	Enzyme	107910	15q21	AR	Ovary	+	Ambiguous	Maternal virilization during pregnancy, absent breast development at puberty, except in partial cases
Glucocorticoid receptor	Nuclear receptor TF	138040	5q31	AR	Ovary	+	Ambiguous	↑ ACTH, 17-hydroxyprogesterone and cortisol; failure of dexamethasone suppression (patient heterozygous for a mutation in CYP21)

OMIM #, Online Mendelian Inheritance in Man number; ACTH, adrenocorticotropin; AD, autosomal dominant (often de novo mutation); AR, autosomal recessive; CAH, congenital adrenal hyperplasia; DSD, disorders of sex development; ND, not determined; TF, transcription factor; WAGR, Wilms, aniridia, genital anomalies, and retardation; X, X-chromosomal; Y, Y-chromosomal. Chromosomal rearrangements likely to include key genes are included.

Data from Lee PA, Houk CP, Ahmed SF, et al. International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. *Pediatrics*. 2006;118:e488-e500; Baxter RM, Arboleda VA, Lee H, et al. Exome sequencing for the diagnosis of 46,XY disorders of sex development. *J Clin Endocrinol Metab*. 2015;100:e333-e344.

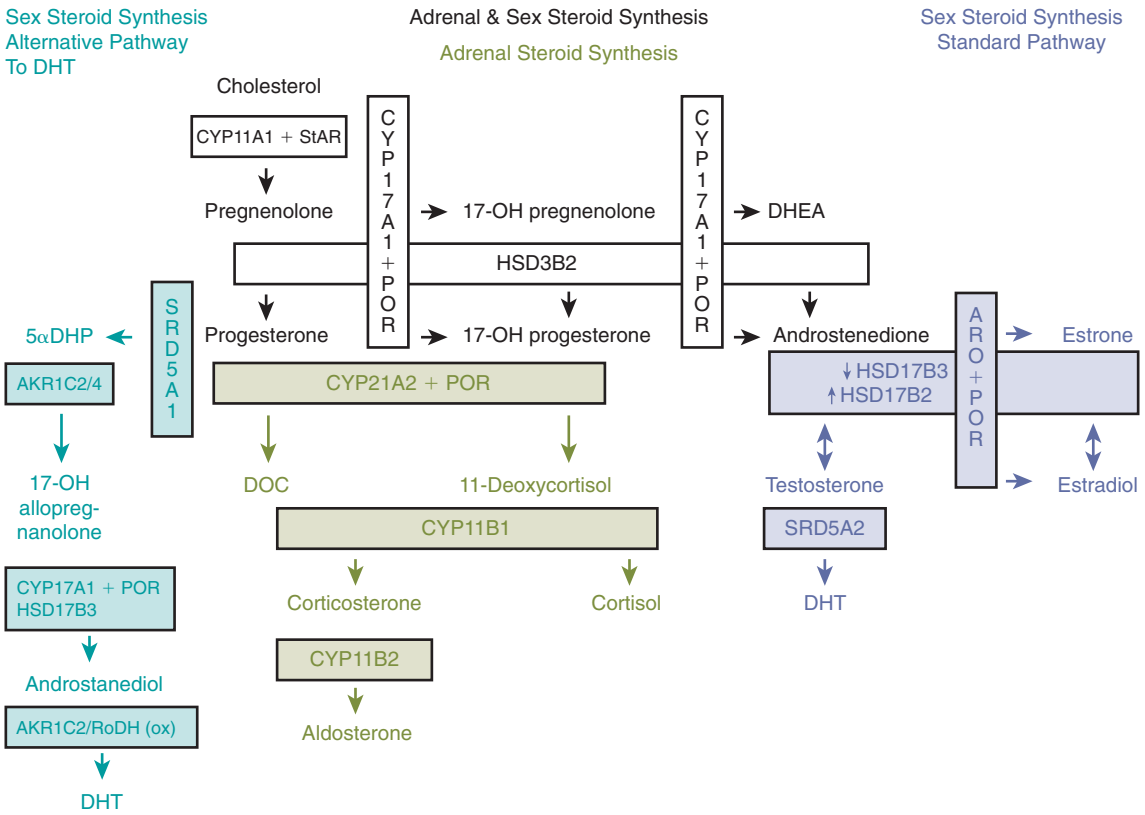


FIGURE 23.5 Steroidogenic Pathways. CYP11A1: cholesterol side chain cleavage. Enzyme activities include 20-hydroxylase, 22-hydroxylase, and 20,22-lyase; CYP17A1: activities include 17α-hydroxylase and 17,20-lyase; HSD3B2: activities include 3β-hydroxysteroid dehydrogenase type II and D5D4-isomerase; CYP21A2: activity is 21-hydroxylase; CYP11B1: activity is 11β-hydroxylase; CYP11B2: activities include 18-hydroxylase (CMOI) and 18-dehydrogenase (CMOII); SRD5A1: activity is 5α-reductase type I; SRD5A2: activity is 5α-reductase type II; HSD17B2: activity is 17β-hydroxysteroid dehydrogenase type II; HSD17B3: activity is 17β-hydroxysteroid dehydrogenase type III; AKR1C2/4 *(blue):* activities are 3α-reductase types I and III; AKR1C2/ToDH 9ox): activities are 3α-reductase and 3-hydroxyepimerase. ARO, aromatase; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; 5αDHP, 5α-dihydroprogesterone; DOC, deoxycorticosterone; POR, P450 oxidoreductase. (Data from Kim MS, Donohoue PA. Adrenal disorders. In: Kappy MS, Allen DB, Geffner ME, eds. *Pediatric Practice Endocrinology*. 2nd ed. New York: McGraw-Hill; 2014; and Flück CE, et al. Why boys will be boys: two pathways of fetal testicular androgen biosynthesis are needed for male sexual differentiation. *Am J Hum Genet*. 2011;89:201-218.)

DIAGNOSTIC APPROACH TO THE PATIENT WITH ATYPICAL OR AMBIGUOUS GENITALIA

Infants with ambiguous or atypical genitalia should be evaluated and treated at a center with multidisciplinary experience in DSD. The appearance of the external genitalia is rarely diagnostic of a particular disorder, and thus does not often allow distinction among the various forms of DSD. The most common causes of 46,XX DSD are virilizing forms of **congenital adrenal hyperplasia (CAH)**. It is important to note that in 46,XY DSD, the specific diagnosis is not found in up to 50% of cases. At 1 experienced center, the etiologies of DSD in 250 patients over 25 years were compiled. The 6 most common diagnoses accounted for 50% of the cases. These included virilizing CAH (14%), androgen insensitivity syndrome (10%), mixed gonadal dysgenesis (8%), clitoral/labial anomalies (7%), hypogonadotropic hypogonadism (6%), and 46,XY small-for-gestational age males with hypospadias (6%). The etiology in cases of 46,XY DSD without a known diagnosis can be further delineated using exome sequencing technologies.

The relative lack of established diagnoses in 46,XY DSD and the resulting lack of specific management emphasizes the need for thorough diagnostic evaluations. These include biochemical characterization of possible steroidogenic enzymatic defects, imaging studies to characterize internal genitalia, and determination of genetic sex as well as other genetic studies as determined by each individual patient with atypical genitalia. The parents need counseling about the potentially complex nature of the baby's condition, and guidance as to how to deal with the curiosity of their well-meaning friends and family members. The evaluation and management should be carried out by a multidisciplinary team of experts that include practitioners in pediatric endocrinology, pediatric surgery/urology, pediatric radiology, newborn medicine/neonatology, genetics, and psychology. *On occasion, the sex of rearing will need to be uncommitted until the diagnostic evaluation is completed.* Once the sex of rearing has been agreed on by the family and team, treatment can be organized. Genetic counseling should be offered when the specific diagnosis is established.

After a complete history and physical exam, the common diagnostic approach includes multiple steps as described in the following outline. These steps are usually performed simultaneously rather than waiting for results of 1 test prior to performing another, in order to expedite the diagnosis. Careful attention to the presence of physical features other than the genitalia is crucial to determine if a diagnosis of a particular multisystem syndrome is possible (Table 23.5 and Fig. 23.6). A summary of many features of commonly encountered causes of DSD is provided in Table 23.6.

(See *Nelson Textbook of Pediatrics,* p. 2752.)

TABLE 23.5 Potential Investigations for Disorders of Sex Development

Approach	Test	Uses
Genetics	FISH* (X- and Y-specific probes)	Rapid analysis of sex chromosome complement on cells
	qfPCR*	Rapid analysis of sex chromosome signal in DNA
	Karyotype*	Analysis of sex chromosomes and autosomes in cells with ability to look for mosaicism by screening multiple cells, as well as detection of major deletions, duplications, and balanced translocations
	Array CGH or SNP microarray*	Analysis of chromosome signal across the genome, with ability to detect smaller copy number variants but not balanced translocations, using DNA
	Multiple ligation probe-dependent amplification	Analysis of the loss of gain of specific exons or whole genes on a predefined panel of probes, such as for DSD genes, using DNA
	Single-gene analysis	Sanger sequencing and analysis of individual genes that are highly likely to be the cause of DSD based on incidence and clinical and biochemical features (e.g., *CYP21A2*)
	Targeted panel sequencing	Analysis of large numbers of known DSD-causing genes using high throughput sequencing of DNA
	Whole exome sequencing	Analysis of all the coding exons in the DNA, which may show changes in known, putative, or novel DSD-associated genes, using high-throughput sequencing
Endocrine	Routine serum biochemistry*; urinalysis*	May reveal a salt-losing crisis or associated renal disorder (e.g., WT1)
	17-Hydroxyprogesterone,* 11-deoxycortisol, 17-hydroxypregnenolone	May help to diagnose CAH or reveal a specific block in an adrenal pathway relevant to DSD
	Renin, ACTH	May show a salt-losing state or primary adrenal insufficiency
	Testosterone,* androstenedione, DHT	Indicates the degree of androgen production and ratios of androgens in the basal state or following hCG stimulation and may help to diagnose a block in androgen production consistent with a specific diagnosis (e.g., 17β-HSD or 5α-reductase deficiencies); can also reveal androgen production in ovotesticular DSD
	Gonadotropins	May indicate an underlying block in steroidogenesis or androgen insensitivity (LH), or impaired Sertoli cell function (FSH)
	AMH, inhibin B	Can be useful markers of testicular integrity: AMH is detectable throughout childhood and is reduced in testicular dysgenesis or absent if streak gonads or anorchia occur; AMH may be high in AIS or reduced androgen production due to steroidogenic defects; AMH may help to reveal the presence of testicular tissue in 46,XX ovotesticular DSD
	Urinary steroids by GC–MS	Can be used to diagnose specific steroidogenic defects in the newborn period (e.g., 21-hydroxylase deficiency, 11β-hydroxylase deficiency, 3β-hydroxysteroid dehydrogenase deficiency, P450 oxidoreductase deficiency, 17α-hydroxylase deficiency); can reveal 5α-reductase deficiency only after 3-6 mo of life
	Dynamic tests: ACTH stimulation	Used to assess the adrenal gland stress response (quantitative) and can be coupled with measurement of steroid metabolites or poststimulation urine steroid analysis to study ratios of metabolites (diagnostic)
	hCG stimulation	Used in short (3 days) or prolonged (3 wk) formats to assess androgen production (quantitative) and androgen biosynthesis pathways (diagnostic); can also be used to assess for the presence of testicular tissue (e.g., anorchia, ovotestis), although AMH is now more often used initially
	FSH stimulation test	Rarely used to investigate the presence of ovarian tissue by measuring inhibin A and estradiol response
Imaging	Abdominopelvic and renal ultrasound*	Can reveal the size, position, and structure of gonads (especially testes), the presence of müllerian structures, and associated changes (such as renal size or anomalies)
	MRI	Sometimes used to assess internal structures, especially in adolescence
	Cystourethroscopy, sinogram	Can reveal the structure of the bladder, vagina, and common channel
Surgical	Laparoscopy	Can reveal internal structures by direct visualization, such as gonads and müllerian structures
	Gonadal biopsies	Can be used to determine the nature of gonads, especially if testicular dysgenesis or ovotestes are suspected

*Indicates first-line investigations for which results are available within days. For images of G-banded karyotypes and FISH analysis, see Fig. 23.6.

ACTH, adrenocorticotropic hormone; AIS, androgen insensitivity syndrome; AMH, antimüllerian hormone; CAH, congenital adrenal hyperplasia; CGH, comparative genomic hybridization; DHT, dihydrotestosterone; DSD, disorders of sex development; FISH, fluorescent in situ hybridization; FSH, follicle-stimulating hormone; GC–MS, gas chromatography–mass spectrometry; hCG, human chorionic gonadotropin; LH, luteinizing hormone; MRI, magnetic resonance imaging; qfPCR, quantitative fluorescent polymerase chain reaction; SNP, single-nucleotide polymorphism.

From Achermann JC, Hughes IA. Pediatric disorders of sex development. In: Melmed S, Polonsky KS, Larsen PR, et al., eds. *Williams Textbook of Endocrinology*. 13th ed. Philadelphia: Elsevier; 2016:949.

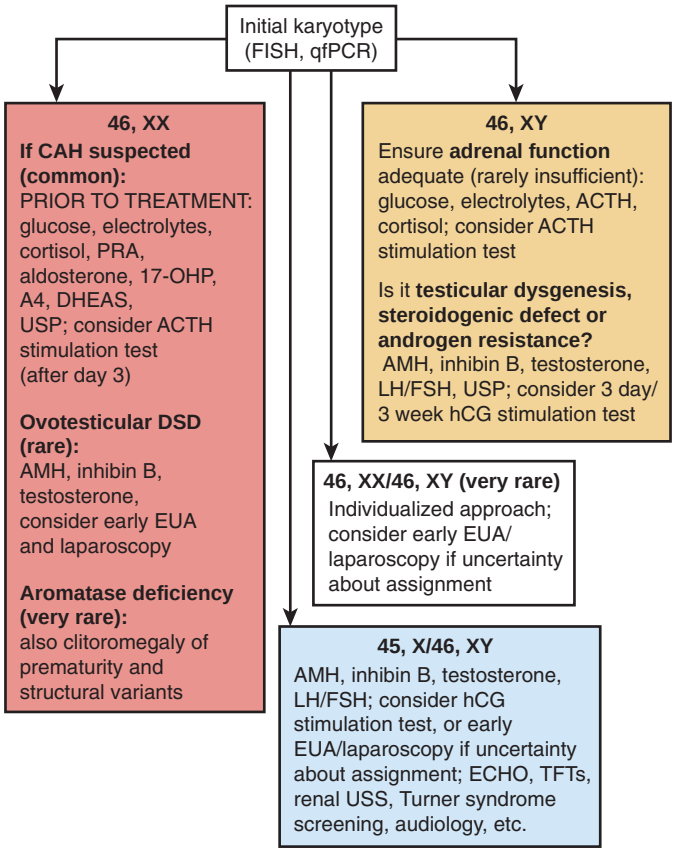


FIGURE 23.6 Overview of potential investigations for a newborn with atypical genitalia or disorders of sex development (DSD) once the initial karyotype or assessment of sex chromosome complement has been made. A4, androstenedione; ACTH, adrenocorticotropic hormone; AMH, antimüllerian hormone; CAH, congenital adrenal hyperplasia; DHEAS, dehydroepiandrosterone sulfate; ECHO, echocardiogram; EUA, examination under anesthetic; FISH, fluorescent in situ hybridization; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone; 17-OHP, 17-hydroxyprogesterone; PRA, plasma renin activity; qfPCR, quantitative fluorescent polymerase chain reaction; TFT, thyroid function test; USP, urine steroid profiling; USS, ultrasound screening. (From Achermann JC, Hughes IA. Pediatric disorders of sex development. In: Melmed S, Polonsky KS, Larsen PR, et al., eds. *Williams Textbook of Endocrinology*. 13th ed. Philadelphia: Elsevier; 2016:948.)

Diagnostic tests include the following:

1. Blood karyotype, with rapid determination of sex chromosomes (in many centers this is available within 24-48 hours) (see Fig. 23.6).
2. Other blood tests (see Table 23.5)
   a. Screen for congenital adrenal hyperplasia: cortisol biosynthetic precursors and adrenal androgens, particularly serum levels of 17-hydroxyprogesterone and androstenedione for 21-hydroxylase deficiency, the most common form. In the United States, all 50 states have a newborn screen for 21-hydroxylase deficiency.
   b. Screen for androgen biosynthetic defects with serum levels of androgens and their precursors.
   c. Assess for gonadal responsiveness to gonadotropin to screen for testicular gonadal tissue: measure serum levels of testosterone and dihydrotestosterone before and after intramuscular injections of hCG.
   d. Molecular genetic analyses for SRY (sex-determining region of the Y chromosome), other Y-specific loci, and when needed, other single-gene defects associated with DSD (see Table 23.4).
   e. Gonadotropin levels (LH and FSH).
   f. AMH and inhibin B levels.
3. The internal anatomy of patients with ambiguous genitalia can be defined with 1 or more of the following studies:
   a. Voiding cystourethrogram (VCUG).
   b. Endoscopic examination of the genitourinary tract.
   c. Pelvic ultrasound; renal and adrenal ultrasound.
   d. Pelvic MRI.
   e. Exploratory laparoscopy to locate and characterize/biopsy the gonads.

BASIC APPROACHES TO THE DIAGNOSIS AND MANAGEMENT OF DISORDERS OF SEX DEVELOPMENT

In the neonate, the presence of atypical genitalia requires immediate attention to determine the etiology and then if necessary, decide on the sex of rearing. In some cases, DSD is associated with other abnormalities that adversely impact the child's health, particularly the salt-losing forms of CAH, adrenal insufficiency related to SF1 defects, and renal abnormalities associated with WT-1 defects.

The family of the infant needs to be informed of the child's condition as early, completely, compassionately, and honestly as possible. Caution must be used to avoid feelings of guilt, shame, and confusion. Guidance needs to be provided to alleviate both short-term and long-term concerns and to allow the child to grow up in a completely supportive environment. The initial care is best provided by the aforementioned team of professionals who remain focused foremost on the needs of the child. Management of the potential emotional and psychologic effects that these disorders can generate in the child and the family is of paramount importance and requires the involvement of physicians, psychologists, and other health care professionals with sensitivity, training, and experience in this field.

While awaiting the results of blood tests, imaging with pelvic ultrasonography and/or MRI is used to determine the presence of a uterus and ovaries. Presence of a uterus and absence of external palpable gonads often suggest a virilized XX female. A search for the source of virilization includes studies of adrenal hormones to rule out varieties of CAH, and studies of androgens and estrogens may be necessary to rule out aromatase deficiency. Virilized XX females with CAH are generally (but not always) reared as females even when Prader 4 or 5 (see Fig. 23.3).

The absence of a uterus, with or without palpable external gonads, may indicate an undervirilized XY male. Measurements of blood levels of gonadotropins, testosterone, AMH, and DHT are necessary to determine whether testicular production of androgen is present and is normal. Undervirilized males who are totally feminized may be reared as females. Certain significantly undervirilized infants, such as those with 5α-reductase deficiency, may be reared as males because these children virilize normally at puberty. Sixty percent of individuals with 5α-reductase deficiency assigned as female in infancy will identify as males as adults. An infant with a comparable degree of undervirilization resulting from an androgen receptor defect, such as androgen insensitivity syndrome (AIS), may be successfully reared as a female, depending on androgen responsiveness.

In some mammals, the female exposed to androgens prenatally or in early postnatal life exhibits nontraditional sexual behavior in adult life. Most, but not all, girls who have undergone fetal masculinization from CAH have female sexual identity, although during childhood they may appear to prefer male typical play activities over female typical play activities.

TABLE 23.6 Atypical/Ambiguous Genitalia: Features Associated with the Most Common Diagnoses

	21-OH* Deficiency	Testicular Dysgenesis with Y Chromosome	Ovo-Testicular DSD	Partial Androgen Insensitivity	Dihydrotestosterone (DHT) Deficiency	Block in Testosterone (T) Synthesis
Clinical Feature						
Palpable gonad(s)	–	+/–	+/–	+	+/–	+
Uterus present†	+	+	Usually	–	–	–
Increased skin pigmentation	+/–	–	–	–	–	–
Sick baby	+/–	–	–	–	–	+/–
Dysmorphic features	–	+/–	–	–	–	–
Diagnostic Test Results						
Serum 17-OHP	Elevated	Normal	Normal	Normal	Normal	Normal
Electrolytes	Possibly abnormal	Normal	Normal	Normal	Normal	Possibly abnormal
Karyotype	46,XX	45,X/46,XY or others	46,XX	46,XY	46,XY	46,XY
Testosterone response to hCG	NA	Positive	Normal or reduced	Positive	Positive	Reduced or absent
Gonadal biopsy	NA	Dysgenic gonad	Ovotestis	Normal testis with +/– Leydig cell hyperplasia DNA screening for AR‡ or post-receptor mutations positive in many cases	Normal testis Elevated T : DHT ratio	Normal testis Levels of testosterone precursors elevated Testosterone level low

*21-Hydroxylase.
†As determined by ultrasound or rectal examination.
‡Androgen receptor.
hCG, human chorionic gonadotropin; NA, not applicable; 21-OH, 21-hydroxylase; 17-OHP, 17-hydroxyprogesterone.

In the past it was thought that surgical treatment of ambiguous genitalia to create a female appearance, particularly when a vagina was present, was more successful than construction of male genitalia. Considerable controversy has developed regarding these decisions. Sexual functioning is to a large extent more dependent on neurohormonal and behavioral factors than the physical appearance and functional ability of the genitalia. Similarly, controversy exists regarding the timing of the performance of invasive and definitive procedures, such as surgery. Whenever possible, without endangering the physical or psychologic health of the child, an expert multidisciplinary team should consider deferring elective surgical procedures and gonadectomies until the child can participate in the informed consent for the procedure. One study of 59 boys and 18 girls with gender dysphoria but without DSD or documentation of genomic or enzymologic abnormalities indicated that most of these children no longer have gender dysphoria after completion of puberty. Among those who do, homosexuality and bisexuality are the most frequent diagnoses.

For patients with DSD who have Y-chromosome material and intraabdominal gonads, gonadectomy is generally recommended due to the risk of gonadal tumors developing with increasing age, many of which are malignant.

The pediatrician, pediatric endocrinologist, and psychologist, along with the appropriate additional specialists, should provide ongoing compassionate, supportive care to the patient and the patient's family throughout childhood, adolescence, and adulthood. Active support groups are available for families and patients with many of the conditions discussed.

SPECIFIC TYPES OF DISORDERS OF SEX DEVELOPMENT

46,XX Disorders of Sex Development

In 46,XX DSD, the sex chromosomes are XX, but the external genitalia are virilized. If the gonads are ovaries, there is no significant AMH production. Thus the uterus, fallopian tubes, cervix, and upper vagina will develop. The varieties and causes of this condition are relatively few. Most cases result from exposure of the female fetus to excessive exogenous or endogenous androgens during early intrauterine life (see Fig. 23.4 and Table 23.2). The changes consist principally of virilization of the external genitalia (clitoral hypertrophy and labioscrotal fusion).

Androgen Exposure/Fetoplacental Source

Congenital adrenal hyperplasia. CAH is the most common cause of genital ambiguity and of 46,XX DSD. CAH is caused by an enzymatic defect in the biosynthesis of cortisol. This results in compensatory ACTH excess, which stimulates hyperplasia of the adrenal cortex in an attempt to normalize cortisol secretion. There is overproduction of adrenal androgen precursors in the forms of CAH that cause genital ambiguity in 46,XX infants. Females with 21-hydroxylase and 11-hydroxylase deficiency are the most highly virilized (see Fig. 23.2).

Minimal virilization also occurs with the type II 3β-hydroxysteroid dehydrogenase (HSD3B2) defect (see Fig. 23.5 for enzymatic pathways). The androgen precursors are converted in extra-adrenal tissues into testosterone and DHT, the potent androgens that bind to the androgen receptor (AR). The treatment for all forms of CAH is cortisol replacement therapy, which reduces ACTH secretion and reverses the androgen excess. Mineralocorticoid replacement may be needed in 21-hydroxylase and HSD3B2 deficiency. The surgical treatment of virilized genitalia in affected females is usually recommended during infancy. However, this remains a controversial topic. Surgical outcomes have improved in the past decades.

CAH due to 21-hydroxylase deficiency (mutations in the *CYP21A2* gene) is one of the most common inherited diseases associated with DSD. It accounts for more than 95% of cases of adrenal steroidogenic defects and is estimated to occur in about 1 in 14,000 live births. In some genetically isolated populations such as Yupik Eskimos, the incidence is much higher. CYP21A2 deficiency usually presents as 1 of 2 clinical syndromes in neonates or very young infants, both of which are associated with glucocorticoid deficiency. If not diagnosed in the 1st couple of weeks, the **salt-wasting form** is associated with dehydration, hyponatremia, hyperkalemia, acidosis, and hypotension with elevated plasma renin activity (PRA) due to mineralocorticoid deficiency. Symptoms of this renal salt loss include lethargy, vomiting, and poor feeding. Adrenal androgen excess results in ambiguous genitalia in affected females. The simple virilizing form also causes prenatal virilization in females but without postnatal salt wasting. In some infants, the distinction between the 2 forms is not clear due to early detection by newborn screening. Female patients with salt-losing CAH tend to have more virilization than do non–salt-losing female patients. Masculinization may be so intense that a complete penile urethra results, and the patient may appear to be a male with bilateral cryptorchidism. Affected males have normal genitalia. **Late-onset forms** of CYP21A2 deficiency present with early pubarche in both sexes, or with hirsutism and menstrual irregularities in older females. These late-onset forms are not causes of DSD.

CAH due to 11β-hydroxylase deficiency (mutations in the *CYP11B1* gene) is the second most common cause of CAH, and accounts for less than 5% of CAH cases. As with other causes of CAH, cortisol synthesis is reduced; however, there is excessive mineralocorticoid (deoxycorticosterone [DOC]) secretion accompanying adrenal androgen overproduction. As a result, patients become hypertensive after infancy because of increased sodium retention.

CAH due to 3β-hydroxysteroid dehydrogenase type II deficiency (mutations in the *HSD3B2* gene) is a rare form of CAH in which synthesis of all steroid hormones is impaired (see Fig. 23.5). Thus, there are deficiencies of glucocorticoids, mineralocorticoids, and potent androgens. Most patients present as neonates or in early infancy. Clinical manifestations are because of both cortisol and aldosterone deficiency as seen in 21-hydroxylase deficiency, including feeding difficulties, vomiting, volume depletion, and subsequent hyponatremia, hyperkalemia, and high PRA. Affected females have mild virilization (an indirect effect of oversecretion of dehydroepiandrosterone [DHEA]). This form of CAH may also cause 46,XY DSD.

P450 oxidoreductase (POR) deficiency is also known as apparent combined CYP21A2 and CYP17A1 deficiency. The underlying defect is a mutation in the *POR* gene that encodes cytochrome P450 oxidoreductase, a mitochondrial cofactor that transfers electrons to CYP21A2 and CYP17A1 during steroidogenesis. This results in a partial deficiency of the enzymes 21-hydroxylase and 17-hydroxylase. Affected girls are born with ambiguous genitalia, suggesting intrauterine androgen excess; however, as opposed to classic CAH, after birth serum androgen concentrations are low, and virilization does not progress. Boys may have undervirilization. Mothers may have virilization during pregnancy with an affected fetus. Bone malformations affecting primarily the head and limbs (**Antley-Bixler syndrome**) may be seen in both boys and girls with POR deficiency.

Aromatase deficiency. In 46,XX females, the rare condition of aromatase deficiency during fetal life leads to 46,XX DSD and results in hypergonadotropic hypogonadism at puberty because of ovarian failure to synthesize estrogen from androgen. Examples of this condition include 2 46,XX infants who had enlargement of the clitoris and posterior labial fusion at birth. In 1 instance, maternal serum and urinary levels of estrogen were very low and serum levels of androgens were high. Cord serum levels of estrogen were also extremely low, and those of androgen were elevated. The 2nd case also had virilization of unknown cause since birth, but the aromatase deficiency was not diagnosed until 14 years of age, when she had further virilization and failed to go into female puberty. At that time, she had elevated levels of gonadotropins and androgens but low estrogen levels, and ultrasonography revealed large ovarian cysts bilaterally. Two siblings with aromatase deficiency have also been described. The 28-year-old XX proband was 177.6 cm tall (+2.5 SD) after having received estrogen replacement therapy. Her 24-year-old brother was 204 cm tall (+3.7 SD), and had a delayed bone age of only 14 years due to failure of epiphyseal fusion, which is estrogen-mediated.

Cortisol resistance due to glucocorticoid receptor gene mutation. A 9-year-old girl with 46,XX DSD and a history of ambiguous genitalia, thought to be due to 21-hydroxylase deficiency CAH, had elevated cortisol levels both at baseline and after dexamethasone, along with hypertension and hypokalemia, suggestive of the diagnosis of generalized glucocorticoid resistance. A novel homozygous mutation in exon 5 of the glucocorticoid receptor was demonstrated. Virilization occurs due to excess ACTH stimulation of adrenal steroid production, as the glucocorticoid receptor defect is also present in the pituitary gland, which senses inadequate cortisol effect to provide negative feedback.

Androgen Exposure: Maternal Source

Virilizing maternal tumors. Rarely, a female fetus can be virilized by a maternal androgen-producing tumor. In a minority of cases, the lesion is a benign adrenal adenoma, but the majority are ovarian tumors, particularly androblastomas, luteomas, and Krukenberg tumors. Maternal virilization may be manifested by enlargement of the clitoris, acne, deepening of the voice, decreased lactation, hirsutism, and elevated levels of androgens. In the infant, there is enlargement of the clitoris of varying degrees, often with labial fusion if the tumor produced excess androgen during the 1st trimester. Mothers of children with unexplained 46,XX DSD should undergo physical examination and measurements of their own levels of plasma testosterone, dehydroepiandrosterone sulfate (DHEAS), and androstenedione.

Administration of androgenic drugs to women during pregnancy. Testosterone and 17-methyltestosterone have been reported to cause 46,XX DSD in some instances. The greatest number of cases has resulted from the use of certain progestational compounds for the treatment of threatened abortion. These progestins have been replaced by nonvirilizing ones.

Disorders of Ovarian Development

46,XX testicular DSD. In this condition, also called XX male, the gonads are testicular, and virilization is typically incomplete. Infertility and/or gonadal failure may develop after childhood. Many cases are due to translocation of SRY sequences onto one of the X chromosomes, often paired with duplication of SOX9. The appropriate sex of rearing may be difficult to determine.

46,XX gonadal dysgenesis. These girls typically present at puberty with lack of breast development and hypergonadotropic

hypogonadism. Normal müllerian structures are present, but ovaries are absent or streaks.

Undetermined/unknown. Rarely, 46,XX DSD can be associated with other congenital anomalies, especially those of the genitourinary or gastroenteric tract, and are thus multifactorial in origin. These include cloacal exstrophy and MURCS association (müllerian hypoplasia, renal agenesis, and cervicothoracic somite abnormalities). Isolated deficiency of müllerian development is known as **Mayer-Rokitansky-Küster-Hauser syndrome**.

46,XY Disorders of Sex Development

In 46,XY DSD, the genotype is XY, and the external genitalia are either not completely virilized, ambiguous (atypical), or completely female. When gonads are found, they typically contain testicular elements; their development ranges from rudimentary to normal. Because the process of normal virilization in the fetus is so complex, it is not surprising that there are many varieties and causes of 46,XY DSD. *The etiology of 46,XY DSD is not identified in up to 50% of cases.*

Defects in Testicular Development

The first step in male differentiation is development of the bipotential gonad into a testis. In the XY fetus, if there is a deletion of the short arm of the Y chromosome or mutation of the *SRY* gene, male gonadal differentiation does not occur. The phenotype is female; müllerian (paramesonephric) ducts are well developed because of the absence of AMH, and gonads consist of undifferentiated streaks. By contrast, even extreme deletions of the long arm of the Y chromosome (Yq-) have been found in normally developed males, most of whom have short stature and azoospermia. This indicates that the long arm of the Y chromosome normally has genes that prevent these manifestations. In many syndromes in which the testes fail to differentiate, Y chromosomes appear morphologically normal on karyotyping.

Wilms tumor suppressor gene* (WT1) *mutations: Denys-Drash, Fraser and WAGR syndromes. The constellation of nephropathy with atypical genitalia and bilateral Wilms tumor typify Denys-Drash syndrome. Müllerian ducts are often present, indicating deficiency of multiple fetal testicular functions. Affected patients with a 46,XX karyotype have normal external genitalia. There is onset of proteinuria in infancy that progresses to nephrotic syndrome and end-stage renal failure by 3 years of age, with focal or diffuse mesangial sclerosis being the most consistent histopathologic finding. Wilms tumor usually develops in children younger than 2 years of age and is frequently bilateral. Gonadoblastomas have also been reported.

A variety of mutations of *WT1* have been found in **Denys-Drash syndrome**. *WT1* functions as a tumor suppressor gene and a transcription factor, and is expressed in the genital ridge and fetal gonads. One report found a zinc finger domain mutation in the *WT1* alleles of a patient with no genitourinary abnormalities, suggesting that some cases of sporadic Wilms tumor may carry the *WT1* mutation. Different mutations of the *WT1* gene, heterozygous mutations at intron 9, have been described in **Fraser syndrome**, a condition of nonspecific focal and segmental glomerulosclerosis, 46,XY gonadal dysgenesis, and frequent gonadoblastoma, but without Wilms tumor.

WAGR syndrome is a contiguous gene deletion syndrome causing Wilms tumor, aniridia, genitourinary malformations, and retardation. These children have a deletion of 1 copy of chromosome 11p13, which may be visible on karyotype analysis. The deleted region encompasses the aniridia gene *(PAX6)* and *WT1*. Only the 46,XY males have genital abnormalities, ranging from cryptorchidism to severe undervirilization. Gonadoblastomas have developed in the dysgenic gonads. Wilms tumor usually occurs by 2 years of age. Some cases also had unexplained obesity, raising the question of an obesity-associated gene in this region of chromosome 11 and naming the syndrome **WAGRO.**

Campomelic syndrome. This form of short-limbed skeletal dysplasia is characterized by anterior bowing of the femur and tibia; small, bladeless scapulae; small thoracic cavities and 11 pairs of ribs, along with malformations of other organs. It is usually lethal in early infancy. About 75% of reported 46,XY patients exhibit a completely female phenotype with the external and internal genitalia both being female. Some 46,XY patients have atypical genitalia. The gonads appear to be ovaries but histologically may contain elements of both ovaries and testes.

The gene responsible for the condition is *SOX9* (SRY-related HMG-box gene). This gene is structurally related to *SRY* and also directly regulates type II collagen gene *(COL2A1)* development. The same mutations may result in different gonadal phenotypes. Gonadoblastoma was reported in a patient with this condition. The inheritance is autosomal dominant.

Steroidogenic Factor 1 *(SF1)* Gene Mutations

Adrenal insufficiency and 46,XY DSD have been described in patients with mutations of the *SF1* gene. In some patients, *SF1* mutations occur without causing adrenal insufficiency. In a number of these families, if the mother shares the *SF1* mutation she has premature ovarian insufficiency.

Other Known Genetic Causes of 46,XY DSD

46,XY DSD has been described in patients with other single gene mutations, as well as deletions of parts of autosomal loci on chromosomes 2q, 9p, and 10q. Examples of a number of these genetic conditions are shown in Table 23.4. The use of exome sequencing of targeted genes has enhanced the detection of specific genetic defects in patients with 46,XY DSD.

XY pure gonadal dysgenesis (Swyer syndrome). The designation *pure* distinguishes this condition from forms of gonadal dysgenesis that are of chromosomal origin and associated with somatic anomalies such as 45,X Turner syndrome and 47,XXY Klinefelter syndrome. Affected patients have normal stature as adults and a completely female phenotype at birth, including vagina, uterus, and fallopian tubes. At pubertal age, breast development and menarche fail to occur, and hypergonadotropic hypogonadism is present. None of the other phenotypic features associated with 45,X are present. Familial cases suggest an X-linked or a sex-limited dominant autosomal transmission. Most of the patients with a known genetic cause have had mutations of the *SRY* gene. The gonads consist of almost totally undifferentiated streaks despite the presence of a cytogenetically normal Y chromosome. The primitive gonad cannot accomplish any testicular function, including suppression of müllerian ducts. There may be hilar cells in the gonad capable of producing some androgens; accordingly, some virilization, such as clitoral enlargement, may occur at the age of puberty. The streak gonads may undergo neoplastic changes, such as **gonadoblastomas** and **dysgerminomas**, and should be removed as soon as the diagnosis is established, regardless of the age of the patient.

XY gonadal agenesis syndrome (embryonic testicular regression syndrome). In this rare syndrome, the external genitalia are slightly atypical but more nearly female. Hypoplasia of the labia; some degree of labioscrotal fusion; a small, clitoris-like phallus; and a perineal urethral opening are present. No uterus, no gonadal tissue, and usually no vagina can be found. At the age of puberty, no sexual development occurs and gonadotropin levels are elevated. Most children have been reared as females. In several patients with XY gonadal agenesis in whom no gonads could be found on exploration, significant rises in testosterone followed stimulation with hCG, indicating Leydig cell function somewhere. Siblings with the disorder are known.

It is presumed that testicular tissue was active long enough during fetal life for AMH to inhibit development of müllerian ducts but not long enough for testosterone production to result in virilization. Testicular degeneration seems to occur between the 8th and the 12th fetal week. Regression of the testes before the 8th week of gestation results in Swyer syndrome; between the 14th and the 20th week of gestation, it results in the rudimentary testis syndrome; and after the 20th week, it results in anorchia with otherwise normal external genitalia.

In **bilateral anorchia**, sometimes referred to as *vanishing testes syndrome*, testes are absent, but the male phenotype is complete; it is presumed that fetal testicular function was active during the critical period of genital differentiation but that sometime later it was damaged. Bilateral anorchia in identical twins and unilateral anorchia in identical twins and in siblings suggest a genetic predisposition. Coexistence of anorchia and the gonadal agenesis syndrome in a sibship is evidence for a relationship between the disorders.

Deficiency of Testicular Hormone Production

Genetic defects have been delineated in the enzymatic steps required for the synthesis of testosterone by the fetal testicular Leydig cells, and a defect in Leydig cell differentiation has also been described. These defects produce 46,XY males with incomplete masculinization. Because levels of testosterone are normally low before puberty except during the period of "minipuberty" at 1-2 months of age, an hCG stimulation test may be needed in children to assess the ability of the testes to synthesize testosterone.

Leydig cell aplasia. Patients with aplasia or hypoplasia of the Leydig cells usually have a female phenotype, but there may be mild virilization. Testes, epididymis, and vas deferens are present; the uterus and fallopian tubes are absent due to normal production of müllerian-inhibiting substance. There are no secondary sexual changes at puberty, but pubic hair may be normal. Plasma levels of testosterone are low and do increase with hCG stimulation; luteinizing hormone (LH) levels are elevated. The Leydig cells of the testes are absent or markedly deficient. The defect may involve a lack of receptors for LH. In children, hCG stimulation is necessary to differentiate the condition from the androgen insensitivity syndromes (AISs), as older children with AIS have low testosterone levels when prepubertal. There is male-limited autosomal recessive inheritance. The human LH receptor is a member of the G protein–coupled superfamily of receptors that contains 7 transmembrane domains. Several inactivating mutations of the LH receptor have been described in males with hypogonadism suspected of having Leydig cell hypoplasia or aplasia.

Congenital adrenal hyperplasia (CAH). **CAH due to lipoid adrenal hyperplasia:** This is the most severe form of congenital adrenal hyperplasia and it derives its name from the appearance of the enlarged adrenal glands resulting from accumulation of cholesterol and cholesterol esters. The rate-limiting process in steroidogenesis is the transport of free cholesterol through the cytosol to the inner mitochondrial membrane, where the P450 side-chain cleavage enzyme (CYP11A1) acts. Cholesterol transport into mitochondria is mediated by the steroidogenic acute regulatory protein (StAR) (see Fig. 23.5). Most patients with lipoid CAH have genetic mutations of StAR. A minority have mutations in CYP11A1.

All serum steroid levels are low or undetectable, and ACTH and PRA levels are very elevated. The phenotype is female in both genetic females and males. Genetic males have no müllerian structures because the testes can produce normal AMH but no steroid hormones. These children present with acute adrenal crisis and salt wasting in infancy. Most patients are 46,XY. In 46,XX patients with StAR defects, ovarian steroidogenesis can occur at puberty, as ovarian estrogen production does not require StAR. These 46,XX patients do not have DSD. All patients have a lifelong requirement for glucocorticoid and mineralocorticoid replacement therapy. Some patients will need estrogen replacement therapy, such as all 46,XX individuals with CYP11A1 mutations, as well as all 46,XY lipoid CAH patients. Intraabdominal testes should be removed.

CAH due to 3β-hydroxysteroid dehydrogenase type II (HSD3B2) deficiency. 46,XY infants with this form of CAH have various degrees of hypospadias, with or without bifid scrotum and cryptorchidism and, rarely, a complete female phenotype. Affected infants usually develop salt-losing manifestations shortly after birth due to an inability to synthesize biologically potent steroid hormones (see Fig. 23.5). Incomplete defects, occasionally seen in infants without salt loss and in boys with premature pubarche, as well as late-onset nonclassic forms have been reported, but these forms do not cause DSD. As described earlier, patients with HSD3B2 deficiency have point mutations of the gene encoding type II 3β-hydroxysteroid enzyme, resulting in impairment of steroidogenesis in the adrenals and gonads. The impairment may be unequal between adrenals and gonads. Normal pubertal changes in some boys could be explained by the normally present type I 3β-hydroxysteroid dehydrogenase present in many peripheral tissues. Infertility is frequent. There is no correlation between degree of salt wasting and degree of phenotypic abnormality. Replacement therapy with adrenal steroids is required from infancy on, and with sex steroids at puberty. In 46,XY patients with intraabdominal testes who are being raised as females, gonadectomy is recommended.

CAH due to deficiency of 17-hydroxylase/17,20-lyase. A single enzyme (CYP17A1) encoded by a single gene has both 17-hydroxylase and 17,20-lyase activities in adrenal and gonadal tissues (see Fig. 23.5). Genetic males with CYP17A1 deficiency usually have a complete female phenotype or, less often, various degrees of undervirilization from labioscrotal fusion to perineal hypospadias and cryptorchidism. Pubertal development fails to occur in both genetic sexes.

In the classic disorder, there is decreased synthesis of cortisol by the adrenals and of sex steroids by the adrenals and gonads. Levels of the mineralocorticoid DOC and corticosterone are markedly increased and lead to the hypertension and hypokalemia characteristic of this form of 46,XY DSD. Although levels of cortisol are low, the elevated ACTH and corticosterone levels prevent symptomatic cortisol deficiency. The renin-aldosterone axis is suppressed because of the strong mineralocorticoid effect of elevated DOC. Virilization does not occur at puberty; levels of testosterone are low, and those of gonadotropins are increased. Because fetal production of AMH is normal, no müllerian duct remnants are present. In 46,XY phenotypic females, removal of intraabdominal testes and replacement therapy with hydrocortisone and estrogenic sex steroids are indicated.

CYP17A1 deficiency has autosomal recessive inheritance. Affected 46,XX females are usually not detected until young adult life, when they fail to experience normal pubertal changes and are found to have hypertension and hypokalemia. This condition should be suspected in patients presenting with primary amenorrhea and hypertension whose chromosomal complement is either 46,XX or 46,XY.

Deficiency of 17-ketosteroid reductase. This enzyme, also called 17β-hydroxysteroid dehydrogenase (17β-HSD), catalyzes the final step in testosterone biosynthesis. It is necessary to convert androstenedione to testosterone and also DHEA to androstenediol, and estrone to estradiol (see Fig. 23.5). Enzymatic defects in the fetal testis give rise to males with complete or near-complete female phenotype in 46,XY patients. Müllerian ducts are absent, and a shallow vagina is present. The diagnosis is based on the ratio of androstenedione to testosterone; in prepubertal children; an hCG stimulation test may be necessary to make the diagnosis.

The inheritance is autosomal recessive. At least 4 different types of 17β-HSD are recognized, each encoded by different genes on different chromosomes. Type III (HSD17B3) is the enzyme defect that is especially common in a highly inbred Arab population in Gaza. The gene for the disorder is expressed only in the testes, where it converts androstenedione to testosterone. Most patients are diagnosed at puberty because of virilization and the failure to menstruate. Testosterone levels at puberty may approach normal, presumably as a result of peripheral conversion of androstenedione to testosterone. Some patients spontaneously adopt a male gender role at puberty.

Type I 17β-HSD converts estrone to estradiol and is found in placenta, ovary, testis, liver, prostate, adipose tissue, and endometrium. Type II, whose gene is on chromosome 16q24, reverses the reactions of types I and III (convert testosterone to androstenedione and estrone to estradiol, respectively). Type IV is similar in action to type II. A late-onset form of 17β-HSD deficiency presents as gynecomastia in young adult males.

Persistent müllerian duct syndrome. In this disorder, there is persistence of müllerian duct derivatives in otherwise completely virilized males. Cases have been reported in siblings and identical twins. Cryptorchidism is present in 80% of affected males; during surgery for this or inguinal hernia, the condition is uncovered when a fallopian tube and uterus are found. The degree of müllerian development is variable and may be asymmetric. Testicular function is normal in most, but testicular degeneration has been reported. Some affected males acquire testicular tumors after puberty. In a study of 38 families, 16 families had defects in the AMH gene. They had low blood AMH levels. In 16 families with high AMH levels, the defect was in the AMH type II receptor gene, with 10 of 16 having identical deletions.

Treatment consists of removal of as many of the müllerian structures as possible without causing damage to the testis, epididymis, or vas deferens.

Smith-Lemli-Opitz syndrome. Smith-Lemli-Opitz syndrome is an autosomal recessive disorder caused by mutations in the sterol Δ7-reductase gene. This prevents normal androgen synthesis. It is characterized by prenatal and postnatal growth retardation, microcephaly, ptosis, anteverted nares, broad alveolar ridges, syndactyly of the 2nd-3rd toes, and severe mental retardation. Its incidence is 1/20,000-1/60,000; 70% are male. 46,XY patients usually have genital ambiguity or completely female external genitals. Müllerian duct derivatives are usually absent. Affected 46,XX patients have normal genitalia. Patients with Smith-Lemli-Opitz syndrome may also develop adrenal insufficiency due to inability to produce sufficient steroid hormones.

Defects in Androgen Action

In the following group of disorders, fetal synthesis of testosterone is normal and defective virilization results from inherited abnormalities in androgen action.

Dihydrotestosterone deficiency. **Deficiency of steroid 5α-reductase type II (SRD5A2)**: SRD5A2 deficiency prevents the conversion of testosterone to dihydrotestosterone (DHT) in androgen target tissues. Decreased production of DHT in utero results in marked ambiguity of external genitalia of affected 46,XY infants because of the absolute requirement for DHT in completion of prenatal virilization. Biosynthesis and peripheral actions of testosterone are normal.

The phenotype most commonly associated with this condition in boys consists of a small phallus, bifid scrotum, urogenital sinus with perineal hypospadias, and a blind vaginal pouch (Fig. 23.7). Testes are in the inguinal canals or labioscrotal folds and are normal histologically. There are no müllerian structures. Wolffian (mesonephric) structures (i.e., the vas deferens, epididymis, and seminal vesicles) are present. Most affected patients have been assigned the female sex of rearing. At puberty, virilization occurs; the phallus enlarges, the testes descend and grow normally, and spermatogenesis occurs, as DHT is ***not*** required for normal virilization at puberty. There is no gynecomastia. Beard growth is scanty, acne is absent, the prostate is small, and recession of the temporal hairline fails to occur. The prenatal virilization of the wolffian ducts is caused by the action of locally produced testosterone itself, although masculinization of the urogenital sinus and external genitals depends on the action of DHT during the critical period of fetal masculinization. Growth of facial hair and of the prostate postnatally also appears to be DHT dependent.

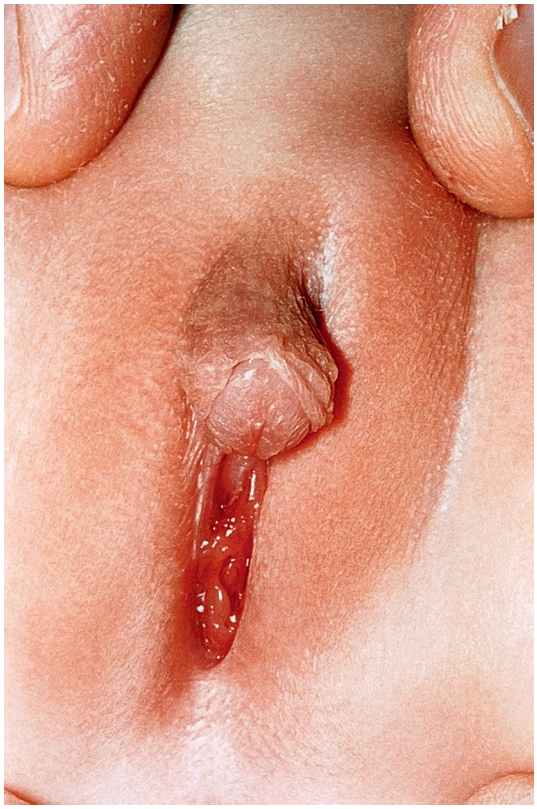


FIGURE 23.7 5α-Reductase deficiency. (From Wales JKH, Wit JM, Rogol AD. *Pediatric Endocrinology and Growth*. 2nd ed. Philadelphia: Elsevier; 2003:165.)

Several different gene defects of SRD5A2 have been identified in patients from throughout the world. Familial clusters have been reported from the Dominican Republic, Turkey, Papua New Guinea, Brazil, Mexico, and the Middle East. There is no reliable correlation between genotype and phenotype.

The disorder is inherited as an autosomal recessive trait but expression is limited to males. Normal homozygous females with normal fertility indicate that in females DHT has no significant role in sex differentiation or in ovarian function later in life. The clinical diagnosis should be made as early as possible in infancy. It is important to distinguish this from partial androgen insensitivity syndrome (PAIS), as patients with PAIS are far less sensitive to androgen treatment than are patients with SRD5A2 deficiency. The biochemical diagnosis of SRD5A2 deficiency is based on finding normal serum testosterone levels, and normal or low DHT levels with markedly increased basal and especially hCG-stimulated testosterone:DHT ratios (>17).

It is important to note that most but not all children with SRD5A2 deficiency reared as females in childhood have changed to identify as male around the time of puberty. It appears that exposures to testosterone in utero, early postnatally, and at puberty have variable

contributions to the formation of their male gender identity. Much more needs to be learned about the influences of hormones such as androgens as well as the influences of cultural, social, psychologic, genetic, and other biologic factors in gender identity and behavior. Infants with this condition should be reared as boys whenever practical. Treatment of male infants with DHT results in phallic enlargement. At this time, DHT is not commercially available in the United States, but can be obtained from European suppliers.

Deficiency of 3α-reductase (AKRC): Another cause of DHT deficiency is a block in an alternative pathway of DHT synthesis (see Fig. 23.5). Patients previously thought to have 46,XY DSD due to isolated deficiency of the 17,20-lyase activity of CYP17A1 have subsequently been characterized as having mutations in the *AKR1C2* gene (3α-reductase type III) or both the *AKR1C2* and *AKR1C4* (3α-reductase type IV) genes. These findings show that both the classical and alternative pathways to DHT production must be intact for normal prenatal virilization.

Androgen receptor defects: androgen insensitivity syndromes (AISs). The AISs are the **most common** forms of 46,XY DSD, occurring with an estimated frequency of 1/20,000 genetic males. This group of heterogeneous X-linked recessive disorders can result from 1 of more than 150 different mutations described in the androgen receptor gene, located on Xq11-12: single point mutations resulting in amino acid substitutions or premature stop codons, frameshift and premature terminations, gene deletions, and splice site mutations. Post-receptor defects have also been described.

The clinical spectrum seen in patients with AIS, all of whom have a 46,XY chromosomal complement, range from phenotypic females (complete AIS or CAIS) to males with various forms of atypical genitalia and undervirilization (partial AIS or PAIS, as well as clinical syndromes such as Reifenstein syndrome) (Fig. 23.8) to phenotypically normal-appearing males with infertility. In addition to normal 46,XY chromosomes, the presence of testes and normal or elevated testosterone and LH levels are common to all such patients.

In CAIS, an extreme form of failure of virilization, genetic males appear female at birth and are invariably reared accordingly as their condition often goes undetected until childhood or adolescence. The external genitalia are female. The vagina ends blindly in a pouch, and the uterus is absent due to the normal production and effect of AMH by the testes. In about one third of patients, unilateral or bilateral fallopian tube remnants are found. The testes are usually intraabdominal but may descend into the inguinal canal; they consist largely of seminiferous tubules. At puberty, there is normal development of breasts, and the habitus is female, but menstruation does not occur and sexual hair is absent. Adult heights of these women are commensurate with those of normal males despite profound congenital deficiency of androgenic effects.

The testes of affected adult patients produce normal to elevated male levels of testosterone that are converted to normal levels of DHT. Failure of normal male external genitalia differentiation during fetal life reflects a defective response to androgens including DHT starting very early in gestation.

Prepubertal girls with this disorder are often detected when inguinal masses prove to be testes or when a testis is unexpectedly found during inguinal herniorrhaphy. *About 1-2% of girls with an inguinal hernia prove to have this disorder.* In infants, elevated LH levels should suggest the diagnosis. In older girls and adults, amenorrhea is the usual presenting symptom. In prepubertal children, the condition must be differentiated from other types of 46,XY undervirilized males in which there is complete feminization. These include 46,XY gonadal dysgenesis (Swyer syndrome), true agonadism, Leydig cell aplasia including LH receptor defects, and 17-ketosteroid reductase deficiency; all these conditions, unlike complete AIS, are characterized by low levels of testosterone as neonates and during adult life and by failure to respond

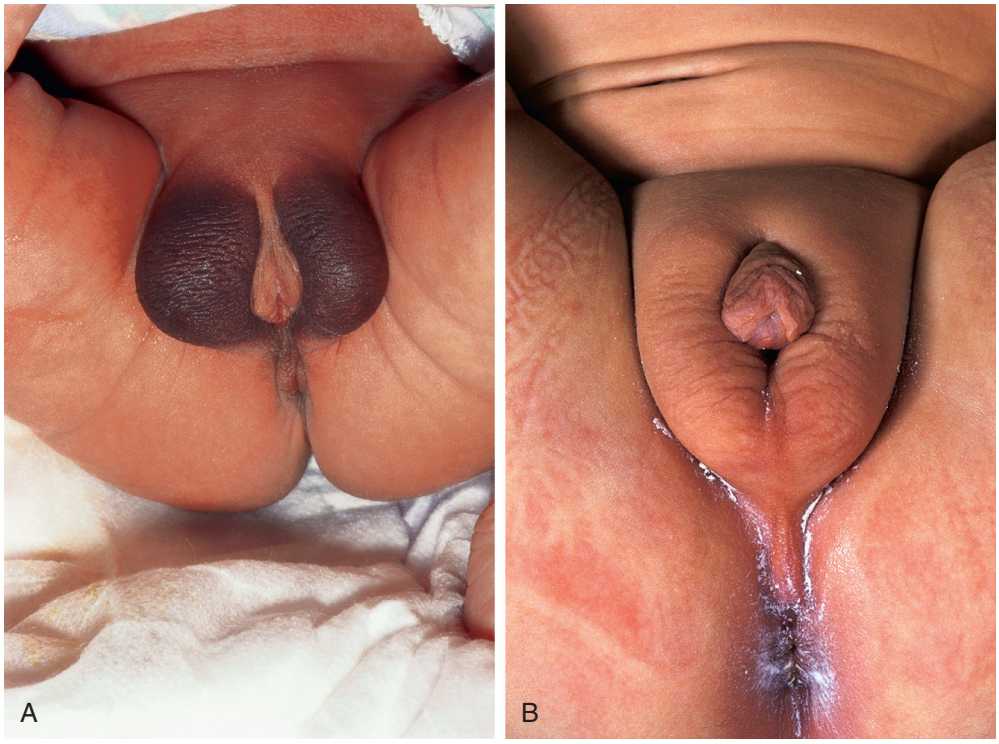


FIGURE 23.8 *A,* Partial androgen insensitivity with descended testes in bifid labioscrotal folds. *B,* Less severe partial androgen insensitivity with severe hypospadias and maldescent of testes. (From Wales JKH, Wit JM, Rogol AD. *Pediatric Endocrinolgy and Growth.* 2nd ed. Philadelphia: Elsevier; 2003:165.)

to hCG during the prepubertal years. Although patients with complete AIS have unambiguously female external genitals at birth, those with partial AIS have a wide variety of phenotypic presentations ranging from perineoscrotal hypospadias, bifid scrotum, and cryptorchidism to extreme undervirilization appearing as clitoromegaly and labial fusion. Some forms of partial AIS have been known as specific syndromes. Patients with Reifenstein syndrome have incomplete virilization characterized by hypogonadism, severe hypospadias, and gynecomastia (Fig. 23.9). Gilbert-Dreyfus and Lubs are additional syndromes classified as partial AIS. In all cases, abnormalities in the androgen receptor gene or post-receptor defects have been identified.

The diagnosis of patients with partial AIS may be particularly difficult in infancy. The postnatal surge in testosterone and LH is diminished in those with complete AIS (CAIS) but not in those with partial AIS (PAIS). In some, especially those sufficiently virilized in infancy, the diagnosis is not suspected until puberty when there is inadequate virilization with lack of facial hair or voice change and the appearance of unusually prominent gynecomastia. Azoospermia and infertility are common. Increasingly, androgen receptor defects are being recognized in adults who have a small phallus and testes and infertility. A single amino acid substitution in the androgen receptor was reported in a large Chinese family in whom some affected members were fertile while others had gynecomastia and/or hypospadias.

In girls or young women with CAIS, the historical recommendation has been that testes should be removed prior to adult life, or as soon as they are discovered. *In one third of patients, malignant tumors, usually seminomas, develop by 50 years of age.* Several teenage girls have acquired seminomas. Replacement therapy with estrogens is indicated at the age of puberty if the gonads were removed prior to this age. Some patients prefer to retain their gonads until after puberty has completed in order to mimic a more natural pubertal progression based on their own body's timing of gonadotropins.

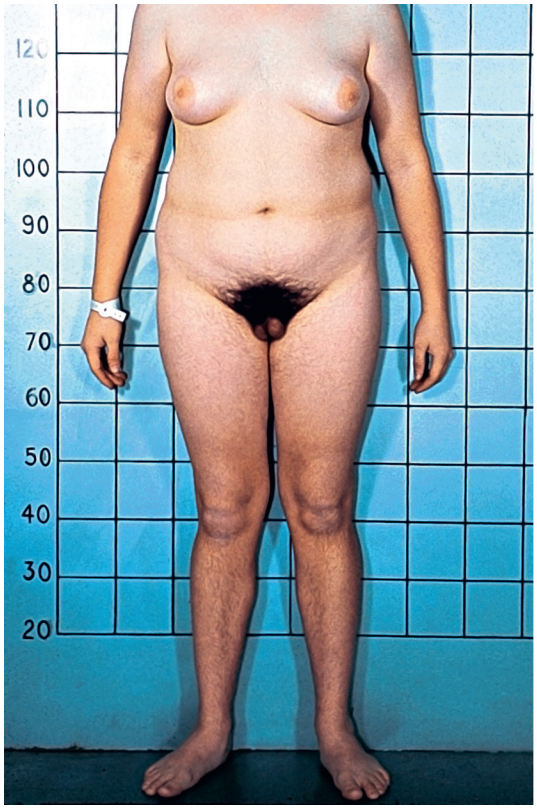


FIGURE 23.9 Partial androgen insensitivity syndrome at adolescence, male sex of rearing. Note gynecomastia from peripheral aromatase conversion of testosterone to estradiol. Abundant pubic hair implies only partial resistance. (From Wales JKH, Wit JM, Rogol AD. *Pediatric Endocrinology and Growth*. 2nd ed. Philadelphia: Elsevier; 2003:165.)

Normal breasts develop in affected girls who have not had their testes removed by the age of puberty. In these individuals, production of estradiol results from aromatase activity on testicular testosterone. The absence of androgenic activity also contributes to the feminization of these women.

The psychosexual and surgical management of patients with partial AIS is extremely complex and depends in large part on the presenting phenotype. Osteopenia is recognized as a late feature of AIS.

Molecular analyses have suggested that phenotype may depend in part on somatic mosaicism of the androgen receptor gene. This was based on the case of a 46,XY patient who had a premature stop codon in exon 1 of the AR gene but who also had evidence of virilization (pubic hair and clitoral enlargement) explained by the discovery of the wild-type alleles on careful examination of the sequencing data. The presence of mosaicism shifts the phenotype to a higher degree of virilization than expected from the genotype of the mutant allele alone. Genetic counseling is thus challenging in families with androgen receptor gene mutations. In addition to lack of genotype-phenotype correlations, there is a high rate (27%) of de novo mutations in families.

The degree of sex hormone-binding globulin reduction after exogenous androgen administration (stanozolol) has been shown to correlate with the severity of the receptor defect and may become a useful clinical tool. Successful therapy with supplemental androgens has been reported in patients with partial AIS and various mutations of the androgen receptor in the DNA-binding domain and the ligand-binding domain.

Mutant androgen receptors are also reported in patients with spinal and bulbar muscular atrophy in whom clinical manifestations including testicular atrophy, infertility, gynecomastia, and elevated LH, FSH, and estradiol levels usually manifest between the 3rd and 5th decades of life. Androgen receptor mutations have also been described in patients with prostate cancer.

Undetermined Causes of 46,XY Disorders of Sex Development

Other 46,XY undervirilized males display great variability of the external and internal genitalia and various degrees of phallic and müllerian development. Testes may be histologically normal or rudimentary, or there may only be 1 testis. Other complex genetic syndromes, many resulting from single-gene mutations, are associated with varying degrees of ambiguity of the genitalia, particularly in the male. These entities must be identified on the basis of the associated extragenital malformations. Examples include **bladder exstrophy** and **Eagle-Barrett syndrome** (formerly known as prune-belly syndrome). Another such complex syndrome is termed ATRX or X-linked α-thalessemia with mental retardation and genital abnormalities.

Ovotesticular Disorders of Sex Development

In ovotesticular DSD, both ovarian and testicular tissues are present, either in the same or in opposite gonads. Affected patients have ambiguous genitalia, varying from normal female with only slight enlargement of the clitoris to almost normal male external genitalia.

About 70% of all patients have a 46,XX karyotype. Ninety-seven percent of affected patients of African descent are 46,XX. Fewer than 10% of persons with ovotesticular DSD are 46,XY. About 20% have 46,XX/46,XY mosaicism. Half of these are derived from more than 1 zygote and are chimeras (chi 46,XX/46,XY). The presence of both paternal and maternal alleles for some blood groups are

demonstrated. An ovotesticular DSD chimera, 46,XX/46,XY, was reported as resulting from embryo amalgamation after in vitro fertilization. Each embryo was derived from an independent, separately fertilized ovum.

Examination of 46,XX ovotesticular DSD patients with Y-specific probes has detected fewer than 10% with a portion of the Y chromosome including the *SRY* gene. Ovotesticular DSD is usually sporadic, but a number of siblings have been reported. The cause of most cases of ovotesticular DSD is unknown.

The most frequently encountered gonad in ovotesticular DSD is an ovotestis, which may be bilateral. If unilateral, the contralateral gonad is usually an ovary but may be a testis. The ovarian tissue is often normal, but the testicular tissue is usually dysgenic. The presence and function of testicular tissue can be determined by measuring basal and hCG-stimulated testosterone levels as well as AMH levels. Patients who are highly virilized and have had adequate testicular function with no uterus are usually reared as males. If a uterus exists, virilization is often mild and testicular function minimal; assignment of female sex may be indicated. Selective removal of gonadal tissue inconsistent with sex of rearing may be possible. In a few families, 46,XY ovotesticular DSD subjects and 46,XX males have been described in the same sibship.

Defects in the ovarian developmental protein R-spondin 1, encoded by the *RSPO1* gene, have also been described in 46,XX ovotesticular DSD.

Pregnancies with living offspring have been reported in 46,XX ovotesticular DSD individuals reared as females, but very few males with ovotesticular DSD have fathered children. About 5% of patients will develop gonadoblastomas, dysgerminomas, or seminomas.

Sex Chromosome Disorders of Sex Development

Some ambiguity of the genitalia is associated with a wide variety of chromosomal aberrations (see Table 23.2), which must always be considered in the differential diagnosis, the most common being the 45,X/46,XY syndrome. It may be necessary to karyotype several tissues to establish mosaicism. The phenotype in 45,X/46,XY individuals may vary from completely female to completely male, and it is reported that there are probably a large number of patients who are never detected and are raised as normal males.

Other conditions included in the broad category of sex chromosome DSD include 45,X Turner syndrome, and 47,XXY Klinefelter syndrome, due to their associated gonadal failure. However, patients with these conditions have normal external genitalia at birth.

RED FLAGS

Danger signs include manifestations of adrenal insufficiency, in addition to a male phenotype without a palpable testis in the scrotum, hyperpigmentation (increased ACTH production), and hypertension. Although normal at birth, male patients with CAH experience an adrenal crisis once circulating placental-maternal steroid hormones are catabolized and excreted. This phenomenon often occurs between the 3rd and 10th days of life. The initial diagnosis in the boy with salt-losing CAH may be sepsis, pyloric stenosis, meningitis, or other more common neonatal conditions.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Allali S, Muller JB, Brauner R, et al. Mutation analysis of NR5A1 encoding steroidogenic factor 1 in 77 patients with 46,XY disorders of sex development (DSD) including hypospadias. *PLoS One*. 2011;6:e24117.

Baxter RM, Arboleda VA, Lee H, et al. Exome sequencing for the diagnosis of 46,XY disorders of sex development. *J Clin Endocrinol Metab*. 2015;100:E333-E344.

Berenbaum SA, Bryk KK, Duck SC, et al. Psychological adjustment in children and adults with congenital adrenal hyperplasia. *J Pediatr*. 2004;144:741-746.

Biason-Lauber A, Konrad D, Navratil F, et al. A WNT4 mutation associated with Müllerian-duct regression and virilization in a 46,XX woman. *N Engl J Med*. 2005;351:792-798.

Bilezikjian LM, Justice NJ, Blackler AN, et al. Cell-type specific modulation of pituitary cells by activin, inhibin and follistatin. *Mol Cell Endocrinol*. 2012;359:43-52.

Bose HS, Pescovitz OH, Miller WL. Spontaneous feminization in a 46,XX female patient with congenital lipoid adrenal hyperplasia due to a homozygous frameshift mutation in the steroidogenic acute regulatory protein. *J Clin Endocrinol Metab*. 1997;82:1511-1515.

Bose HS, Sugawara T, Strauss JF, et al. The pathophysiology and genetics of congenital lipoid adrenal hyperplasia. *NEJM*. 1996;335:1870-1878.

Bouvattier C, Carel JC, Lecointre C, et al. Postnatal changes of T, LH, and FSH in 46,XY infants with mutations in the AR gene. *J Pediatr Endocrinol Metab*. 2002;87:29-32.

Brinkmann AO. Molecular basis of androgen insensitivity. *Mol Cell Endocrinol*. 2001;179:105-1099.

Canto P, Vilchis F, Chavez B, et al. Mutations of the 5α-reductase type II gene in eight Mexican patients from six different pedigrees with 5α-reductase-2 deficiency. *Clin Endocrinol*. 1997;46:155-160.

Chu J, Zhang R, Zhao Z, et al. Male fertility is compatible with an Arg840 Cys substitution in the AR in a large Chinese family affected with divergent phenotypes of AR insensitivity syndrome. *J Clin Endocrinol Metab*. 2002;87:347-351.

Clarkson MJ, Harley VR. Sex with two SOX on: SRY and SOX9 in testis development. *Trends Endocrinol Metab*. 2003;13:106.

Damiani D, Fellous M, McElreavey K, et al. True hermaphroditism: Clinical aspects and molecular studies in 16 cases. *Eur J Endocrinol*. 1997;136:201-204.

Eggers S, Sinclair A. Mammalian sex determination – Insights from humans and mice. *Chromosome Res*. 2012;20:215-238.

El-Khairi R, Achermann JC. Steroidogenic factor -1 and human disease. *Semin Reprod Med*. 2012;30:374-381.

Fagerholm R, Santtila P, Miettinen PJ, et al. Sexual function and attitudes toward surgery after feminizing genitoplasty. *J Urol*. 2011;185:1900-1904.

Fluck CE, Meyer-Boni M, Pandley AV, et al. Why boys will be boys: Two pathways of fetal testicular androgen biosynthesis are needed for male sexual differentiation. *Am J Hum Genet*. 2011;89:201-218.

Gul D. Third case of WAGR syndrome with severe obesity and constitutional deletion of chromosome (11)(p12p14). *Am J Med Genet*. 2002;107:70-71.

Habert R, Lejeune H, Saez J. Origin, differentiation and regulation of fetal and adult Leydig cells. *Mol Cell Endocrinol*. 2001;179:47-74.

Harrington J, Palmert MR. Distinguishing constitutional delay of growth and puberty from isolated hypogonadotropic hypogonadism: Critical appraisal of available diagnostic tests. *J Clin Endocrinol Metab*. 2012;97:3056-3067.

Hochberg Z, Chayen R, Reiss N, et al. Clinical, biochemical and genetic findings in a large pedigree of male and female patients with 5α-reductase 2 deficiency. *J Clin Endocrinol Metab*. 1996;81:2821-2827.

Hughes IA, Davies JD, Bunch TI, et al. Androgen insensitivity syndrome. *Lancet*. 2012;380:1419-1428.

Imbeaud S, Belville C, Messika-Zeitoun L, et al. A 27 base-pair deletion of the anti-mullerian type 1 receptor gene is the most common cause of the persistent mullerian duct syndrome. *Hum Mol Genet*. 1996;5:1269-1277.

Kim MS, Donohoue PA. Adrenal disorders. In: Kappy MS, Allen DB, Geffner ME, eds. *Pediatric Practice Endocrinology*. 2nd ed. New York: McGraw-Hill; 2014.

Kremer H, Karaaij R, Toledo SPA, et al. Male pseudohermaphroditism due to a homozygous missense mutation of the luteinizing hormone receptor gene. *Nat Genet*. 1995;9:160-164.

Krob G, Braun A, Kuhnle U. True hermaphroditism: Geographical distribution, clinical findings, chromosomes and gonadal histology. *Eur J Pediatr*. 1994;153:2-10.

Lee PA, Houk CP, Ahmed SF, et al. International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. *Pediatrics*. 2006;118:e488-e500.

Lee PA, Witchel SF. Genital surgery among females with congenital adrenal hyperplasia: Changes over the past five decades. *J Pediatr Endocrinol Metab*. 2002;15:1473-1477.

Looijenga LHJ, Hersmus R, LeLeeuw BH, et al. Gonadal tumours and DSD. *Best Pract Res Clin Endocrinol Metab*. 2010;24:291-310.

McPherson EW, Clemens MM, Gibbons RJ, et al. X-linked α-thalassemia/mental retardation (ATR-X) syndrome: A new kindred with severe genital anomalies and mild hematologic expression. *Am J Med Genet*. 1995;55:302-306.

Mebarki F, Sanchez R, Rheaumes E, et al. Non-salt-losing male pseudohermaphroditism due to the novel homozygous N100S mutation in the type II 3 β-hydroxysteroid dehydrogenase gene. *J Clin Endocrinol Metab*. 1995;80:2127-2134.

Meier M, Moller G, Adamski J. Perspectives in understanding the role of 17β-hydroxysteroid dehydrogenases in health and disease. *Ann N Y Acad Sci*. 2009;1155:15-24.

Mendonca BB, Inacio M, Costa EMF, et al. Male pseudohermaphroditism due to steroid 5α-reductase 2 deficiency. *Medicine (Baltimore)*. 1996;75:64-76.

Mendonca BB, Leite MV, DeCastro M, et al. Female pseudohermaphroditism caused by a novel homozygous mutation of the GR gene. *J Clin Endocrinol Metab*. 2002;87:1805-1809.

Miller WL. P450 oxidoreductase deficiency: a new disorder of steroidogenesis with multiple clinical manifestations. *Trends Endocrinol Metab*. 2004;15:311-315.

Moisan AM, Ricketts ML, Tardy V, et al. New insight into the molecular basis of 3β-hydroxysteroid dehydrogenase deficiency: Identification of eight mutations in the HSD3 gene in eleven patients from seven new families and comparison of the functional properties of twenty-five mutant enzymes. *J Clin Endocrinol Metab*. 1999;84:4410-4425.

Mullis PE, Yoshimura N, Kuhlmann B, et al. Aromatase deficiency in a female who is compound heterozygote for two new point mutations in the P450arom gene: Impact of estrogens on hypergonadotropic hypogonadism, multicystic ovaries, and bone densitometry in childhood. *J Clin Endocrinol Metab*. 1997;82:1739-1745.

Ogilvy-Stuart AL, Brain CE. Early assessment of ambiguous genitalia. *Arch Dis Child*. 2004;89:401-407.

Parisi MA, Ramsdell LA, Burns MW, et al. A gender assessment team: Experience with 250 patients over a period of 25 years. *Genet Med*. 2007;9:348-357.

Parma P, Radi O, Vidal V, et al. R-spondin-1 is essential in sex determination, skin differentiation and malignancy. *Nat Genet*. 2006;38:1304-1309.

Piferrer F. Epigenetics of sex determination and gonadogenesis. *Dev Dyn*. 2013;242:360-370.

Rajpert-De Meyts E. Expression of anti-müllerian hormone during normal and pathological gonadal development: Association with differentiation of Sertoli and granulosa cells. *J Clin Endocrinol Metab*. 1999;84:3836-3844.

Royer-Pekora B, Beier M, Henzler M, et al. Twenty-four new cases of WT1 germline mutations and review of the literature: Genotype/phenotype correlations for Wilms tumor development. *Am J Med Genet*. 2004;127A:249-257.

Simard J, Sanchez R, Durocher F, et al. Structure-function relationships and molecular genetics of the 3 beta-hydroxysteroid dehydrogenase family. *J Steroid Biochem Mol Biol*. 1995;55:489-505.

Sinclair AH, Berta P, Palmer MS, et al. A gene from the human sex-determining region encodes a protein with homology to a conserved DNA-binding motif. *Nature*. 1990;346:240-244.

Smith EP, Boyd J, Frank GR, et al. Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. *NEJM*. 1994;331:1056-1061.

Stenvers KL, Findlay JK. Inhibins: From reproductive hormones to tumor suppressors. *Trends Endocrinol Metab*. 2010;21:174-180.

Sun SS, Schubert CM, Chumlea WC, et al. National estimates of the timing of sexual maturation and racial differences among US children. *Pediatrics*. 2002;110:911-919.

Tajima T, Fujieda K, Kouda N, et al. Heterozygous mutation in the cholesterol side chain cleavage enzyme (P450scc) gene in a patient with 46,XY sex reversal and adrenal insufficiency. *J Clin Endocrinol Metab*. 2001;86:3820-3825.

Teixeira J, Maheswaran S, Donahue PK. Müllerian inhibiting substance: An instructive development hormone with diagnostic and possible therapeutic applications. *Endocr Rev*. 2001;22:657-674.

Wallien MS, Cohen-Kettenis PT. Psychosexual outcome of gender-dysphoric children. *J Am Acad Child Adolesc Psychiatry*. 2008;47:1413-1423.

White PC, Speiser PW. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Endocr Rev*. 2000;21:245-291.

Winter JSD, Hughes IA, Reyes FL, et al. Pituitary-gonadal relations in infancy: 2. Patterns of serum gonadal steroid concentrations in man from birth to 2 years of age. *J Clin Endocrinol Metab*. 1976;42:679.

Wisniewski AB, Migeon CJ, Meyer-Bahlburg HF, et al. Androgen insensitivity syndrome: Long-term medical, surgical and psychosexual outcome. *J Clin Endocrinol Metab*. 2000;85:2664-2669.

Yanase T, Simpson ER, Waterman MR. 17-Alpha-hydroxylase/17,20-lyase deficiency: From clinical investigation to molecular definition. *Endocr Rev*. 1991;12:91-108.

24

Intellectual and Developmental Disability

Mark Simms

DEFINITIONS

Intellectual disability (ID) has replaced the older term mental retardation (MR), reflecting a more enlightened and progressive attitude toward individuals with disabilities. ID is characterized by significant limitations in intellectual functioning and in adaptive behavior that begin before age 18 years, and are expressed in conceptual, social, and practical adaptive skills. The impairments of ID extend beyond what is measured on a standardized test of intelligence, and must take into account the context of an individual's typical environment and their cultural and linguistic backgrounds. Adaptive functioning includes 3 broad domains: conceptual, social, and practical. The **conceptual domain** involves academic competence, the acquisition of practical knowledge, and judgment in novel situations. The **social domain** involves awareness of others' thoughts and feelings, empathy, friendships, and social judgment. The **practical domain** involves the ability to manage one's own affairs, including school and work responsibilities, money management, and recreation (Table 24.1). Although ID is a lifelong condition, it is recognized that "with appropriate personalized supports over a sustained period, the life functioning of the person with intellectual disability generally will improve." In a long-term study comparing ID and non-ID siblings, those with mild ID (intelligence quotient [IQ] between 64 and 75) were just as likely to find stable employment, to have similar total family incomes, to have stable marriages, and to raise children as their siblings. However, they reported higher rates of psychologic distress and lower rates of participation in formal organizations. Table 24.2 provides descriptions of typical adult functioning in individuals with varying degrees of ID.

The term **developmental disability** includes a diverse group of lifelong physical and mental impairments that negatively affect an individual's ability to function as well as their peers. These conditions begin during childhood (before 22 years of age), and interfere with mobility, acquisition of self-care ability, communication skills, social skills, general learning ability, and independent living. The specific types of conditions and categories of disabilities vary widely. The National Institute for Child Health and Development (NICHD) includes the following conditions: neurologic disorders: cerebral palsy, muscular dystrophy, epilepsy, genetic syndromes, autism, and degenerative disorders; sensory disorders: blindness and deafness; metabolic disorders: phenylketonuria (PKU); and cognitive disorders: intellectual impairment, learning disabilities, and attention-deficit/hyperactivity disorder (ADHD). Developmental disabilities may be isolated, as in a child with impaired vision, or may be multiple, as in a child with delays in motor, cognitive, language, and social functioning. There may be considerable overlap in specific disorders in terms of the affected functions (Fig. 24.1). In young children, developmental delays may result from a wide range of causes, including early environmental understimulation, chronic physical illness, neuromuscular disorders, central nervous system (CNS) abnormalities, genetic syndromes, etc. Some etiologies are fully or partly amenable to early educational and medical interventions, while others may lead to permanent intellectual impairment or progressive deterioration of functioning. Therefore, until a young child has had the benefit of early intervention services and he or she has matured to the point where formal cognitive, language, and adaptive measures are stable and predictive of future functioning, the descriptive term **global developmental delay** (GDD) is preferred.

EPIDEMIOLOGY

Intellectual Disability

The overall prevalence of ID varies from 1-3%, depending on the criteria used and the age of the individual at the time of evaluation. For example, standardized tests of intelligence have a mean of 100 and standard deviation of 15 points. Statistically, 2.5% of individuals should have an IQ score below 2 standard deviations (70 points) and fit the cognitive criterion for ID. However, because the standard error of measurement is approximately 5 points, extending the IQ score upward to 75 points would almost double the prevalence of ID. This might be countered by secondary criteria involving deficits in adaptive behaviors, since many children with IQ scores in the mildly low range (55-70) will not qualify for a diagnosis of ID because they have adequate adaptive functioning.

Many studies have documented a higher rate of mild ID in economically disadvantaged children that stems from a few highly significant sociodemographic factors. In 1 study, approximately half of the excess prevalence of mild ID among African-American 10-year-old children in the mid-1980s was related to the mother's level of education and her age at the time of delivery, birth order, sex of the child, and family's income level.

Developmental Disability

Developmental disabilities affect approximately 1 in 6 children in the United States (13.8%). The prevalence rates vary by specific condition: Learning disabilities (7.66%) and ADHD (6.69%) are the most

(See *Nelson Textbook of Pediatrics,* p. 216.)

(See *Nelson Textbook of Pediatrics,* p. 3412.)

common, while ID, epilepsy, autism, deafness, cerebral palsy, and blindness each affect less than 1%. Boys have more than twice the prevalence of any developmental disability, and children insured by Medicaid have a nearly 2-fold higher prevalence of disability compared with those with private insurance. The overall prevalence of disability increased by 17% between 1997 and 2008, mostly due to a nearly 4-fold change in autism (from 0.19% to 0.74%). In addition, the prevalence of Down syndrome increased by 31% (from 0.09% to 0.12%). Table 24.3 lists the prevalences of selected conditions.

DIAGNOSIS

Identification of a specific cause for delayed development in a child is important and may provide insight into prognosis, recurrence risk, therapies, counseling, and linkage with a supportive group. From a community perspective, having a specific diagnosis for an affected individual helps in the development of treatment and prevention strategies. Identification of the child's functional abilities, strengths and weaknesses, overall physical health, and environmental factors is critical for optimizing the child's health, development, and functioning. In addition, the origin of developmental disability is not apparent in many children, or there may be multiple possible causal factors or multiple disabilities present. For example, 23% of children with developmental disabilities have 2 disabilities, and 6% have 3 or more. Even if a specific diagnosis cannot be made, early identification of developmental delay can lead to a program of early intervention or remediation that may improve the child's ultimate functioning. To identify those disorders, which are amenable to intervention, an international consortium has developed both a web-based tool and a mobile application (app) to assist expert clinicians and general practitioners alike in the evaluation and management of children with ID (http://www.treatable-id.org/).

TABLE 24.1 Diagnosis of Intellectual Disability

Diagnostic Criteria

All 3 Criteria Must Be Met

A. Deficits in intellectual function, such as reasoning, problem solving, planning, abstract thinking, judgment, academic learning, and learning from experience, confirmed by both clinical assessment and individualized standardized testing.

B. Deficits in adaptive functioning that result in failure to meet developmental and sociocultural standards for personal independence and social responsibility. Without ongoing support, the adaptive deficits limit functioning in 1 or more activities of daily life, such as communication, social participation, and independent living, across multiple environments, such as home, school, work, and community.

C. Onset of intellectual and adaptive deficits during the developmental period.

Assumptions

1. Assessments performed on the child are sensitive to differences in culture, language, communication, and behavior.
2. The demands and constraints of the child's environment (home, neighborhood, school) must be considered.
3. Even children with limitations have strengths that should be considered.

Data from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-V)*. 5th ed. Arlington, VA: American Psychiatric Association; 2013.

IDENTIFICATION

Children who experience significant complications in the perinatal period or who are born with obvious congenital anomalies are at risk for developmental disabilities. In addition, newborn screening programs may identify children with rare but significant problems who require early treatments and interventions. Children with no apparent risk factors or obvious physical or neurologic symptoms may be

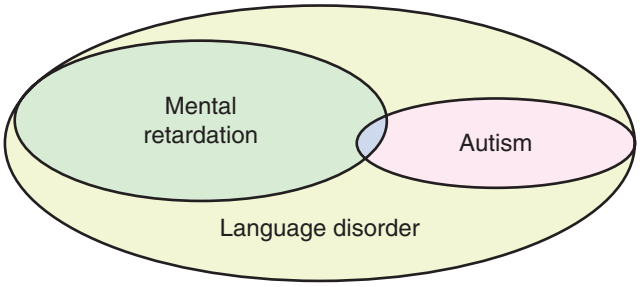


FIGURE 24.1 Relationship of autism, language disorders, and intellectual disability. (Modified from Simms MD, Schum RL. Preschool children who have atypical patterns of development. *Pediatr Rev.* 2000;21:147-158.)

TABLE 24.2 Severity of Intellectual Disability and Adult Age Functioning

Level	Mental Age as an Adult*	Adult Adaptation
Mild	9-11 yr	Reads at 4th-5th grade level; simple multiplication/division; writes simple letters, lists; completes job applications; basic independent job skills (arrive on time, stay at task, interact with coworkers); uses public transportation, may qualify for driver's license; keeps house, cooks using recipes
Moderate	6-8 yr	Sight-word reading; copies information, e.g., address from card to job application; matches written number to number of items; recognizes time on clock; communicates; some independence in self-care; housekeeping with supervision or cue cards; meal preparation, can follow picture recipe cards; job skills learned with much repetition; uses public transportation with some supervision
Severe	3-5 yr	Needs continuous support and supervision; may communicate wants and needs, sometimes with augmentative communication techniques
Profound	<3 yr	Limitations of self-care, continence, communication, and mobility; may need complete custodial or nursing care

* *International Statistical Classification of Diseases and Related Health Problems*. 10th revision. World Health Organization; 2010.
From Schum RL. Grand Rounds Presentation at Children's Hospital of Wisconsin; 2003.

TABLE 24.3 Prevalence of Select Conditions Associated with Developmental Delay

Condition	Prevalence/100,000	Comments
Cerebral palsy	250-270	Represents many causes
Significant hearing loss	150	In neonatal period
Down syndrome	98-125	Prevalence at birth
Fragile X syndrome	117	Predominantly in boys
Meningomyelocele	60-100	Prevalence at birth
Klinefelter syndrome	100	15% have intelligence quotient (IQ) <80
Fetal alcohol syndrome	60-800	Present at birth
Congenital HIV infection	5-50	Preventable with maternal and neonatal therapy
Blindness	41-88	At 10 yr of age
Infantile hydrocephalus	64	Prevalence at birth
Neurofibromatosis	33	5% have intellectual disability
Trisomy 18	30	Prevalence at birth
Trisomy 13	20	Prevalence at birth
Turner syndrome	20	IQ may be normal
Prader-Willi syndrome	13-20	In childhood
Galactosemia	14	In infancy
Phenylketonuria	6-12	In infancy
Anophthalmia	6	Consider other anomalies
Rett syndrome	4-5	In girls 2-18 yr of age
Histidinemia	3	At birth
Acrocephalosyndactylia (Apert syndrome)	1-2	Present at birth

identified through a process of surveillance and screening during routine child health care visits.

Developmental Risk Factors

Young children's development may be adversely affected by biologic and/or sociocultural risk factors (Table 24.4). Many risk factors can be graded according to severity (e.g., degree of prematurity, intracranial hemorrhage, intrauterine growth restriction), but it is often the cumulative effect of multiple factors that ultimately determines a child's developmental outcome, even when 1 or more "severe" risks are present. For example, it has been shown that low 5-minute Apgar scores, in the absence of other symptoms of neonatal encephalopathy, correlate poorly with long-term neurologic dysfunction. Sociocultural risks also can have profound effects on development and may interact with biologic risk factors to create a greater effect than any single factor alone (so-called "double jeopardy").

Developmental Protective Factors

During the process of developmental surveillance, the clinician should identify and acknowledge the influence of protective and supportive factors that may contribute to positive outcomes. For example, barring catastrophic circumstances, child-rearing conditions that support and enrich early development may compensate for biologic deficits. Sociocultural factors, such as small family size, higher level of parental education, and fewer changes in residence have a more powerful positive effect than many biologic risks and seem to be important predictors of developmental functioning beyond infancy. The brains of infants and young children are remarkably resilient and normal cognitive and language outcomes are often seen, even in the face of perinatal stroke or similar focal brain injuries. Neural plasticity also extends to situations of extreme environmental deprivation,

TABLE 24.4 Risk Factors for Developmental Disabilities

Biologic	Sociocultural
Male sex	Low parental education
Maternal age above 30 yr old	Maternal depression
Multiple pregnancies	Maternal substance abuse
High birth order	Low socioeconomic status
Preterm birth	Lack of prenatal care
Low birthweight (<750 g)	Inadequate environmental stimulation
Intrauterine growth restriction	
Small head circumference	
Brain malformations	
Holoprosencephaly	
Schizencephaly	
Lissencephaly	
Neonatal complications	
Neonatal encephalopathy	
Intracranial hemorrhage	
Symptomatic hypoglycemia	
Severe hyperbilirubinemia	
Congenital infections	
Acquired central nervous system infections	
Iron and iodine deficiencies	
Brain injury	
Malnutrition	

TABLE 24.5 Developmental Protective Factors

Biologic	Sociocultural
Neural plasticity	Small family size
Comprehensive and supportive health care	Higher level of parental education
	Few changes in residence
Early intervention services	Parental support system

providing interventions occur early enough. In addition, preschool early intervention programs that are designed to mitigate the factors that place children at risk for poor outcomes have been shown to have significant short- and long-term educational, behavioral, and economic benefits (Table 24.5).

SCREENING FOR SPECIFIC ABNORMALITIES

Deficits in vision, hearing, and language can have devastating effects on development; early intervention to ameliorate these problems can improve outcomes. All children should be screened on a regular basis for these conditions.

Visual Deficits

Children at high risk for development of deficits in vision (see Chapter 32) include those with strabismus (especially after 4 months of age), hydrocephalus, congenital infection, neonatal encephalopathy, congenital anomaly of the CNS, prematurity with overexposure to oxygen, and family history of a childhood onset of visual impairment. All neonates should routinely undergo an evaluation of their fundi for the presence of a red reflex, which can be obscured by cataract or tumor, as well as inspection of the globe, which may be affected by congenital glaucoma. Infants with nystagmus who do not follow visually by 3 months of age, who have dissociation between visual behavior and motor behavior, or whose parents express concern about their vision should undergo a formal ophthalmologic evaluation.

Preschool children should undergo periodic evaluations of extraocular movements to rule out strabismus and amblyopia; the evaluation should include visual inspection of the child's eyes, the Hirschberg light test, and the cover-uncover test. As early in the child's development as possible, specific tests of monocular and binocular vision such as Allen cards (3-5 years), the Snellen chart (>5 years), or the Titmus test (>4 years) should be performed.

Loss of Hearing

Early detection of hearing loss is critical for optimizing the language development of these children. Universal newborn hearing screening programs (UNHSP) have been in place since the 1990s to detect infants born with moderate, severe, or profound bilateral hearing impairment. More than 95% of all children born in the United States are screened for hearing loss shortly after birth. Although the prevalence of congenital deafness is low in the general population (1-3/1,000 infants), it is higher in infants who require neonatal intensive care services (2-4/100 infants). More than half of babies with permanent congenital hearing impairment do not have prospectively identifiable risk factors and would be missed without UNHSP. They would not receive hearing intervention within the 1st 6 months of life, a period that is critical for speech, language, and later learning development. Hearing loss can be acquired during infancy or childhood from infection (cytomegalovirus [CMV], meningitis), trauma (particularly basal skull and temporal bone fractures), ototoxic drugs (aminoglycosides, furosemide), or damaging noise levels. A number of **genetic syndromes** are associated with deafness (Waardenburg, Alport, Pendred, and Jervell and Lange-Nielsen) and progressive or late-onset hearing loss can occur in neurofibromatosis, Usher syndrome, Hunter syndrome, Friedreich ataxia, or Charcot-Marie-Tooth syndrome (Table 24.6). The American Academy of Pediatrics (AAP) recommends that children with 1 or more "risk factors" should have hearing screening again at 24-30 months, even if they passed the newborn screening test. In addition, parental concern about hearing loss has a sensitivity of approximately 44%. If parents express concern about their child's ability to hear and if the child has had recurrent episodes of otitis media, mastoiditis, or 1 of the perinatal or familial risk factors, a formal audiometric screening should be performed. Table 24.7 lists the latest acceptable age ("limit ages") for the appearance of skills related to hearing; absence of these milestones may indicate a disorder of hearing. *Deaf infants may smile, coo, and babble; however, their vocalizations usually cease after 8 months of age.*

TABLE 24.6 Risk Indicators Associated with Permanent Congenital, Delayed-Onset, and/or Progressive Hearing Loss in Children

1. Caregiver concern* regarding hearing, speech, language, or developmental delay.
2. Family history* of permanent childhood hearing loss.
3. Neonatal intensive care of >5 days or any of the following, regardless of length of stay: ECMO,* assisted ventilation, exposure to ototoxic medications (gentamicin and tobramycin) or loop diuretics (furosemide/Lasix), and hyperbilirubinemia that requires exchange transfusion.
4. In utero infections such as CMV,* herpes, rubella, syphilis, and toxoplasmosis.
5. Craniofacial anomalies, including those that involve the pinna, ear canal, ear tags, ear pits, and temporal bone anomalies.
6. Physical findings, such as a white forelock, that are associated with a syndrome known to include sensorineural or permanent conductive hearing loss.
7. Syndromes associated with hearing loss or progressive or late-onset hearing loss,* such as neurofibromatosis, osteopetrosis, and Usher syndrome; other frequently identified syndromes include Waardenburg, Alport, Pendred, and Jervell and Lange-Nielsen.
8. Neurodegenerative disorders* such as Hunter syndrome or sensory motor neuropathies such as Friedreich ataxia and Charcot-Marie-Tooth syndrome.
9. Culture-positive postnatal infections associated with sensorineural hearing loss,* including confirmed bacterial and viral (especially herpes viruses and varicella) meningitis.
10. Head trauma, especially basal skull/temporal bone fracture* that requires hospitalization.
11. Chemotherapy.*
12. Recurrent or persistent otitis media for at least 3 mo.

*Risk indicators that are of greater concern for delayed-onset hearing loss.
ECMO, extracorporeal membrane oxygenation; CMV, cytomegalovirus.
From American Academy of Pediatrics, Joint Committee on Infant Hearing. *Pediatrics.* 2007;120(4):898-921.

Speech and Language Disorders

Disorders of speech and language development, prevalent in 3-20% of preschool children, are the most common reason for referral to early intervention programs and are correlated with subsequent learning

(See *Nelson Textbook of Pediatrics,* p. 3073.)

(See *Nelson Textbook of Pediatrics,* p. 207.)

TABLE 24.7 Latest Acceptable Age for Skills Related to Hearing*

Age (mo)†	Activity
3	Not startling to loud sounds
6	Not smiling to voice; not vocalizing
9	Does not localize speech or other sounds
12	Not babbling multiple sounds and syllables
18	No words
24	<50% of speech understandable

*A child who does not demonstrate the activity by the stated age should have formal audiometry performed.
†Corrected for gestational age.
Modified from the Arizona Speech, Language, Hearing Association.

TABLE 24.8 Speech-Language Screening for Pediatricians

Refer for a Speech-Language Evaluation if:		
At Age	**Receptive**	**Expressive**
15 mo	Does not look/point at 5-10 objects/people named by a parent	Not using 3 words
18 mo	Does not follow simple directions ("Get your shoes")	Not using Mamma, Dadda, or other names
24 mo	Does not point to pictures or body parts when they are named	Not using 25 words
30 mo	Does not verbally respond or nod/shake head to questions	Not using unique 2-word phrases, including noun-verb combinations
36 mo	Does not understand prepositions or action words; does not follow 2-step directions	Vocabulary <200 words; does not ask for things by name; echolalia to questions; regression of language after acquiring 2-word phrases

From Schum RL. Language screening in the pediatric office setting. *Pediatr Clin North Am.* 2007;54:425-436.

problems. Speech refers to the mechanics of oral communication (sound production); language includes the understanding, processing, and production of communication (words). Speech problems may include articulation (pronunciation) deficits (phonologic or apraxic speech disorders), fluency disorders (stuttering), or unusual voice quality. Language delays may be confined to expression with normal receptive abilities, or may involve both expressive and receptive abilities. Language delays may be a feature of GDD/ID, autism spectrum disorders (ASDs), hearing impairment, or may be the result of an isolated disorder (specific language impairment).

Children with speech and language delays often experience emotional and social adjustment difficulties related to their inability to communicate effectively with parents and peers. In general, children with normal comprehension of language and normal nonverbal cognitive abilities have an excellent prognosis, while those with receptive delays are at risk for language-based learning disabilities (reading comprehension and writing disorders) (Table 24.8).

OTHER CONDITIONS

Prenatal and Newborn Screening Programs

Prenatal Screening

Prenatal screening has undergone significant changes with the advent of "next generation sequencing" (NGS) technologies. The traditional screening takes the form of biochemical and ultrasound tests, which may detect fetuses at high risk for chromosome anomalies and neural tube defects. In the 1st trimester (11-14 weeks' gestation), measurement of maternal serum levels of human chorionic gonadotropin (hCG) and pregnancy-associated plasma protein A (PAPP-A), and a sonogram measurement of the fluid underneath the skin along the back of the fetus' neck (nuchal translucency) may identify Down syndrome, trisomy 13, or trisomy 18. In the 2nd trimester (15-22 weeks' gestation), a quad screen (α-fetoprotein, hCG, estriol, and inhibin A levels) may identify Down syndrome and neural tube defects (spina bifida, encephalocele). An abnormal result on these screenings is typically followed by high-resolution ultrasonography, chorionic villus sampling or amniocentesis, genetic testing (chomosome analysis or microarray), and genetic counseling. NGS technologies allow for noninvasive prenatal testing (NIPT) on maternal blood samples, also called *cell-free* fetal DNA prenatal testing. These technologies identify possible chromosomal and microdeletion disorders through maternal blood screening. If an abnormality is detected, a confirmatory test is still required through more invasive techniques such as amniocentesis. In addition, prenatal genetic carrier screening can be performed for a large number of disorders; at present, these are the only standard of care for individuals at high risk for certain genetic conditions (e.g., Tay-Sachs).

Newborn Screening

Uniform newborn screening has been highly successful in identifying children with rare but serious conditions who can benefit from early intervention. All 50 states, U.S. territories, and the U.S. military routinely test for inborn errors of metabolism (IEM), congenital hypothyroidism, congenital adrenal hyperplasia, severe T-cell immunodeficiency (SCID), cystic fibrosis, and hemoglobinopathies. Test samples should be collected between 24-48 hours of age, but results may be influenced by a variety of maternal and infant factors. For example, tests for congenital adrenal hyperplasia are sensitive to the weight of the infant and the use of steroids. Screening for hypothyroidism (thyroid-stimulating hormone [TSH]) may be falsely low in premature or low-birthweight infants. In addition, use of antibiotics and total parenteral nutrition (TPN) may interfere with interpretation of newborn metabolic screening tests. While all states screen for a "core panel" of 29 conditions, they vary in testing for other conditions. An additional 26 conditions have been recommended for inclusion in the U.S. Health and Human Services Recommended Uniform Screening Panel. Normal newborn screening test results do not eliminate the possibility that a clinically symptomatic child could have 1 of the disorders in the state's panel. Clinicians should familiarize themselves with the specific tests that are routinely performed in each state.

IDENTIFICATION OF CHILDREN WITH DEVELOPMENTAL DISABILITIES IN PRIMARY HEALTH CARE SETTINGS

Not all developmentally disabling conditions can be identified at or shortly after birth through newborn screening programs. Many disorders may not manifest until children are preschool or school age, and some infrequent disorders cause regression or deterioration of function beginning at different ages. Therefore, identification of

children with developmental disabilities is a continuous process that should take place throughout childhood.

Parents, caretakers, or teachers who have concerns about the child's behavior or his or her failure to meet age-appropriate developmental expectations often identify children with developmental disabilities. In 1 study, 14% of parents waiting for well child visits had a concern about their child's learning or cognition. Multiple studies have found parental concern to identify correctly 74-80% of preschool age children (0-6 years old) with cognitive delays, speech and language delays, and learning disabilities. Conversely, the absence of parental concern correctly identified 70-80% of children without a significant disability. Thus, reliance on parental concern alone as a means of identification (sensitivity and specificity) matches acceptable standards for more formal developmental screening tests. However, sole reliance on parental concerns will miss a substantial number of children with developmental concerns, especially those with more subtle disabilities, for a variety of reasons. Parents may be unaware of their child's delays, they may lack the confidence to raise their concerns to the health care provider, or the provider may dismiss these concerns and not pursue further investigation. In particular, children without obvious physical impairments may not be identified until they enter a formal school program. Complicating matters further, children with developmental disabilities may experience significant behavioral or emotional difficulties that "mask" (or distract from) their underlying developmental difficulties.

Developmental Screening

Developmental screening involves the routine application of a brief standardized tool when there is no obvious concern. Developmental screening tests for use by health care providers have been available for several decades, but they are rarely administered by pediatricians, and generally lack sufficient sensitivity to identify subtle disorders while falsely identifying a significant number of nonaffected children. Instead, physicians are more likely to rely on their own clinical judgment, which detects fewer than 30% of children with significant developmental disabilities, or on informal and nonstandardized lists of developmental milestones. A more practical and widely accepted alternative is the use of parent-completed developmental questionnaires, such as the Ages and Stages Questionnaire (ASQ) or the Parents' Evaluations of Developmental Status (PEDS) that can be scored by nonphysician staff and interpreted by the health care provider.

Developmental Surveillance

Developmental surveillance is a "flexible, continuous process whereby knowledgeable professionals perform skilled observations of children throughout all encounters during child health care." The goal of developmental surveillance is to identify children who may benefit from further diagnostic evaluations and early intervention services. To be effective, surveillance requires clinicians to be knowledgeable about child development and to recognize both variations of and deviations from normal patterns. Identification of children in need of further evaluation is believed to be improved by incorporating into the process developmental risk factors based on the child's medical history, family history, as well as social and environmental circumstances. Additionally, clinicians are encouraged to include the observations and impressions of preschool teachers, public health nurses, and other professionals involved in the child's care.

The AAP recommends a combination of both developmental surveillance at every well child visit and standardized developmental screening at the 9-, 18-, and 30-month visits (Fig. 24.2). At any point in this process, children who elicit concern about their development should be referred for further diagnostic evaluations and for early intervention and educational programs.

COMPREHENSIVE DEVELOPMENTAL ASSESSMENT

Children identified with developmental delays should receive a comprehensive, multidisciplinary evaluation including assessments of neurodevelopmental, cognitive, and communication functioning. These assessments should focus on both the child's strengths and functional abilities as well as on weaknesses and disabilities. Based on the findings from these evaluations, further subspecialty consultations (e.g., neurology, genetics, physical medicine and rehabilitation, ophthalmology, occupational and physical therapy, speech therapy) can be arranged, and a plan for specific laboratory investigations developed. The goals of the evaluations are to identify a specific etiologic diagnosis, prognosis, recurrence risk, and interventions to promote the child's optimal development. Parents may also benefit from associating with a disease-specific support group.

Neurodevelopmental Pediatric Assessment

History

Pediatric evaluation of a child with GDD or ID consists of a complete history and physical examination. Schedule the evaluation as a separate visit with sufficient uninterrupted time (at least 45-60 minutes) to focus on issues related to the child's behavior and development. Unless the child's and family's histories are well known to the provider, parents can be asked to complete detailed history questionnaires, developmental and behavioral rating scales, and to provide any additional information from outside sources (e.g., prior medical records, consultation reports, educational evaluations, etc.) prior to this visit that will contribute to assembling a complete record of the child's care. Previsit preparation may help parents to refresh their memory regarding their child's development and to focus their questions and concerns during the evaluation.

Many disabilities have their origin in the prenatal period, so the pregnancy and birth history are reviewed carefully for possible developmental risk factors (Table 24.9). Difficulty in conception or history of recurrent pregnancy loss may suggest the presence of an inherited chromosome anomaly. Maternal illnesses (toxoplasmosis, other [syphilis, varicella-zoster, parvovirus B19], rubella, CMV, and herpes [TORCH] infections; HIV infection) preceding or continuing through pregnancy, or exposure to potentially harmful or teratogenic substances (tobacco, alcohol, illicit drugs, radiation exposure, or medications) should be noted. Other pregnancy complications such as intrauterine growth restriction (which may reflect chronic placental insufficiency, uterine anatomic abnormality, or fetal genetic anomaly); bleeding (especially in the 3rd trimester), which can be caused by placenta previa; placental abruption; or hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome; hypertension (especially leading to eclampsia); complications of maternal diabetes; or limited prenatal care may be associated with poor fetal outcomes. In the perinatal period, signs of fetal distress during labor (heart rate and movement abnormalities associated with uterine contractions), low Apgar scores, neonatal seizures, or the need for extensive neonatal resuscitation may be the result of acute fetal CNS injury or preexisting congenital abnormalities that first manifest at the time of birth. The method of delivery and the reason(s) for nonvaginal delivery may reflect on fetal status at the time of birth. Neonatal physical measurements (weight, length, and head circumference) when compared with gestational age are helpful in determining whether the child experienced intrauterine growth restriction. Severe medical complications in the neonatal period such as the presence of neonatal encephalopathy syndrome including seizures and multiorgan compromise, intraventricular hemorrhage, neonatal infections, prolonged requirement for mechanical ventilation, need for extracorporeal

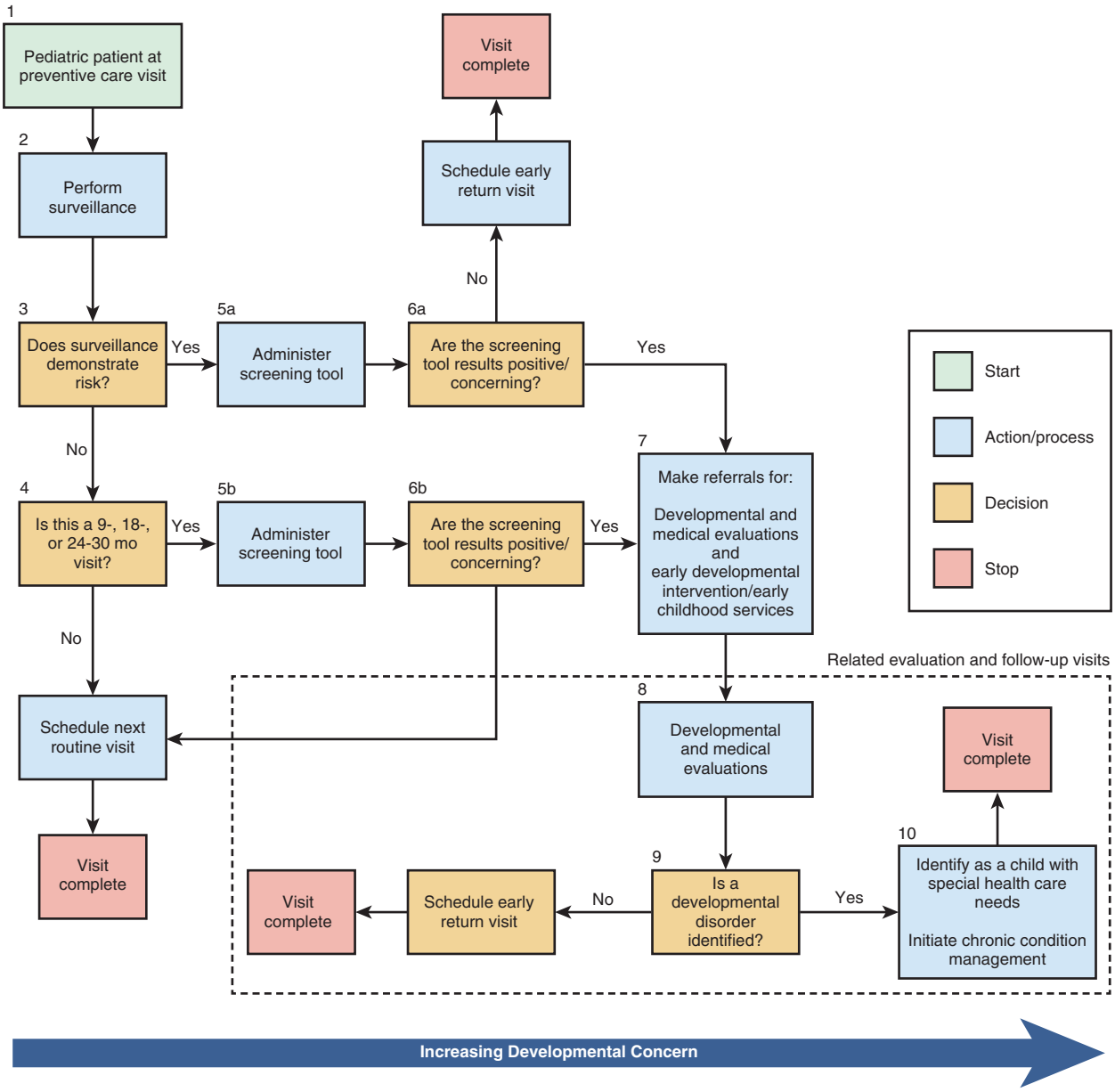


FIGURE 24.2 Developmental surveillance and screening algorithm within a pediatric preventive care visit. Numbers refer to steps in the algorithm. (From Council on Children with Disabilities, et al. Identifying infants and young children with developmental disorders in the medical home: an algorithm for developmental surveillance and screening. *Pediatrics.* 2006;118:407.)

membrane oxygenation (ECMO), the presence of complex cardiac anomalies, and necrotizing enterocolitis may be associated with increased risk of developmental disabilities (Table 24.10). Conversely, an infant who did not require care in a neonatal intensive care unit (NICU) or prolonged stay in the hospital following birth likely experienced no significant perinatal developmental risk factors. When available, reviewing medical records from the neonatal period may be helpful in clarifying what actually transpired at the time of the infant's birth.

The social and economic circumstances of the family may reveal factors that place the infant at risk for developmental disabilities. The clinician should ask about the highest educational levels achieved by both parents, marital status or stability of the parents' relationship, parental mental health concerns, history of "high-risk behaviors" (illicit drug use), housing status, and presence of a parental support system (close friends and extended family members) to help with care of the infant.

The 1st weeks and months of life are a "transition period" for both the infant and the family. Children with developmental disabilities may begin to manifest symptoms in this period with difficulties nursing, excessive colic, poor weight gain, onset of seizures, or delayed achievement of motor milestones. Review of prior growth records may help differentiate between a congenital or acquired disorder. A history of recurrent illness, family/social or environmental stress, trauma (especially to the CNS), or epilepsy may be associated with poor development. *True regression, the loss of previously acquired skills, should be distinguished from failure of development.* Newly emerging skills may fluctuate until they are firmly established. In cases of true regression, multiple areas of functioning are affected and do not reemerge over time.

TABLE 24.9 Information to Obtain About a Child with Suspected Developmental Disabilities

Item	Possible Significance
Parental Concerns	Parents are quite accurate in identifying developmental problems
Current Levels of Developmental Functioning	Used to monitor child's progress
Temperament	May interact with disability or be confused with developmental delay
Prenatal History	
Alcohol ingestion	Fetal alcohol syndrome; an index of caretaking risk
Illegal drug, toxin, medication exposure	Developmental toxin (e.g., phenytoin); may be an index of caretaking risk
Radiation exposure	Damage to the CNS
Nutrition	Inadequate fetal nutrition
Prenatal care	Index of the social situation
Injuries, hyperthermia	Damage to the CNS
Smoking	Possible CNS damage
HIV exposure	Congenital HIV infection
Maternal PKU	Maternal PKU effect
Maternal illness	Toxoplasmosis, rubella, CMV, HIV, herpesvirus infections
Perinatal History	
Gestational age, birthweight	Biologic risk from prematurity and small for gestational age
Labor and delivery	Hypoxia or index of abnormal prenatal development
Apgar scores	Hypoxia, cardiovascular impairment
Specific perinatal adverse events; see Table 24.10	Increased risk for CNS damage
Neonatal History	
Illness: seizures, respiratory distress, hyperbilirubinemia, metabolic disorder; see also Table 24.10.	Increased risk for CNS damage
Malformations	May represent syndrome associated with developmental delay
Family History	
Consanguinity	Autosomal recessive condition more likely
Mental functioning	Increased hereditary and environmental risks
Illnesses (e.g., metabolic disease)	Hereditary illness associated with developmental delay
Family member died young or unexpectedly	May suggest inborn errors of metabolism or storage disease
Family member requires special education	Hereditary causes of developmental delay
Social History	
Resources available (e.g., financial, social support)	Necessary to maximize child's potential
Educational levels of parents	Family may need help to provide stimulation
Mental health problems	May exacerbate child's conditions
High-risk behaviors (illicit drug use, sexual promiscuity)	Increased risk for congenital infection; index of caretaking risk
Other stressors (e.g., marital discord)	May exacerbate child's conditions or compromise care
Other History	
Sex of the child	Important for X-linked conditions
Developmental milestones	Index of developmental delay, regression may indicate a progressive condition
Head injury	Even moderate trauma may be associated with developmental delay or learning disabilities
Serious infections (e.g., meningitis)	May be associated with developmental delay
Toxic exposure (e.g., lead)	May be associated with developmental delay
Physical growth	May indicate malnutrition; obesity, growth failure caused by genetic disorder
Recurrent otitis media	Associated with hearing loss and abnormal speech development
Visual and auditory functioning	Sensitive index of impairments in vision and hearing
Nutrition	Malnutrition during infancy may lead to delayed development
Chronic conditions such as renal or cyanotic cardiac	May be associated with delayed development

CMV, cytomegalovirus; CNS, central nervous system; HIV, human immunodeficiency virus; PKU, phenylketonuria.

TABLE 24.10 Findings that May Be Used to Identify Neonates at Increased Risk for Developmental Delay

Item	Comment
Apgar scores	<3 at 5 min or <5 at 10 min, and HIE
Abnormal EEG	
Neonatal seizures	Hypoglycemia, hypoxia, intracranial hemorrhage, or infection confer high risk
Intracranial	Grade III or higher; PVL hemorrhage
Hydrocephalus	Especially with other anomalies, thin cortical mantle, or parenchymal lesions
Central nervous system	Seen on CT scan or ultrasonography system anomalies
Prematurity	<32 wk
Small for gestational age	<3rd percentile (intrauterine growth age retardation)
Dysmorphic	3 or more minor or 1 or more major features
Chromosomal	Trisomies, fragile X, XO anomaly
Ventilation required	Longer than 2 wk
Small head	<3rd percentile circumference
Meningitis/encephalitis	Bacterial (group B streptococci, *Escherichia coli*) Viral (herpes simplex)
Hypoglycemia	Symptomatic
Congenital infection	Cytomegalovirus, toxoplasmosis, syphilis, rubella, herpes simplex, varicella-zoster, HIV
Hyperbilirubinemia	Requiring exchange transfusions
Associated medical problems	Such as retinopathy of prematurity, heart disease, bronchopulmonary dysplasia, necrotizing enterocolitis

EEG, electroencephalography; HIE, hypoxic-ischemic encephalopathy; PVL, periventricular leukomalacia.

Ages of achievement of common milestones in motor, language, cognitive, and social development should be reviewed. Parents of infants and toddlers may have more accurate recollections of their child's milestones than parents of older children. In some cases, parents may recall comparing their child's milestones to another child's (sibling, relative, neighbor), or may only recall their child's "major" milestones, such as ages at which the child began walking independently, waving "bye-bye," using 1st words, or talking in sentences.

A 3-generation family pedigree should be reviewed to identify other individuals with conditions similar to the child's, developmental/learning disabilities, or early deaths. Consanguinity may increase the risk of a recessive disorder. A family's ethnic ancestry may suggest potential etiology, since a number of conditions occur at increased frequency among certain ethnic groups (e.g., Tay-Sachs disease among Ashkenazi Jews).

Social and environmental factors such as parental physical or mental illness (including substance abuse), death of a close family member, divorce, domestic abuse, parental incarceration, multiple changes of dwelling, placement in foster care, or having a sibling with a serious chronic illness may have significant adverse effects on a child's development.

It is important to know whether the child has received any type of educational or therapeutic interventions and the impact those programs have had on his or her behavior and development.

For young children, a description of their play interests, self-help skills, and social interactions with parents, peers, and caretakers/teachers may provide valuable information about the child's level of overall development. A review of common activities of daily living (ADL), including dressing, eating, toileting, and motor skills, often provides insight about the integrity of the child's cognitive, communication, and neuromotor development. School experiences, academic readiness skills, educational achievement, and behavior patterns at home and school often reflect the cognitive and language development of school-age children and adolescents.

Physical Examination

The physical examination should begin with observations of the general appearance of the child, including overall state of health, visual and auditory responsiveness to the surroundings, and interactions with parents. When the child is at rest, subtle abnormalities of body proportions and movement patterns may be observed. Careful attention should also be paid to physical measurements (length/height, weight, *and head circumference*) with values plotted on standard reference curves. Both poor growth and excessive growth may be associated with metabolic disorders or genetic syndromes. Head circumference measurements may be abnormal (greater or less than 2 standard deviations [SD] from the mean) or disproportionate for body size (head circumference should correlate with length/height of the child). Although large or small head size may be associated with significant pathology, a benign form of familial micro- and macrocephaly may be ruled out if 1 or both parents share the same trait. **Dysmorphic features** may suggest a recognizable pattern of deformation or malformation (Table 24.11) (see Chapter 25). If the child has an unusual appearance, biologic family members should be examined either directly or from photographs to determine any resemblance. Additionally, examining serial photographs of a child at different ages can help to identify "coarsening" of facial features due to a storage disease (mucopolysaccharidosis). Abnormalities of skin pigmentation may suggest the presence of a neurocutaneous disorder (phakomatosis) associated with developmental disability (neurofibromatosis, tuberous sclerosis, Sturge-Weber syndrome) (see Chapter 30). A Wood's lamp examination may be helpful if a depigmented lesion is identified (ash-leaf spots in tuberous sclerosis). Measurements of facial features, such as inner canthal distance, palpebral fissure length, auricular size and position, and development of the philtrum and upper lip, may be associated with structural anomalies of craniofacial development caused by genetic or teratogenic exposure (fetal alcohol syndrome). The oral structures should be examined for the presence of cleft palate (velocardiofacial syndrome, Stickler syndrome), macroglossia (Beckwith-Wiedemann syndrome), or recessed jaw (Pierre-Robin sequence). Anomalies of the neck may indicate vertebral abnormalities (Klippel-Feil syndrome) or genetic disorders (Turner syndrome, Noonan syndrome, Down syndrome). Cardiac anomalies are associated with a large number of syndromes. The abdominal exam may reveal evidence of an enlarged liver (associated with glycogen storage diseases, sphingolipidoses, or mucopolysaccharidoses). Examination of the back should include the "forward bend test" for scoliosis, and the presence of dimpling or a hirsute area in the lower spine that could represent an occult form of spinal dysraphism (tethered cord or other spinal cord anomaly). Anomalies of the extremities (limb proportions, hands, feet, and nails) are associated with a wide range of birth defects and syndromes. The presence of multiple malformations may be an important key to identifying a specific developmental disorder or syndrome. Although minor physical anomalies may be associated with developmental delay, most children with minor anomalies develop normally (Table 24.12).

TABLE 24.11 Physical Examination of a Child with Suspected Developmental Disabilities

Item	Possible Significance
General appearance	May indicate significant delay in development or obvious syndrome
Stature	
Short stature	Malnutrition, many genetic syndromes are associated with short stature (e.g., Turner and Noonan syndromes)
Obesity	Prader-Willi syndrome
Large stature	Sotos syndrome
Head	
Macrocephaly	Alexander syndrome, Canavan disease, Sotos syndrome, gangliosidosis, hydrocephalus, mucopolysaccharidosis, subdural effusion
Microcephaly	Virtually any condition that can restrict brain growth (e.g., malnutrition, Angelman syndrome, de Lange syndrome, fetal alcohol effects)
Face	
Coarse, triangular, round, or flat face; hypotelorism or hypertelorism, slanted or short palpebral fissure; unusual nose, maxilla, and mandible	Specific measurements may provide clues to inherited, metabolic, or other diseases such as fetal alcohol syndrome, cri du chat (5p–) syndrome, or Williams syndrome
Eyes	
Prominent	Crouzon syndrome, Seckel syndrome, fragile X syndrome
Cataract	Galactosemia, Lowe syndrome, prenatal rubella, hypothyroidism
Cherry-red spot in macula	Gangliosidosis (GM_1), metachromatic leukodystrophy, mucolipidosis, Tay-Sachs disease, Niemann-Pick disease, Farber lipogranulomatosis, sialidosis type III
Chorioretinitis	Congenital infection with cytomegalovirus, toxoplasmosis, or rubella
Corneal cloudiness	Mucopolysaccharidosis types I and II, Lowe syndrome, congenital syphilis
Ears	
Low-set or malformed pinnae	Trisomies such as Down syndrome, Rubinstein-Taybi syndrome, CHARGE syndrome, cerebrooculofacioskeletal syndrome, fetal phenytoin effects
Hearing	Loss of acuity in mucopolysaccharidosis; hyperacusis in many encephalopathies
Heart	
Structural anomaly or hypertrophy	CHARGE syndrome, velocardiofacial syndrome, glycogenosis type II, fetal alcohol effects, mucopolysaccharidosis type I; chromosomal anomalies such as Down syndrome; maternal PKU; chronic cyanosis may impair cognitive development
Liver	
Hepatomegaly	Fructose intolerance, galactosemia, glycogenosis types I-IV, mucopolysaccharidosis types I and II, Niemann-Pick disease, Tay-Sachs disease, Zellweger syndrome, Gaucher disease, ceroid lipofuscinosis, gangliosidosis
Genitalia	
Macro-orchidism	Fragile X syndrome
Hypogenitalism	Prader-Willi syndrome, Klinefelter syndrome, CHARGE syndrome
Extremities	
Hands, feet, dermatoglyphics, and creases	May indicate a specific entity such as Rubinstein-Taybi syndrome or be associated with chromosomal anomaly
Joint contractures	Signs of muscle imbalance around the joints; e.g., with meningomyelocele, cerebral palsy, arthrogryposis, muscular dystrophy; also occurs with cartilaginous problems such as mucopolysaccharidosis
Skin	
Café-au-lait spots	Neurofibromatosis Tuberous sclerosis Chromosomal aneuploidy McCune-Albright syndrome Fanconi anemia Silver-Russell syndrome Ataxia telangiectasia Bloom syndrome Basal cell nevus syndrome Gaucher disease Chediak-Higashi syndrome Hunter syndrome Multiple endocrine neoplasia type 2b Bannayan-Riley-Ruvalcaba syndrome Maffucci syndrome
Seborrheic or eczematoid rash	Phenylketonuria, histiocytosis
Hemangiomas and telangiectasia	Sturge-Weber syndrome, Bloom syndrome, ataxia-telangiectasia
Hypopigmented macules, streaks, adenoma sebaceum	Tuberous sclerosis, hypomelanosis of Ito
Hair	
Hirsutism	de Lange syndrome, mucopolysaccharidosis, fetal phenytoin effects, cerebrooculofacioskeletal syndrome, trisomy 18
Neurologic	
Asymmetry of strength and tone	Focal lesion, hemiplegic cerebral palsy
Hypotonia	Prader-Willi syndrome, Down syndrome, Angelman syndrome, gangliosidosis, early cerebral palsy, muscle disorders (dystrophy or myopathy)
Hypertonia	Neurodegenerative conditions involving white matter, cerebral palsy, trisomy 18
Ataxia	Ataxia-telangiectasia, metachromatic leukodystrophy, Angelman syndrome

CHARGE, **c**oloboma, **h**eart defects, **a**tresia choanae, **r**etarded growth, **g**enital anomalies, **e**ar anomalies (deafness); CATCH-22, **c**ardiac defects, **a**bnormal face, **t**hymic hypoplasia, **c**left palate, **h**ypocalcemia—defects on chromosome 22; PKU, phenylketonuria.

TABLE 24.12 Examples of Minor Anomalies and Associated Syndromes*†

Head	Flat occiput: Down syndrome, Zellweger syndrome; prominent occiput: trisomy 18 Delayed closure of sutures: hypothyroidism, hydrocephalus Craniosynostosis: Crouzon syndrome, Pfeiffer syndrome Delayed fontanel closure: hypothyroidism, Down syndrome, hydrocephalus, skeletal dysplasias
Face	Midface hypoplasia: fetal alcohol syndrome, Down syndrome Triangular facies: Russell-Silver syndrome, Turner syndrome Coarse facies: mucopolysaccharidoses, Sotos syndrome Prominent nose and chin: fragile X syndrome Flat facies: Apert syndrome, Stickler syndrome Round facies: Prader-Willi syndrome
Eyes	Hypertelorism: fetal hydantoin syndrome, Waardenburg syndrome Hypotelorism: holoprosencephaly sequence, maternal phenylketonuria effect Inner canthal folds/Brushfield spots: Down syndrome; slanted palpebral fissures: trisomies Prominent eyes: Apert syndrome, Beckwith-Wiedemann syndrome Lisch nodules: neurofibromatosis Blue sclera: osteogenesis imperfecta, Turner syndrome, hereditary connective tissue disorders
Ears	Large pinnae/simple helices: fragile X syndrome Malformed pinnae/atretic canal: Treacher Collins syndrome, CHARGE syndrome Low-set ears: Treacher Collins syndrome, trisomies, multiple disorders
Nose	Anteverted nares/synophrys: de Lange syndrome; broad nasal bridge: fetal drug effects, fragile X syndrome Low nasal bridge: achondroplasia, Down syndrome Prominent nose: Coffin-Lowry syndrome, Smith-Lemli-Opitz syndrome
Mouth	Long philtrum/thin vermilion border: fetal alcohol effects Cleft lip and palate: isolated or part of a syndrome Micrognathia: Pierre-Robin sequence, trisomies, Stickler syndrome Macroglossia: hypothyroidism, Beckwith-Wiedemann syndrome
Teeth	Anodontia: ectodermal dysplasia Notched incisors: congenital syphilis Late dental eruption: Hunter syndrome, hypothyroidism Talon cusps: Rubinstein-Taybi syndrome Wide-spaced teeth: de Lange syndrome, Angelman syndrome
Hair	Hirsutism: Hurler syndrome Low hairline: Klippel-Feil sequence, Turner syndrome Sparse hair: Menkes disease, argininosuccinic acidemia Abnormal hair whorls/posterior whorl: chromosomal aneuploidy (e.g., Down syndrome) Abnormal eyebrow patterning: Cornelia de Lange syndrome
Neck	Webbed neck/low posterior hairline: Turner syndrome, Noonan syndrome
Chest	Shield-shaped chest: Turner syndrome
Genitalia	Macro-orchidism: fragile X syndrome Hypogonadism: Prader-Willi syndrome
Extremities	Short limbs: achondroplasia, rhizomelic chondrodysplasia Small hands: Prader-Willi syndrome Clinodactyly: trisomies, including Down syndrome Polydactyly: trisomy 13, ciliopathies Broad thumb: Rubinstein-Taybi syndrome Syndactyly: de Lange syndrome Transverse palmar crease: Down syndrome Joint laxity: Down syndrome, fragile X syndrome, Ehlers-Danlos syndrome Phocomelia: de Lange syndrome
Spine	Sacral dimple/hairy patch: spina bifida
Skin	Hypopigmented macules/adenoma sebaceum: tuberous sclerosis Café-au-lait spots and neurofibromas: neurofibromatosis Linear depigmented nevi: hypomelanosis of Ito Facial port-wine hemangioma: Sturge-Weber syndrome Nail hypoplasia or dysplasia: fetal alcohol syndrome, trisomies

*Increased incidence of minor anomalies have been reported in cerebral palsy, intellectual disability, learning disabilities, and autism.
†The presence of 3 or more minor anomalies implies a greater chance that the child has a major anomaly and a diagnosis of a specific syndrome. CHARGE, **c**oloboma, **h**eart defects, **a**tresia choanae, **r**etarded growth, **g**enital anomalies, **e**ar anomalies (deafness).
Modified from Levy SE, Hyman SL. Pediatric assessment of the child with developmental delay. *Pediatr Clin North Am.* 1993;40:465-477.

The neuromotor examination should include observation of muscle bulk and presence or absence of muscle atrophy associated with myopathy. The assessment of cranial nerves includes evaluation for visual responsiveness, pupillary reactivity, presence of red reflexes, fullness of eye movements, and evidence of strabismus. Ptosis, asymmetry of facial expression, or abnormal tongue movement (deviation or fasciculation) suggests muscle weakness or partial paralysis. Muscle strength may be assessed by observing the child move about and manipulate objects. In the 1st year of life, motor milestones include the ability to sit independently, crawl, cruise, and walk. By 18 months, children should be able to squat and recover. The Gowers maneuver is helpful in assessing strength of the quadriceps muscles. Decreased muscle tone may be reflected in poor posture or hypermobile joints. Decreased stretch reflex responsiveness may be due to lower motor neuron disease or myopathy. In infants, the persistence of primitive reflexes or the absence of protective postural reflexes is suggestive of neuromotor dysfunction. In older children, the presence of increased stretch reflexes, clonus, and positive Babinski reflexes are signs of upper motor neuron dysfunction associated with spasticity. Normal gait requires intact and coordinated motor and sensory ability. Unsteady gait or tremor may be a sign of muscle weakness or abnormal cerebellar function or basal ganglia disease. Asymmetry of gait may reflect hemiplegia. Observing the child reaching for objects, extending the arms outstretched, or performing the finger-to-nose test may reveal tremors or difficulty with eye-hand coordination.

Neurodevelopmental Examination

Many pediatricians and developmental specialists incorporate a number of "informal" age-appropriate tasks into their evaluation that provide an opportunity to examine the child's development and behavior. This part of the examination may take 10-15 minutes. Parents should always be present while examining preschool children to provide comfort and reassurance. Older children (6 years and above) may respond better without their parents present for this part of the examination. It is important to recognize that a child's responses on "informal measures" in the context of a pediatric developmental assessment are not an adequate substitute for formal psychologic and communication evaluations. However, the clinician may observe how the child interacts with the examiner and parents, the child's ability to understand and communicate with the examiner and with the parents, and make some observations of the child's attention span, persistence with tasks, and frustration tolerance.

FORMAL NEURODEVELOPMENTAL ASSESSMENTS

Psychologic Evaluation

Evaluation by a child psychologist can provide an assessment of a child's strengths and weaknesses across a broad range of cognitive areas. For infants and young children, global measures of development are the most valuable, since the structure of intelligence develops from relatively "general" and homogeneous ability to more complex and differentiated functions over time. Few tasks on measures used for preschool children reflect "pure" abilities in any particular skill. Rather, tasks for infants reflect the child's ability to utilize a combination of cognitive, language, and motor skills to respond. However, tests vary in their ability to separate these component functions. The Bayley Scales of Infant and Toddler Development-3rd Edition (Bayley III) is a widely used tool for assessing children 0-42 months of age. There are several normed measures of verbal and nonverbal abilities that can be used with children older than 2 years of age. Many factors can contribute to the child's performance. Observing how the child responds to a task can be as informative as the accuracy of the response. It is generally recognized that intelligence testing prior to age 6 years is not highly predictive of test results at older ages, but the evaluation provides a measure of the child's abilities at that point in time. In addition, a psychologist is able to observe the child's behavior, attention span, organizational skills, persistence, and frustration tolerance during the evaluation. These informal observations may help to determine the presence or absence of emotional or behavioral problems that stem from, or coexist with, the child's developmental disabilities.

Results of psychologic tests are not indicative of specific etiologies (genetic or acquired biologic conditions) and cannot determine whether a child has suffered a "brain injury," even in the context of a potentially traumatic event. Serial cognitive measures, particularly when there is premorbid information that has changed over time, may suggest the effects of trauma or a progressive disease process.

Speech-Language and Oral Motor Evaluation

The ability to understand and communicate with others has a very strong influence on a child's emotional, behavioral, and social functioning. Communication abilities may or may not reflect the child's intellectual ability. A speech-language pathologist can evaluate a wide range of communication and oral motor skills in children. For example, even prior to the use of words, infants display "preverbal" communication abilities (gestures), and may recognize a number of spoken words. Older children may suffer from delays in understanding of language (language disorders) or from disorders of speech sound production (apraxia, dysarthria). Many children with neurologic disabilities have oral motor coordination disorders (dysphagia) that interfere with chewing and swallowing and place them at risk for poor weight gain and/or pulmonary aspiration. Drooling management is also a problem for many children with oral motor coordination delays. While it is more common for receptive language ability to exceed expressive language ability, children with Williams syndrome and with spina bifida/hydrocephalus may display conversational skills that exceed their cognitive deficits ("cocktail conversation"). In both conditions, "basic" language abilities (vocabulary and grammar) are relatively well developed, while "higher-level" language functions (semantic knowledge and pragmatic aspects of communication) are deficient.

DIAGNOSTIC STRATEGY

Once a comprehensive profile of the child's strengths and weaknesses has been identified through neurodevelopmental, psychologic, and speech-language evaluations, the next step is to establish a developmental diagnosis.

Cognitive, language, and motor abilities typically develop in a coordinated fashion. Discrepancies in development between different areas of function may point to a specific area of concern or suggest possible clinical diagnoses (Table 24.13). Many disabilities can be identified by their characteristic pattern of development over time (e.g., hypotonia/hyperphagia in Prader-Willi syndrome, regression/microcephaly/hand-wringing behavior in Rett syndrome). In general, motor milestones do not correlate well with intellectual ability, since most children with ID walk at a normal age. Language abilities, when well developed, are usually an excellent indicator of intellectual function. Problem-solving skills (referred to as "adaptive" or "visual-motor" skills) often correlate with nonverbal cognitive abilities. Finally, psychosocial milestones often reflect language ability. A child with delays in all areas likely has a cognitive deficit, while a child whose communication skills are at variance with nonverbal cognitive abilities likely has a language disorder.

TABLE 24.13 Differential Diagnosis of Atypical Patterns of Development

	Intellectual Disability	Developmental Language Disorder	Specific Language Impairment	Autism Spectrum Disorder	Social Pragmatic Communication Disorder
Cognitive ability	Delayed	Normal/delayed	Normal	Normal/delayed	Normal
Language ability	Delayed	Disordered	Disordered	Disordered	Normal
Social ability	Normal	Normal	Normal	Abnormal	Abnormal
Family history	Negative	Speech/language	Speech/language	Affective disorder	Social deficits

Modified from Simms MD, Schum RL. Preschool children who have atypical patterns of development. *Pediatr Rev.* 2000;21:147-158.

TABLE 24.14 Select "Extrinsic" Conditions Associated with Developmental Regression

Neoplasms and their therapy
Leukemia
Tumors
Histiocytosis
Increased intracranial pressure
Hydrocephalus, including ventricular shunt malfunctions
Subdural hematoma or effusion
Infections
Encephalitis, including HIV infection
Meningitis
Endocrine disorders
Hypothyroidism
Adrenocortical insufficiency
Collagen vascular disease (e.g., systemic lupus erythematosus)

Delays isolated to a single, specific area such as expressive language are more likely to be transient than are generalized delays. If the child's development has deteriorated (regressed), a progressive encephalopathy may be present. Progressive disorders may be the result of metabolic or storage diseases, or due to a genetic syndrome (Rett syndrome). In contrast, static encephalopathies are usually the result of structural abnormalities due to abnormal development or trauma (Tables 24.14 and 24.15).

More than 300 neurodegenerative disorders have been described; additional classification based on progression and age is noted in Table 24.16 and in Figs. 24.3 and 24.4. Neurodegenerative disorders are often categorized as involving white matter, gray matter, basal ganglia, or the entire CNS. White matter diseases (e.g., adrenoleukodystrophy) affect long tracts and manifest with loss of motor skills, spasticity, disturbed gait, areflexia (if peripheral nerve also involved), or ataxia, whereas gray matter diseases (e.g., ceroid lipofuscinoses) manifest with seizures and abnormalities of cognition, vision, and hearing. Many disorders classified as "white matter" or "gray matter" manifest with a mixed picture of signs and symptoms. Diseases that involve primarily the basal ganglia, such as Huntington disease, manifest with mental deterioration, behavioral changes, rigidity, ataxia, dysarthria, seizures, and incoordination. As these diseases progress, neurologic signs and symptoms become more widespread and less specific.

To date, approximately 450 genes have been implicated in GDD/ID. Of these, 400 are associated with "syndromic" GDD/ID (i.e., cases in which abnormalities are identified on examination such as micro- or macrocephaly, dysmorphic features, congenital anomalies, abnormal neurologic examination, seizures, structural brain abnormalities, sensory deficits [vision or hearing], or autism). Approximately 50 genes have been associated with "nonsyndromic" GDD/ID.

A distinction should be made between a clinical diagnosis that is based on descriptions and measurements of various functional abilities and an etiologic diagnosis that attributes the problem(s) to a specific cause. For most developmental disabilities, a specific etiology cannot be established with absolute certainty. For example, clinical diagnoses such as cerebral palsy or ID can result from multiple etiologies, and conversely, the same etiology can manifest in a variety of ways. As medical diagnostic technologies have improved, the number of individuals for whom an etiologic diagnosis can be established has increased. Even when a specific etiologic diagnosis cannot be determined, an accurate clinical diagnosis is often helpful in designing treatment recommendations, since most treatments are based on an educational-developmental model and are successful for a range of underlying biomedical causes.

Although most parents will pursue further evaluations when they are concerned about their child's development, not all are willing or able to have their child undergo medical diagnostic testing procedures when he or she is very young. Instead, parents typically want to know what they can do to help their child "catch up" with his or her peers. This concept is often reinforced by referring to the problem as a developmental "delay." Unless there are signs of regression or failure to thrive that would make diagnostic testing urgent, "watchful waiting" while the child enters a program of interventions is a very reasonable strategy. If, despite these measures, the developmental concerns persist, families may be more willing to obtain further diagnostic testing. It is often helpful to share with parents that the probability of establishing a medical diagnosis with current technology is only 20-25%, unless specific syndromes or disorders are suspected from the history and physical examination. Further, in most situations, a specific diagnosis may not result in a cure for the basic disorder. However, if a specific etiology can be established, it may result in effective treatments and preventive measures, even when a cure for the underlying condition is not possible. For example, medical treatment for the circadian rhythm dysfunction associated with Smith-Magenis syndrome can be very successful in improving sleep patterns and daytime behaviors. In addition, children can be monitored on an expectant basis for complications that occur frequently with specific disorders (Wilms tumor in Beckwith-Wiedemann syndrome).

LABORATORY TESTING

With the rapid advances in diagnostic testing technologies over the past decade, evaluation strategies have undergone considerable scrutiny to determine the most effective approach to determining an etiologic diagnosis for individuals with GDD/ID. In general, when a specific diagnosis is suspected based on the history and physical

TABLE 24.15 Select "Intrinsic" Conditions Associated with Developmental Regression

Age at Onset (yr)	Conditions	Comments
<2, with hepatomegaly (see Chapter 14)	Fructose intolerance	Vomiting, hypoglycemia, poor feeding, failure to thrive (when given fructose)
	Galactosemia	Lethargy, hypotonia, icterus, cataract, hypoglycemia (when given lactose)
	Glycogenosis (glycogen storage disease) types I-IV	Hypoglycemia, cardiomegaly (type II)
	Mucopolysaccharidosis types I and II	Coarse facies, stiff joints
	Niemann-Pick disease, infantile type	Gray matter disease, failure to thrive
	Tay-Sachs disease	Seizures, cherry-red macula, edema, coarse facies
	Zellweger (cerebrohepatorenal) syndrome	Hypotonia, high forehead, flat facies
	Gaucher disease type II	Extensor posturing, irritability
	Carbohydrate-deficient glycoprotein syndromes	Dysmyelination, cerebellar hypoplasia
<2, without hepatomegaly	Krabbe disease	Irritability, extensor posturing, optic atrophy, and blindness
	Rett syndrome	Girls with deceleration of head growth, loss of hand skills, hand wringing, impaired language skills, gait apraxia
	Maple syrup urine disease	Poor feeding, tremors, myoclonus, opisthotonos
	Phenylketonuria	Light pigmentation, eczema, seizures
	Menkes kinky hair disease	Hypertonia, irritability, seizures, abnormal hair
	Subacute necrotizing encephalopathy of Leigh	White matter disease
	Cerebrooculofacioskeletal syndrome (of Pena and Shokeir)	Reduced white matter, failure to thrive
	Canavan disease	White matter disease
	Pelizaeus-Merzbacher disease	White matter disease
2-5	Niemann-Pick disease types III and IV	Hepatosplenomegaly. gait difficulty
	Wilson disease	Liver disease, Kayser-Fleischer ring; deterioration of cognition is late
	Gangliosidosis type II	Gray matter disease
	Ceroid lipofuscinosis	Gray matter disease
	Mitochondrial encephalopathies (e.g., myoclonic epilepsy with ragged red fibers [MERRF])	Gray matter disease
	Ataxia-telangiectasia	Basal ganglia disease
	Huntington disease (chorea)	Basal ganglia disease
	Hallervorden-Spatz syndrome	Basal ganglia disease
	Metachromatic leukodystrophy	White matter disease
	Adrenoleukodystrophy	White matter disease, behavior problems, deteriorating school performance, quadriparesis
5-15	Adrenoleukodystrophy	Same as for adrenoleukodystrophy in 2-5-yr-olds
	Multiple sclerosis	White matter disease
	Neuronal ceroid lipofuscinosis, juvenile and adult (Spielmeyer-Vogt and Kufs disease)	Gray matter disease
	Schilder disease	White matter disease, focal neurologic symptoms
	Refsum disease	Peripheral neuropathy, ataxia, retinitis pigmentosa
	Sialidosis type II, juvenile form	Cherry-red macula, myoclonus, ataxia, coarse facies
	Subacute sclerosing panencephalitis	Diffuse encephalopathy, myoclonus; may occur years after measles

TABLE 24.16 Causes of Developmental Regression

Onset Before Age 2 Years

Acquired Immune Deficiency Syndrome Encephalopathy*

Autism Spectrum Disorder

Disorders of Amino Acid Metabolism
- Guanidinoacetate methyltransferase deficiency*
- Homocystinuria (21q22)*
- Maple syrup urine disease (Intermediate and thiamine response forms)*
- Phenylketonuria
- Guanidinoacetate methyltransferase deficiency*

Disorders of Lysosomal Enzymes
- Ganglioside storage disorders
  - GM_1 gangliosidosis
  - GM_2 gangliosidosis (Tay-Sachs disease, Sandhoff disease)
- Gaucher disease type II (glucosylceramide lipidosis)*
- Globoid cell leukodystrophy (Krabbe disease)
- Glycoprotein degradation disorders
- I-cell disease
  - Mucopolysaccharidoses*
  - Type I (Hurler syndrome)*
  - Type III (Sanfilippo disease)
- Niemann-Pick disease type A (sphingomyelin lipidosis)
- Sulfatase deficiency disorders
  - Metachromatic leukodystrophy (sulfatide lipidoses)
  - Multiple sulfatase deficiency

Carbohydrate-Deficient Glycoprotein Syndromes

Hypothyroidism*

Mitochondrial Disorders
- Alexander disease
- Mitochondrial myopathy, encephalopathy, lactic acidosis, stroke
- Progressive infantile poliodystrophy (Alpers disease)
- Subacute necrotizing encephalomyelopathy (Leigh disease)
- Trichopoliodystrophy (Menkes disease)

Neurocutaneous Syndromes
- Chediak-Higashi syndrome
- Neurofibromatosis*
- Tuberous sclerosis*

Other Disorders of Gray Matter
- Infantile ceroid lipofuscinosis (Santavuori-Haltia disease)
- Infantile neuroaxonal dystrophy
- Lesch-Nyhan disease*
- Progressive neuronal degeneration with liver disease
- Rett syndrome

Other Disorders of White Matter
- Aspartoacylase deficiency (Canavan disease)
- Galactosemia: transferase deficiency*
- Neonatal adrenoleukodystrophy
- Pelizaeus-Merzbacher disease
- Progressive cavitating leukoencephalopathy

Progressive Hydrocephalus*

Onset After Age 2 Years

Disorders of Lysosomal Enzymes
- Gaucher disease type III (glucosylceramide lipidosis)
- Globoid cell leukodystrophy (late-onset Krabbe disease)
- Glycoprotein degradation disorders
- Aspartylglycosaminuria
- Mannosidosis type II
- GM_2 gangliosidosis (juvenile Tay-Sachs disease)
- Metachromatic leukodystrophy (late-onset sulfatide lipidoses)
- Mucopolysaccharidoses types II and VII
- Niemann-Pick type C (sphingomyelin lipidosis)

Infectious Disease
- AIDS encephalopathy*
- Congenital syphilis*
- Subacute sclerosing panencephalitis

Other Disorders of Gray Matter
- Ceroid lipofuscinosis
  - Juvenile
  - Late infantile (Bielschowsky-Jansky disease)
- Huntington disease
- Mitochondrial disorders
  - Late-onset poliodystrophy
  - Myoclonic epilepsy and ragged-red fibers
- Progressive neuronal degeneration with liver disease
- Xeroderma pigmentosum

Other Disorders of White Matter
- Adrenoleukodystrophy
- Alexander disease
- Cerebrotendinous xanthomatosis
- Progressive cavitating leukoencephalopathy
- Epileptic aphasia
  - Landau-Kleffner syndrome

*The most common conditions and the ones with disease modifying treatments.

Modified from Pina-Garza JE. *Fenichel's Clinical Pediatric Neurology: A Signs and Symptoms Approach*. 7th ed. Philadelphia: Saunders; 2013.

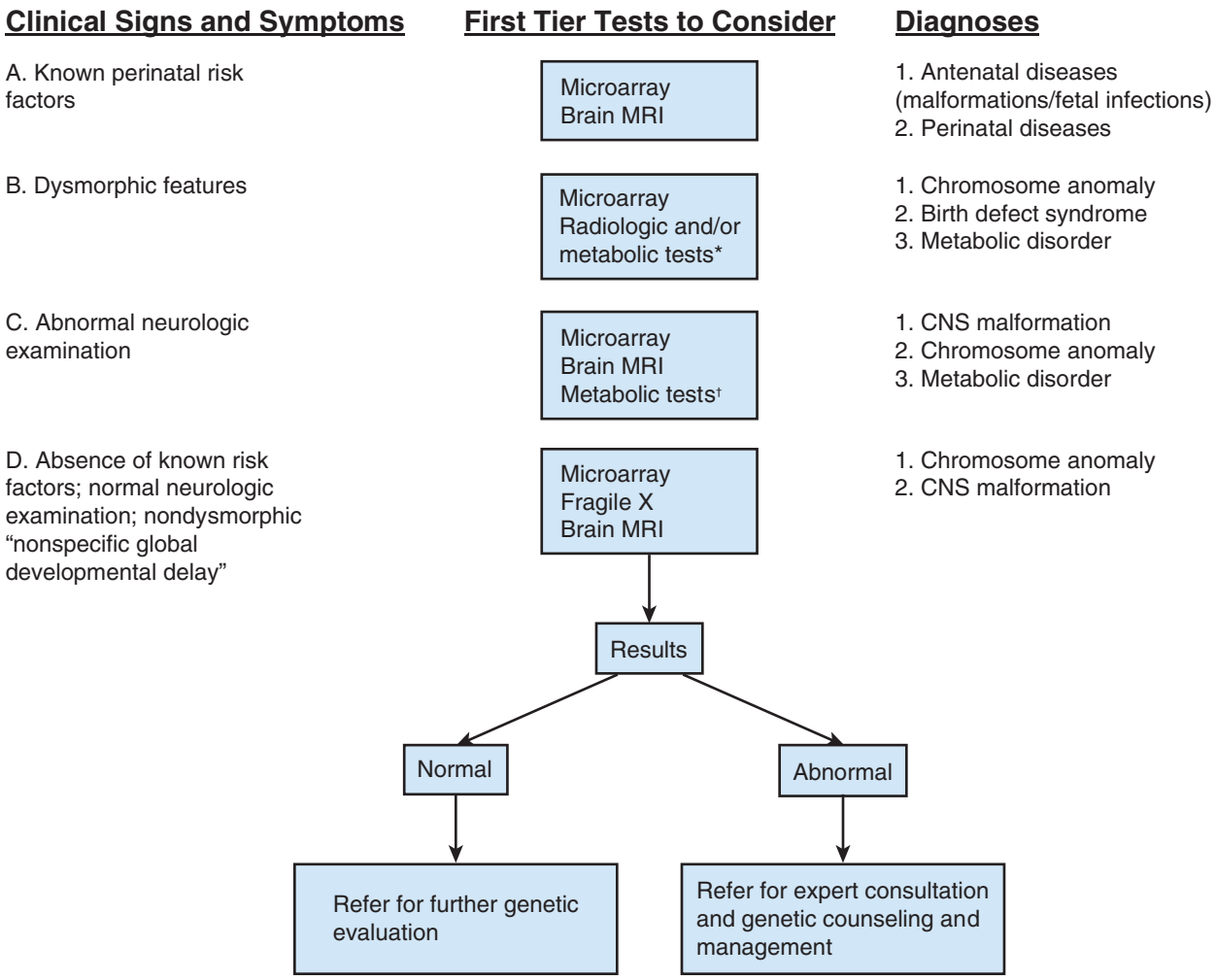


FIGURE 24.3 Evaluation of infants with developmental delay without regression. *Mucopolysaccharide screening. †Urine organic acids; plasma amino acids; acylcarnitine profile. CNS, central nervous system; MRI, magnetic resonance imaging.

examination, a "targeted" approach to confirm that condition (single-gene tests, specific metabolic studies, neuroimaging, etc.) is warranted (Tables 24.17 and 24.18). If no clinical diagnosis is suspected, current guidelines for comprehensive evaluation recommend a "tiered approach."

Genetic Tests

The 1st tier for all children with "nonspecific" GDD/ID should consist of genetic testing with chromosomal microarray (CMA) and Fragile X (Fra X) tests. If a specific diagnosis is not established from CMA/Fra X testing, referral for consultation with a geneticist should also be arranged. Next genome sequencing (NGS) technology has made available broad screening panels within a group of phenotypes (e.g., X-Linked Intellectual Disability [XLID] panel), but improved bioinformatics and accessibility to whole-exome sequencing (WES) are evolving into a new diagnostic era for children with disabilities. Diagnosis in up to 30% of affected children with syndromic GDD/ID can be achieved with WES; a clear causative etiology in autism or isolated GDD/ID is most often not found (see Fig. 24.3). The diagnostic yield of CMA in unexplained ID is 15-20%. The technology will not detect balanced translocations if there is no loss or gain of chromosomal material. Copy number variations (CNV) may identify known genetic disorders, but also patterns that have not yet been associated with GDD/ID. In this case, it may be necessary to test both parents to determine if the CNV was inherited or de novo. If the same CNV is found in an unaffected parent, it is more challenging to interpret the significance of the variant. There are numerous case reports of unaffected parent carriers and wide variability in phenotypic expression. If the variant is de novo in the child, it is more likely to be significant.

Metabolic Tests

Routine neonatal screening for metabolic disorders may identify infants with inborn errors of metabolism (IEM) that are associated with GDD. However, not all children with IEM are found shortly after birth, and normal results do not eliminate the possibility that one of the screened for IEM is present. As with genetic testing, "targeted" biochemical lab testing can be performed when a specific disease is considered (7-dehydrocholesterol for Smith-Lemli-Opitz syndrome, very-long-chain fatty acids for peroxisomal disorders, T_4/TSH for hypothyroidism, creatinine kinase for Duchenne muscular dystrophy, mucopolysaccharides for lysosomal storage disorders such as Hunter or Hurler disease). In general, few metabolic conditions result in GDD/ID in the absence of other neurologic symptoms (Table 24.19). To date, 89 IEM have been identified that are amenable to treatment of the underlying defect and/or pathogenetic mechanism (Table 24.20). Of these, 54 (60%) can be identified by blood tests (plasma amino acids,

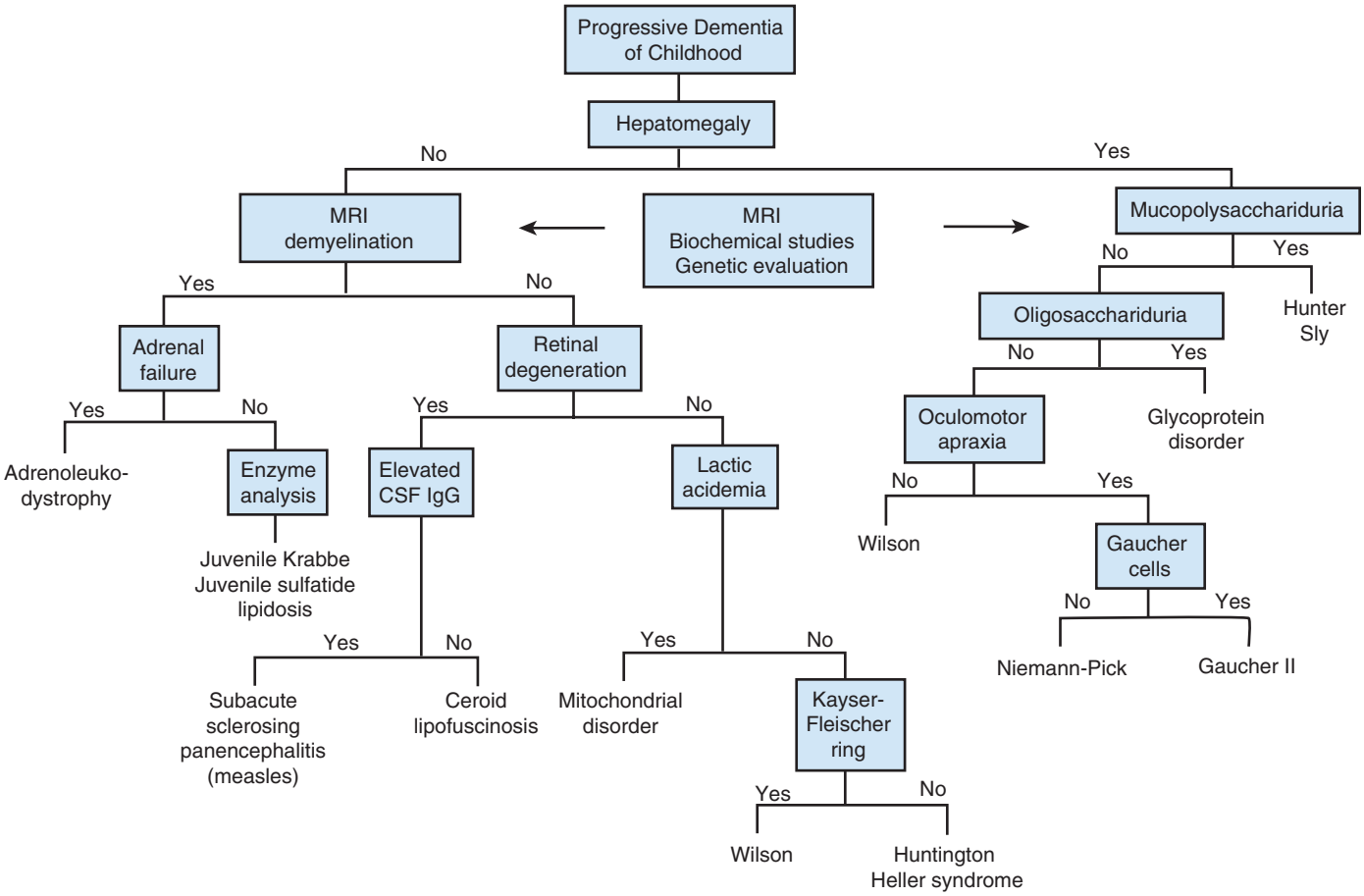


FIGURE 24.4 Evaluation of children with progressive dementia. CSF, cerebrospinal fluid; IgG, immunoglobulin G; MRI, magnetic resonance imaging. (Modified from Fenichel GM. *Clinical Pediatric Neurology: A Signs and Symptoms Approach*. 2nd ed. Philadelphia: WB Saunders; 1993:138.)

TABLE 24.17 Chromosomal Abnormalities in Which Developmental Delay Is a Major Feature

Condition	Incidence	Comments
Trisomy 21	1/700	Down syndrome
Fragile X syndrome	1/800	Macro-orchidism, hyperactivity, autistic-like behavior
47,XXY (Klinefelter syndrome)	1/1000	Small testes, problems in language skills
47,XXX	1/1000	Girls with learning and language problems may have 48,XXXX
45,X (Turner syndrome)	1/2000	Girls with short stature, broad neck, gonadal dysgenesis; visuospatial deficits common
Prader-Willi syndrome (abnormality of contiguous genes on chromosome 15; inherited from deletions of paternal chromosomes—monoparental disomy)	1/5000	Hypotonia in infancy, obesity, short stature, mild intellectual disability
Angelman syndrome (chromosome anomaly similar to that in Prader-Willi syndrome; inherited from maternal deletion in chromosome 15—monoparental disomy)	Unknown	Ataxia, prognathism, absence of speech, severe intellectual disability, inappropriate laughter
Trisomy 18	1/8000	Multiple congenital anomalies, severe developmental delay
Trisomy 13	1/20,000	Multiple congenital anomalies, severe developmental delay
5p– (cri du chat syndrome)	1/100,000	High-pitched cry, small stature, speech and language delays
4p– (Wolf-Hirschhorn syndrome)	1/100,000	Midline deficiencies, profound intellectual disability, seizures
11p– (Wilms tumor, aniridia)	1/100,000	Ambiguous genitalia, aniridia, cataracts
17p– (Miller-Dieker syndrome)	1/100,000	Lissencephaly, microcephaly, seizures, cryptorchidism

TABLE 24.18 Suggested Evaluation of the Child with Intellectual Disability/Global Developmental Delay

Test	Comments
In-depth history	Includes pre-, peri-, and postnatal events (including seizures); developmental attainments; and 3-generation pedigree in family history
Physical examination	Particular attention to minor or subtle abnormalities; neurologic examination for focality and skull abnormalities Behavioral phenotype
Vision and hearing evaluation	Essential to detect and treat; can mask as developmental delay
Gene microarray analysis	A 7.8% yield overall (10% in syndromic and 6.5% in nonsyndromic intellectual disability) Better resolution than karyotype. May identify up to twice as many abnormalities as karyotyping. Excellent in detecting de novo microdeletions or microduplications
Karyotype	Yield: 4% in global developmental delay/intellectual disability Best for inversions and balanced insertions, reciprocal translocations, and polyploidy
Fragile X screen	Combined yield, 2% Preselection on clinical grounds can increase yield to 7.6%
X-linked candidate intellectual disability genes	May explain up to 10% of intellectual disability Yield may be as high as 42% if there is a definite family history and as high as 17% from a possibly linked kindred
Exomic gene sequencing	Detects inherited and de novo point mutations, especially in nonsyndromic severe intellectual disability
Neuroimaging	MRI preferred. Positives increased by abnormalities of skull contour or microcephaly and macrocephaly, or focal neurologic examination. Overall, has a higher yield Identification of specific etiologies is rare. Most conditions that are found do not alter the treatment plan. Need to weigh risk of sedation against possible yield
Thyroid (T_4, TSH)	Near 0% in settings with a universal newborn screening program
Serum lead	If there are identifiable risk factors for excessive environmental lead exposure
Metabolic testing	Yield: 0.2-4.6% based on clinical indicators and tests performed Urine organic acids, plasma amino acids, ammonia, lactate, and a capillary blood gas. Focused testing based on clinical findings is warranted Tandem mass spectrometry newborn screening has allowed for identification of many disorders in the perinatal period and has decreased yield in older children. Other disorders have emerged; e.g., congenital disorders of glycosylation and disorders of creatine synthesis and transport
MECP2 for Rett syndrome	1.5% of females with severe intellectual disability 0.5% of males
EEG	May be deferred in absence of history of seizures
Repeated history and physical examination	Can give time for maturation of physical and behavioral phenotype. New technology may be available for evaluation

EEG, electroencephalogram; CGH, comparative genomic hybridization; MECP2, methyl CpG binding protein 2; T_4, thyroxine; TSH, thyroid-stimulating hormone.

Modified from Michelson DJ, Shevell MI, Sherr EH, et al. Evidence report: Genetic and metabolic testing on children with global developmental delay: Report of the Quality Standards Subcommittee of The American Academy of Neurology and The Practice Committee of Child Neurology. *Neurology*. 2011;77:1629-1635; Curry CJ, Stevenson RE, Aughton D, et al. Evaluation of mental retardation: recommendations of a consensus conference: American College of Medical Genetics. *Am J Med Genet*. 1997;12:72:468-477; Shapiro BK, Batshaw ML. Mental retardation. In: Burg FD, Ingelfinger JR, Polin RA, et al, eds. *Gellis and Kagan's Current Pediatric Therapy*. 18th ed. Philadelphia: Saunders; 2005, used with permission; and Shevell M, Ashwal S, Donley D, et al. Practice parameter: evaluation of the child with global developmental delay. *Neurology*. 2003;60:367-380.

homocysteine, copper, ceruloplasmin) and urine (creatine metabolites, glycosaminoglycans, oligosaccharides, organic acids, and pyrimidines). The remaining 35 (40%) are identified by specific tests and molecular analysis. A digital app (TIDE BC) is available free (http://www.treatable-id.org) from the App Store, and provides an information portal about these diseases and their treatments. Although the yield from metabolic studies in "nonsyndromic" GDD/ID is relatively low (0.2-5%), IEM are amenable to treatment, so metabolic testing should be considered in all cases of unexplained GDD/ID.

Neuroimaging

Ultrasonography

An ultrasound study of the head performed before the anterior fontanel closes can provide a general anatomic picture of the brain, including a view of the posterior fossa. This technique is insensitive to lesions involving the subdural space, and its success depends more on the skill of the interpreter than that of the other imaging studies. It does not expose the child to radiation, nor is sedation required in most instances. Its primary uses include identifying and monitoring intraventricular

TABLE 24.19 Features Suggestive of Inherited Neurometabolic Disorders

Encephalopathy	Systemic Features
Intellectual disability	Urinary odor
Developmental regression	Intrauterine growth retardation
Cerebral palsy	Failure to thrive
Spastic diplegia	Poor sucking
Spastic quadriplegia	Vomiting repeatedly
Depressed sensorium	Weak cry
Lethargy	Cardiomyopathy
Irritability	Hepatomegaly
Stupor	Fatty liver
Coma	Fibrosis/cirrhosis
Dementia	Hepatosplenomegaly
Hypotonia	Renal Tubular Acidosis
Seizures	Susceptibility to Infections
Myoclonus	Bone Marrow Depression
Infantile spasms	Neutropenia
Extrapyramidal symptoms	Thrombocytopenia
Dystonia	Pancytopenia
Opisthotonos	Seborrhea
Choreoathetosis	Alopecia
Microcephaly	Abnormal Hair
Macrocephaly	Pili torti
Speech problems	Trichorrhexis nodosa
Eye-related problems	
Abnormal movements	
Apraxia	
Cherry-red spot	
Nystagmus	
Optic atrophy	
Tapetoretinal degeneration (hereditary)	

Modified from Chaves-Carballo E. Detection of inherited neurometabolic disorders. A practical clinical approach. *Pediatr Clin North Am.* 1992;39:801-820.

hemorrhage and hydrocephalus; these functions are useful, especially in the preterm infant.

Computed Tomography Scans

CT provides more detail than ultrasonography, including details of bone structures and the subdural space. Using contrast material will further delineate structures such as tumors, or differentiate white from gray matter. However, CT exposes the child to radiation, and most young children require sedation to undergo this procedure.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) provides the greatest detail of the nonbone aspects of the CNS. The scanning time is longer than for CT, and most young children require sedation. The contrast material used, gadolinium, is generally safer than the contrast agents used for CT. MRI is superior to CT in the evaluation of the posterior fossa. MRI is used for imaging the spinal cord. MRI can differentiate abnormalities of gray and white matter, as well as deep and cortical gray matter lesions. Special techniques include magnetic resonance angiography, which can identify blood flow, and cerebrospinal fluid flow imaging, which can identify flow in conditions such as Chiari II malformation. Magnetic resonance spectroscopy identifies metabolites in the brain such as lactate, *N*-acetylaspartate, and choline. Conditions such as phenylketonuria, maple syrup urine disease, and Canavan disease have distinctive patterns on spectroscopy.

TABLE 24.20 Conditions in Which Early Treatment May Significantly Improve the Course of the Disease

Condition	Treatment
Galactosemia	Lactose-free diet
Fructosemia	Fructose-free diet
Hypoglycemia from any cause	Prevent hypoglycemia and/or provide glucose
Lead intoxication	Separate child from source of lead; chelation therapy
Hypothyroidism	Thyroid replacement
Phenylketonuria	Phenylalanine-free diet
Maternal phenylketonuria	Phenylalanine-free diet during pregnancy
Maple syrup urine disease	Diet restricted in branched-chain amino acids + dialysis or exchange transfusion
Recurrent otitis media	Antibiotic prophylaxis, pressure-equalizing tubes
Malnutrition	Adequate nutrition
Increased intracranial pressure (e.g., hydrocephalus, neoplasm)	Shunt ventricles or cystic structure
Congenital HIV infection	Prenatal/postnatal treatment with AZT (zidovudine)
Congenital toxoplasmosis	Prenatal treatment with spiramycin, pyrimethamine, and sulfonamide
Dopa-responsive dystonia	Responds to levodopa; may be misdiagnosed as cerebral palsy
Metachromatic leukodystrophy	Bone marrow transplantation
Niemann-Pick disease	Bone marrow transplantation, liver transplantation, implanted amniotic epithelial cells
Adrenoleukodystrophy	Bone marrow transplantation
Mucopolysaccharidosis type I	Bone marrow transplantation
Glycogen storage disease type IV	Liver transplantation
Menkes disease	Parenteral copper histidinate
Lesch-Nyhan syndrome	Allopurinol + bone marrow transplantation
Krabbe disease	Bone marrow transplantation

HIV, human immunodeficiency virus.

Indications for Various Imaging Modalities

Many studies have identified abnormalities in the brains of children with developmental delay on MRI that were not evident on CT. These abnormalities include delayed myelination, focal lesions, and hypoplastic white matter. In approximately 33% of children with developmental delay, the MRI is abnormal. This increases if the child has microcephaly or associated neurologic findings such as focal motor deficits, seizures, or a pattern of regression/degeneration. Neuroimaging in

children with GDD may reveal evidence of cerebral injury, brain malformation, or markers of cerebral dysgenesis. Injury may be due to hypoxic-ischemic encephalopathy ("watershed" or deep gray matter lesions in term infants and periventricular leukomalacia common in premature infants) or signs of intrauterine infection. Malformations may result from disorders of ventral induction (holoprosencephaly, agenesis of the corpus callosum, septo-optic dysplasia), migrational abnormalities (lissencephaly, schizencephaly, pachygyria, polymicrogyria, band heterotopias), and aberrant white matter development (demyelinating/dismyelinating syndromes). At times, neuroimaging may provide information about the possible timing of the event (whether injury or dysgenesis). Serial imaging studies may help to distinguish a static from a progressive course and aid in prognosis. However, in many instances, abnormal findings may not be sufficient for determining the specific underlying cause of the disability. Furthermore, there may be a very weak correlation between neuroimaging findings and the child's clinical picture. As an unintended consequence, neuroimaging studies may reveal incidental findings that are unrelated to the child's developmental delay, for example, nonspecific findings such as mild ventriculomegaly and enlargement of the subarachnoid spaces, or patchy areas of white matter gliosis of uncertain origin (Table 24.21). In many instances, these are benign variations of normal or clinically insignificant anomalies. In some cases, these findings may require consultation with a pediatric neurosurgeon, but it is important to avoid unnecessary additional tests or interventions whenever possible.

Other Tests

Most neurometabolic disorders can be identified through serum, plasma, and urine tests in conjunction with neuroradiologic investigations. However, other tests can be helpful for identifying specific diseases. Analysis of cerebrospinal fluid for elevated protein levels may help in the diagnosis of a disease affecting white matter; the presence of measles antibody can help identify subacute sclerosing panencephalitis. On occasion, cerebrospinal fluid evaluation of lactate, pyruvate, and amino acids may be helpful. Peripheral nerve conduction tests and electromyography may help confirm that the condition is associated with peripheral neuropathy. Diminished deep tendon reflexes and prolonged nerve conduction times are noted in Krabbe disease, Refsum disease, metachromatic leukodystrophy, and infantile neuroaxonal dystrophy (see Chapter 29).

Skin and muscle biopsies may identify conditions in which abnormal material is stored in cells, such as neuronal ceroid lipofuscinosis. Brainstem auditory evoked response is useful as an evaluation of hearing in infants and is used to evaluate brainstem functioning. Visual evoked response can be useful in determining the integrity of the visual pathways; however, it cannot determine visual acuity.

TABLE 24.21 Types of Abnormalities Identified by Neuroimaging

- Malformations of Cortical Development:
  - Midline defects: holoprosencephaly; callosal agenesis; cerebellar hypoplasia
  - Migration defects: lissencephaly; bands; schizencephaly; pachygyria/microgyria
  - Hydrocephalus, hemimegalencephaly
  - Neurocutaneous syndromes: tuberous sclerosis; neurofibromatosis
  - Trauma: hypoxic-ischemic encephalopathy; stroke
- Metabolic and Neurodegenerative Disorders:
  - Cortical gray matter: lysosomal enzyme defects (lipidoses: GM_1 gangliosidosis, neuronal ceroid lipofuscinosis) and mucolipidoses
  - Corpus striatum (caudate and putamen): mitochondrial disorders, organic acidopathies, aminoacidopathies, Wilson disease, juvenile Huntington disease
  - Globus pallidus: Hallervorden-Spatz disease, methylmalonic acidemia, hyperbilirubinemia
  - White matter (leukoencephalopathies): peroxisomal disorders (adrenoleukodystrophies), lysosomal leukodystrophies (metachromatic, globoid cell); other white matter diseases (Pelizaeus-Merzbacher, Canavan, Alexander, Cockayne)
- Congenital infection: cytomegalovirus; human immunodeficiency virus; toxoplasmosis
- Neoplastic disorders

Discussing a Developmental Diagnosis with Parents

When a specific developmental diagnosis is established, it should be shared with the family in an objective but sensitive manner. Facts about the condition and prognostic information should be presented with an explanation of the margin of uncertainty around any disorder. Each child is unique; therefore, making a prognosis for an individual child solely based on data is risky. When appropriate, parents should be reassured that they did not do anything to cause the child's disease, since feelings of guilt in this situation are universal. All parents want some measure of hope and assurance that they will have help from competent professionals who will care for their child.

When the child is an infant or toddler, a frank discussion about the child's profile of developmental strengths and weaknesses relating skills to a "developmental age" may help parents to align their expectations to the child's functional abilities. All parents want to help their child grow and develop to his or her potential, and the clinician should make a plan for follow-up to evaluate the child's progress. For children under age 3 years, follow-up in 6 months will provide a time frame in which significant change can be observed. For older children, yearly intervals are appropriate.

SPECIFIC CONDITIONS

Cerebral Palsy

Cerebral palsy (CP) is the leading cause of motor disability in children. CP is a clinical diagnosis characterized by significant impairment of movement and posture that begins in infancy or early childhood. Worldwide, CP affects 1-5 in every 1000 live births. The cause is often brain dysgenesis or injury (prenatal or perinatal from hypoxic-ischemic encephalopathy, intraventricular hemorrhage, or periventricular leukomalacia). There is an inverse relationship between birthweight and CP, ranging from 51-73/1000 in very low birthweight (<1500 g) neonatal survivors to 1-2/1000 in normal birthweight (>2500 g) infants. The effects of improvements in neonatal intensive care have both increased the survival of low birthweight and premature infants, and have decreased the incidence of CP among survivors. However, more than half of children diagnosed with CP were born at term or near term, and there has not been a decrease in CP prevalence over time. In a large population-based study in Western Australia, approximately 76% of children with CP were born at term after an uncomplicated perinatal course without evidence of neonatal encephalopathy. A recent study identified clinically significant CNV in 31% of children with no obvious etiology (so-called "cryptogenic" CP). Thus, the etiology of CP appears to be multifactorial with a largely prenatal onset including genetic, environmental, inflammatory, and infectious influences on fetal development.

(See *Nelson Textbook of Pediatrics,* p. 2896.)

Although the underlying pathology is nonprogressive, the clinical manifestations may change over time. For example, an infant with CP may initially present as hypotonic but then develop spasticity, and functional disability may increase if joint contractures or scoliosis develops. CP is associated with a wide range of other disabilities, including sensory impairment (hearing and vision), dysphagia, epilepsy, and ID (40-65%).

Some IEM present with features of CP ("CP mimics") and are amenable to treatment that can improve the neurologic outcome. A number of symptoms should raise the "index of suspicion" that an IEM may be responsible for the clinical picture of CP:

- Severe symptoms in the absence of a history of perinatal injury
- Normal brain MRI findings
- Abnormalities isolated to the globus pallidus
- Neurodevelopmental regression or progressively worsening symptomatology
- Isolated muscular hypotonia
- Rigidity as opposed to spasticity
- Paraplegia
- A pattern of disease inheritance or consanguinity

Autism Spectrum Disorder

Individuals with ASD have pervasive impairments in reciprocal social communication and social interactions, and circumscribed interests and repetitive patterns of behavior and activities that limit or impair their daily functioning. The disorder is present from early childhood, although approximately 25-30% of children with ASD experience a regression of skills, often between the ages of 15 and 24 months. Regression may be gradual or rapid, and usually encompasses the loss of communication (words and gestures) and social skills (eye contact). However, the regression does not appear to be progressive, and most children "plateau" at this regressed state (Table 24.22). The prevalence of ASD among children aged 8 years is 1:68, with a male-to-female ratio of 4.5:1. ASD is a neurodevelopmental disorder with multifactorial etiology, with genetic factors playing a significant role. It occurs with high frequency in a number of known genetic disorders (Down syndrome, Fra X syndrome, tuberous sclerosis, Rett syndrome, Angelman syndrome). Hereditary factors also play a role, since ASD also has an elevated recurrence rate within certain families. Other biologic risk factors for ASD include children born to older parents and children born prematurely or with low birthweight.

Fragile X Syndrome

FRAXA syndrome is the most commonly diagnosed genetic cause of ID in males. It affects 1 in 4000 males and 1 in 8000 females. FRAXA syndrome is found in all racial and ethnic groups. The disorder is the result of an inheritable unstable DNA in the *FMR1* gene of the X chromosome. Normal individuals may have less than 40 triplet repeats. Females with between 55 and 200 repeats are said to have *FMR1* premutation, since the number of repeats is likely to expand in cells that become eggs. Males with greater than 200 repeats are clinically symptomatic and will likely have a moderate degree of ID. In addition, speech and language delays, attention difficulty, anxiety disorder, and autism are associated with FRAXA syndrome. Full-mutation females may have a mild degree of ID. Because characteristic physical symptoms of FRAXA are difficult to identify in infants and young children, routine molecular testing for the *FMR1* gene may identify 2-6% of males and 2-4% of females with nonspecific ID. In older children and adults, characteristic physical features and a distinct "behavioral phenotype" may suggest a diagnosis of FRAXA syndrome (Table 24.23).

TABLE 24.22 Autism Spectrum Disorder

Diagnostic Criteria

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive):
   1. Deficits in social-emotional reciprocity, ranging, for example, from an abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
   2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
   3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

   Specify current severity: Severity is based on social communication impairments and restricted, repetitive patterns of behavior.

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least 2 of the following, currently or by history (examples are illustrative, not exhaustive):
   1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
   2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take the same route or eat the same food every day).
   3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).
   4. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

   Specify current severity: Severity is based on social communication impairments and restricted, repetitive patterns of behavior.

C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for the general developmental level.

From American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-V)*. 5th ed. Arlington, VA: American Psychiatric Association; 2013.

(See *Nelson Textbook of Pediatrics,* p. 176.)

TABLE 24.23 Scoring System for Screening Individuals for Fragile X Syndrome*

Category	Score	Criteria
Family history	2	Retarded sibling, maternal uncle, aunt, nephew, niece, 1st cousin
	1	Any other affected relative
	0	No family history of retardation
Personality	2	Shyness, lack of eye contact followed by friendliness, verbosity, and echolalia
	1	Some of these characteristics
	0	No characteristic
Ears	2	Large and protruding
	1	Large, not protruding
	0	Other
Face	2	Long jaw, high and wide forehead
	1	Only 1 finding
	0	No findings
Body habitus	2	Slim, tall, rounded shoulders, hyperextensible fingers, lack of body hair, **or** obese with female fat distribution, striae, soft skin, lack of body hair (in boys and men)
	2	Slim **or** obese (girls and women)
	1	Only some features
	0	No features

*A score of 5 or greater has a sensitivity of 0.88 and specificity of 0.98 in comparison with chromosome analysis.

Inborn Errors of Metabolism and Storage Diseases

IEM may manifest as an acute encephalopathy (from an organic acidemia or hyperammonemia) or as a chronic progressive encephalopathy (cardiomyopathy, spasticity, hyperreflexia, liver dysfunction), often as a result of mitochondrial disorders or storage diseases (see Table 24.19).

- *Sphingolipidoses* (Tay-Sachs disease, Niemann-Pick disease, GM_1 gangliosidosis) are associated with a cherry-red retinal spot, organomegaly, and ID.
- *Glycoprotein degradation disorders* (e.g., mannosidosis, fucosidosis) may variably manifest with coarse facies, ID, hepatosplenomegaly, and vacuolated lymphocytes.
- *Mucopolysaccharidoses* (e.g., the Hurler, Hunter, and Sanfilippo syndromes) may manifest with coarse facies, ID, hepatosplenomegaly, dysostosis multiplex, and corneal clouding.
- *Neuronal ceroid lipofuscinosis* may manifest with ID, vision loss, ataxia, and myoclonic seizures.
- *Peroxisomal disorders* (Zellweger syndrome, X-linked adrenoleukodystrophy, Refsum disease) variably manifest with ID, encephalopathy, seizures, blindness, dysmorphic features, and deafness.

IEM should also be suspected in children with acute neurologic abnormalities in whom there is unexplained vomiting, an unusual smell to the urine or body odor, acidosis, or renal stones.

Congenital Infections

Bacteria, parasites, or viruses acquired before, during, or after birth may cause CNS infection and injury. The diagnosis is based on the clinical manifestations (Table 24.24) and culture or serologic evidence of infection (Table 24.25).

Postnatal Infections

CNS infection during infancy or childhood may cause encephalitis or meningoencephalitis with resultant ID. Bacterial (pneumococcus, *Mycobacterium tuberculosis*, meningococcus) and viral (herpes simplex type 1 or 2, eastern or western equine encephalitis virus, West Nile virus, St. Louis encephalitis virus, HIV; in rare cases, mumps, enteroviruses, or California encephalitis virus) cases occur in infancy and early childhood and variably have neurodevelopmental sequelae. Secondary problems caused by the infection such as hearing or visual loss must also be considered. Late sequelae or prior viral infection such as measles or rubella panencephalitis may appear 10-20 years after the initial CNS disease and manifest as dementia, poor school performance, and progressive encephalopathy.

TREATMENT

The treatment of a child with a developmental or intellectual disability includes routine health maintenance, treatment of the underlying condition (if possible), treatment of associated conditions (such as hyperactivity, seizures, or drooling), relief of symptoms, anticipatory guidance to prevent secondary conditions, and environmental, educational, and family support. The overriding goal is to optimize the functional status and prognosis of the child.

Health maintenance for children with developmental disabilities should be the same as that provided for all children, including immunizations, regular monitoring of physical growth and development, and screening for conditions such as anemia, tuberculosis, and lead intoxication. Use of standardized growth charts will reflect the child's individual pattern over time. Specific growth charts are available for some conditions, including Down syndrome, Prader-Willi syndrome, and FRAXA syndrome. Nutritional recommendations are available for children with CP.

Very few conditions (see Table 24.20) that lead to developmental delay can be "cured." However, medical treatment of associated conditions can help reduce pain and discomfort. For example, many children with CP have drooling and spasticity. Drooling can be controlled by the use of glycopyrrolate, scopolamine patch, or surgery to the salivary glands. Spasticity can be managed with oral baclofen, periodic injections of botulinum toxin, tizanidine, or dorsal root rhizotomy. Behavioral or psychiatric problems may benefit from counseling, support, or psychopharmacologic medications. These medications can be used to reduce arousal symptoms and to improve affect, perceptual functioning, cognitive processing, communication, and behavior (Table 24.26). Attention must be paid to the use of medications in specific conditions. For example, valproic acid is more likely to cause hepatotoxicity in GM_2 gangliosidosis, spinocerebellar degeneration, Friedreich ataxia, Lafora body disease, Alpers disease, and myoclonic epilepsy with ragged red fibers. Parents and capable children should be informed about the medication prescribed, including side effects. Some written guidelines for parents and youth are available for psychopharmacologic medications.

Anticipatory guidance for parents of children with developmental disabilities involves the same categories used in all children but may be modified because of the unique features of the child's condition. For example, parents of children with CP should be aware of the possibility that their child may be at risk for poor weight gain and aspiration pneumonia because of oral-motor dysphagia, for strabismus, spinal scoliosis and deformities (contractures) of the foot, knee, and hip because of muscle spasticity, osteoporosis, decubitus ulcers, epilepsy, and learning difficulties.

Although there are many different causes, children with developmental disabilities and their families share many common characteristics, including chronicity of the condition (with no cure in most instances); inability to participate in peer activities; parental feelings of guilt and loss of the "ideal" child; increased expense to care for a

TABLE 24.24 Distinguishing Features of Perinatal Congenital Infections

Agent	Maternal Epidemiology	Neonatal Features
Toxoplasma gondii	Heterophile-negative mononucleosis Exposure to cats or raw meat or immunosuppression High-risk exposure at 10-24 wk gestation	Hydrocephalus, abnormal spinal fluid, intracranial calcifications, chorioretinitis, jaundice, hepatosplenomegaly, fever, ID if symptomatic Many infants asymptomatic at birth Treatment: pyrimethamine plus sulfadiazine
Rubella virus	Unimmunized seronegative mother; fever ± rash Detectable defects with infection: by 8 wk, 85% 9-12 wk, 50% 13-20 wk, 16% Virus may be present in the infant's throat for 1 yr Prevention: vaccine	Intrauterine growth restriction, microcephaly, microphthalmia, cataracts, glaucoma, "salt-and-pepper" chorioretinitis, hepatosplenomegaly, jaundice, PDA, deafness, blueberry muffin rash, anemia, thrombocytopenia, leukopenia, metaphyseal lucencies, B- and T-cell deficiency, ID Infant may be asymptomatic at birth
Cytomegalovirus (CMV)	Primary infection may be asymptomatic Heterophile-negative mononucleosis; infant may have viruria for 1-6 yr	Sepsis, intrauterine growth restriction, chorioretinitis, microcephaly, periventricular calcifications, blueberry muffin rash, anemia, thrombocytopenia, neutropenia, hepatosplenomegaly, jaundice, deafness, pneumonia Many asymptomatic at birth, ID if symptomatic Prevention: CMV-negative blood products
Herpes simplex type 2 virus	STD; primary genital infection may be asymptomatic; intrauterine infection rare, acquisition at time of birth more common	Intrauterine infection: chorioretinitis, skin lesions, microcephaly, ID Postnatal infection: encephalitis, localized or disseminated disease, skin vesicles, keratoconjunctivitis, ID if CNS infection Treatment: acyclovir
Varicella-zoster virus	Intrauterine infection with chickenpox during 1st trimester Infant develops severe neonatal varicella when maternal illness occurs 5 days before or 2 days after delivery	Microphthalmia, cataracts, chorioretinitis, cutaneous and bone aplasia/hypoplasia/atrophy, cutaneous scars, ID Zoster as in an older child Prevention of neonatal condition: VZIG Treatment of ill neonate: acyclovir
Treponema pallidum (syphilis)	STD Maternal primary asymptomatic: painless "hidden" chancre Penicillin, not erythromycin, prevents fetal infection	Presentation at birth as nonimmune hydrops, prematurity, anemia, neutropenia, thrombocytopenia, pneumonia, hepatosplenomegaly Late neonatal presentation as snuffles (rhinitis), rash, hepatosplenomegaly, condylomata lata, metaphysitis, cerebrospinal fluid pleocytosis, keratitis, periosteal new bone, lymphocytosis, hepatitis; ID possible Late-onset abnormalities: teeth, eye, bone, skin, CNS, ear Treatment: penicillin
Parvovirus B19	Etiology of 5th disease; fever, rash, arthralgia in adults	Nonimmune hydrops, fetal anemia Treatment: in utero transfusion
Human immunodeficiency virus (HIV)	AIDS: most mothers are asymptomatic and HIV-positive; high-risk history: prostitute, drug abuse, sexual partner of bisexual person, or hemophiliac	AIDS symptoms develop between 3-6 mo of age in 25-40%; failure to thrive, recurrent infection, hepatosplenomegaly, neurologic abnormalities, ID Management: IVIG, trimethoprim-sulfamethoxazole, antiretroviral therapy Prevention: maternal and infant antiretroviral therapy
Hepatitis B virus	Vertical transmission common; may result in cirrhosis, hepatocellular carcinoma	Acute neonatal hepatitis; many become asymptomatic carriers Prevention: HBIG, vaccine
Borrelia burgdorferi	Lyme disease, erythema chronicum migrans, meningitis, arthritis, carditis	Prematurity, rash, cortical blindness, fetal death?

TABLE 24.24 Distinguishing Features of Perinatal Congenital Infections—cont'd

Agent	Maternal Epidemiology	Neonatal Features
Neisseria gonorrhoeae	STD, infant acquires at birth Treatment: cefotaxime, ceftriaxone	Gonococcal ophthalmia, sepsis, meningitis Prevention: silver nitrate, erythromycin eye drops Treatment: intravenous ceftriaxone
Chlamydia trachomatis	STD, infant acquires at birth Treatment: oral erythromycin	Conjunctivitis, pneumonia Prevention: erythromycin eye drops Treatment: oral erythromycin
Mycobacterium tuberculosis	Positive PPD skin test, recent converter, positive chest roentgenogram, positive family member Treatment: INH and rifampin ± ethambutol	Congenital rare septic pneumonia; acquired primary pulmonary TB; ID if CNS symptoms; if asymptomatic, follow PPD Prevention: INH, BCG, separation Treatment: INH, rifampin, pyrazinamide
Trypanosoma cruzi (Chagas disease)	Central South American native, immigrant, travel Chronic disease in mother	Failure to thrive, heart failure, achalasia Treatment: nifurtimox

AIDS, acquired immunodeficiency syndrome; BCG, bacillus Calmette-Guérin; CNS, central nervous system; HBIG, hepatitis B immune globulin; ID, intellectual disability; INH, isoniazid; IVIG, intravenous immunoglobulin; PDA, patent ductus arteriosus; PPD, purified protein derivative; STD, sexually transmitted disease; TB, tuberculosis; VZIG, varicella-zoster immune globulin.
Modified from Kliegman RM. Fetal and neonatal medicine. In: Behrman RE, Kliegman RM, eds. *Nelson Essentials of Pediatrics*. 2nd ed. Philadelphia: WB Saunders; 1994.

TABLE 24.25 Diagnosis of Congenital Infections

Serologic Findings

Syphilis: nontreponemal (VDRL) or treponemal (FTA-ABS)
Toxoplasmosis: ELISA, Sabin-Feldman dye test
Rubella: latex agglutination, enzyme immunoassay
Cytomegalovirus: ELISA
Herpes simplex viruses: several methods
Varicella-zoster virus: fluorescent antimembrane antibody
Lyme disease: ELISA
Human parvovirus B19: ELISA or RIA
Arboviruses: antibody capture ELISA (blood or CSF)

Serologic Studies Should Include

An acute sample from the infant for agent-specific IgM and IgG
A convalescent sample from the infant for agent-specific antibodies
A maternal sample for agent-specific IgG

Virologic Findings (Culture and PCR)

Cytomegalovirus: urine, saliva, blood leukocytes, occasionally CSF
Rubella virus: urine, nasopharyngeal secretions
Herpes simplex viruses: skin lesions, throat, rectum, CSF, blood
Varicella-zoster virus: skin lesions
Enteroviruses: CSF, throat, stool, blood
Arboviruses: blood, CSF
When the agent is unknown, samples should include urine, throat washing, CSF, blood, rectal swab, and fluid from skin vesicles, if present.

CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; FTA-ABS, fluorescent treponemal antibody absorption; IgG, immunoglobulin G; IgM, immunoglobulin M; PCR, polymerase chain reaction; RIA, radio-immunoassay; VDRL, Venereal Disease Research Laboratory.
From Bale JF, Murph JR. Congenital infections and the nervous system. *Pediatr Clin North Am.* 1992;39:669-690.

TABLE 24.26 Psychopharmacologic Agents That May Be Useful in the Treatment of Children with Developmental Disabilities

Medication	Possible Indications
Carbamazepine	Mania, bipolar disorder, impulsivity, aggression, seizures, trigeminal neuralgia
Clomipramine	Obsessive-compulsive disorder, depression
Clonazepam	Mania, bipolar disorder, seizure
Clonidine, guanfacine	Manic episodes, attention-deficit/hyperactivity disorder, aggression
Sertraline, other SSRIs, risperidone, olanzapine, aripiprazole	Obsessive-compulsive disorder, depression, anxiety Aggressive, self-injurious behavior
Methylphenidate	Attention-deficit/hyperactivity disorder: dextroamphetamine Aggression, impulsivity
Valproic acid	Bipolar disorder, especially rapidly cycling

SSRIs, selective serotonin reuptake inhibitors.

disabled child; lost economic opportunities (such as the inability of a parent to return to work because he or she must care for the child at home); need for personal care (because the child cannot be left alone or with a sitter); confusing systems of health care, insurance coverage, and governmental agencies and rules; and social isolation.

Environmental support may be needed and may take the form of family therapy, financial counseling, and referral to a disease-oriented volunteer support group or in a "Big Brothers/Big Sisters" program. Formal support includes early intervention for children from birth to 3 years of age, preschool intervention through the school district for children 3-5 years of age, and special education services provided under the Individuals with Disabilities Education Act (IDEA) and Section 504 of the Rehabilitation Act for school-age children. Families may also need assistance in transitioning their adolescent child from

TABLE 24.27 Providing Primary Care to Children with Developmental Disabilities Using the Mnemonic "Md's DD BASICS"

MD's DD BASICS	Things to Check	Potential Consultant(s)
Motor	Ambulation, seating, position, spine	Orthopedist, physiatrist, PT, OT
Diet	Weight, fat stores, diet, feeding problems	Nutritionist/dietitian, speech pathologist, OT
Seizures	Seizure record; drug levels and side effects	Neurologist
Dermatology	Skin breakdown	Nursing, plastic surgeon
Dentistry	Teeth, gums	Dentist
Behavior	Aggression, self-injury, sleep, pica, interfering behavior	Psychologist, psychiatrist
Advocacy	Finances, family support, program aid	Social worker
Sensory	Vision, hearing	Ophthalmologist, audiologist
Infections	Immunizations, environment, lungs, urine	Infection control nurse
Constipation	Stools, gastroesophageal reflux	Gastroenterologist
Sexuality	Menses, sexual activity, masturbation, contraception, prevention of sexually transmitted diseases	Gynecologist, habilitation program

OT, occupational therapist; PT, physical therapist.
Modified from Sulkes S. MD's DD BASICS: identifying common problems and preventing secondary disabilities. *Pediatr Ann.* 1995;24:245-254.

TABLE 24.28 Medical Checklist for a Child with Down Syndrome

Age	Condition	Monitoring
Birth to 2 mo	Etiology, recurrence risk	Chromosome analysis and genetic counseling
	Hypothyroidism	TSH, T_3, and T_4
	Congenital heart defect	Pediatric cardiology evaluation, including echocardiography
	Family stress	Referral to Down Syndrome Association
2-12 mo	Refractive errors, cataracts	Pediatric ophthalmologic evaluation
	Hearing loss; recurrent otitis media	Auditory brainstem evoked response
	Delayed development	Formal developmental evaluations
1-12 yr	Delayed development	Enrollment in early intervention program
	Hypothyroidism	Annual TSH
	Hearing loss	Auditory testing: annually between 1 and 3 yr and every 2 yr between 3 and 13 yr
	Refractive error	Ophthalmologic examination every 2 yr
	Atlantoaxial instability	Cervical spine roentgenography at 2 and 12 yr
	Routine care	Dental examination at 2 yr, then every 6 mo (prophylaxis for subacute bacterial endocarditis, if indicated)
12-18 yr	Hypothyroidism	TSH annually
	Decreased hearing	Auditory testing every 2 yr
	Refractive error	Ophthalmologic examination every 2 yr
	Mitral valve prolapse	Echocardiography

T_3, triiodothyronine; T_4, thyroxine; TSH, thyroid-stimulating hormone.

school to a work or independent living situation. At each stage in the child's life, the clinician should review the services the child is receiving and determine whether the family might benefit from additional support. The mnemonic "MD's DD BASICS" provides a list of content areas for review at each visit (Table 24.27). Checklists to monitor the care of children with specific problems such as Down syndrome are also available, often through the AAP (Table 24.28).

Complementary and Alternative Therapies

Because conventional medical care cannot cure many conditions associated with developmental disability, a wide range of "complementary and alternative medications" (CAM) and therapies have arisen. The rate of CAM use by children with special health care needs is ~30-70%. CAM may include biochemical therapies (herbal remedies, vitamin and mineral supplements), nutritional supplements, biomechanical therapies (massage, chiropractic), bioenergetic therapies (acupuncture, homeopathy), and lifestyle/mind-body therapies including dietary manipulations (Feingold diet, sugar elimination diet), relaxation training, and biofeedback. In some instances, CAM may include potentially toxic treatments (antifungal medications, chelation, vitamin B_{12} injections). In most instances, families use CAM to supplement conventional services and treatments. While the research basis for the effectiveness or harm of CAM is limited, it is also true that the literature addressing the appropriate and effective use of "mainstream" pharmacologic agents to treat children with developmental disabilities is also quite limited. Clinicians should ask about all therapies the family is using to help the child. Unless there are identified health risks, clinicians should refrain from disparaging the use of CAM. Acknowledging and discussing the use of CAM is not the same as recommending or prescribing them. It is better to know what treatments and services a child is receiving and to factor them into an overall plan of care than to be unaware of what the family is doing for their child. The clinician should keep an "open mind" about CAM, but maintain a focus on the safety and efficacy of all treatments for children with developmental disabilities.

PITFALLS AND HAZARDS IN DEVELOPMENTAL DIAGNOSIS

The identification of "risk factors" does not imply a specific etiology or diagnosis. It is important to avoid a logical fallacy (post hoc attribution) and not base a diagnosis on a specific cause unless there is positive evidence to confirm that cause. For example, a history of a low 5-minute Apgar score with no other symptoms of neonatal encephalopathy is not likely to be the cause of a child's subsequent developmental disability.

Dysmorphic and physically disabled children are often assumed to have GDD/ID, and conversely, children with normal facial appearance and motor skills may not be identified early as having GDD/ID. Cognitive development is usually unaffected in a number of striking dysmorphic syndromes (e.g., Treacher Collins syndrome, achondroplasia).

Identifying a child as being "at risk" for developmental delay may alter the family's perceptions, making the child vulnerable. This might lead to constraints on the child's experiences and diminished expectations of performance. When a child is born with a single risk factor, such as prematurity, the parents may be afraid to place demands on the child, creating a vicious cycle of "learned helplessness" and immature behaviors.

Parents of children who are informed that their child is not normal often grieve for their "lost" (typically developing) child. This process of grieving involves stages that include denial, sadness, anger, and guilt. One parent may be experiencing persistent anger while another is still sad or depressed. This difference in stages may make communication between them exceedingly difficult. Grieving may occur at times other than the initial diagnosis, for example, on the 1st day of kindergarten. These feelings may be expressed in nonfunctional ways, such as denial that leads to unending shopping for professionals who will "cure" the child or anger that is expressed at the clinician, thereby thwarting efforts at building a trusting and supportive relationship. However, many authorities believe that these emotions are essential steps that allow the parents to release the old dreams and secure new ones. The goal of the therapeutic clinician is to accept the parents at whatever stage they are in and to help them understand the normalcy of the stages.

SUMMARY AND RED FLAGS

Developmental disabilities are common. Identifying children with developmental delay involves both specific attention to children with biologic and/or sociocultural risks and routine developmental surveillance and screening during well child visits. All children with suspected developmental delay should receive a formal multidisciplinary assessment that includes a systematic diagnostic approach with a "tiered" strategy for laboratory and neuroimaging evaluations. Developmental regression, vomiting, seizures, or lethargy suggests the presence of a potentially life-threatening metabolic disorder. Parents need to understand that it is not always possible to identify a single defined disease process responsible for their child's developmental disability. Even if a specific etiology is not found, comprehensive clinical assessments can identify the child's profile of strengths and weaknesses. Children with developmental disabilities will require meticulous monitoring over time and coordination of care to optimize their functional status. All children with developmental disabilities will benefit from early intervention, therapeutic, and special education services to help maximize their developmental potential and to promote independence and personal autonomy.

Red flags include developmental regression (see Tables 24.14 and 24.15), developmental delay associated with vomiting or lethargy (see Table 24.19), and recognition of a treatable cause of delay or CP (see Table 24.20).

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Aase JM. *Diagnostic Dysmorphology*. New York: Plenum Medical Book; 1990.

Akins RS, Krakowiak P, Angkustsiri K, et al. Utilization patterns of conventional and complementary/alternative treatments in children with autism spectrum disorders and developmental disabilities in a population-based study. *J Dev Behav Pediatr*. 2014;35:1-10.

American Academy of Pediatrics, Committee on Fetus and Newborn; American College of Obstetricians and Gynecologists and Committee on Obstetric Practice. The Apgar score. *Pediatrics*. 2006;117:1444-1447.

American Academy of Pediatrics Task Force on Newborn and Infant Hearing. Newborn and infant hearing loss: detection and intervention. *Pediatrics*. 1999;103:527-530.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-V)*. 5th ed. Arlington, VA: American Psychiatric Association; 2013.

Aylward GP. The relationship between environmental risk and developmental outcome. *J Dev Behav Pediatr*. 1992;13:222-229.

Badawi N, Felix JF, Kurinczuk JJ, et al. Cerebral palsy following term newborn encephalopathy: a population-based study. *Dev Med Child Neurol*. 2005;47:293-298.

Ballantyne AO, Spilkin AM, Hesselink J, et al. Plasticity in the developing brain: intellectual, language and academic functions in children with ischaemic perinatal stroke. *Brain*. 2008;131:2975-2985.

Baron IS, Leonberger KA. Assessment of intelligence in the preschool period. *Neuropsychol Rev*. 2012;22:334-344.

Battaglia A, Carey JC. Diagnostic evaluation of developmental delay/mental retardation: an overview. *Am J Med Genet*. 2003;117C:3-14.

Battaglia A, Doccini V, Bernardini L, et al. Confirmation of chromosomal microarray as a first-tier clinical diagnostic test for individuals with developmental delay, intellectual disability, autism spectrum disorders and dysmorphic features. *Eur J Paediatr Neurol*. 2013;17:589-599.

Berry SA. Newborn screening. *Clin Perinatol*. 2015;42:441-453.

Bick J, Zhu T, Stamoulis C, et al. Effect of early institutionalization and foster care on long-term white matter development: a randomized clinical trial. *JAMA Pediatr*. 2015;169:211-219.

Blasco PA. Pitfalls in developmental diagnosis. *Pediatr Clin North Am*. 1991;38:1425-1438.

Centers for Disease Control and Prevention. Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2010. *MMWR Morb Mortal Wkly Rep*. 2014;63(SS02):1-21.

Centers for Disease Control and Prevention. Economic costs associated with mental retardation, cerebral palsy, hearing loss, and vision impairment, United States, 2003. *MMWR Morb Mortal Wkly Rep*. 2004;53(03):57-59.

Chan E. The role of complementary and alternative medicine in attention-deficit hyperactivity disorder. *J Dev Behav Pediatr*. 2002;23:S37-S45.

Council on Children with Disabilities, Section on Developmental Behavioral Pediatrics, Bright Futures Steering Committee, et al. Identifying infants and young children with developmental disorders in the medical home: an algorithm for developmental surveillance and screening. *Pediatrics*. 2006;118:405-420.

Curry CJ, Stevenson RE, Aughton D, et al. Committee of the ACMG. Evaluation of mental retardation: recommendations of a consensus conference. *Am J Med Genet*. 1997;72:468-477.

Day RE, Schutt WH. Normal children with large heads—Benign familial megalencephaly. *Arch Dis Child*. 1979;54:512-517.

De Leersnyder H, Bresson JL, de Blois MC, et al. Beta-1-adrenergic antagonists and melatonin reset the clock and restore sleep in a circadian disorder, Smith-Magenis syndrome. *J Med Genet*. 2003;40:74-78.

Dudova I, Kasparova M, Markova D, et al. Screening for autism in preterm children with extremely low and very low birth weight. *Neuropsychiatr Dis Treat*. 2014;10:277-282.

Dworkin PH. British and American recommendations for developmental monitoring: the role of surveillance. *Pediatrics*. 1989;84:1000-1010.

Editorial. Developmental surveillance. *Lancet*. 1986;1:950-951.

Escalona SK. Babies at double hazard: Early development of infants at biologic and social risk. *Pediatrics*. 1982;70:670-676.

Fletcher JM, Barnes M, Dennis M. Language development in children with spina bifida. *Semin Pediatr Neurol*. 2002;9:201-208.

Frankenburg WK, Dodds JB. The Denver Developmental Screening Test. *J Pediatr*. 1967;71:181-191.

Gesell A, Amatruda C. *Developmental Diagnosis*. New York: Paul Hoeber; 1941.

Glascoe FP. The value of parents' concerns to detect and address developmental and behavioural problems. *J Paediatr Child Health*. 1999;35:1-8.

Glascoe FP. Early detection of developmental and behavioral problems. *Pediatr Rev*. 2000;21:272-280.

Graham JM. *Smith's Recognizable Patterns of Human Deformation*. 3rd ed. Elsevier; 2007.

Harlor AD, Bower C, The Committee on Practice and Ambulatory Medicine, et al. Clinical Report—Hearing assessment in infants and children: recommendations beyond neonatal screening. *Pediatrics*. 2009;124:1252-1263.

Henderson LB, Applegate CD, Wohler E, et al. The impact of chromosomal microarray on clinical management: a retrospective analysis. *Genet Med*. 2014;16:657-664.

Hickson GB, Altemeier WA, O'Connor S. Concerns of mothers seeking care in private pediatric offices: opportunities for expanding services. *Pediatrics*. 1983;72:619-624.

Hreidarsson SJ, Shapiro BK, Capute AJ. Age of walking in the cognitively impaired. *Clin Pediatr (Phila)*. 1983;22:248-250.

Huffman LC, Sutcliffe TL, Tanner ISD, et al. Management of symptoms of children with autism spectrum disorders: a comprehensive review of pharmacologic and complementary-alternative medicine treatments. *J Dev Behav Pediatr*. 2011;32:56-68.

Idring S, Magnusson C, Lundberg M, et al. Parental age and the risk of autism spectrum disorders: findings from a Swedish population-based cohort. *Int J Epidemiol*. 2014;43:107-115.

James HE, Perszyk A. Concepts on childhood microcrania: a clinical overview for the neurosurgeon who is evaluating a child with a small head. *Pediatr Neurosurg*. 2011;47:354-358.

Johnson CP, Myers SM, Council on Children with Disabilities. Identification and evaluation of children with autism spectrum disorders. *Pediatrics*. 2007;120:1183-1215.

Jones KL, Jones MC, del Campo M. *Smith's Recognizable Patterns of Human Malformation*. 7th ed. Elsevier; 2013.

Karoly LA, Kilburn MR, Cannon JS. *Proven benefits of early interventions*. Rand Corporation; 2005 <www.rand.org/content/dam/rand/pubs/research_briefs/2005/RAND_RB9145.pdf>.

Kemper KJ, Vohra S, Walls R. The use of complementary and alternative medicine in pediatrics. *Pediatrics*. 2008;122:1374-1386.

Kuzniewicz MW, Wi S, Qian Y, et al. Prevalence and neonatal factors associated with autism spectrum disorders in preterm infants. *J Pediatr*. 2014;164:20-25.

Lathi RB, Hazard FK, Heerema-McKenney A, et al. First trimester miscarriage evaluation. *Semin Reprod Med*. 2011;29:463-469.

Leach EL, Shevell M, Bowden K, et al. Treatable inborn errors of metabolism presenting as cerebral palsy mimics: systematic literature review. *Orphanet J Rare Dis*. 2014;9:197.

Lee RW, Poretti A, Cohen JS, et al. A diagnostic approach for cerebral palsy in the genomic era. *Neuromolecular Med*. 2014;16:821-844.

Linver MR, Brooks-Gunn J, Kohen DE. Family processes as pathways from income to young children's development. *Dev Psychol*. 2002;38:719-734.

Luckasson R, Borthwick-Duffy S, Buntinx WHE, et al. *Mental Retardation: Definition, Classification, and Systems of Supports*. 9th ed. Washington, DC: American Association on Mental Retardation; 1992.

Maher CO, Piatt JH, Section on Neurologic Surgery. Incidental findings on brain and spine imaging in children. *Pediatrics*. 2015;135:e1084-e1096.

Martin GR, Beekman RH, Mikula EB, et al. Implementing recommended screening for critical congenital heart disease. *Pediatrics*. 2013;132:e185-e192.

Michelson DJ, Shevell MI, Sherr EH, et al. Evidence report: genetic and metabolic testing on children with global developmental delay. *Neurology*. 2011;77:1629-1635.

Miller DT, Adam MP, Aradhya S, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet*. 2010;86:749-764.

Moeschler JB, Shevell M, Committee on Genetics. American Academy of Pediatrics. Clinical Report. Comprehensive evaluation of the child with intellectual disability or global developmental delays. *Pediatrics*. 2014;134:e903-e918.

Montgomery TR. The dysmorphology examination. In: Accardo PJ, ed. *Capute and Accardo's Neurodevelopmental Disabilities in Infancy and Childhood*. Vol. 1. 3rd ed. Baltimore: Paul H. Brookes; 2008:311-320.

Moster D, Lie RT, Markestad T. Joint association of Apgar scores and early neonatal symptoms with minor disabilities at school age. *Arch Dis Child Fetal Neonatal Ed*. 2002;86:F16-F21.

Murphy CC, Yeargin-Allsopp M, Decoufle P, et al. The administrative prevalence of mental retardation in 10-year-old children in metropolitan Atlanta, 1985 through 1987. *Am J Public Health*. 1995;85:319-323.

Nelson HD, Bougatsos C, Nygren P. Universal newborn hearing screening: systematic review to update the 2001 US Preventive Services Task Force recommendations. *Pediatrics*. 2008;122:e266-e276.

Newborn Screening Authoring Committee. Newborn screening expands: recommendations for pediatrician and medical homes—Implications for the system. *Pediatrics*. 2008;121:192-217.

Nordenbaek C, Jorgensen M, Kyvik KO, et al. A Danish population-based twin study on autism spectrum disorders. *Eur Child Adolesc Psychiatry*. 2014;23:35-43.

Pakula AT, Van Naarden Braun K, Yeargin-Allsopp M. Cerebral palsy: classification and epidemiology. *Phys Med Rehabil Clin N Am*. 2009;20:425-452.

Palfrey JS, Singer JD, Walker DK, et al. Early identification of children's special needs: a study in five metropolitan communities. *J Pediatr*. 1987;111:651-659.

Pimperton H, Blythe H, Kreppner J, et al. The impact of universal newborn hearing screening on long-term literacy outcomes: a prospective cohort study. *Arch Dis Child*. 2014;doi:10.1136/archdischild-2014-307516.

Purser HRM, Thomas MSC, Snoxall S, et al. Definitions versus categorization: assessing the development of lexico-semantic knowledge in Williams syndrome. *Int J Lang Commun Disord*. 2011;46:361-373.

Rapin I, Segalowitz SJ. On the nature and scope of child neuropsychology. In: Segalowitz SJ, Rapin I, eds. *Handbook of Neuropsychology*. Vol. 8. 2nd ed. Part I. Child Neuropsychology. New York: Elsevier; 2002:1-6.

Riggs ER, Wain KE, Riethmaier D, et al. Chromosomal microarray impacts clinical management. *Clin Genet*. 2014;85:147-153.

Rodriguez DP, Poussaint TY. Neuroimaging of the child with developmental delay. *Top Magn Reson Imaging*. 2007;18:75-92.

Sand N, Silverstein M, Glascoe FP, et al. Pediatricians' reported practices regarding developmental screening: do guidelines work? Do they help? *Pediatrics*. 2005;116:174-179.

Schaefer GB, Bodensteiner JB. Radiological findings in developmental delay. *Semin Pediatr Neurol*. 1998;5:33-38.

Schaefer GB, Sheth RD, Bodensteiner JB. Cerebral dysgenesis: an overview. *Neurol Clin*. 1994;12:773-788.

Schalock RL, Luckasson RA, Shogren KA, et al. The renaming of mental retardation: understanding the change to the term intellectual disability. *Intellect Dev Disabil*. 2007;45:116-124.

Segel R, Ben-Pazi H, Zeligson S, et al. Copy number variations in cryptogenic cerebral palsy. *Neurology*. 2015;84:1660-1668.

Scheiner AP, Sexton ME. Prediction of developmental outcome using a perinatal risk inventory. *Pediatrics*. 1991;88:1135-1143.

Seltzer MM, Floyd F, Greenberg J, et al. Life course impacts of mild intellectual deficits. *Am J Ment Retard*. 2005;110:451-468.

Shevell M, Ashwal S, Donley D, et al. Practice parameter: evaluation of the child with global developmental delay. *Neurology*. 2003;60:367-380.

Silove N, Collins F, Ellaway C. Update on the investigation of children with delayed development. *J Paediatr Child Health*. 2013;49:519-525.

Smith RD. The use of developmental screening tests by primary-care pediatricians. *J Pediatr*. 1978;93:524-527.

Soden SE, Saunders CJ, Willig LK, et al. Effectiveness of exome and genome sequencing guided by acuity of illness for diagnosis of neurodevelopmental disorders. *Sci Transl Med*. 2014;6(265):265ra168.

Srour M, Shevell M. Genetics and the investigation of developmental delay/intellectual disability. *Arch Dis Child*. 2014;99:386-389.

Stevenson RE, Schwartz CE. X-linked intellectual disability: unique vulnerability of the male genome. *Dev Disabil Res Rev*. 2009;15:361-368.

Stiles J. Neural plasticity and cognitive development. *Dev Neuropsychol*. 2000;18:237-272.

Tarini BA, Zikmund-Fisher BJ, Saal HM, et al. Primary care providers' initial evaluation of children with global developmental delay: a clinical vignette study. *J Pediatr*. 2015;167:1404-1408.

Tarpey PS, Smith R, Pleasance E, et al. A systematic, large-scale resquencing screen of X-chromosome coding exons in mental retardation. *Nat Genet*. 2009;41(5):535-543.

Thorpe HS, Werner EE. Developmental screening of preschool children: a critical review of inventories used in health and educational program. *Pediatrics*. 1974;53:362-370.

Valente EM, Ferraris A, Dallapiccola B. Genetic testing for paediatric neurological disorders. *Lancet*. 2008;7:1113-1126.

Van Karnebeek CD, Jansweijer MC, Leenders AG, et al. Diagnostic investigations in individuals with mental retardation: a systematic literature review of their usefulness. *Eur J Hum Genet*. 2005;13:6-25.

Van Karnebeek CDM, Scheper FY, Abeling NG, et al. Etiology of mental retardation in children referred to a tertiary care center: a prospective study. *Am J Ment Retard*. 2005;110(4):253-267.

Van Karnebeek CDM, Shevell M, Zschocke J, et al. The metabolic evaluation of the child with an intellectual developmental disorder: diagnostic algorithm for identification of treatable causes and new digital resource. *Mol Genet Metab*. 2014;111:428-438.

Van Karnebeek CDM, Stockler S. Treatable inborn errors of metabolism causing intellectual disability: a systematic literature review. *Mol Genet Metab*. 2012;105:368-381.

Yeargin-Allsopp M, Drews CD, Decoufle P, et al. Mild mental retardation in black and white children in metropolitan Atlanta: a case-control study. *Am J Public Health*. 1995;85:324-328.

25

Dysmorphology

Donald Basel

Dysmorphology evolved as a subset of clinical genetics that focused on standardizing the descriptive terminology used to define deviations from normal structural development in the context of syndromic disorders. These traits were termed *birth defects* and result from malformations, deformations, or disruptions, which generally have a significant and obvious effect on appearance (Table 25.1 and Fig. 25.1). To identify the abnormal state, one has to be familiar with normal developmental stages, the timing of specific organ development, and developmental vulnerable periods (Fig. 25.2). The dysmorphic physical examination is directed to overcome some of the clinical challenges of identifying and describing birth defects by providing a framework in which to differentiate normal human variable morphology from the abnormal in the context of a specific diagnosis.

An international initiative to standardize the nosology used in clinical dysmorphology has been adapted to the Internet as an online resource supported by the National Human Genome Research Institute (NHGRI): https://elementsofmorphology.nih.gov/. These terms in themselves are of no clinical utility (aside from communicating the appropriate malformation to other providers) but when used with available database tools, can be a powerful adjunct to determining the final diagnosis. Examples of these terms are noted in Table 25.2. The importance of reaching a diagnosis is to provide insight into the nature of the condition, enable appropriate counseling of recurrence risk, guide the necessary management recommendations, and provide the family with an overall framework of the natural history and prognosis of the disorder.

DIAGNOSTIC APPROACHES

Often the geneticist-dysmorphologist is asked to view a child with the expectation that the total picture will lead to an instant identification of a syndrome or condition. Instant identification happens more frequently with the more common or better known conditions. Most often a diagnosis is difficult with many complex disorders; knowledge, skill, attention to detail, the use of the current tools, review of literature, and standard reference sources are required for diagnosis.

Human Variation

Normal human variation is enormous. A common sense argument can be made for variation by pointing out the ability of people to recognize and differentiate thousands of individuals whom they have met; computer programs for facial recognition are based on this premise. Nonetheless, humans differ little from one another at their DNA level; variation is currently estimated at approximately 0.1% or 1 base of DNA/1000 bases, which equates to roughly 6 coding variants/gene. The advent of molecular and biochemical diagnostic methods for identifying genes and gene products has begun to ease the burden on the geneticist by providing diagnostic and confirmatory tests for syndrome identification. Sequencing of the Human Genome clarified many prior preconceived notions regarding human genetics. Prior to the completion of the project, it was estimated that humans had approximately 100,000 genes, whereas in reality this number is closer to 23,000 genes. Of these genes, less than half have been associated with human disease and many have no clear function assigned to them at this time. This gene coding portion of the genome only accounts for approximately 1% of the total genomic code, which consists of roughly 6 billion nucleotides. DNA analysis when available may provide the genotype and confirm the diagnosis, but it cannot unerringly define the phenotype.

There is still much to learn about our genetic code and how genes are expressed and regulated; even if we could perform genomic sequencing on every patient, there would be a number of patients in whom the molecular diagnosis remained elusive. The current diagnostic rate for exome sequencing is approximately 25%, this improves to about 30% with exome trios in which selected relatives are sequenced along with the affected individual and used to assess allele segregation with the phenotype.

There are common genetic pathways that relate genes within a pathway to common groups of disorders. This has provided an explanation to clinicians why seemingly disparate disorders share certain disease associations but remain clinically distinct. An example of this is the **RASopathies** (Fig. 25.3), in which *germline* pathogenic variants in *KRAS* can result in the classic Noonan phenotype or cardiofaciocutaneous syndrome. There is genetic heterogeneity in this group of disorders which share several overlapping features. In addition, *somatic* mosaicism for genes in this pathway has been identified to cause several capillary/vascular malformation disorders. Another example is the allelic disorders involving the *TRPV4* gene, which include brachyolmia type 3, digital arthropathy–brachydactyly, hereditary motor and sensory neuropathy type IIc, metatropic dysplasia, parastremmatic dwarfism, scapuloperoneal spinal muscular atrophy, spondyloepiphyseal dysplasia Maroteaux type, spinal muscular atrophy, and spondylometaphyseal dysplasia Kozlowski type. The wide phenotypic variability ranging from primary skeletal dysplasias to isolated neuromuscular disease speaks to the complexities of gene regulation and tissue-specific expression.

In addition to the primary gene code, there are tertiary elements that can be *imprinted*, in which gene expression is controlled by parent of origin or even be affected by the environment, the concept of **epigenetic** control. Further variability exists in genomic **copy number variations**, some of which are considered normal variants, while others result in recognizable microdeletion or microduplication disorders such as velocardiofacial syndrome (VCFS) and Smith–Magenis syndrome.

Not all congenital malformations or birth defects are primarily genetic. Teratogenic exposure, vascular events, and extrinsic factors, such as amniotic bands, all have the potential to result in deviations from normal morphologic development (Fig. 25.4).

(See *Nelson Textbook of Pediatrics,* p. 899.)

TABLE 25.1 Mechanisms, Terminology, and Definition of Dysmorphology

Terminology	Definition	Example
Malformation sequence	Single, local tissue morphogenesis abnormality that produces a chain of subsequent defects	DiGeorge sequence of primary 4th brachial arch and 3rd and 4th pharyngeal pouch defects that lead to aplasia or hypoplasia of the thymus and parathyroid glands, aortic arch anomalies, and micrognathia
Deformation sequence	Mechanical (uterine) forces that alter structure of intrinsically normal tissue	Oligohydramnios produces deformations by in utero compression of limbs (dislocated hips, equinovarus foot deformity), crumpled ears, dislocated nose, or small thorax
Disruption sequence	In utero tissue destruction after a period of normal morphogenesis	Amnionic membrane rupture sequence, leading to amputation of fingers/toes, tissue fibrosis, and destructive tissue bands
Dysplasia sequence	Poor organization of cells into tissues or organs	Neurocutaneous melanosis sequence with poor migration of melanocyte precursor cells from the neural crest to the periphery, manifesting as melanocytic hamartomas of skin, meninges, and so forth
Malformation syndrome	Appearance of multiple malformations in unrelated tissues without an understandable unifying cause; with enhanced genetic investigation, a single etiology may become identified	Trisomy 21 Teratogens

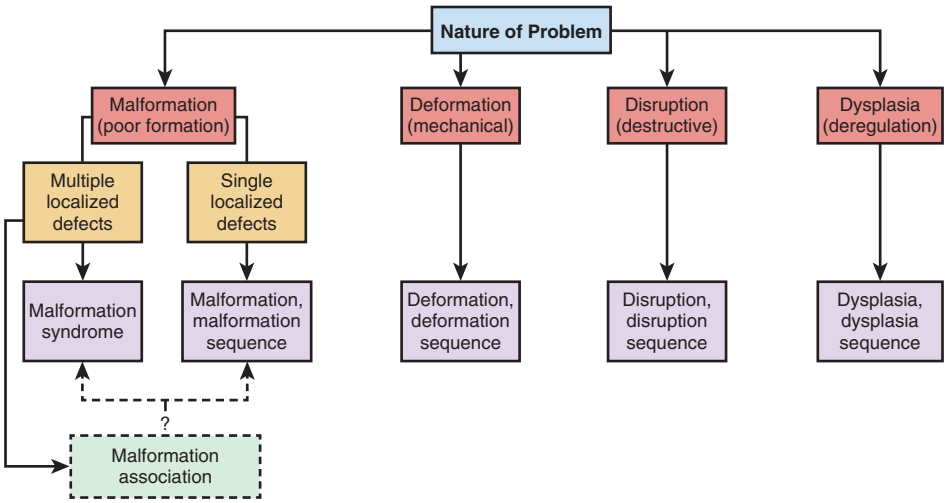


FIGURE 25.1 Most patients with multiple structural defects will fall into one of these categories (e.g., malformation; deformation; disruption; or dysplasia). The prognosis, management, and recurrence-risk counseling may vary considerably among these categories. (From Jones KL, Jones MC, Del Campo M, eds. *Smith's Recognizable Patterns of Human Malformation*. 7th ed. Philadelphia: Elsevier; 2013:3.)

TERATOLOGY

Teratogens are agents that affect normal development and can give rise to congenital birth defects. For the most part, teratogens are considered to be chemical agents, such as thalidomide or alcohol. However, perinatal infections with cytomegalovirus would fall into this broad category as would significant radiation exposure. The minority of fetuses exposed to potential teratogens show effects, even if exposed at the same time with the same dose of the agent (e.g., alcohol, 30%; thalidomide, 20%; hydantoins, 10%; warfarin, 8%; lithium, 7%; and diazepam, 1%). The exact determinants why some fetuses are affected are poorly understood.

Embryologic timing is one of the critical elements that define the final outcome. There are broadly 3 periods identified in fetal development (see Fig. 25.2).

Implantation: Period of fertilization through gastrulation and formation of the embryonic plate (first 2 weeks after fertilization). Significant interference with development during this time usually results in loss of conceptus.

Embryonic: This is the period of primary tissue differentiation, and thus, the period at greatest risk for major malformations (weeks 3 through 8).

Fetal: At this time, primary organogenesis is complete, but growth and neuronal migration proceed. The central nervous system (CNS) is at risk and many of the minor birth defects arise during this time (9 weeks through birth).

Some teratogens may have delayed effects, and these do not result in an overt congenital malformation; diethylstilbestrol (DES) exposure in a female fetus can predispose to vaginal clear cell carcinoma in puberty.

(See *Nelson Textbook of Pediatrics,* p. 814.)

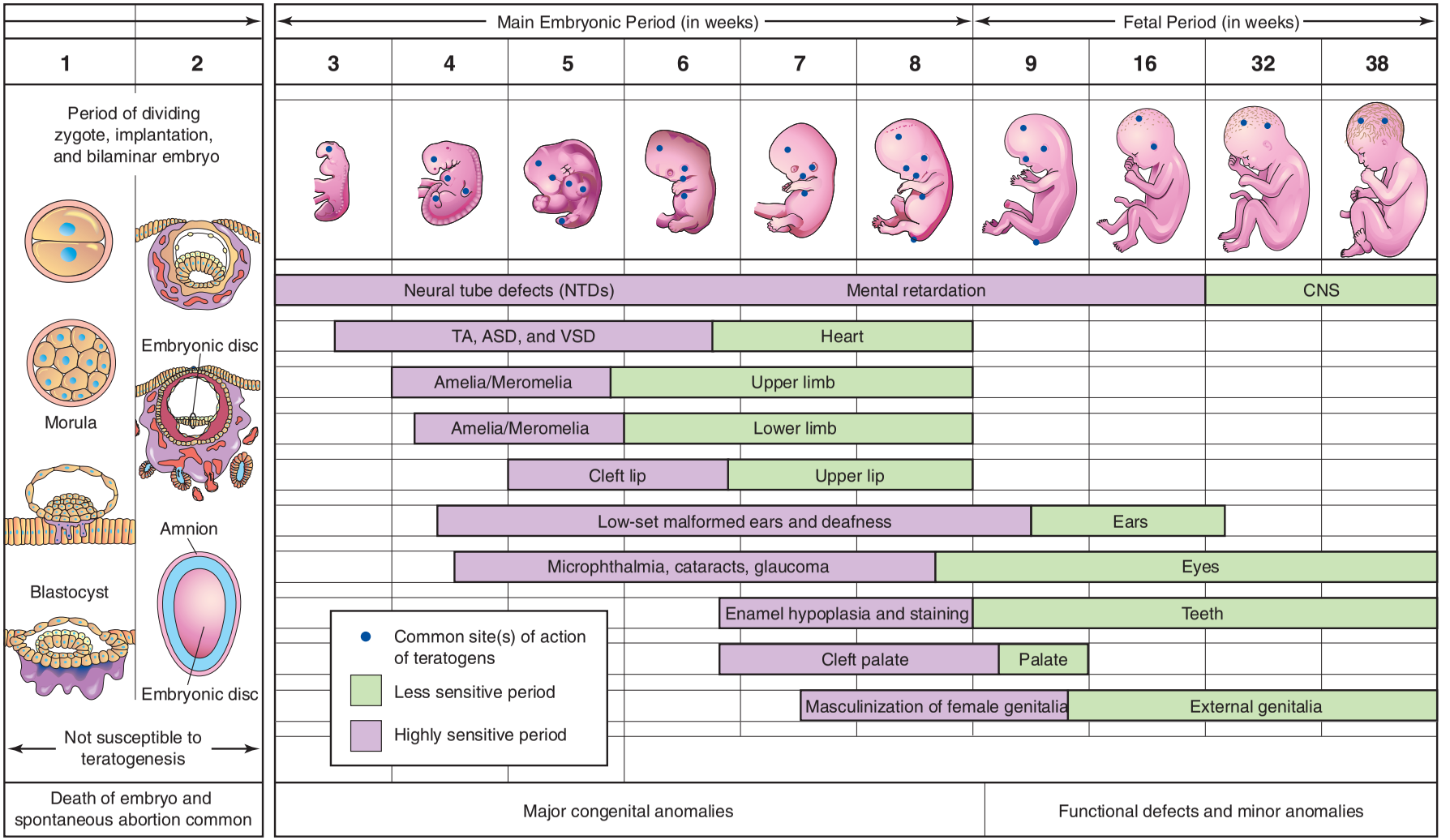


FIGURE 25.2 Critical Periods in Human Prenatal Development. During the first 2 weeks of development, the embryo is usually not susceptible to teratogens; a teratogen damages all or most of the cells, resulting in death of the embryo, or damages only a few cells, allowing the conceptus to recover and the embryo to develop without birth defects. During highly sensitive periods *(mauve),* major birth defects may be produced (e.g., amelia, absence of limbs, neural tube defects, spina bifida cystica). During stages that are less sensitive to teratogens *(green),* minor defects may be induced (e.g., hypoplastic thumbs). ASD, atrial septal defect; CNS, central nervous system; TA, truncus arteriosus; VSD, ventricular septal defect. (From Moore KL, Persaud TVN, et al. *The Developing Human*. 10th ed. Philadelphia: Elsevier; 2016.)

TABLE 25.2 Glossary of Selected Terms Used in Dysmorphology

Terms Pertaining to the Face and Head

Brachycephaly: A condition in which head shape is shortened from front to back along the sagittal plane; the skull is rounder than normal

Canthus: The lateral or medial angle of the eye formed by the junction of the upper and lower lids

Columella: The fleshy tissue of the nose that separates the nostrils

Glabella: Bony midline prominence of the brows

Nasal alae: The lateral flaring of the nostrils

Nasolabial fold: Groove that extends from the margin of the nasal alae to the lateral aspects of the lips

Ocular hypertelorism: Increased distance between the pupils of the 2 eyes

Palpebral fissure: The shape of the eyes based on the outline of the eyelids

Philtrum: The vertical groove in the midline of the face between the nose and upper lip

Plagiocephaly: A condition in which head shape is asymmetric in the sagittal or coronal planes; can result from asymmetry in suture closure or from asymmetry of brain growth

Scaphocephaly: A condition in which the head is elongated from front to back in the sagittal plane; most normal skulls are scaphocephalic

Synophrys: Eyebrows that meet in the midline

Telecanthus: A wide space between the medial canthi

Terms Pertaining to the Extremities

Brachydactyly: A condition of having short digits

Camptodactyly: A condition in which a digit is bent or fixed in the direction of flexion (a "trigger finger"–type appearance)

Clinodactyly: A condition in which a digit is crooked and curves toward or away from adjacent digits

Hypoplastic nail: An unusually small nail on a digit

-melia: A suffix meaning "limb" (e.g., amelia—missing limb; brachymelia—short limb)

Polydactyly: The condition of having 6 or more digits on an extremity

Syndactyly: The condition of having 2 or more digits at least partially fused (can involve any degree of fusion, from webbing of skin to full bony fusion of adjacent digit)

From Behrman RE, Kliegman RM. *Nelson Essentials of Pediatrics*. 4th ed. Philadelphia: Saunders; 2002:149.

Embryogenesis

The developmental timing of the event that results in the final phenotype is one of the critical determinants of the phenotypic outcome. When considering embryologic processes, timing is one element but other important concepts are important to aid understanding of the final outcome. The timing is important because multiple developmental processes are occurring at the same time and thus a number of malformations present concomitantly as a result of interference with everything developing at the same embryonic time; radial ray defects may be seen with cardiac septal defects as in Holt–Oram syndrome. The common embryologic origin of various elements can give rise to overlapping disorders with shared elements: branchial arch developmental field defects in VCFS or disorders caused by abnormal neural crest cell migration. Critical embryologic events can give rise to disorders due to failure of a specific embryologic process: Neural tube defects arise as a result of abnormal neural tube fusion/closure.

BIRTH DEFECTS

It is estimated that approximately 15% of newborns have 1 minor anomaly; 0.8% have 2 minor anomalies, and 0.5% have 3. The more minor anomalies that are present, the greater is the probability that an underlying syndrome or a major organ anomaly is also present. Statistically, this equates to a 5-fold risk if 2 minor anomalies are present and a 20-30% probability that there is a major anomaly (congenital heart disease, renal, CNS, limb) if 3 minor anomalies are present. Approximately 50% of major anomalies involve the head and neck region. The Centers for Disease Control and Prevention statistics for the United States assert that a baby is born with a birth defect every 4.5 minutes; in 2010, birth defects accounted for about 1 in 5 infant deaths in the United States. Examples and potential etiologies are noted in Table 25.3.

Persons in the same family or ethnic groups may superficially resemble one another; any attempt at identifying a condition as an abnormality should include inspection of close relatives. *Unusual morphologic findings in a child who resembles his or her parents does not exclude a dysmorphic condition.* The parents might have variation in expression of the disorder or there could be additional features which are distinct that need to be separated from the common familial morphology.

CLINICAL CLASSIFICATION

Single-System Defects

- Most common of all birth defects
- Isolated to a single organ system
- Clinically similar to organ malformations seen in syndromes due to common pathways and same-organ end-point
- Examples: isolated cleft lip/palate; congenital heart disease; distal limb anomalies

Association

- Statistically ascertained nonrandom co-occurrences of multiple anomalies in which a single underlying cause is not identifiable. Usually, a diagnosis of exclusion.
- Creates an awareness to evaluate for associated anomalies
- <1% risk for recurrence
- Example: VATER/VACTERL (vertebral, anal atresia, cardiac, tracheoesophageal fistula, renal anomalies, limb malformations—typically radial ray) (Figs. 25.5 and 25.6)

Sequence

- A cascade of effects from a single localized abnormality in early morphogenesis that results in multiple congenital anomalies
- Example: Potter sequence secondary to renal agenesis and severe oligohydramnios (Figs. 25.7 and 25.8)

Syndrome

- The presence of multiple structural/functional defects due to a single cause.
- Example: Down syndrome caused by trisomy for chromosome 21 (Fig. 25.9) or other trisomies (Fig. 25.10 and Tables 25.4, 25.5, and 25.6)

Complex

- Denotes a malformation arising from the effects of an event affecting a single developmental field in the embryo. Typically relates to aberrant vasculature or vascular events
- Example: sacral agenesis, Poland anomaly

(See *Nelson Textbook of Pediatrics,* p. 899.)

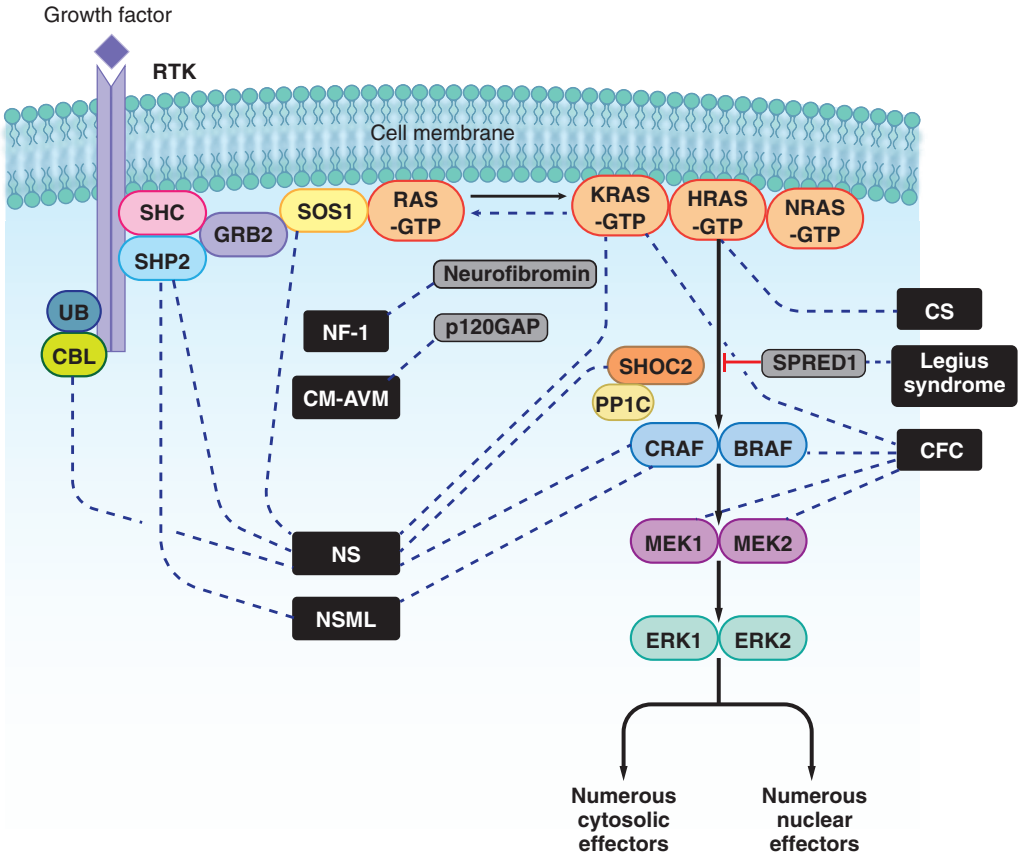


FIGURE 25.3 The RAS/MAPK signal transduction pathway. The MAPK signaling pathway of protein kinases is critically involved in cellular proliferation, differentiation, motility, apoptosis, and senescence. The RASopathies are medical genetic syndromes caused by mutations in genes that encode components or regulators of the Ras/MAPK pathway (indicated by *dashed lines*). These disorders include neurofibromatosis type 1 (NF1), Noonan syndrome (NS), Noonan syndrome with multiple lentigines (NSML), capillary malformation–arteriovenous malformation syndrome (CM-AVM), Costello syndrome (CS), cardiofaciocutaneous syndrome (CFC), and Legius syndrome. RAS/MAPK, RAS protein family/mitogen-activated protein kinase. (From Rauen KA. The RASopathies. *Annu Rev Genomics Hum Genet*. 2013;14:355-369.)

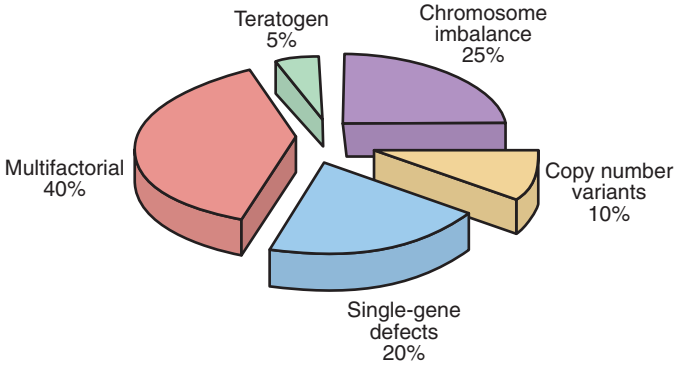


FIGURE 25.4 Causes of Congenital Malformation. (From Nussbaum RL, et al. *Thompson and Thompson Genetics in Medicine*. 8th ed. Philadelphia: Elsevier; 2016.)

DYSMORPHIC EVALUATION

The first step toward a dysmorphic evaluation is an index of suspicion. In a neonate with birth defects, this is often a logical step, but in a child with failure to thrive or short stature, someone has to initiate a more detailed evaluation for a syndromic entity or it will be delayed. It is not uncommon for a young female to be diagnosed with monosomy X (Turner syndrome) when she fails to enter puberty.

Components of Dysmorphic Evaluation

Detailed History

- A family health history (3-generation pedigree analysis) (Figs. 25.11 and 25.12) (about 5% of children have a biologic father who is not the reported partner)
- Pregnancy history with detail to exposures (teratogens) and general health (gestational diabetes)
- Birth history and neonatal status
- Participation in state newborn screening
- General growth and developmental history; *regression is very important to document*
- Complete medical history, including details of the minutiae of symptom presentation and progression

Some sensitivity surrounding the history taking should be exercised as it is common for a parent to perceive responsibility for the outcomes. Most birth defects occur sporadically without a family history. Autosomal recessive disorders typically happen in 1 or more siblings without a family history; many autosomal dominant conditions occur as new mutations. Sex-linked conditions may have no prior family occurrence or an occurrence identified in a remote relative such as the maternal grandmother's brother.

TABLE 25.3 Causes of Congenital Malformations

Monogenic (7.5% of Serious Anomalies)
X-linked hydrocephalus
Achondroplasia
Ectodermal dysplasia
Apert disease
Treacher Collins syndrome

Chromosomal (6% of Serious Anomalies)
Trisomies 21, 18, 13
XO, XXY
Deletions 4p– 5p–, 7q–, 13q–, 18p–, 18q–, 22q–
Prader–Willi syndrome (50% have partial deletion of chromosome 15)

Maternal Infection (2% of Serious Anomalies)
Intrauterine infections (e.g., herpes simplex, CMV, varicella-zoster, rubella, and toxoplasmosis)

Maternal Illness (3.5% of Serious Anomalies)
Diabetes mellitus
Phenylketonuria
Hyperthermia

Uterine Environment (% Unknown)
Deformation
Uterine pressure, oligohydramnios: clubfoot, torticollis, congenital hip dislocation, pulmonary hypoplasia, 7th nerve palsy

Disruption
Amniotic bands, congenital amputations, gastroschisis, porencephaly, intestinal atresia

Twinning
Conjoined twins, intestinal atresia, porencephaly

Environmental Agents (% Unknown)
Polychlorinated biphenyls
Herbicides
Mercury
Alcohol

Medications (% Unknown)
Thalidomide
Diethylstilbestrol
Phenytoin
Warfarin
Cytotoxic drugs
Isotretinoin (vitamin A)
D-Penicillamine
Valproic acid

Unknown Etiologies
Polygenetic
Anencephaly/spina bifida
Cleft lip/palate
Pyloric stenosis
Congenital heart disease

Imprinting of Genes
Prader–Willi syndrome
Beckwith–Wiedemann syndrome

Sporadic Syndrome Complexes (Anomalads)
CHARGE syndrome
VATER syndrome
Pierre Robin syndrome
Prune-belly syndrome

Nutritional
Low folic acid–neural tube defects

CMV, cytomegalovirus; CHARGE, coloboma, heart defects, atresia choanae, retarded growth, genital anomalies, ear anomalies (deafness); VATER, vertebral defects, anal atresia, tracheoesophageal fistula with esophageal atresia, and radial and renal anomalies.
From Behrman RE, Kliegman RM. *Nelson Essentials of Pediatrics*. 4th ed. Philadelphia: Saunders; 2002:148.

Family health history. It is customary to start with the siblings of the patient (**the proband**), proceed to the parents and the parents' siblings and their children, and then consider the 4 grandparents and their siblings. This approach is more helpful than the generic question, "Does anyone in the family have anything like this?" Many parents may be unaware of neonatal deaths in older relatives (the proband's grandparents or uncles and aunts). Most people are unfamiliar with the term *consanguinity*, but the examiner can ask whether there are ancestors in common or inquire about the place of origin and the size of the community from which the families derive. Maiden names of women should always be noted. Self-identified, remote ancestry may help identify a fruitful area to investigate because certain conditions may be more common in certain ethnic population groups. Consanguinity refers to couples who have ancestors in common within 2 or 3 generations, whereas group identity is not consanguinity.

Pregnancy and birth history. Maternal health and concurrent illness with treatment is a critical part of the evaluation. Details of participation in prenatal screening programs and prenatal evaluations can help resolve uncertainties that arise during the evaluation. On occasion, a discrepancy is discovered between an ultrasound report and a neonatal clinical finding: for example, a "normal" cerebellum reported at 17 weeks of gestation and absence of the cerebellum at term. Before concluding that some process happened between 17 and 40 weeks of gestation, it is important to review the actual studies done at 17 weeks. This type of investigation can help pinpoint the timing of in utero problems or can eliminate erroneous hypotheses if the study of the fetus at 17 weeks was actually incomplete or inconclusive. Viral and other infectious illnesses and rashes are germane to note, as are times of exposure during the pregnancy. Parvovirus B19, rubella virus, cytomegalovirus, *Toxoplasma* species, herpes simplex virus, varicella virus, and *Treponema pallidum* (syphilis) are microorganisms that can

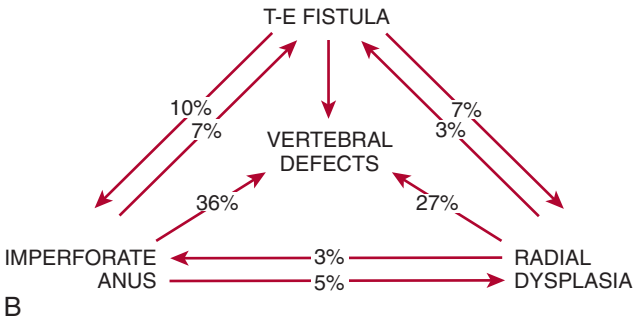


FIGURE 25.5 VATER association as initially set forth. *A,* Young infant with vertebral anomalies, anal atresia, esophageal atresia with tracheoesophageal fistula, radial aplasia on the left, and thumb hypoplasia on the right. *B,* Relative frequencies of some of the other VATER association defects when the patient is ascertained by virtue of having 1 of the defects. *C,* Same patient at 2 years of age, with normal intelligence. (From Jones KL, Jones MC, Del Campo M, eds. *Smith's Recognizable Patterns of Human Malformation*. 7th ed. Philadelphia: Elsevier; 2013:852.)

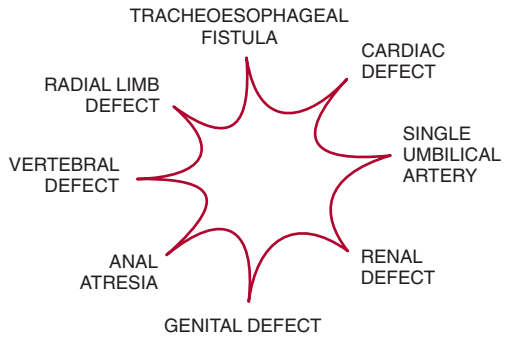


FIGURE 25.6 *Left,* Expanded VACTERL association of defects. *Right,* Note the relatively severe thumb *(radial)* defect of the right hand and the much more subtle "radial" defect of the left hand *(arrow)*. The arrow depicts a hypoplastic thenar eminence and crease. (From Jones KL, Jones MC, Del Campo M, eds. *Smith's Recognizable Patterns of Human Malformation*. 7th ed. Philadelphia: Elsevier; 2013:853.)

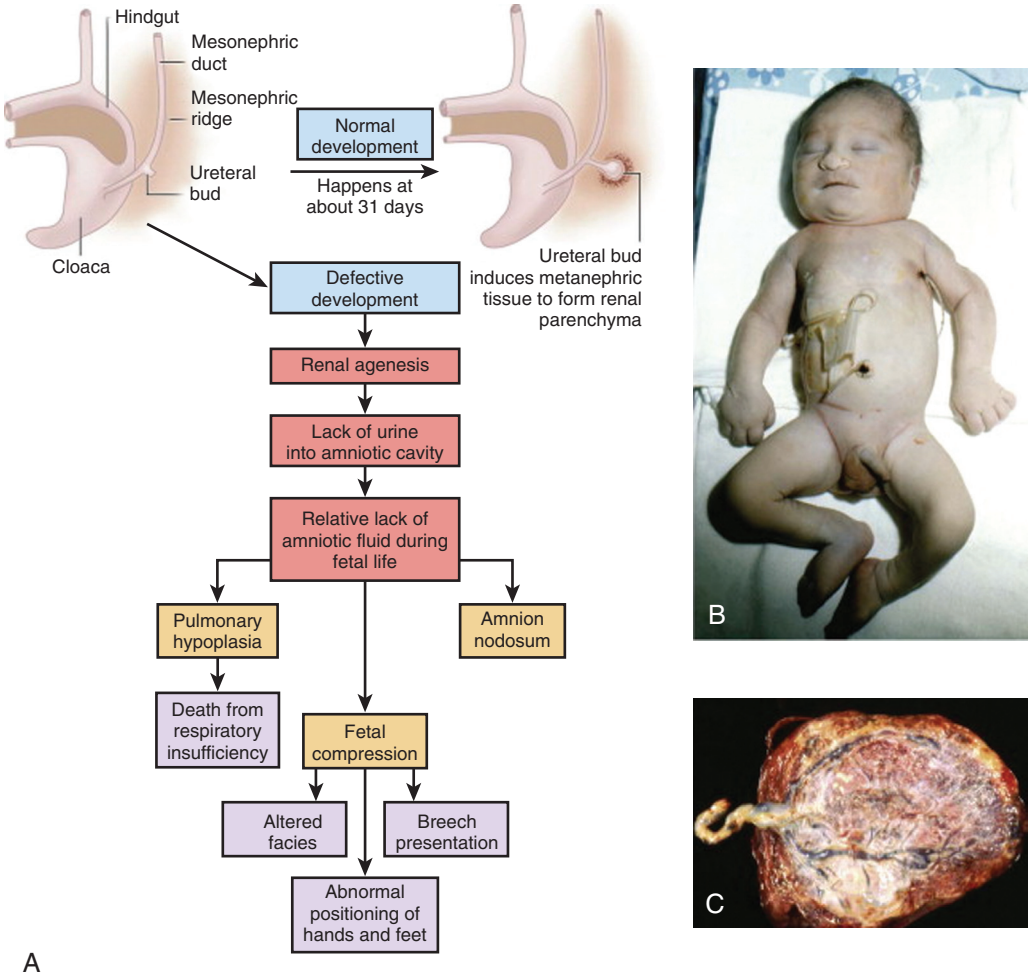


FIGURE 25.7 *A–C,* The consequences of renal agenesis. Note the multiple deformational defects in *B,* and the amnion nodosum (brown-yellow granules from vernix that have been ribbed into defects of the amniotic surface) in *C.* (From Jones KL, Jones MC, Del Campo M, eds. *Smith's Recognizable Patterns of Human Malformation.* 7th ed. Philadelphia: Elsevier; 2013:821.)

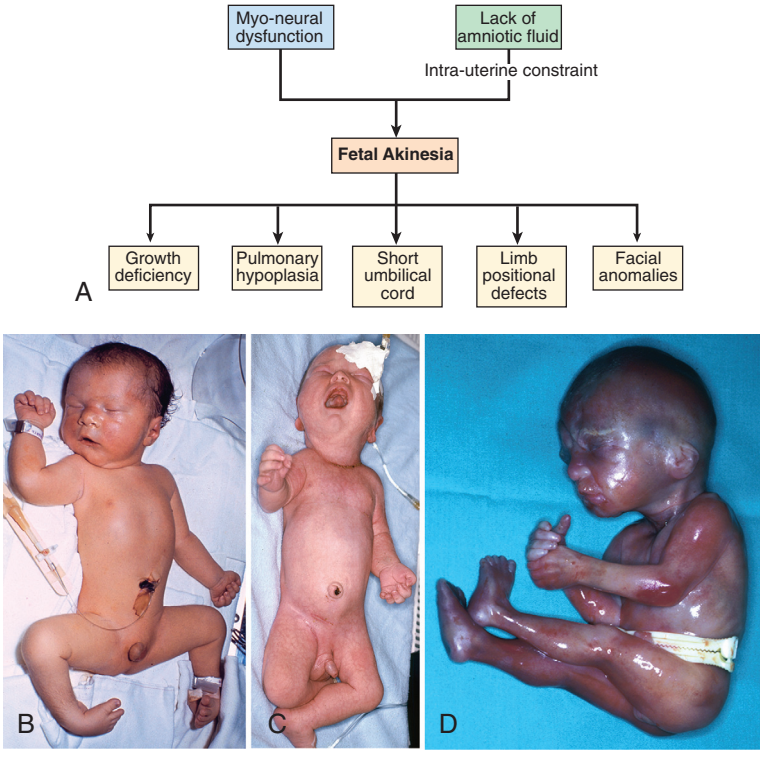


FIGURE 25.8 *A,* This diagram demonstrates the etiologically heterogeneous phenotype that results from fetal akinesia. *B,* This infant was born with myotonic dystrophy to a mother with the same condition. He had multiple joint contractures with thin bones and respiratory insufficiency. *C,* This infant was immobilized in a transverse lie after amnion rupture at 26 weeks. *D,* This fetus had bilateral renal agenesis resulting in oligohydramnios. (From Graham JL. *Smith's Recognizable Patterns of Human Malformation.* 3rd ed. Philadelphia: Elsevier; 2007:287; Figure 47-2.)

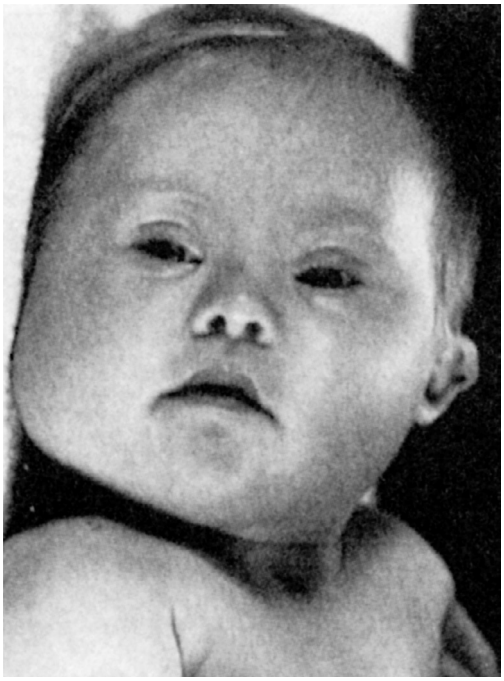


FIGURE 25.9 Facial appearance of a child with Down syndrome. (From Wiedemann HR, Kunze J, Dibbern H. *Atlas of Clinical Syndromes: A Visual Guide to Diagnosis*. 3rd ed. St. Louis: Mosby; 1989.)

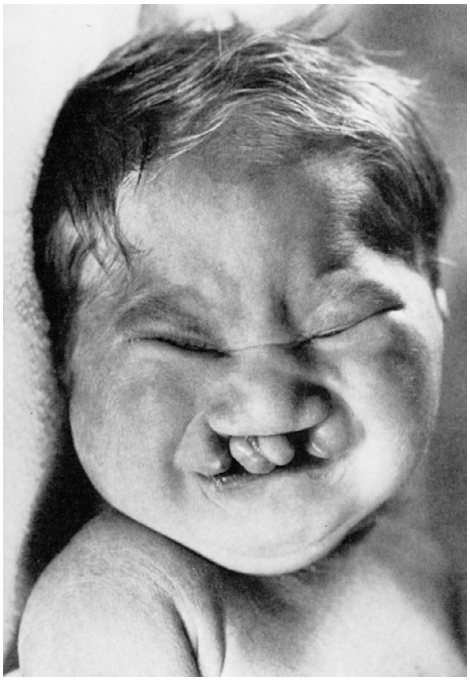


FIGURE 25.10 Facial appearance of a child with trisomy 13. (From Wiedemann HR, Kunze J, Dibbern H. *Atlas of Clinical Syndromes: A Visual Guide to Diagnosis*. 3rd ed. St. Louis: Mosby; 1989.)

TABLE 25.4 Clinical Findings That May Be Present with Trisomy 21*

Stature smaller than that of peer age group	Lax joints, including laxity of the atlantoaxial articulation (the latter predisposing the patient to C1–C2 dislocation)
Developmental delays	Short, broad hands, feet, and digits; single palmar crease, clinodactyly
Congenital heart disease (e.g., endocardial cushion defect and ventricular septal defect)	Exaggerated space between 1st and 2nd toes
Structural abnormalities of the bowel (e.g., tracheoesophageal atresia, duodenal atresia, annular pancreas, duodenal web, and Hirschsprung disease)	Velvety, loosely adhering mottled skin (cutis marmorata) in infancy; coarse, dry skin in adolescence
Central hypotonia	Statistically increased risk for leukemia, Alzheimer disease, hypothyroidism
Brachycephaly	
Delayed closure of fontanels	
Small midface, hypoplastic frontal sinuses, myopia, and small (short) ears	

*An individual may exhibit any combination of these findings. There is no correlation between the number of physical findings and eventual level of mental performance. The increased risk for leukemia is significant, but probably no >1% for any individual. Alzheimer disease is relatively common in persons with trisomy 21 who die in middle adult life, but its frequency in all adults with Down syndrome is not known.
From Behrman RE, Kliegman RM. *Nelson Essentials of Pediatrics*. 4th ed. Philadelphia: Saunders; 2002:142.

be teratogenic or affect organ function. Fetal exposure to these organisms at a vulnerable time can be critical; conversely, exposures after formation of an organ are not expected to have a morphologic effect on the organ. Perinatal anoxia is often blamed for infants' problems, but infants with a syndrome or genetic condition may be predisposed to perinatal problems, including fetal distress or neonatal adaptive difficulties.

Developmental history. A developmental history establishes the pattern for acquisition of developmental milestones. A screening tool such as the Denver Developmental Assessment Test can assist in the evaluation of younger children. It is important to establish whether a child is making progress, remaining static, or showing signs of **developmental regression** by losing landmarks of development. The last possibility is the most ominous for prognosis and warrants aggressive evaluation for diagnosis and possible treatment.

Prior medical concerns including all evaluations and investigations to date should be reviewed. It is often necessary to delay the initial consult so that past medical records can be made available for thorough review.

Examination

The details of morphology are documented in much more detail than is ordinarily the case in a general physical examination. Diagnosis is often based on the language used in the description. Even if a diagnosis

TABLE 25.5 Ultrasonographic and Pathologic Findings of Trisomic Conditions

Abnormality	Trisomy 21	Trisomy 18	Trisomy 13
IUGR	+	++	++
CNS abnormalities	–	+	++
Holoprosencephaly	–	–	++
Mild ventricular dilatation	+	+	+
Agenesis of the corpus callosum	–	+	+
Dandy–Walker variant	–	++	+
Spina bifida, NTD	–	++	+
Face	–	+	++
Cyclopia	–	–	++
Cleft lip or palate	–	+	++
Microphthalmia	–	++	+
Duodenal atresia	++	–	–
Esophageal atresia	+	++	–
Cardiac defects	+	++	++
Echogenic intracardiac foci	+	–	++
Diaphragmatic hernia	–	++	+
Cystic hygroma	+	+	+
Hydrops	+	+	+
Omphalocele	–	+	+
Echogenic bowel	++	+	+
Short femur or humerus	+	++	–
Radial aplasia or limb reduction	–	++	+
Clenched hands or wrists	–	++	+
Polydactyly	–	–	++
Club feet or rocker-bottom feet	–	++	++
Renal abnormalities	+	+	++
Choroid plexus cysts	+?	++	–
Single umbilical artery	–	++	++

IUGR, intrauterine growth restriction; CNS, central nervous system; NTD, neural tube defect.
From Nyberg DA, Souter VL. Sonographic markers of fetal aneuploidy. *Clin Perinatol*. 2002;27:762.

TABLE 25.6 Findings That May Be Present in Trisomy 13 and Trisomy 18

	Trisomy 13	Trisomy 18
Head and face	Scalp defects (e.g., cutis aplasia) Microphthalmia, corneal abnormalities Cleft lip and palate in 60–80% of cases Microcephaly Microphthalmia Sloping forehead Holoprosencephaly (arhinencephaly) Capillary hemangiomas Deafness	Small and premature appearance Tight palpebral fissures Narrow nose and hypoplastic nasal alae Narrow bifrontal diameter Prominent occiput Micrognathia Cleft lip or palate Microcephaly
Chest	Congenital heart disease (e.g., VSD, PDA, and ASD) in 80% of cases Thin posterior ribs (missing ribs)	Congenital heart disease (e.g., VSD, PDA, and ASD) Short sternum, small nipples
Extremities	Overlapping of fingers and toes (clinodactyly) Polydactyly Hypoplastic nails, hyperconvex nails	Limited hip abduction Clinodactyly and overlapping fingers; index over 3rd, 5th over 4th; closed fist Rocker-bottom feet Hypoplastic nails
General	Severe developmental delays and prenatal and postnatal growth retardation Renal abnormalities Nuclear projections in neutrophils Only 5% live >6 mo	Severe developmental delays and prenatal and postnatal growth retardation Premature birth, polyhydramnios Inguinal or abdominal hernias Only 5% live >1 yr

ASD, atrial septal defect; PDA, patent ductus arteriosus; VSD, ventricular septal defect.
From Behrman RE, Kliegman RM. *Nelson Essentials of Pediatrics*. 4th ed. Philadelphia: Saunders; 2002:142.

is not clear, the description is the starting point of the evaluation. It is helpful to have an anatomic outline for assessing morphology in an orderly and systematic manner.

There are few opportunities to follow a predetermined flow for the examination in most young children, but it is important to maintain a level of structure to the data collection process so as not to overlook a critical finding. It is also good practice to obtain photographs of the face with frontal and side profiles for later reflection and utilization of newer facial recognition tools.

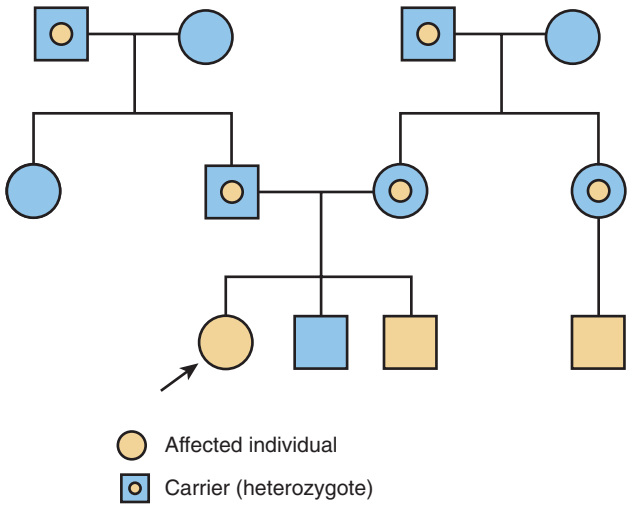


FIGURE 25.11 Pedigree showing affected individuals and carriers. (From Marcdante KJ, Kliegman RM. *Nelson Essentials of Pediatrics*. 7th ed. Philadelphia: Elsevier; 2015:147; Figure 47-1.)

Initial Inspection

General observation of the patient is important. The office visit is a small snapshot in the life of the person being evaluated. Subtle movements, behaviors, and social interactions may be key to the underlying diagnosis. Children with Williams syndrome are exceptionally sociable with verbose language skills and frequently have a coarse character to their voice, whereas on the opposing end, children with autism may not permit you to perform a complete physical examination and the greatest opportunity to evaluate movements and physical traits is while you are initially interviewing the parents or caregivers.

Anthropometrics

The Centers for Disease Control and Prevention has published growth curves for children and adolescents that are based upon a heterogeneous U.S. population more representative of various ethnic and ancestral groups than were previous charts. There are separate curves for height, weight, head circumference, and stature for boys and girls aged 0-36 months, and there are corresponding curves for boys and girls aged 2-18 years, in addition to curves for body mass index, but without curves for head circumference. There are also references for anthropometric measurements of various body parts from the fetus to adult age. If a child's measurements are discrepant from the norms—that is, *over the 97th percentile* or *under the 3rd percentile*—it is possible to transpose the actual measurement up or down to the 50th percentile on the same line to determine the height age or weight age equivalent. Height can be plotted versus weight on the stature curve to determine whether these parameters are proportional. Thus, a child can be identified as small or tall for age and appropriate or inappropriate in weight (either too heavy or too thin) for height. A child with short stature and proportionate weight has proportionate short stature. Head growth is an important factor in assessing brain growth as well as skull growth

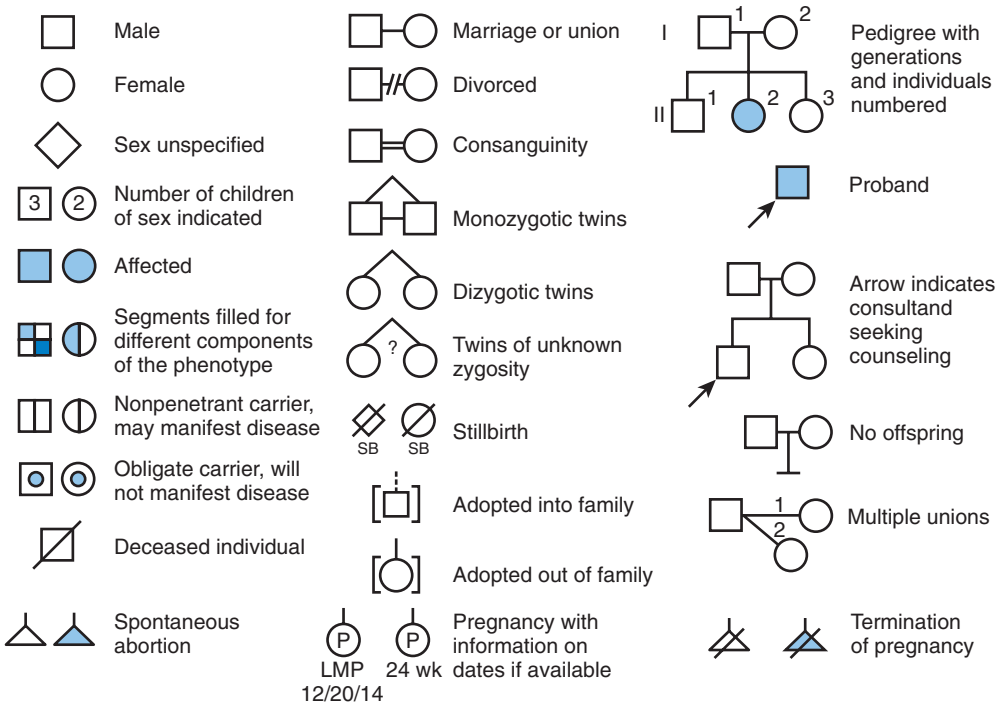


FIGURE 25.12 Symbols commonly used in pedigree charts. Although there is no uniform system of pedigree notation, the symbols used here are according to recent recommendations made by professionals in the field of genetic counseling. (From Nussbaum RL, McInnes RR, Willard HF, eds. *Thompson and Thompson Genetics in Medicine*. 8th ed. Philadelphia: Elsevier; 2016:109.)

and suture closure. Abnormally small head size (**microcephaly**) and abnormally large head size (**macrocephaly**) are considered in proportion to stature with consideration for chronologic age. A child 7 years of age but with a height age of 4 years and proportionate weight and head circumference does not truly have microcephaly but proportionate short stature. Standardized tables exist in various reference resources for several ethnic groups that allow for assessment across racial barriers. Additionally standardized charts exist for known syndromes so that normal growth can be appropriately evaluated in a child with a known diagnosis.

A helpful diagnostic assessment for children of discrepant size is the **bone age**, determined by radiograph: generally of the left hand and wrist, according to the standards of Gruleich and Pyle, but occasionally, for infants, by radiograph of the hemiskeleton.

The data collection should include the following highlights with more detail completed as needed.

Head and Neck

- Hair: distribution, texture, pigmentation, low posterior hairline (Fig. 25.13)
- Skull: shape, fontanel
- Neck: mobility, adenopathy, thyroid, embryonic remnants (branchial arch)

FIGURE 25.13 Turner syndrome. *A–C,* Note prominent ears, loose folds of skin in posterior neck with low hairline, broad chest with widely spaced nipples. (Courtesy Dr. Lynne M. Bird, Children's Hospital, San Diego; From Jones KL, Jones MC, Del Campo M, eds. *Smith's Recognizable Patterns of Human Malformation.* 7th ed. Philadelphia: Elsevier; 2013:81.)

Face

- Forms the largest and most important aspect of the dysmorphic evaluation.

General "Rules"

- 1/3s = forehead-nasion : nasion-subnasale : subnasale-chin = 1 : 1 : 1
- Perpendicular from pupils should meet corners of mouth
- Inner canthal distance should allow space for an additional eye (on magnetic resonance imaging [MRI] space between globes should allow an additional globe)
- Top of ear should align with eyebrow/line through pupils should align with root of outer helix.
- Forehead: slope, breadth, height, prominence
- Eyebrows: thickness/fullness, arch
- Eye: distance (hyper- or hypotelorism), color, pupil shape, presence of epicanthus or telecanthus, alignment (up- or down-slanting)
- Ears: overall shape/architecture, position, rotation, pits, creases, hearing
- Nose: root, bridge, tip, columella, nasolabial fold, alae nasi, philtrum
- Mouth: lips thickness and shape, lip pits, mucosal lesions, dental alignment, dentition, palate, uvula
- Chest: shape, pectus, nipples, breathing
- Abdomen: organomegaly, masses, hernia
- Genitalia: structure, size, Tanner stage, anus, and perineum
- Musculoskeletal: spine alignment, joint mobility (Fig. 25.14 and Table 25.7), proportions, finger length, palmar surfaces, nail health.
- Neurologic evaluation: complete including development, behavior and modified mini-mental examination, and observation for unique movements or behaviors.

If a child has an unusual appearance and the differences do not seem to be familial variations as judged by observing the parents, it is necessary to describe how the child appears different. When the variation is a discontinuous variable—that is, a birth defect (e.g., there is an extra digit on the ulnar side of each hand; there is a cleft of the lip on the left that extends into the left nostril, and there is a notch in the gum behind the cleft)—the task is easier. Such birth defects may be considered major abnormalities. The subtle malformations are often minor abnormalities, but both major and minor findings are relevant to diagnosis. Some conditions may be obvious on inspection alone, especially to an experienced observer. Typical manifestations of Down syndrome (Figs. 25.15 and 25.16; see also Tables 25.4 and 25.5 and Fig. 25.9), trisomy 13 or 18 (Figs. 25.17 and 25.18; see also Table 25.6 and Fig. 25.10), severe manifestations of Cornelia de Lange syndrome, and those of Williams syndrome may represent a quick diagnosis; however, even these classical syndromes may manifest in atypical and subtle ways, and careful assessment is necessary to identify them. The expectation that, with enough experience, a physician, even a geneticist or a dysmorphologist, can unerringly identify every case of a common syndrome (even one so common and well known as trisomy 21) is not true. Human diversity is so great that even the most experienced clinicians are glad for confirmatory tests. Most cases of trisomy 21 can be identified by inspection, but there is not the same degree of certainty about every dysmorphic patient.

ASSEMBLING THE DATA

After the history and examination are complete, the abnormal findings are listed. In general, the order is in a sequence ranked by perceived importance. In determining the order, the clinician may consider the magnitude of the deviation, but uniqueness is important in differentiating conditions. Subtleties can be significant; for example, **inverted nipples** (common in carbohydrate-deficient glycoprotein syndrome) or **redundant umbilical skin** (in company with abnormal anterior chamber of the eye and abnormally shaped teeth in Rieger syndrome) can be very helpful in identifying a condition.

The description of history and morphology becomes the working diagnosis. Even if the clinician cannot find a match in the standard references concerning the syndrome identification, a descriptive diagnosis is invaluable for providing the constellation of findings that delineate the problems.

MINIMAL DIAGNOSTIC CRITERIA

The key phenotypic elements of a syndrome, which unquestionably identify it and differentiate it from all other similar conditions, have been termed the *minimal diagnostic criteria*. In the absence of a definitive laboratory test, establishing the diagnostic criteria is a logical and ideal goal for achieving uniformity of diagnosis.

Unfortunately, minimal diagnostic criteria are difficult to decide upon and are enumerated for only a few conditions. Reasonably successful efforts for identifying diagnostic criteria for 2 relatively common conditions, **neurofibromatosis type 1 (NF1)** (Table 25.8) and **Marfan syndrome** (Table 25.9), have been achieved and updated through consensus conferences. The molecular abnormalities for each condition have been identified, but the absence of a molecular result does not exclude the diagnosis, and in the case of Marfan syndrome, the molecular finding itself is not sufficient for a diagnosis.

In NF1, a family history that includes an affected parent is a major help (and major criterion) for diagnosis. When there is no positive family history, an index case requires additional criteria. The criteria are quite specific and include easily documented findings. However, criteria do not include learning disabilities, intellectual disability, scoliosis, short stature, asymmetric limb growth, endocrine and neuroendocrine tumors, hypertension, or epilepsy, any of which may be present in NF1. These conditions are germane but not unique to NF1.

The concept of minimal diagnostic criteria is laudable but difficult to achieve. When available, the minimal diagnostic criterion is the confirmatory laboratory test; however, the confirmatory laboratory test does not necessarily define the parameters of the phenotype of the syndrome as is noted in the example of Marfan syndrome and *FBN1* gene variants.

TOOLS TO ASSIST THE DIAGNOSTIC ODYSSEY

Reference books on syndromology, human malformations, and deformations are excellent resources for assistance with diagnosis; however, most illustrations in texts focus on individuals with the most exaggerated findings to illustrate the condition. Birth defects are discrete (discontinuous) variables, but human features occur in a continuum. Diagnosis becomes a process of identifying the variables by a systematic evaluation of the entire individual.

Technology has eliminated some of the art forms once common practice (e.g., dermatoglyphics or the analysis of finger and palm ridge patterns).

The advent of broader molecular screening tools for diagnosis has limited the initial quest for a clinical diagnosis as the relatively high prevalence of copy number variations (microdeletion/duplication disorders) has established chromosome microarrays as the first-line standard of care in the evaluation of a child with multiple congenital anomalies, developmental delays, or autism spectrum behaviors. This is supported by the American College of Medical Genetics as well as the U.S. Food and Drug Administration (FDA). Common

FIGURE 25.14 Beighton Hypermobility Score. *A,* Passive dorsiflexion of the fifth metacarpophalangeal joint. Score is positive if ≥90 degrees (bilateral testing). *B,* Passive hyperextension of the elbow. Score is positive if ≥10 degrees (bilateral testing). *C,* Passive hyperextension of the knee. Score is positive if ≥10 degrees (bilateral testing). *D,* Passive apposition of the thumb to the flexor side of the forearm, while the shoulder is 90 degrees flexed, elbow extended, and hand pronated. Score is positive if the whole thumb touches the flexor side of the forearm (bilateral testing). *E,* Forward flexion of the trunk with the knees straight. Score is positive if the hand palms rest easily on the floor. (From Smits-Engelsman B, Klerks M, Kirby A. Beighton score: a valid measure for generalized hypermobility in children. *J Pediatr.* 2010;158:119-123.)

TABLE 25.7 9-Point Beighton Score of Hypermobility

Description	Bilateral Testing	Scoring (Max. Points)
Passive dorsiflexion of the 5th metacarpophalangeal joint to ≥90 degrees	Yes	2
Passive hyperextension of the elbow >190 deg in females and >180 deg in males	Yes	2
Passive hyperextension of the knee >190 deg in females and >180 deg in males	Yes	2
Passive apposition of the thumb to the flexor side of the forearm, while the shoulder is flexed 90 degrees, elbow is extended, and hand is pronated	Yes	2
Forward flexion of the trunk, with the knees straight, so that the hand palms rest easily on the floor	No	1
Total		**9**

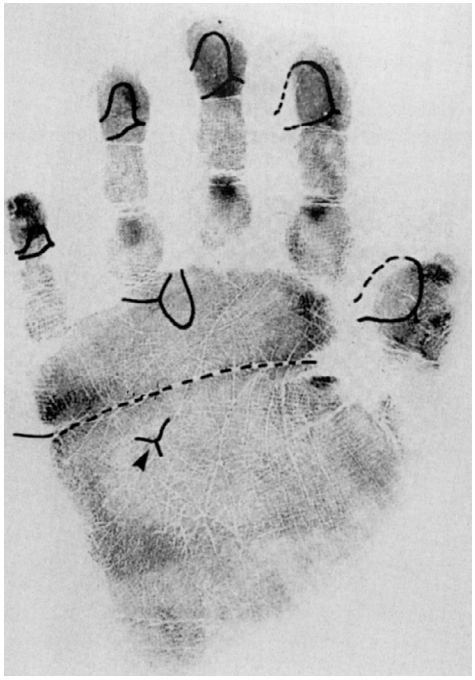


FIGURE 25.15 Characteristic dermal patterns of the palm of a child with Down syndrome: a single flexion crease (simian crease), axial triradius *(arrowhead)* in distal position, a pattern area on the palm between the third and fourth digits, and ulnar loops on all 10 digits. (From Nussbaum RL, McInnes RR, Willard HF. *Thompson and Thompson Genetics in Medicine*. 6th ed. Philadelphia: Saunders; 2001:160.)

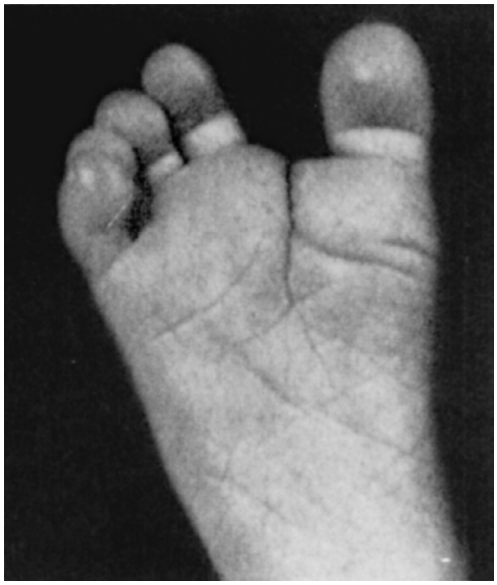


FIGURE 25.16 "Prehensile" foot in a 1-month-old child. (From Wiedemann HR, Kunze J, Dibbern H. *Atlas of Clinical Syndromes: A Visual Guide to Diagnosis*. 3rd ed. St. Louis: Mosby; 1989.)

FIGURE 25.17 Trisomy 18: Overlapping finger and hypoplastic nails. (From Wiedemann HR, Kunze J, Dibbern H. *Atlas of Clinical Syndromes: A Visual Guide to Diagnosis*. 3rd ed. St. Louis: Mosby; 1989.)

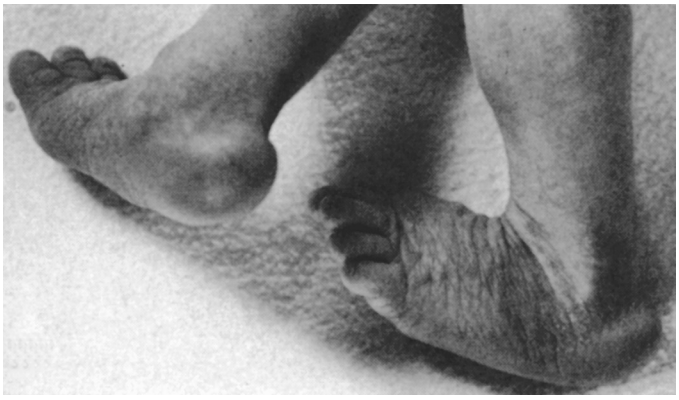


FIGURE 25.18 Trisomy 18: Rocker-bottom feet (protruding calcanei). (From Wiedemann HR, Kunze J, Dibbern H. *Atlas of Clinical Syndromes: A Visual Guide to Diagnosis*. 3rd ed. St. Louis: Mosby; 1989.)

(See *Nelson Textbook of Pediatrics*, p. 3179.)

TABLE 25.8 Diagnostic Criteria for Neurofibromatosis Type 1*

1. Family history (an affected parent)
2. 6 or more café-au-lait spots
   >0.5 cm in prepubertal children
   >1.5 cm in postpubertal children
3. 1 or more plexiform neurofibromas
4. 2 or more neurofibromas
5. Freckling of the armpits or in skin folds
6. 2 or more Lisch modules of the iris
7. Optic glioma
8. Osseous dysplasia of the sphenoid bone and/or long bones

*There must be positive findings in 2 or more categories.
From National Institutes of Health Consensus Developmental Conference. Neurofibromatosis conference statement. *Arch Neurol.* 1988;45:575.

chromosomal deletion and duplication disorders can be identified in this way (Table 25.10).

Utilization of specific genetic databases such as POSSUM (Pictures of Standard Syndromes and Undiagnosed Malformations) or LMD (London Medical Databases) relies on cross-referencing the presence of specific dysmorphologic features to create differential diagnoses. These resources, however, require an annual subscription and are curated by affiliated academic programs. Free resources that use the standardized ontologic nosology include OMIM (Online Mendelian Inheritance in Man; http://www.omim.org/) and Phenomizer (http://compbio.charite.de/phenomizer/), which similarly allow the end user to generate lists of potential diagnoses.

Novel technologic approaches such as utilization of facial recognition software in order to generate possible differential diagnoses are being developed and are playing an increasingly important role as experienced dysmorphologists become an endangered species. The most successful implementation of a mobile application called Face2Gene (http://www.fdna.com/face2gene/). This software is compliant with the Health Insurance Portability and Accountability Act (HIPAA) and gaining more acceptance as a powerful clinical tool in the dysmorphic evaluation as it utilizes facial heat mapping signatures to generate visual differential diagnoses that allow complex database analysis using standardized ontology to search clinical findings in OMIM, LMD, and POSSUM.

Genetic Testing

The catalog of available tests has expanded exponentially over the past decade, and as large-scale sequencing becomes more accessible and affordable, genomic analysis is not far away from becoming standard of care. The primary limitation of this testing is our current ability to interpret all the variation and to connect relevance of this variation to the clinical phenotype being evaluated. It thus remains important to collect and identify crucial/significant data elements that assist in the interpretation of the tests ordered. Broad panels encompassing common phenotypes are available for complex heterogeneic disorders such as epilepsy or cardiomyopathy. To assist in the identification of laboratories offering specific testing, a company offering global laboratory listing was established (https://www.genetests.org/).

Testing itself should be judiciously selected to confirm a diagnosis or gather more information to enable a diagnosis to be formulated. Before any laboratory or imaging testing is done, the examiner should address the question "Does the description correlate with a described condition or syndrome?" Often, the working diagnosis is the succinct and relevant description of the child, which amounts to a list of

TABLE 25.9 Revised Ghent Criteria for the Diagnosis of Marfan Syndrome

The revised criterion place more emphasis on aortic root dilatation/dissection and ectopia lentis

I: In the **absence of family history**: MFS DX if:
- (1) Aortic root dilated/dissected (Z ≥2) AND Ectopia Lentis (EL)*
- (2) Aortic root dilated/dissected (Z ≥2) AND FBN1
- (3) Aortic root dilated/dissected (Z ≥2) AND Syst (≥7 points)*
- (4) Ectopia Lentis with normal aortic root AND FBN1 mutation associated with Aortic root dilated/dissection

II: In the **presence of family history**: MFS DX if:
- (5) EL AND FH of MFS
- (6) Systemic feature score (≥7 points) AND FH of MFS*
- (7) Ao (Z ≥2 above 20 years old, ≥3 below 20 years) + FH of MFS*

***Caveat**: without discriminating features of Shprintzen–Goldberg syndrome, Loeys–Dietz syndrome, or Vascular EDS **AND** after TGFBR1/2, collagen biochemistry, COL3A1 testing if indicated.

(Other conditions/genes will emerge with time.)

Scoring of systemic features: Max total: 20 points; score ≥7 points indicates systemic involvement
- Wrist AND thumb sign **[3]** (wrist OR thumb sign **[1]**)
- Pectus carinatum deformity **[2]** (pectus excavatum or chest asymmetry **[1]**)
- Hindfoot deformity **[2]** (plain pes planus **[1]**)
- Pneumothorax **[2]**
- Dural ectasia **[2]** *(sensitive, but not specific; not considered equal to lens dislocation or aortic root enlargement)*
- Protrusio acetabuli **[2]** *AP Pelvis:* medial protrusion of the acetabulum at least 3-mm beyond the ilioischial line
- ↓US/LS** **AND** ↑arm span/height (>1.05) AND no severe scoliosis **[1]**
- Scoliosis (≥2 degrees) or thoracolumbar kyphosis **[1]**
- Reduced elbow extension **[1]** 170 degrees or less upon full extension
- Facial features (3/5) **[1]** (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)
- Skin striae **[1]** *(abnormal position or excessive)*
- Myopia > 3 diopters **[1]**
- Mitral valve prolapse (all types) **[1]**

US/LS** (normal upper to lower segment ratios)
White adults, 0.85; black adults, <0.78
Children 0–5 yo <1; 6–7 yo <0.95; 8-9 yo <0.9

Major Differential Diagnoses

Ectopia Lentis syndrome: EL with or without Syst AND with an FBN1 not known with Ao or no FBN1

MASS phenotype: Ao (Z < 2) AND Syst (≥5 with at least 1 skeletal feature) without EL

Mitral Valve Prolapse syndrome: MVP AND Ao (Z <2) AND Syst (<5) without EL

Differential expanded, conditions with:

aortic aneurysms: LDS, bicuspid aortic valve, familial thoracic aortic aneurysm, vEDS, arterial tortuosity

ectopia lentis: ectopia lentis syndrome, Weill–Marchesani syndrome, homocystinuria, Stickler syndrome systemic features: Shprintzen–Goldberg syndrome, CCA, LDS, MASS phenotype and MVPS

Ao, aortic root dilatation/dissection; AP, anteroposterior; CCA, Congenital Contractural Arachnodactyly; DX, diagnosis; EDS, Ehlers-Danlos syndrome; FH, family history; LDS, Loeys-Dietz syndrome; LS, lower segment; MASS, Mitral valve, myopia, Aorta, Skin and Skeletal features; MVPS, Mitral Valve Prolapse syndrome; Syst, systemic feature score; US, upper segment; vEDS, Vascular type of Ehlers-Danlos syndrome; yo, years old.
From Loeys BL, Dietz HC, Braverman AC, et al. The revised Ghent nosology for the Marfan syndrome. *J Med Genet.* 2010;47:476-485.

TABLE 25.10 Some Chromosomal Deletion Syndromes for Which There Is a Commercially Available DNA Probe for Fluorescent In Situ Hybridization Analysis

Condition	Brief Description	Probe
Williams syndrome	Proportionate short stature, mild–moderate to severe intellectual disability, cocktail patter for conversation, stellate pattern of iris pigmentation, supravalvular aortic stenosis, recessed nasal bridge, and wide mouth with full lips	7q11
WAGR syndrome	Wilms tumor, aniridia, growth delay, intellectual disability, and genitourinary anomalies	11p13
Prader–Willi syndrome Angelman syndrome	Distinct syndromes with common or overlapping areas of deletion; phenotype depends on gender of the parent of origin of the deletion. *Prader–Willi syndrome:* hypotonia in infancy, short stature, obesity, mild–moderate and occasionally, severe intellectual disability, small hands and feet (caused by paternal deletion of 15q11-13 or maternal uniparental disomy for chromosome 15). *Angelman syndrome:* severe intellectual disability, absence of speech, ataxia, tremulous movements, large mouth, frequent drooling (caused by maternal deletion of chromosome 15q11-13 or paternal uniparental disomy)	15q11
Smith–Magenis syndrome	Brachycephaly, prognathism, self-destructive behavior, wrist biting, pulling out nails, head banging, indifference to pain, severe intellectual disability, hyperactivity, social behavior problems	17p11.2
Miller–Dieker syndrome	Microcephaly, narrow temples, hypotonia/hypertonia, abnormal posturing, seizures, severe to profound intellectual disability, poor growth, lissencephaly and other brain abnormalities on CT or MRI	17p13
Velocardiofacial (VCF) syndrome (overlaps with DiGeorge syndrome)	*VCF:* cleft palate, congenital heart disease, learning and/or behavior problems, long face, prominent nose, limb hypotonia, slender hands with tapering fingers. *DiGeorge syndrome:* T cell deficiency, immunoglobulin deficiency	22q11

CT, computed tomography; MRI, magnetic resonance imaging; WAGR, Wilms tumor, aniridia, genitourinary anomalies, and mental retardation.

TABLE 25.11 Genetics Developmental Delay Evaluation

Tier One	Acylcarnitine profile Amino acids (plasma) Ammonia Urine organic acids Ceruloplasmin Copper (blood)—if abnormal repeat with 24 hr urine DNA microarray Homocysteine (blood) Lactic acid and Pyruvic acid (blood) to determine lactate : pyruvate ratio in mitochondrial disorders
Tier Two	Mucopolysaccharides screen Congenital disorders of carbohydrate glycosylation Chromosome Fragile X Prader–Willi and Angelman (methylation testing) Creatine/guanidinoacetate (blood) Creatine/guanidinoacetate (urine) Purine pyrimidine panel (urine) Very long chain fatty acids (blood)

TABLE 25.12 Genetic Testing in Congenital Heart Disease

Patient Features	What to Order
CHD with features suggestive of trisomy 21 or 45X	Karyotype
CHD with features of trisomy 13 or 18	STAT chromosome FISH 21/18/13
Conotruncal congenital heart lesion • Interrupted aortic arch • Pulmonary atresia with ventricular septal defect • Tetralogy of Fallot • Truncus arteriosus • Malaligned ventricular septal defect and/or features typical of 22q11.2 deletion syndrome	DNA microarray
Heterotaxy	DNA microarray Next generation sequencing heterotaxy panel
CHD with or without dysmorphic features/multiple anomalies	DNA microarray

CHD, congenital heart disease; FISH, fluorescent in situ hybridization.

findings arranged in order of importance or significance from the perspective of the examiner.

A further advance in molecular understanding is the identification of metabolic disorders that are associated with intellectual disability but have proven treatments. The publication by Dr. van Karnebeel: *The Treatable Intellectual Disability* (www.treatable-id.org) digital tool to enhance diagnosis and care for rare diseases impacted the initial testing recommendations for children with intellectual disability, and recommendations for initial evaluations as listed in Tables 25.11 and 25.12 have become more broadly implemented. Thus metabolic screening for disorders that would not have been detected through national newborn screening programs is routinely used in the evaluation of children with intellectual disability.

Diagnostic imaging is invaluable in assessing CNS malformations, cardiac structure and function, skeletal deformity, and abdominal organs. The rapid advances in imaging technology and resolution are additionally enabling functional studies as well as real-time metabolic analysis with spectroscopy when using MRI to study the brain.

Bone age testing is indicated with short stature, growth delay, or large stature. Complete skeletal surveys are one of the only ways to help delineate skeletal dysplasias but require expert interpretation.

Specialized laboratory testing is reserved to aid specific diagnostic investigation (e.g., muscle biopsy, fibroblast culture for enzyme analysis, electron microscopy of arterial walls or blood buffy coat). These specialized tests are performed by a small number of laboratories to aid the diagnosis of rare disorders and should ideally be left to the expert physician.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Bone Age and Physical Measurements

Bonthron D, Fitzpatrick D, Porteous M, et al. *Clinical Genetics: A Case-Based Approach*. Philadelphia: WB Saunders; 1998.

Bronstein RA, Cornstock CH. Central nervous system anomalies. *Clin Perinatol*. 2000;27:791-812.

Bukowski R, Saade GR. Hydrops fetalis. *Clin Perinatol*. 2000;27:1007-1032.

Dar P, Gross SJ. Craniofacial and neck anomalies. *Clin Perinatol*. 2000;27:813-838.

Devine PC, Malone FD. Noncardiac thoracic anomalies. *Clin Perinatol*. 2000;27:865-900.

Dugoff L, Thieme G, Hobbins JC. Skeletal anomalies. *Clin Perinatol*. 2000;27:979-1006.

Emanuel BS, Saitta SC. From microscopes to microarrays: dissecting recurrent chromosomal rearrangements: the RASopathies annual review of genomics and human genetics. *Nat Rev Genetics*. 2007;8:869-883.

Frazer KA, Murray SS, Schork NJ, et al. Human genetic variation and its contribution to complex traits. *Nat Rev Genetics*. 2009;10:241-251.

Gleason PF, Eddleman KA, Stone JL. Gastrointestinal disorders of the fetus. *Clin Perinatol*. 2000;27:901-920.

Goodman RM, Gorlin RJ. *The Malformed Infant and Child—An Illustrated Guide*. New York: Oxford University Press; 1983.

Gorlin RJ, Cohen MM Jr, Hennekam RCM. *Syndromes of The Head and Neck*. 4th ed. New York: Oxford University Press; 2001.

Greulich WW, Pyle SI. *Radiographic Atlas of Skeletal Development of The Hand and Wrist*. 2nd ed. Stanford, CA: Stanford University Press; 1959.

Hall JG, Froster-Iskenius UG, Allanson JE. *Handbook of Normal Physical Measurements*. New York: Oxford University Press; 1989.

Jacobs AM, Toudjarska I, Racine A, et al. A recurring FBN1 gene mutation in neonatal Marfan syndrome. *Arch Pediatr Adolesc Med*. 2002;156:1081-1084.

Jones KL. *Smith's Recognizable Patterns of Human Malformations*. 5th ed. Philadelphia: WB Saunders; 1997.

Jones KL, Jones MC, Del Campo M, eds. *Smith's Recognizable Patterns of Human Malformation*. 7th ed. Philadelphia: Elsevier; 2013.

Keats TEE. *Atlas of Roentgenographic Measurement*. St. Louis: Mosby-Yearbook; 1990.

Malone FD, D'Alton ME. Anomalies peculiar to multiple gestations. *Clin Perinatol*. 2000;27:1033-1046.

McKusick VA. *Mendelian Inheritance in Man*. 12th ed. Baltimore: Johns Hopkins University Press; 1998. Available online as: OMIM: Online Mendelian Inheritance in Man, <http://www3.ncbi.nim.nih.gov/OMIM/>.

Nyberg DA, Souter VL. Sonographic markers of fetal aneuploidy. *Clin Perinatol*. 2000;27:761-789.

Robinson JN, Abuhanad AZ. Abdominal wall and umbilical cord anomalies. *Clin Perinatol*. 2000;27:947-978.

Roizen NJ, Patterson D. Down's syndrome. *Lancet*. 2003;361:1281-1288.

Saphier CJ, Gaddipati S, Liat E, et al. Prenatal diagnosis and management of abnormalities in the urologic systems. *Clin Perinatol*. 2000;27:921-946.

Simpson JL, Elias S. *Genetics in Obstetrics and Gynecology*. 3rd ed. Philadelphia: WB Saunders; 2003.

Simpson LL. Structural cardiac anomalies. *Clin Perinatol*. 2000;27:839-864.

Sontag LW, Snell D, Anderson M. Skeletal maturation. *Am J Dis Child*. 1939;58:949.

Stevenson RE, Hall JG, Goodman RM. *Human Malformations and Related Anomalies*. Vols. 1 and 2. New York: Oxford University Press; 1993.

Syndrome References

Van Karnebeel CDM, Houben RFA, Lafek M, et al. The treatable intellectual disability AAP. www.treatable-id.org: A digital tool to enhance diagnosis and care for rare diseases. *Orphanet J Rare Dis*. 2012;7:47.

26

Irritable Infant

Angela L. Rabbitt

An irritable infant is a challenge to the caregiver and medical provider and is a common presenting complaint in early infancy. An irritable infant is defined here as a patient younger than 1 year of age who according to the caregiver, cries excessively or is excessively fussy. There are many causes, but most irritable infants do not have significant underlying pathologic processes. However, there are serious entities that must not be missed (Table 26.1).

Medical providers should also recognize the profound anxiety and stress that infant crying may place on families and other caregivers. Although excessive crying generally resolves with time, the family's beliefs about the cause of the crying can have a lasting effect on the way they interact with the child and their beliefs about the infant's health. Caregivers who perceived their infant's crying as excessive or inconsolable described higher rates of depression, strained family relationships, and guilt about their inability to calm the infant. Excessive crying may even trigger thoughts of harming the infant and is reported as a common trigger for child physical abuse. Additionally, infants with early cry-fuss problems in combination with family dysfunction are at higher risk for ongoing behavioral problems, highlighting the need for early identification and intervention in this population. Therefore, the provider's response when evaluating an irritable infant should be focused on diagnosing potentially treatable medical conditions and on addressing the caregiver's understanding and response to the crying.

DIAGNOSTIC APPROACH

Less than 5-10% of infants who present for medical care due to excessive crying will have a serious underlying etiology. However, a thorough medical evaluation is needed to identify the minority of infants with treatable issues, and in healthy infants a thorough evaluation may reassure caregivers.

The initial evaluation of an irritable infant starts with a careful history and physical examination with the intent of ruling out potentially emergent conditions and stabilizing the patient if indicated (Fig. 26.1). The physical examination should include a complete examination of all body systems with the clothing removed. Table 26.2 lists elements of the history and physical examination suggestive of emergent and common diagnoses that may present with a chief complaint of crying. The history should be comprehensive, given the wide array of possible diagnoses to consider. The history should include questions about the characteristics of the cry (the time of day, duration, whether it is associated with feeds) and any changes to the infant's typical crying pattern. Infants with a sudden increase in the frequency and duration of inconsolable crying compared to normal are more likely to have an underlying medical condition. Clinicians should also ask caregivers why they think the infant is crying in order to specifically address any fears about the infant's health.

In the majority of cases, the history and/or physical examination will suggest the diagnosis, which can be confirmed with the judicious use of laboratory and imaging studies. However, providers should be aware of potentially serious diagnoses that may present with vague symptoms of fussiness and few other signs or symptoms on physical examination, including neurologic conditions and certain fractures. In very young infants, the neurologic exam is a poor screening tool to detect subtle neuropathology, and intracranial injury may not be accompanied by external evidence of trauma. An accurate history of injury may be concealed or unknown to the presenting caregiver in cases of physical abuse, and the child may present for medical care after the symptoms of acute injury have resolved. In addition to questions about recent symptoms, medical providers should ask about any remote history of suspicious bruising or other injury. A history of previous neurologic symptoms, such as episodes of unexplained seizures, apnea, altered mental status, developmental delay, or periods of extreme lethargy, may suggest an occult head injury or other nontraumatic neuropathology. Consider a skeletal survey and/or head imaging in infants with this history.

Growth parameters, including head circumference, should be obtained. Increasing head circumference percentile may point to increased intracranial pressure in infants with otherwise vague symptoms. Though conditions such as constipation, gastroenteritis, and gastroesophageal reflux are most often benign, poor growth or developmental delay may indicate more severe disease or that another medical condition is causing the symptoms.

A urinary tract infection (UTI) may also present with vague symptoms of irritability in infants. This may be one of the few conditions in which laboratory or imaging leads to a diagnosis in the absence of a suggestive clinical picture. Some suggest that a urinalysis and culture should be a standard screening test in infants who present with crying.

When the history and physical examination do not suggest a diagnosis, additional laboratory or radiographic evaluation may be needed. In particular, if the infant is ill-appearing, has evidence of poor growth or developmental delay, or is persistently inconsolable beyond the initial assessment, laboratory and radiographic studies should be done (Table 26.3). Patients may need to be monitored in the hospital until a diagnosis can be established. Some tests to consider include:

- A complete blood cell count with differential, erythrocyte sedimentation rate, and/or C-reactive protein measurement (for infection or inflammation, sickle cell disease)
- Analysis of cerebrospinal fluid (for meningitis or encephalitis)
- Blood culture
- Serum pH and complete metabolic panel, amylase, and lipase (for Electrolyte abnormalities, metabolic diseases, abdominal trauma)
- Urinalysis and culture
- Stool guaiac (for intussusception, gastroenteritis, cow's milk allergy)
- A skeletal survey

TABLE 26.1 Differential Diagnosis in the Irritable Infant

Emergent/Urgent Diagnoses	Nonemergent/Urgent Diagnoses
Eyes, Ears, Nose, Throat	
Choanal atresia	Otitis externa
Corneal abrasion	Teething
Foreign body	
Glaucoma	
Otitis media	
Respiratory	
Airway obstruction (croup, foreign body)	Upper respiratory tract infection
Lower respiratory tract infection (pneumonia, bronchiolitis)	
Cardiovascular	
Congestive heart failure	
Supraventricular tachycardia	
Anomalous coronary artery	
Myocarditis	
Kawasaki disease	
Gastrointestinal System	
Incarcerated hernia	Constipation
Gastrointestinal obstruction (intussusception, volvulus, pyloric stenosis, Hirschsprung disease)	Uncomplicated gastroenteritis
	Anal fissure
Abdominal trauma	Gastroesophageal reflux
Peritonitis	Inappropriate feeding volume or technique
	Milk or soy protein allergy
Genitourinary System	
Testicular torsion	
Ovarian torsion	
Urinary tract infection	
Musculoskeletal System	
Osteomyelitis	Minor, soft tissue injury
Septic arthritis	Discitis
Fractures	
Skin	
Cellulitis	Impetigo
Tourniquet syndrome (digit, genitalia)	Dermatitis
	Insect bites
	Minor injury
Central Nervous System	
Encephalitis	
Meningitis	
Increased intracranial pressure (trauma, hydrocephalus, intracranial hemorrhage)	
Intracranial mass	
Miscellaneous	
Drug ingestion	Vaccine reaction
Neonatal abstinence syndrome	Poor caregiver-infant interaction
Inborn error of metabolism	Normal crying
Sepsis	
Sickle cell crisis	
Physical abuse	

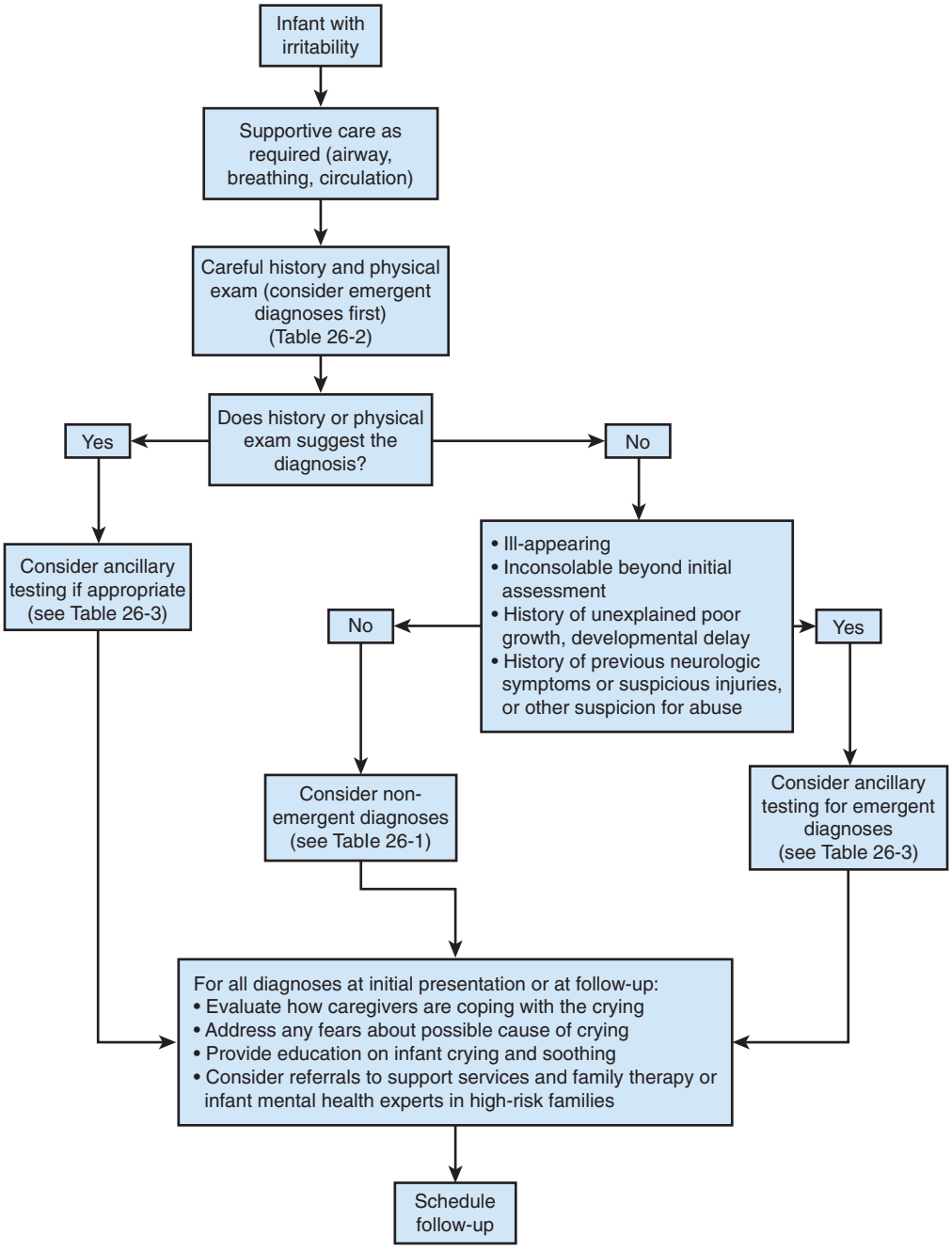


FIGURE 26.1 Initial approach to the irritable infant.

TABLE 26.2 Clinical Presentation of Selected Diagnoses in Infants Presenting with Crying

Review of Systems	Possible Physical Exam Findings	Diagnoses to Consider
Eyes, Ears, Nose, Throat		
• Pain or irritation of 1 eye • Chronic or intermittent tearing	• Photophobia • Tearing • Foreign body seen on lid inversion • Corneal enlargement or clouding • Ocular enlargement • Optic nerve cupping • Photophobia	• Foreign body • Corneal abrasion • Glaucoma
• Difficulty breathing and cyanosis during feeds; symptoms improve with crying	• Inability to pass a nasogastric tube • Decreased air movement through nares	• Choanal atresia
• Otorrhea • Fever • Ear tugging • Decreased appetite	• Bulging or immobile tympanic membrane • Abnormal color or perforated tympanic membrane • Otorrhea	• Otitis media • Otitis externa
• Excessive drooling • Decreased appetite	• Inflamed gums • Tooth eruption • Erythema over frenulum	• Teething • Lacerated frenulum
Respiratory		
• Trouble breathing, cough, congestion	• Abnormal breath sounds • Respiratory distress	• Airway obstruction (foreign body, croup) • Pneumonia • Bronchiolitis
Cardiovascular		
• Tachypnea and diaphoresis with feeds • Trouble breathing • Easy fatigability • Pallor, cyanosis	• Tachycardia • Respiratory distress • Poor perfusion • Abnormal heart sounds • Abnormal breath sounds • Hepatomegaly • Cardiomegaly	• Congestive heart failure • Supraventricular tachycardia • Anomalous coronary artery • Myocarditis
Gastrointestinal System		
• Constipation (hard stools, <2 per wk)	• Nonspecific exam • Stool mass in left lower quadrant • Anal fissure	• Constipation
• Delayed passage of meconium, poor growth, vomiting	• Abdominal distention • Tight anal canal with empty ampulla	• Hirschsprung disease
• Vomiting • Poor feeding with or without poor weight gain • Crying associated with feeds • Diarrhea	• Nonspecific exam • Hematochezia	• Milk and/or soy protein allergy • Gastroesophageal reflux disease • Gastroenteritis
• Vomiting • Poor feeding • Abdominal pain	• Abdominal distention • Abdominal tenderness, guarding • Abdominal or pelvic mass	• Intestinal obstruction (volvulus, intussusception) • Peritonitis
• History of injury • No history or history of prior suspicious injury in abusive trauma	• With or without evidence of injury on exam • Nonspecific abdominal exam	• Abdominal trauma
• Forceful vomiting • Hungry between episodes of emesis	• Dehydrated • Palpable pyloric sphincter	• Pyloric stenosis
• Improper formula volume or mixing • Frustration with feeds • Poor latch • Feeding aversion • Poor growth • Vomiting • Excess gas	• Nonspecific exam	• Inappropriate feeding volume or technique

TABLE 26.2 Clinical Presentation of Selected Diagnoses in Infants Presenting with Crying—cont'd

Review of Systems	Possible Physical Exam Findings	Diagnoses to Consider
Genitourinary System		
• Testicular swelling	• Testicular swelling, tenderness	• Testicular torsion
• Previous urinary tract infection	• Suprapubic tenderness • Nonspecific exam	• Urinary tract infection
Musculoskeletal System		
• Decreased movement of an extremity • Increased crying with movement	• Swelling, tenderness, warmth, erythema, pain or crepitus with palpation or movement • Nonspecific exam	• Fractures • Soft tissue injury • Osteomyelitis • Septic arthritis • Diskitis
Skin		
• Rash • Purulent drainage • Itching	• Swelling, tenderness, warmth, erythema, rash	• Infection • Dermatitis • Insect bites
• Swollen appendage	• Well-demarcated line separating normal tissue from a distal dusky edematous appendage • Ligature deeply imbedded in a groove covered by edematous tissue	• Tourniquet syndrome
• Sudden onset of irritability • History of injury • No history of injury or prior suspicious injury in abusive trauma	• Bruising, laceration, burns	• Abusive or nonabusive trauma
• Hernia	• Dusky or nonreducible umbilical or inguinal bulge	• Incarcerated hernia
Central Nervous System		
• Lethargy • Vomiting • Seizures • With or without fever	• Abnormal neurologic exam • Ill-appearing • Papilledema • Enlarged head circumference	• Meningitis • Encephalitis • Increased intracranial pressure (hydrocephalus, intracranial hemorrhage) • Intracranial mass
• No history, or history of prior suspicious injury • Prior history of symptoms of increased intracranial pressure	• Nonspecific exam • Retinal hemorrhages (present in 85% of patients with abusive head trauma) • With or without other injuries	• Abusive or nonabusive head trauma
Miscellaneous		
• Medication administration • Illicit drug use by caregivers	• Nonspecific exam • Altered mental status • Tachycardia • Respiratory or cardiac compromise • Seizures	• Drug ingestion
• Maternal drug use in a newborn • Poor feeding • Vomiting • Sneezing, hiccups, diarrhea • Poor sleep • Tremors • Seizures	• Nonspecific exam	• Neonatal abstinence syndrome
• Vomiting • Poor growth • Developmental delay or regression • Seizures	• Dehydration and shock • Organomegaly • Abnormal neurologic exam • Jaundice • Dysmorphic features • Abnormal odor • Tachypnea	• Inborn error of metabolism

TABLE 26.2 Clinical Presentation of Selected Diagnoses in Infants Presenting with Crying—cont'd

Review of Systems	Possible Physical Exam Findings	Diagnoses to Consider
Miscellaneous (cont'd)		
• Lethargy • With or without fever • Seizures	• Ill-appearing • Cardiorespiratory compromise	• Sepsis
• Infant or family history of sickle cell disease • Trouble breathing	• Respiratory distress • Splenomegaly • Swelling and tenderness of the hands and feet	• Sickle cell crisis
• Recent immunizations	• Nonspecific exam	• Vaccine reaction
• Dysfunctional or chaotic home environment • Significant caregiver stress	• Nonspecific exam	• Poor infant-caregiver interaction
• Content between crying bouts • Feeding well • Normal development	• Nonspecific exam	• Normal infant crying

- Computed tomographic (CT) scan or magnetic resonance imaging (MRI) of the head (for intracranial hemorrhage, mass, or hydrocephalus)
- Comprehensive urine drug screen

In the **consolable infant** without history or physical examination findings suggestive of a serious condition, nonemergent causes of crying are more likely (see Table 26.1). The most likely diagnosis in infants younger than 4 months of age is above average crying in a normal infant. However, because a definitive diagnosis has not been established, infants should receive a follow-up evaluation within 24 hours to ensure that a more serious illness was not missed and to address any additional concerns or questions about the crying. This element is especially critical if the clinician has any doubt concerning the establishment of the correct diagnosis.

ADDRESSING CAREGIVERS' RESPONSE TO CRYING

The distress, frustration, and anxiety that persistent or inconsolable crying may cause caregivers should be recognized and acknowledged with empathy, regardless of the cause. After addressing any urgent medical needs, caregivers should be educated about the normal pattern of infant crying and methods to soothe the infant.

Normal infant crying progressively increases after 2 weeks and peaks in the 2nd month of life, then gradually decreases by the 4th or 5th month. It generally peaks in the late afternoon and evening within the 1st 6 months of life. At times it may be unrelated to the needs of the infant. Therefore, even in healthy infants some episodes of fussiness will not be soothed with typical caregiver attempts to soothe, such as feeding, cuddling, carrying, and diapering, and may occur for up to 4-5 hours per day. This pattern of crying is consistent among normal infants regardless of caretaking styles, cultural groups, and socioeconomic status, and has been demonstrated even in some nonhuman mammalian species. The pattern may reflect a developmental stage characterized by infants' increased reactivity to their environment and an immature ability to self-regulate. Though this crying pattern seems to be universal, the frequency and duration of crying varies significantly between infants. This variation is due to a number of factors, including infant temperament, the caregivers' response to crying, and likely other unidentified factors.

Caregivers should be reassured that physical contact in the form of carrying and feeding on demand within the 1st months of life will not spoil the infant, but may reduce the amount of crying over the long term by creating a more secure attachment between the infant and caregiver. Room sharing, with the infant's crib or bassinet in the caregiver's bedroom, may also decrease infant crying in the 1st 3 months of life. Some other calming, evidence-based techniques include swaddling young infants and decreasing stimulation. A consistent daily routine may assist infants' ability to self-regulate, resulting in decreased duration of crying bouts. Parents can also try to respond to excessive crying by giving the baby a pacifier, rocking the infant in a calm environment, or providing some background noise or vibration. Promptly initiating soothing measures before the crying becomes inconsolable may help to decrease the duration of crying.

Although responding promptly to infant distress may decrease crying, at times even healthy infants will not be soothed with these interventions. The caregivers' inability to soothe the infant is often their primary source of negative feelings such as frustration, anger, or guilt, creating a loss of confidence in parenting skills and feelings of resentment toward the infant. Infants then respond to caregiver anxiety with increased crying. Caregivers may be reassured by information that bouts of fussing do not necessarily indicate illness or pain, but may simply reflect the infant's inability to regulate the crying once it has started. Medical providers can also reassure caregivers that most infant cry-fuss problems are transient and not necessarily predictive of ongoing behavior problems in childhood. In a prospective, community based study of outcomes in infants with sleep and cry-fuss problems, only 5% of mothers reported persistent problems at age 2.

The clinician must be aware that parental distress from prolonged, unexplained crying can lead to the use of ineffective, inappropriate, or even dangerous remedies. Fennel extract, oral sucrose, and herbal tea may show promise as a way to decrease crying; additional study of these treatments and possible negative effects is needed. If these supplements replace infant formula, they may lead to malnutrition and electrolyte abnormalities. Treatments that have been shown to have no significant or reproducible effect in treating crying are simethicone, dimethicone, fiber-enriched formula, chiropractic treatment, or the introduction of lactase enzyme into the infant's milk. Treatment with anticholinergic drugs (dicyclomine hydrochloride, dicycloverine, and cimetropium bromide) was effective in reducing infant crying, but is associated with unacceptable side effects. In addition, several reports have been published of hospitalization or death in infants treated for excessive crying with sedating medications such as dextromethorphan and diphenhydramine, dimenhydrinate, and opiates. Clinicians should counsel parents about the dangers of using these medications in young infants.

TABLE 26.3 Initial Ancillary Testing or Referrals to Consider for Specific Diagnoses

Potential Diagnoses	Ancillary Testing or Consultations to Consider
Eyes, Ears, Nose, Throat	
Corneal abrasion or foreign body	Fluorescein stain
Glaucoma	Ophthalmology consult
Foreign body	Radiographs and/or ENT consult
Respiratory	
Pneumonia or bronchiolitis	Chest radiography, pulse oximetry, nasopharyngeal viral testing
Airway obstruction (croup, foreign body)	Chest and/or neck radiography, pulse oximetry, ENT consult for bronchoscopy
Cardiovascular	
Congestive heart failure Supraventricular tachycardia Anomalous coronary artery Myocarditis	Chest radiography, pulse oximetry, electrocardiogram, echocardiography, CBC, CMP, BNP, Cardiology consult
Gastrointestinal System	
Incarcerated hernia	Ultrasonography with Doppler
Gastrointestinal obstruction (intussusception, volvulus, pyloric stenosis, Hirschsprung disease), peritonitis, abdominal trauma	CBC, CMP, amylase, lipase, abdominal and pelvic radiography, abdominal and pelvic CT, air contrast enema for intussusception, Surgical consult
Milk and/or soy protein allergy	Hemoccult testing
Genitourinary System	
Testicular torsion	Ultrasonography with Doppler, Surgical consult
Ovarian torsion	Pelvic ultrasonography or CT, Surgical consult
Urinary tract infection	UA with culture, CBC, blood culture
Musculoskeletal System	
Osteomyelitis Septic arthritis	CBC, ESR, CRP, blood culture, radiography, MRI, Orthopedics and Infectious Disease consult
Fractures	Skeletal survey
Diskitis	ESR, spine radiographs, spine MRI
Skin	
Cellulitis, infection	CBC, wound culture
Central Nervous System	
Encephalitis Meningitis	Lumbar puncture, head CT or MRI, CBC, blood culture
Increased intracranial pressure (abusive or nonabusive trauma, hydrocephalus, intracranial hemorrhage), neoplasm	Head CT or MRI
Miscellaneous	
Drug ingestion	Comprehensive urine drug screen (with confirmatory testing)
Neonatal abstinence syndrome	Urine or meconium drug screen
Inborn error of metabolism	CBC, ABG, CMP, serum ammonia, serum uric acid, UA, serum amino acids, urine organic acids, serum acylcarnitine profile, lactate, Genetics consult
Sepsis	CBC, LP, UA, urine and blood culture,
Sickle cell crisis	CBC, reticulocyte count, chest radiography, pulse oximetry
Physical abuse	Injury surveillance: Skeletal survey; head CT or MRI in infants <6 mo of age or current or prior symptoms of head injury; AST, ALT, amylase, lipase, UA; urine drug investigation screen with confirmatory testing, Child Protection Team consult

ABG, arterial blood gas; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMP, basic metabolic panel; BNP, brain naturetic peptide; CBC, complete blood count; CMP, comprehensive metabolic panel; CRP, C-reactive protein; CT, computed tomography; ENT, Otolaryngologist; ESR, erythrocyte sedimentation rate; LP, lumbar puncture; MRI, magnetic resonance imaging; UA, urinalysis.

Given the stress that crying can place on a family and the fact that all families will inevitably be faced with the challenge of a fussy infant, this education should be a routine part of each well child evaluation in the 1st year of life. It should not only be given to the caregiver who presents with the child for medical care, but to all adults who will be caring for the child.

SPECIFIC DIAGNOSES

Child Maltreatment

Parental perceptions of prolonged or inconsolable crying place the infant at risk of abuse; parents may smother, slap, or shake their baby in response to crying. Crying is a common stimulus for abusive head trauma, and the abuse is often repeated because the head injury stops the crying.

Any injury in a nonmobile infant raises concern for abusive trauma and should prompt an evaluation for additional injuries. In mobile children, most accidental bruising occurs over bony prominences on the anterior surface of the body. Bruising to the ears, neck, genitals, and buttocks is unusual in nonabused children (Table 26.4). Patterned injuries and any significant, unexplained injury also may suggest abuse (Figs. 26.2, 26.3, and 26.4). The purpose of additional testing when infants present with suspicious findings is injury surveillance and identification of medical conditions that may mimic abusive trauma. The absence of additional injury does not rule out abuse. Even in isolation, the presence of a suspicious injury places the infant at risk for more severe ongoing abuse. In infants who were ultimately diagnosed with physical abuse, almost 30% of the infants had a history of previous, more minor suspicious injuries. Medical providers were reportedly aware of these injuries in 40% of cases, but did not recognize them as concerning (Table 26.5). If there are doubts about whether an injury should be considered suspicious or what tests are indicated, providers should consult a child abuse specialist.

Medical providers are in a unique position to identify infants at risk for maltreatment when they present for medical care, and to provide education and resources to high-risk families. In infants hospitalized for abusive head trauma, the majority of a victim's caregivers sought medical care for excessive crying prior to the abuse. Multiple phone calls and visits to the pediatrician for excessive crying is a warning sign that it is causing significant distress in the family. Ask caregivers how the crying is affecting the family and address any feelings of guilt or frustration. Clinicians can also ask how caregivers typically respond to the crying. All families who present with a fussy infant should be encouraged to seek support and periodic relief from the infant's care. Instruct the caregivers to safely place the infant in a crib or other safe location and walk away for a short time if they feel frustrated and at risk of harming the infant.

Even when child maltreatment is not a concern, more intensive educational and behavior modification interventions directed toward families with persistently fussy infants have shown promise as a way to reduce crying, improve parent-child relationships, and positively influence behavioral development in infants. Successful programs generally

TABLE 26.4 Location of Cutaneous Injuries

Inflicted	Accidental
Upper arms	Shins
Trunk	Hips (iliac crest)
Upper anterior leg	Lower arms
Side of face	Prominences of spine
Ears and neck	Forehead
Genitalia	Under chin

Modified from Pascoe JM, Hildebrandt HM, Tarrier A, et al. Patterns of skin injury in non-accidental and accidental injury. *Pediatrics*. 1979;64:245.

FIGURE 26.2 Lash marks from an electric cord. Such marks are distinctive. The deep lacerations, which are looped if the cord is looped, result in deep tissue damage, and there is the potential for keloid formation on healing. (From Johnson CF. Inflicted injury versus accidental injury. *Pediatr Clin North Am.* 1990;37:791-815.)

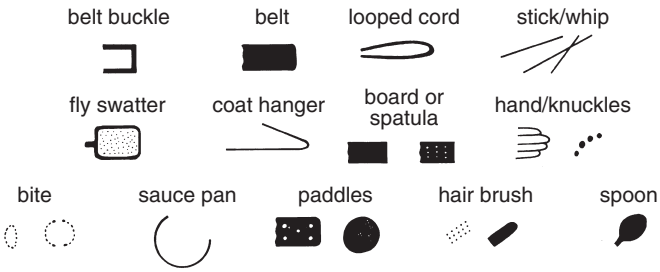


FIGURE 26.3 Marks from burns. (From Johnson CF. Inflicted injury versus accidental injury. *Pediatr Clin North Am.* 1990;37:791-815.)

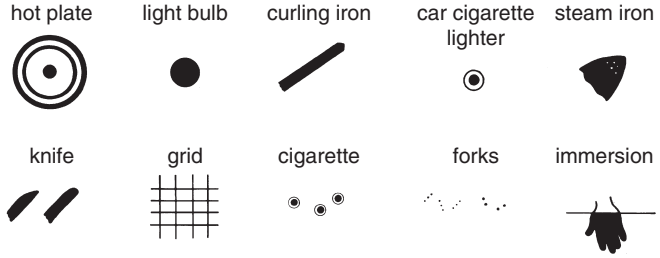


FIGURE 26.4 Marks from objects. (From Johnson CF. Inflicted injury versus accidental injury. *Pediatr Clin North Am.* 1990;37:791-815.)

(See *Nelson Textbook of Pediatrics,* p. 236.)

TABLE 26.5 Pitfalls in Child Abuse Evaluation: 12 Costly Errors

1. A desire to not make the diagnosis
2. Failure to assemble past information on medical conditions and medical encounters
3. Too great a reliance on the information developed by others
4. Transference-countertransference with custodial parent (formation of alliances or development of hostilities)
5. Overinterpretation or underinterpretation of signs and symptoms
6. Overinterpretation or underinterpretation of physical findings
7. Failure to know about conditions mistaken for sexual abuse
8. Faulty laboratory techniques resulting in either false-positive or false-negative reports
9. Use of techniques easily challenged in court
10. Impatience about arriving at a diagnostic conclusion
11. Failure to understand normative data with regard to psychosexual development
12. Failure to prepare adequately for court appearances

assess and address caregiver needs, sources of vulnerability, and infant health. They also provide respite and educate families about infant crying, soothing, and ongoing emotional care. In addition, multidisciplinary approaches may include family therapy or referrals to perinatal and infant mental health experts who can support parent-infant interactions.

Infantile Colic

A uniform definition for infantile colic is lacking but many use the definition derived from Wessel's Criteria, where crying occurs for at least 3 hours a day, at least 3 days a week, for at least 3 weeks in an otherwise healthy infant. Crying from colic generally occurs in the evenings, usually starts between 3 and 21 days of age, and subsides by 3-4 months of age. During crying bouts, parents describe that colicky infants often flex their legs over the abdomen, or may arch their backs with a "pained" look on their face. However, many of these criteria, including the appearance of pain, are also common features of normal infant crying. It is not clear whether the appearance of pain in these infants is due to a true organic etiology or related to caregivers' anxiety about the duration and unsoothable nature of the cry.

A single clear cause of colic remains elusive. Some suggest that the crying from colic is a response to pain from gastrointestinal dysfunction, such as milk protein or lactose intolerance, gastroesophageal reflux disease, abnormal peristalsis, or excessive gas. However, objective testing for these disorders has not revealed significant differences between colicky and noncolicky infants, and treatments have been inconsistently effective. Immaturity of the central nervous system and infant migraine are also suggested causes. Others theorize that colic symptoms are not caused by a single condition, but rather are a common end-point for multiple processes, including *infant temperament* and *caregivers' responses* to the crying. In this view, the term "colic" is used to describe a constellation of common symptoms rather than an underlying disease. Because of the significant overlap in the pattern and characteristics of crying in infants diagnosed with colic and normal infants, others suggest that colic represents a point further along a continuum of normal infant behavior. This perspective suggests that, in healthy infants, the clinical focus should be shifted from attempting to diagnose and treat a particular medical condition to providing education and support to caregivers. From a practical standpoint, the clinician should follow the same method of evaluation that would be initiated for any crying infant regardless of whether or not the crying meets the definition of colic. The duration and frequency of crying in this population can be particularly distressing for caregivers, and education on soothing and coping with the crying should be emphasized.

Feeding and Gastrointestinal Dysfunction

A subset of otherwise healthy infants who present with excessive crying will have some form of gastrointestinal (GI) dysfunction. A history of crying that is associated with vomiting, hematochezia, or is temporally related to feeds may increase the likelihood. Common causes include constipation, gastroesophageal reflux disease (GERD), eosinophilic esophagitis, excessive gas, and cow's and/or soy milk protein allergy or intolerance. Congenital lactose intolerance is rare, but infants may develop transient intolerance from inflammation of the intestinal villi due to gastroenteritis or a milk protein allergy. In infants with hematochezia, a milk protein allergy is most likely. However, in less clear-cut cases, improper feeding volume or technique can cause symptoms that may be misdiagnosed as GERD or a milk protein allergy. Formula changes and pharmacologic interventions may not be without undesirable consequences, including premature cessation of breast-feeding or the development of parental anxiety concerning the possibility of an intrinsic abnormality in their infant.

When GI dysfunction is suspected, and after potentially serious medical conditions are ruled out, clinicians should first evaluate feeding volume and technique. Over- or underfeeding may contribute to infant irritability. Using a slow-flow nipple can cause excessive air intake in a very vigorous feeder. Appropriate burping, feeding the infant in an upright position, using a formula thickener, and using bottles with collapsible bags may also help reduce fussing from excessive intestinal gas or GERD. Poor attachment, latch, and oral motor dysfunction may contribute to feeding problems, fussing, and even infant aversion to feedings. Consider consultation with a lactation specialist in breast-feeding infants.

Unfortunately, no specific laboratory test exists for diagnosing protein allergy in relation to excessive infant crying, and the symptoms of GERD are often nonspecific. In fact, inflammation of the GI tract from cow's milk protein allergy may be the cause of the vomiting and symptoms of pain in up to 40% of infants diagnosed with GERD. Guidelines caution against empiric treatment with acid-reducing medications as a way to diagnose GERD in young infants with nonspecific symptoms due to potential side effects with the overuse of these medications, and because their efficacy in decreasing crying is low. There is evidence that a trial of whey hydrolysate formula, or a milk- and egg-free diet in breast-feeding mothers, may decrease crying compared to controls in otherwise healthy infants with suspected GI dysfunction. The introduction of soy formula may not resolve symptoms because a significant number of infants with milk protein allergies are also allergic to soy protein. There is also increasing evidence that probiotics may be beneficial to reduce low-grade intestinal inflammation and crying in some infants, especially those with symptoms of GERD or constipation. When potentially serious medical conditions have been excluded, and the infant's feeding volume and technique are appropriate, it is reasonable to try these interventions. Changes should be implemented one at a time and continued for at least 2 weeks to evaluate the effects of each change. In infants with persistent symptoms, clinicians can consider a trial of a proton pump inhibitor and/or referral to a gastroenterologist.

Teething

Many complaints, ranging from fever to irritability, have been ascribed to teething. The most common symptoms associated with teething are

(See *Nelson Textbook of Pediatrics,* p. 1972.)

(See *Nelson Textbook of Pediatrics,* p. 1776.)

irritability, excessive drooling, and loss of appetite. Some studies do support the belief that teething is associated with low-grade fever and diarrhea, but this finding is not consistent. No symptom or cluster of symptoms can reliably exclude other medical conditions; therefore, teething should be considered a diagnosis of exclusion.

Management consists of allowing the infant to bite on any appropriate hard object, such as a teething ring. Objects that are small or may break into pieces such as teething biscuits or frozen foods are not recommended due to the risk of choking. Chilling the object in the refrigerator may reduce gum inflammation and pain. However, plastic teething rings should not be frozen or boiled unless directed by the manufacturer. Extreme temperatures may damage plastic teething rings and cause fluid to leak, and frozen rings may injure gums. An oral systemic analgesic such as acetaminophen may provide additional relief, but topical anesthetic agents are no longer recommended due to potential serious side effects with the overuse of these medications.

Drug Reactions

Some therapeutic medications and illicit drugs may cause infant irritability when directly ingested or when transferred to the infant through breast milk. Substances associated with irritability include cocaine, amphetamines, opiates, fluoxetine, clemastine, and caffeine. Pseudoephedrine use in breast-feeding mothers may be associated with infant irritability, but this finding is not consistent among studies. However, when directly ingested by infants, pseudoephedrine can cause irritability as well as other more serious and life-threatening complications. In the evaluation of the irritable infant, a careful infant and maternal drug history are important to obtain along with a comprehensive urine drug screen if indicated.

In the neonate, irritability may also be a symptom of drug withdrawal or the continued effects of in utero exposure. Drugs associated with neonatal abstinence syndrome (NAS) include benzodiazepines, methamphetamine, heroin, methadone, buprenorphine, and other prescription opioid analgesics. Some antidepressants and anxiolytics have been found to potentiate withdrawal in infants as well. Manifestations include irritability, jitteriness, sneezing and congestion, emesis, seizures, poor feeding, hiccups, diarrhea, sleeplessness, hyperactivity, and tremors. Caregivers often describe the crying as high-pitched and inconsolable. NAS usually begins in the 1st week of life and may last for up to a month, depending on the type of substance used. This initial phase may be followed by a relapsing course that includes ongoing irritability and may last for several months. Newborns exposed to cocaine may display similar symptoms of irritability soon after birth, but these likely represent continued effects of the drug rather than withdrawal symptoms.

Mild cases of NAS are often treated with behavioral management such as reducing stimulation, swaddling, demand feeding, and other calming techniques. Pharmacotherapy is required when supportive therapy fails, or if more serious side effects such as seizures and dehydration develop. Education on coping with infant crying and methods to soothe the infant, as well as close monitoring of the home environment, are particularly important in this population due to the challenges of caring for an infant with irritability from NAS and to the lack of caregiver resources and coping skills often associated with maternal drug use.

SUMMARY AND RED FLAGS

Although at times a simple diagnosis is easily established, the infant with excessive irritability often presents a significant challenge. Establishment of the likely diagnosis, combined with exclusion of significant pathophysiologic processes (see Table 26.1), is a prerequisite to the formulation of an appropriate management plan. Through a logical and stepwise approach, the clinician can usually establish the cause and develop a treatment plan. When the clinician cannot determine the underlying cause, close follow-up monitoring should result in optimal patient care.

Red flags include inconsolability, abnormal level of consciousness, abnormal vital signs, evidence of trauma or anemia, abdominal tenderness or distention, eye tearing, photophobia or conjunctival irritation, and abnormalities of growth including increasing head circumference percentile. Consolability by being held by a parent is often reassuring. In contrast, *paradoxical crying or irritability* when being held suggests that the holding process aggravates a painful process such as a fracture, osteomyelitis, or meningitis.

In all cases, clinicians should evaluate the level of distress that the crying is causing caregivers and should provide education and support. Families with a history of maltreatment, mental illness or drug use in caregivers, caregivers with limited social support, or those who frequently seek medical care or report significant distress and frustration from the crying are at a higher risk for adverse outcomes. When these risk factors are identified, a multidisciplinary approach involving education and resources for the caregivers, medical care for the infant, and family therapy or referrals to perinatal and infant mental health experts can improve parent-infant interactions and long-term outcomes for the child.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Child Maltreatment

Adamsbaum C, Grabar S, Mejean N, et al. Abusive head trauma: judicial admissions highlight violent and repetitive shaking. *Pediatrics*. 2010;126:546-555.

Barr RG. Crying as a trigger for abusive head trauma: a key to prevention. *Pediatr Radiol*. 2014;44(suppl 4):S559-S564.

Barr RG, Trent RB, Cross J. Age-related incidence curve of hospitalized Shaken Baby Syndrome cases: convergent evidence for crying as a trigger to shaking. *Child Abuse Negl*. 2006;30:7-16.

Christian CW, Committee on Child Abuse and Neglect. The evaluation of suspected child physical abuse. *Pediatrics*. 2015;15(5):e1337-e1354.

Christian CW, Block R. Abusive head trauma in infants and children. *Pediatrics*. 2009;123:1409-1411.

Fairbrother N, Barr RB, Pauwels J, et al. Maternal thoughts of harm in response to infant crying: an experimental analysis. *Arch Womens Ment Health*. 2015;18:447-455.

Laskey A, Holsti M, Runyan DK, et al. Occult head trauma in young suspected victims of physical abuse. *J Pediatr*. 2004;144(6):719-722.

McGovern MC, Smith MBH. Causes of apparent life threatening events in infants: a systematic review. *Arch Dis Child*. 2004;89:1043-1048.

Reijneveld SA, van der Wal MF, Brugman E, et al. Infant crying and abuse. *Lancet*. 2004;364:1340-1342.

Rubin DM, Christian CW, Bilaniuk LT, et al. Occult head injury in high-risk abused children. *Pediatrics*. 2003;111:1382-1386.

Sheets LK, et al. Sentinel injuries in infants evaluated for child physical abuse. *Pediatrics*. 2013;131(4):701-707.

Starling SP, Patel S, Burke BL, et al. Analysis of perpetrator admissions to inflicted traumatic brain injury in children. *Arch Pediatr Adolesc Med*. 2004;158(5):454-458.

Talvik I, Alexander RC, Talvic T. Shaken baby syndrome and baby's cry. *Acta Paediatr*. 2008;97:782-785.

Infantile Crying and Colic

Alvarez M, St. James-Roberts I. Infant fussing and crying patterns in the first year in an urban community in Denmark. *Acta Paediatr*. 1996;85:463-466.

Barr RG. The normal crying curve: what do we really know? *Dev Med Child Neurol*. 1990;32:356-362.

Barr RG. Colic and crying syndromes in infants. *Pediatrics*. 1998;102(5):1282-1286.

Barr RG, Hopkins B, Green JA. *Crying as a Sign, a Symptom, and a Signal: Clinical, Emotional and Developmental Aspects of Infant and Toddler Crying*. Cambridge University Press; 2000.

Barr RG, Konner M, Bakeman R, et al. Crying in Ikung San infants: a test of the cultural specificity hypothesis. *Dev Med Child Neurol*. 1991;33:601-610.

Barr RG, Rotman A, Yaremko J, et al. The crying of infants with colic: a controlled empirical description. *Pediatrics*. 1992;90:14-21.

Brazelton TB. Crying in infancy. *Pediatrics*. 1962;29:579-588.

Cohen-Silver J, Ratnapalan S. Management of infantile colic: a review. *Clin Pediatr (Phila)*. 2009;48(1):14-17.

Douglas PS, Hill PS. The crying baby: what approach? *Curr Opin Pediatr*. 2011;23:523-529.

Evanoo G. Infant crying: a clinical conundrum. *J Pediatr Health Care*. 2007;21(5):333-338.

Fleisher DR. Infant colic. In: Faure C, Di Lorenxo C, Thapar N, eds. *Pediatric Neurogastroenterology: Gastrointestinal Motility and Functional Disorders in Children*. New York: Springer; 2013:347-354.

Freedman SB, Al-Harthy N, Thull-Freedman J. The crying infant: diagnostic testing and frequency of serious underlying disease. *Pediatrics*. 2009;123(3):841-848.

Hall B, Chesters J, Robinson A. Infantile colic: a systematic review of medical and conventional therapies. *J Paediatr Child Health*. 2012;48:128-137.

Hemmi MH, Wolke D, Schneider S. Associations between problems with crying, sleeping and/or feeding in infancy and long-term behavioral outcomes in childhood: a meta-analysis. *Arch Dis Child*. 2011;96:622-629.

Herman H, Le A. The crying infant. *Emerg Med Clin N Am*. 2007;(25):1137-1159.

Hunziker UA, Barr RG. Increased carrying reduces infant crying: A randomized controlled trial. *Pediatrics*. 1986;77:641-648.

Keefe MR, et al. Effectiveness of an intervention for colic. *Clin Pediatr (Phila)*. 2006;45:123-133.

Leung AKC. Infantile colic: a review. *J R Soc Promot Health*. 2004;124(4):162-166.

Lucassen PL, Assendelft WJ, Gubbels JW, et al. Effectiveness of treatments for infantile colic: systematic review. *BMJ*. 1998;316:1563-1569.

Patrick S, Garcia J, Griffin L. The role of family therapy in mediating adverse effects of excessive and inconsolable neonatal crying on the family system. *Fam Syst Health*. 2010;28(1):19-29.

Perry R, Hunt K, Ernst E. Nutritional supplements and other complementary medicines for infantile colic: a systematic review. *Pediatrics*. 2011;127(4):720-733.

Poole SR. The infant with acute, unexplained, excessive crying. *Pediatrics*. 1991;88(3):450-455.

Long T, Johnson M. Living and coping with excessive infantile crying. *J Adv Nurs*. 2001;34(2):155-162.

Steutel NF, Benninga MA, Langendam MW, et al. Reporting outcome measures in trials of infant colic. *J Pediatr Gastroenterol Nutr*. 2014;59:341-346.

St. James-Roberts I. *The Origins, Prevention and Treatment of Infant Crying and Sleep Problems: An Evidence-Based Guide for Healthcare Professionals and the Families They Support*. New York: Routledge; 2012.

St James-Roberts I, Alvarez M, Hovish K. Emergence of a developmental explanation for prolonged crying in 1- to 4-month-old infants: review of the evidence. *J Pediatr Gastroenterol Nutr*. 2013;57(suppl 1):S30-S36.

St. James-Roberts I, Conroy S, Wilsher K. Bases for maternal perceptions of infant crying and colic behavior. *Arch Dis Child*. 1996;75:375-384.

St. James-Roberts I, Morris S, Owen C, et al. Use of a behavioural programme in the first 3 months to prevent infant crying and sleep problems. *J Paediatr Child Health*. 2001;37:289-297.

Van Sleuwen BE, L'hoir MP, Engelberts AC, et al. Comparison of behavior modification with and without swaddling as interventions for excessive crying. *J Pediatr*. 2006;149(4):512-517.

Wake M, et al. Prevalence, stability, and outcomes of cry-fuss and sleep problems in the first 2 years of life: prospective community-based sample. *Pediatrics*. 2006;117(3):836-842.

Wessel MA, Cobb JC, Jackson EB, et al. Paroxysmal fussing in infancy, sometimes called colic. *Pediatrics*. 1954;14(5):421-434.

Wolke D, Gray P, Meyer R. Excessive infant crying: a controlled study of mothers helping mothers. *Pediatrics*. 1994;94(3):322-332.

Gastrointestinal Causes of Irritability

Indrio F, et al. Prophylactic use of a probiotic in the prevention of colic, regurgitation, and functional constipation: a randomized clinical trial. *JAMA Pediatr*. 2014;168(3):228-233.

Onyeador N, Paul PS, Sandhu KB. Paediatric gastroesophageal reflux clinical practice guidelines. *Arch Dis Child Educ Pract Ed*. 2014;99:190-193.

Salvatore S, Vandenplas Y. Gastroesophageal reflux and cow milk allergy: is there a link? *Pediatrics*. 2002;110(5):972-984.

Teething

Macknin ML, Piedmonte M, Jacobs J, et al. Symptoms associated with infant teething: a prospective study. *Pediatrics*. 2000;105(4):747-752.

Medication or Drug Reactions

American Academy of Pediatrics: Committee on Drugs. The transfer of drugs and other chemicals into human milk. *Pediatrics*. 2001;108(3):776-789.

Drug Safety Communications. FDA recommends not using lidocaine to treat teething pain and requires new Boxed Warning. Silver Spring, MD: US Food and Drug Administration; June 26, 2014.

Gunn VL, Taha SH, Liebelt EL, et al. Toxicity of over-the-counter cough and cold medications. *Pediatrics*. 2001;108(3):e52.

Incaudo GA. Diagnosis and treatment of allergic rhinitis and sinusitis during pregnancy and lactation. *Clin Rev Allergy Immunol*. 2004;27:159-177.

Kocherlakota P. Neonatal abstinence syndrome. *Pediatrics*. 2014;134(2):e547-e561.

Martin TC, Rocque M. Accidental and non-accidental ingestion of methadone and buprenorphine in childhood: a single center experience, 1999-2009. *Curr Drug Saf*. 2011;6:12-16.

Trajanovska M, Manias E, Cranswick N, et al. Use of over-the-counter medicines for young children in Australia. *J Paediatr Child Health*. 2010;46:5-9.

27

Unusual Behaviors

Ryan Byrne and Kirstin Kirschner

The history is the most important tool for identifying a psychiatric disorder. The initial focus in conducting the history is to establish rapport and to ensure the child's safety with respect to the risk of suicide or physical or sexual abuse. After safety is ensured, the history should focus on delineating the specific behaviors of concern, on identifying any stressors that may be precipitating the behavior (Table 27.1), and on recognizing any associated symptoms that may differentiate which disorder or disorders are causing the behavior. In addition to primary psychiatric diagnoses, the clinician should focus on possible medical causes of the behaviors in question, including medication side effects, substance abuse, and medical illnesses (Tables 27.2 and 27.3). Comorbidity is common in children with psychiatric illnesses, and as such, the clinician should consider whether a combination of medical and psychiatric diagnoses may be producing the patient's symptoms.

Information should be obtained from multiple sources whenever possible, including parents and any other adults who have spent a significant amount of time with the child, such as teachers. The child should be interviewed separately so as to provide a better chance of obtaining his or her perspective and of uncovering a history of abuse or destructive behaviors, such as substance abuse, self-harm, or high-risk sexual activity. As some psychiatric disorders demonstrate a strong genetic predisposition, a detailed psychiatric family history should be obtained. Psychiatric illness in family members may be undiagnosed; hence, the clinician should inquire about the presence of symptoms in addition to formal diagnoses in the family.

The following validated principles should guide history taking, particularly when discussing sensitive topics such as substance use, sexual abuse, and suicidal ideation or intent:

1. **Behavioral incident**: The clinician should break down complex patterns of behavior into discrete incidents and focus on concrete details chronologically. Doing so allows the clinician to objectively establish the sequence of behaviors behind sensitive events, particularly when the patient's subjective responses to the events may influence recall or reporting.
2. **Shame attenuation**: The clinician should assume a stance of unconditional positive regard so as to minimize the influence of guilt or shame while discussing taboo subjects.
3. **Gentle assumption**: By framing questions based on the assumption that a behavior exists, the clinician may overcome patient hesitation to acknowledge the presence of that behavior.
4. **Symptom amplification**: Similar to gentle assumption, by assuming a high frequency of the behavior and inquiring in a concrete manner (e.g., "How many days a week do you drink? 5-6?"), the clinician may make the patient feel more at ease by acknowledging the existence of a particular behavior, particularly if a patient is troubled by the frequency of the behavior.
5. **Denial of the specific:** By asking specific questions, the clinician may elicit more accurate information by prompting recollection of particular behaviors that may otherwise be denied when asked in general terms. For example, asking the patient whether they have ever used marijuana may be more likely to elicit a positive response than asking the patient whether they have ever used illegal drugs.
6. **Normalization:** By simply describing common patterns of symptoms or behaviors, the clinician may help the patient feel more at ease by endorsing the presence of similar patterns in his or her behaviors.

The history allows the clinician to define patterns of behavior that suggest a differential diagnosis. The *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition (DSM-5), contains descriptive diagnostic criteria based on the presence or absence of various symptoms and aids the clinician in assigning a specific diagnosis to these behavior patterns and symptom clusters. Terms frequently used in the diagnosis of psychotic illnesses are noted in Table 27.4.

CONDITIONS CHARACTERIZED BY DISRUPTIVE BEHAVIORS

Disruptive behaviors are broadly categorized by whether they violate the rights of others and are then further classified by whether there is associated difficulty in regulating emotions or behaviors (Fig. 27.1).

Conditions That Do Not Violate the Rights of Others

Attention-deficit/hyperactivity disorder. The cardinal features of attention-deficit/hyperactivity disorder (ADHD) are hyperactivity, distractibility, and impulsivity. Manifestations of these symptoms must be present in more than 1 setting (e.g., school and home) and must interfere with functioning or development. ADHD is more frequent in males than in females, with a ratio of about 2:1 in children. However, females may be underdiagnosed as they are more likely to present with inattention than with hyperactivity. The DSM-5 specifies that there must be a persistent pattern of inattention and/or hyperactivity–impulsivity with 6 or more symptoms in either category lasting at least 6 months. Adolescents 17 years of age or older require only 5 symptoms; however, symptoms should be present prior to 12 years of age.

Inattention

1. Lack of attention to detail or inaccurate work
2. Difficulty sustaining attention
3. Failure to listen when spoken to directly
4. Lack of follow-through
5. Disorganization
6. Avoidance of activities requiring sustained attention
7. Frequent loss of items
8. Easy distraction by extraneous stimuli
9. Forgetfulness

TABLE 27.1 Common Precipitants of Psychiatric Symptoms

Substance abuse
Stress
Death or illness of family or friend
Interpersonal conflict
Rejection or abandonment
Significant change in routine

TABLE 27.2 The MIDAS Mnemonic for Screening for Medical Illness

M:	Do you take any **M**edications?
I:	Do you have any medical **I**llnesses?
D:	Do you have a primary care **D**octor?
A:	Have you ever had any **A**llergies, reactions or side effects?
S:	Have you ever had any **S**urgery?

From Carlat DJ. *The Psychiatric Interview*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2011.

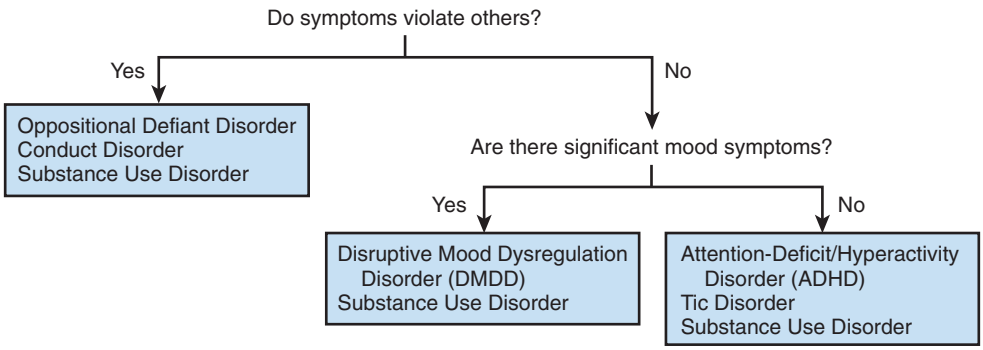


FIGURE 27.1 Evaluation of disruptive behaviors.

Hyperactivity/Impulsivity

1. Frequent fidgeting or squirming
2. Frequent need to walk around
3. Restlessness or need to run around/climb
4. Difficulty engaging in quiet activities
5. Acting "on the go," restlessness, or difficulty of caregivers to keep up with
6. Talking excessively
7. Frequently interrupting
8. Difficulty waiting turn
9. Intrusiveness

The chronicity of the **hyperactivity** in this disorder may be subtle. Although children with ADHD tend to move around more than other children, the hyperactivity may be of concern only in certain situations in which the child is expected to be quiet (e.g., in school or places of worship). Some children with ADHD can sit and be attentive in quiet and relaxed situations, whereas a noisy and active setting, such as an unstructured classroom, precipitates inappropriate behavior. As these children become older, they often become less overtly hyperactive. For instance, an adolescent may mostly feel restless without acting upon that feeling in a disruptive manner. This restlessness may contribute significantly to academic underachievement. Despite intentions for diligent studying, the restlessness may cause the affected teenager to feel the need to walk around, distracting from studying.

Impulsivity significantly contributes to morbidity. The impulsivity applies not only to actions but also to emotions. An impulsive child whose emotions change quickly is at risk for physically aggressive behaviors, such as hitting or biting. In school-aged children, the impulsive aggression is often manifested as explosive behavior. Because of their explosive behavior, inability to wait their turn in a game, and difficulty regulating emotions when interacting with teachers, these children have great difficulty with both peer and teacher relations. Impulsivity can also be potentially life threatening because the child may act before considering the consequences. Impulsivity may manifest as risk-taking behaviors in both children (e.g., running into the street after a ball without checking for traffic) and adolescents (e.g., high-risk sexual activity or substance abuse).

Hyperactivity and impulsivity in children are often readily apparent to adults; however, the manifestations of **inattention and distractibility** are often not as overt. In young children, inattentive behavior can consist of shifting from 1 activity to another and having difficulty finishing tasks. The parents may incorrectly consider these actions to represent lack of motivation. In adolescence, inattentive behavior may result in poor school performance. These children may forget to do homework or may need excessively long periods to complete assignments because of their inability to focus on their work and may be mislabeled as being lazy.

The challenge in diagnosing ADHD lies in defining when specific behaviors are abnormal, particularly when those behaviors may not be apparent in all situations or contexts. The clinician should not rely solely on observations obtained in the clinic setting, but should instead gather information from multiple sources, including parents, teachers, daycare workers, and even a direct classroom observation from a trained health care professional. The classroom teacher represents an excellent resource for determining whether the patient's level of activity and degree of impulsivity are abnormal. Standardized behavioral checklists filled out by the parents and teachers quantify the degree of abnormal behaviors with regard to an age-specific reference population.

Before establishing a diagnosis of ADHD, the clinician must rule out other psychiatric and medical causes of the patient's symptoms. With respect to psychiatric conditions, the differential diagnosis of ADHD includes learning disorders, oppositional behavior, mood disorders, anxiety disorders, and substance abuse. *Because of the high association of learning disorders with ADHD, each evaluation should include an assessment for learning problems.*

With respect to medical conditions, the differential diagnosis of ADHD includes iron deficiency, lead toxicity, thyroid disorders, seizures, hearing loss, and substance abuse. Screening for symptoms of **sleep-disordered breathing** is essential because chronically ineffective

(See *Nelson Textbook of Pediatrics,* p. 200.)

TABLE 27.3 Selected Neurologic and Systemic Causes of Depression and/or Psychosis

Category	Disorders
Head trauma	Traumatic brain injury Subdural hematoma
Infectious	Lyme disease Prion diseases Neurosyphilis Viral infections/encephalitides (HIV infection/encephalopathy, herpes encephalitis, cytomegalovirus, Epstein-Barr virus) Whipple disease Cerebral malaria Systemic infection
Inflammatory	Autoimmune encephalitis Systemic lupus erythematosus Sjögren syndrome Temporal arteritis Hashimoto encephalopathy Sydenham chorea Sarcoidosis
Neoplastic	Primary or secondary cerebral neoplasm Systemic neoplasm Paraneoplastic encephalitis
Endocrine/acquired metabolic	Hepatic encephalopathy Uremic encephalopathy Dialysis dementia Hypo/hyperparathyroidism Hypo/hyperthyroidism Addison disease/Cushing disease Postpartum Vitamin deficiency: vitamin B_{12}, folate, niacin, vitamin C, thiamine Gastric bypass–associated nutritional deficiencies Hypoglycemia Hyponatremia
Vascular	Stroke Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
Degenerative	Progressive supranuclear palsy Huntington disease Corticobasal ganglionic degeneration Multisystem atrophy/striatonigral degeneration/olivopontocerebellar atrophy Idiopathic basal ganglia calcifications/Fahr disease
Demyelinating/Dysmyelinating	Multiple sclerosis Acute disseminated encephalomyelitis Adrenoleukodystrophy Metachromatic leukodystrophy
Inherited metabolic	Wilson disease Posterior horn syndrome Tay-Sachs disease Neuronal ceroid lipofuscinosis Niemann–Pick type C Acute intermittent porphyria Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) Cerebrotendinous xanthomatosis Homocystinuria Ornithine transcarbamylase deficiency
Epilepsy	Ictal Interictal Postictal Forced normalization Postepilepsy surgery Lafora progressive myoclonus epilepsy
Medications	Analgesics Androgens (anabolic steroids) Antiarrhythmics Anticonvulsants Anticholinergics Antibiotics Antihypertensives Antineoplastic agents Corticosteroids Dopamine agonists Oral contraceptives Sedatives/hypnotics Selective serotonin reuptake inhibitors (SSRIs) (serotonin syndrome)
Drugs of abuse	Alcohol Amphetamines Cocaine Hallucinogens Marijuana and synthetic cannabinoids Methylenedioxymethamphetamine (MDMA) (Ecstasy) Phencyclidine
Drug withdrawal syndromes	Alcohol Barbiturates Benzodiazepines Amphetamines SSRIs
Toxins	Heavy metals Inhalants
Other	Normal-pressure hydrocephalus Ionizing radiation Decompression sickness

Modified from Perez DL, Murray ED, Price BH. Depression and psychosis in neurological practice. In: Daroff RB, Jankovic J, Mazziotta JC, Pomeroy SL, eds. *Bradley's Neurology in Clinical Practice.* 7th ed. Philadelphia: Elsevier; 2015.

(See *Nelson Textbook of Pediatrics,* p. 184.)

TABLE 27.4 Psychiatric Terms

Abulia is the state of reduced impulse to act and think associated with indifference about consequences of action.
Affect is the examiner's observation of the patient's emotional state. Frequently used descriptive terms include the following:
- **Constricted** affect is reduced range and intensity of expression.
- **Blunted** affect is further reduced. Usually, there is little facial expression and a voice that is monotone and lacking normal prosody.
- **Flat** describes severely blunted affect in which there is no affective expression.
- **Inappropriate** affect is an incongruous expression of emotion or behavior relative to the content of a conversation or social norms.
- **Labile** affect exhibits abrupt and sudden changes in both type and intensity of emotion.

Anxiety is the feeling of apprehension caused by anticipation of danger that may be internal or external.
Apathy is dulled emotional tone associated with detachment or indifference.
Comportment refers to self-regulation of behavior through complex mental processes that include insight, judgment, self-awareness, empathy, and social adaptation.
Compulsion is the uncontrollable impulse to perform an act repetitively.
Confusion is the inability to maintain a coherent stream of thought owing to impaired attention and vigilance. Secondary deficits in language, memory, and visual spatial skills are common.
Delusion is a false, unshakable conviction or judgment that is out of keeping with reality and with socially shared beliefs of the individual's background and culture. It cannot be corrected with reasoning.
Depression is a sustained psychopathological feeling of sadness often accompanied by a variety of associated symptoms, particularly anxiety, agitation, feelings of worthlessness, suicidal ideation, abulia, psychomotor retardation, and various somatic symptoms and physiologic dysfunctions and complaints that cause significant distress and impairment in social functioning.
Hallucination is a false sensory perception not associated with real external stimuli.
Mood is the emotional state experienced and described by the patient and observed by others.
Obsession is the pathologic persistence of an irresistible thought or feeling that cannot be eliminated from consciousness by logical effort. It is associated with anxiety and rumination.
Paranoia is a descriptive term designating either morbid-dominant ideas or delusions of self-reference concerning 1 or more of several themes, most commonly persecution, love, hate, envy, jealousy, honor, litigation, grandeur, and the supernatural.
Prosody is the melodic patterns of intonation in language that convey shades of meaning.
Psychosis is the inability or impaired ability to distinguish reality from hallucinations and/or delusions.
Thought process and content. Common descriptive terms include the following:
- **Circumstantial** thought follows a circuitous route to the answer. There may be many superfluous details, but the patient eventually reaches the answer.
- **Linear** thought demonstrates goal-directed associations and is easy to follow.
- **Loose associations** are thoughts that have no logical or meaningful connection with ensuing thoughts.
- **Tangential** thoughts are initially clearly linked to a current thought but fail to maintain goal-directed associations; the patient never arrives at the desired point or goal.
- **Clang associations** describe speech in which the sounds of words are similar but not the meanings. The words have no logical connection to each other.
- **Flight of ideas** describes a rapid stream of thoughts that tend to be related to each other.
- **Magical thinking** describes the belief that thoughts, words, or actions have power to influence events in ways other than through reality-based mechanisms.
- **Thought blocking** is characterized by abrupt interruptions in speech during conversation before an idea or thought is finished. After a pause, the individual indicates no recall of what was being said or what was going to be said.

From Perez DL, Murray ED, Price BH. Depression and psychosis in neurological practice. In: Daroff RB, Jankovic J, Mazziotta JC, Pomeroy SL, eds. *Bradley's Neurology in Clinical Practice.* 7th ed. Philadelphia: Elsevier; 2015.

or inefficient sleep can produce symptoms of inattention and hyperactivity.

Tic disorders. Tics are motor movements or vocalizations that are sudden, rapid, recurrent, nonrhythmic, and involuntary. Tics often become worse during stress but may improve during activities requiring moderate physical or mental activity. Tics need to be differentiated from other abnormal movements, such as chorea, athetosis, dystonia, myoclonus, and hemiballismus, which may be associated with an underlying neurologic condition or may be medication-induced. **Simple motor tics** are defined as repetitive movements of single muscle groups. They may consist of eye blinking, neck jerking, or shoulder shrugging. **Complex motor tics** are repetitive movements of several muscle groups in coordination, such as repetitive grooming behaviors, deep knee bends, or smelling of objects. **Simple vocal tics** are defined as nonverbal noises, such as throat clearing or grunting sounds, whereas **complex vocal tics** are intelligible words. Complex vocal tics may manifest as **coprolalia**, the repetitive, stereotyped vocalization of obscenities.

The DSM-5 categorizes tic disorders as follows:

1. **Provisional tic disorder:** motor and/or vocal tics lasting less than a year
2. **Chronic motor or vocal tic disorder:** either motor or vocal tics lasting longer than a year
3. **Tourette disorder:** both motor and vocal tics lasting longer than a year

Tourette disorder consists of multiple motor and vocal tics of at least 1 year in duration. The incidence of this condition is 4-5 per 10,000. In some families, this illness is inherited as an autosomal dominant condition, with 70% penetrance in females and near complete penetrance in males. Because of this difference in penetrance, Tourette disorder is 1.5-3 times more common in males than in females. The median age at presentation is 7 years, though some children may present as early as 2 years. While coprolalia is popularly thought to be a common feature of Tourette disorder, fewer than 10% of affected patients have this form of complex vocal tics.

The DSM-5 criteria for Tourette disorder are as follows:

1. Multiple motor and vocal tics lasting longer than a year with no tic-free intervals longer than 3 months
2. Symptom onset before age 18 years
3. No medical cause for the tics

Tics may lead to the patient being socially ostracized. Children with chronic tic disorders frequently have other psychologic conditions, such as ADHD or obsessive-compulsive disorder (OCD), which may lead to further difficulties in peer interactions and frequent frustration of teachers and family members. Such stressors can worsen the tics, which can further compound the problem.

Disruptive mood dysregulation disorder. While the predominant characteristic of disruptive mood dysregulation disorder (DMDD) is chronic, persistent, and severe irritability, it is often the behavioral issues that prompt presentation to a clinician. DMDD often manifests as irritable, depressed mood and temper tantrums with a low frustration tolerance. The DSM-5 requires the following for diagnosis:

1. Severe recurrent temper outbursts that manifest with verbal or behavioral aggression out of proportion to the situation in intensity or duration
2. Behavior is inconsistent with developmental level
3. Behavior occurs on average 3 or more times per week
4. The mood between outbursts is persistently irritable or angry
5. Symptoms present for 12 or more months
6. Symptoms present in at least 2 settings
7. Age of onset of symptoms must be before age 10 years, but diagnosis should not be made before age 6 years or after age 18 years

The overall prevalence of DMDD among children and adolescents is as high as 5%. Rates are higher in males and school-aged children than in females and adolescents. DMDD can cause significant difficulties with school performance and family/peer relationships. Many children with DMDD will also meet criteria for ADHD, oppositional defiant disorder (ODD), or anxiety disorders. The diagnosis of DMDD should be distinguished from bipolar disorder, which must have distinct episodes of mania or hypomania (Table 27.5). The age of the patient can also help differentiate DMDD and bipolar disorders because bipolar disorders rarely present prior to adolescence.

Substance Use Disorder. Substance use can lead to a wide range of disturbances in mood and behavior. The hallmark of a substance use disorder is the continued use of a substance despite it causing ongoing negative cognitive, behavioral, and physiologic symptoms. The other hallmark of substance use disorder is the significance of the negative behaviors, such as verbal or physical aggression, defiance, lying, or stealing. Sometimes these behaviors will reach the point of violating family and friends.

Conditions That Violate the Rights of Others

Oppositional defiant disorder. The characteristic feature of ODD is a persistent pattern of both defiant behavior and an angry or irritable mood. Affected individuals exhibit at least 4 of the following behaviors in a consistent manner over a 6-month period:

1. Frequently losing temper
2. Often arguing with authority figures
3. Defying rules
4. Deliberately annoying adults
5. Blaming others for his or her actions
6. Becoming easily annoyed by others
7. Being angry
8. Being vindictive

ODD should not be diagnosed if the patient meets the DSM-5 criteria for conduct disorder or if the symptoms occur in the context of a mood, anxiety, or psychotic disorder, in which children exhibit oppositional behavior as a reaction to their illness.

TABLE 27.5 Diagnostic Features of Primary Psychiatric Disorders

The following conditions require clinically significant distress or impairment in social or occupational functioning:

- **Schizophrenia** is a disorder that lasts for at least 6 mo and includes at least 1 mo of active symptoms (2 or more of the following: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, or negative symptoms).
- **Schizoaffective disorder** is a disorder in which a mood episode and the active symptoms of schizophrenia occur together and were preceded or are followed by at least 2 wk of delusions or hallucinations without prominent mood symptoms.
- **Major depressive disorder** is characterized by 1 or more major depressive episodes (at least 2 wk of depressed mood or loss of interest accompanied by at least 4 additional symptoms of depression). Additional symptoms of depression may include significant weight changes, sleep dysfunction, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or guilt, diminished concentration, and suicidal ideation or thoughts of death.
- A **manic episode** is defined by an abnormally and persistently elevated, expansive, or irritable mood persisting for at least 1 wk (or less if hospitalization is required). At least 3 of the following symptoms must be present if the mood is elevated or expansive (4 symptoms are required if the mood is irritable): inflated self-esteem or grandiosity, decreased need for sleep, pressured speech, flight of ideas, distractibility, increased goal-directed activities or psychomotor agitation, and excessive involvement in pleasurable activities with a high potential for painful consequences. Psychotic features may be present.
- **Bipolar I disorder** is characterized by the presence of both manic and major depressive episodes or manic episodes alone.
- **Bipolar II disorder** is characterized by the presence of major depressive episodes alternating with episodes of hypomania.
- **Hypomania** is characterized by an abnormally and persistently elevated, expansive, or irritable mood persisting for at least 4 days. Other criteria required for diagnosis are identical to that of a manic episode except that the symptoms are not so severe as to cause marked impairment in social or occupational functioning, hospitalization is not required, and no psychotic symptoms are present.

From Perez DL, Murray ED, Price BH. Depression and psychosis in neurological practice. In: Daroff RB, Jankovic J, Mazziotta JC, Pomeroy SL, eds. *Bradley's Neurology in Clinical Practice.* 7th ed. Philadelphia: Elsevier; 2015.

Prevalence ranges from 1-11%, depending on the population. In prepubertal children, it occurs more frequently in boys; however, in adolescents, its incidence is equal in both sexes. Most children present before 8 years of age. Affected preschool-aged children sometimes exhibit increased motor activity, difficulty being comforted, and overreacting to situations. Affected school-aged children have low self-esteem and a low tolerance for frustration. The disorder commonly occurs in families with a history of mood or psychotic disorders—particularly maternal depression—and with chronic disruptive behaviors, such as ADHD or conduct disorder.

Children with this disorder are at marked risk for other psychologic disorders, such as ADHD. In addition, these patients may be at increased risk for conduct disorder, antisocial personality disorder as adults, substance abuse, major depressive disorder, and suicide.

Conduct disorder. A child has conduct disorder if he or she has repetitively violated the rights of others and of society. Children with this diagnosis have performed 3 or more of the following behaviors

within the past year and with at least 1 occurring in the previous 6 months:

1. Aggression toward people or animals, such as intimidation, initiation of fights, use of weapons, cruelty to people, cruelty to animals, rape, confrontational theft or mugging
2. Destruction of property, such as arson or vandalism
3. Deceitfulness or theft, such as breaking into houses or cars or stealing items of nontrivial value
4. Serious violation of rules, such as curfew violation, running away, or truancy before the age of 13 years (for running away to qualify as a symptom, it must occur twice, or once if it was lengthy, and must not be an attempt to escape sexual or physical abuse)

Conduct disorder is classified as **childhood onset** if symptoms occur before 10 years of age and **adolescent onset** if symptoms occur at or after 10 years of age. It is further subdivided by severity of offense: mild (e.g., truancy), moderate (e.g., vandalism, nonconfrontational theft), and severe (e.g., rape, confrontational theft). The prevalence of conduct disorder is higher in males than in females. Children initially present with lying, initiating fights, and truancy; as they get older, they progress to more violent acts. Boys are more likely to exhibit acts of violence, such as fighting and stealing, than are girls, who are more likely to exhibit truancy, runaway behavior, and high-risk sexual activity. Half of these children may develop **antisocial personality disorder**, which is a severe conduct disorder of adulthood that is usually associated with criminal activity. The earlier the onset of conduct disorder, the greater the risk of developing antisocial personality disorder as an adult. These children also have a high frequency of depression, suicidal ideation, personality disorders, anxiety disorders, ADHD, and substance abuse.

Although the cause of conduct disorder is unknown, both genetic and psychosocial factors play a role. A history of parental rejection, difficult infant temperament, physical or sexual abuse, early institutional living, and lack of appropriate discipline are associated with the development of conduct disorder. A biochemical or genetic cause for this condition has been postulated due to the high prevalence of this condition in families with psychiatric disorders.

CONDITIONS CHARACTERIZED BY DISRUPTION IN MOOD

Mood disorders are divided into those characterized by a depressed mood and those characterized by extremes of mood lability. When assessing mood disturbances, it is essential to screen for symptoms suggestive of bipolar illness as these patients have a risk of becoming manic when treated with antidepressants (Fig. 27.2). The evaluation of any patient with a disruption in mood should include an assessment of the risk of suicide.

Conditions Characterized by Depressed Mood

Depressive disorders that may present in childhood include DMDD, major depressive disorder, premenstrual dysphoric disorder, persistent depressive disorder (i.e., dysthymia), substance/medication-induced depressive disorder, adjustment disorder with depressed mood, and depressive disorder related to another medical condition.

Major depressive disorder. Major depressive disorder is associated with serious risks of both suicide and significant social and academic impairment (see Table 27.5). Presentations may be subtle. Even though a child may be pervasively sad, he or she may also present with behavior problems and irritability. Patients may also present with somatic complaints, psychosis, or both. The psychotic symptoms are typically mood-congruent auditory hallucinations and delusions of guilt, medical illnesses, or deserving punishment. DSM-5 criteria for major depressive disorder consist of at least a 2-week period of a depressed mood—or irritability in some children—or loss of interest in pleasurable activities, resulting in significant impairment. During this period, the patient has to have at least 5 of the following symptoms:

1. Depressed mood or irritability in some children
2. Loss of interest or pleasure
3. Loss of appetite or overeating
4. Insomnia or hypersomnia
5. Fatigue or loss of energy
6. Feelings of worthlessness or guilt

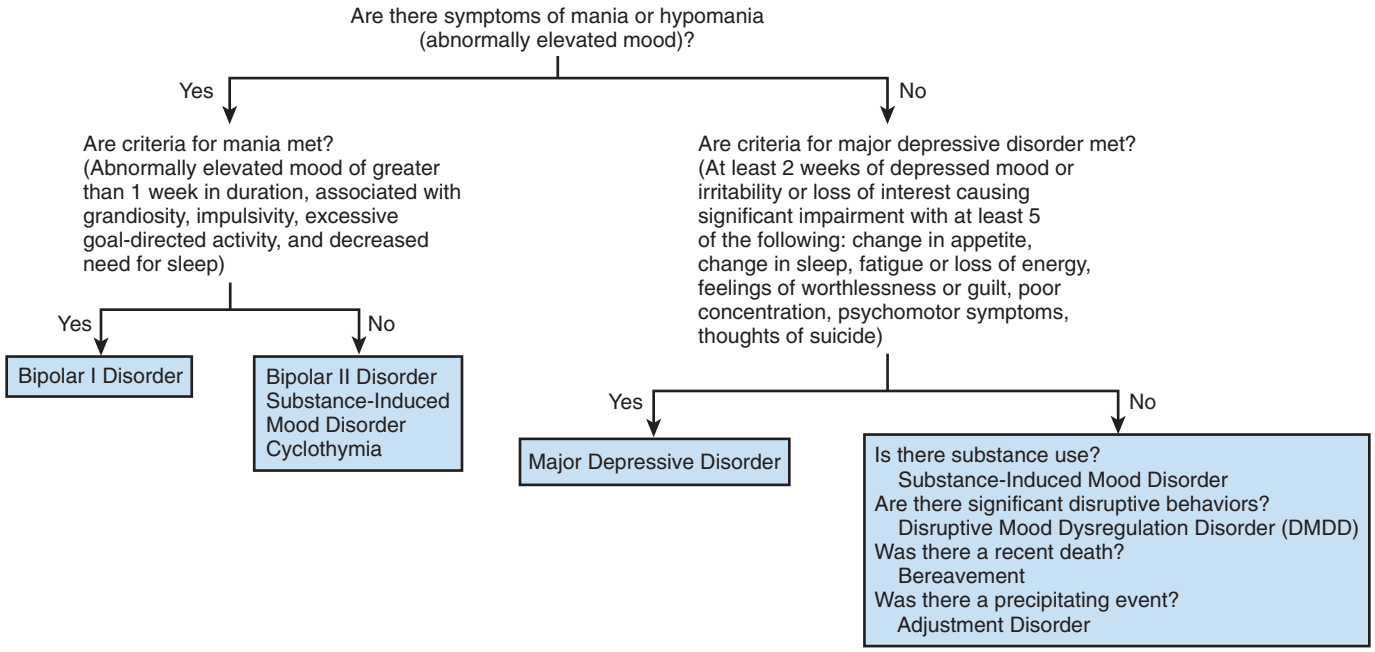


FIGURE 27.2 Evaluation of mood disorders.

(See *Nelson Textbook of Pediatrics,* p. 151.)

7. Poor concentration or indecisiveness
8. Suicidal ideation or thoughts of death
9. Psychomotor agitation or retardation

These symptoms should not be secondary to bereavement, medical conditions, substance abuse, or bipolar disorders. Emotional reaction to adverse stressors is a normal part of life. The clinician must decide whether the reaction to the stressor is normal, an adjustment disorder, or major depression.

The occurrence of major depressive disorders in adolescence is as high as 5%. There is also a 3-fold increase in major depression in children who have a parent with depression. The differential diagnosis of major depression encompasses various medical disorders, including neurologic disorders, endocrine disorders such as hypothyroidism or hyperparathyroidism, side effects from medications such as H_2-blockers or isotretinoin, and substance abuse or use (see Table 27.3). Numerous psychiatric conditions are comorbid with major depression. Among these are ODD, conduct disorder, ADHD, anxiety disorders, eating disorders, and substance abuse.

Major depressive disorder can manifest at any age; however, most patients present in early adulthood. Children usually present with somatic complaints, social withdrawal, and irritability, whereas adolescents often present with psychomotor retardation, thoughts of guilt and worthlessness, and excessive sleep. Approximately 15% of children with major depression eventually develop bipolar disorders. Fifty percent of children with major depression have multiple episodes, frequently associated with significant stressors. Approximately 25% of patients with certain chronic medical conditions such as cancer or diabetes develop major depressive disorder during the course of the illness. The main difficulty in diagnosing major depression is that the gravity of the depressive mood is often not always apparent to the parent and the clinician. Given that children and adolescents often present with irritability, sullenness, or mean-spiritedness, the parents and/or clinician may attribute this behavior to typical adolescent behavior. These children do not always appear sad and the clinician should have a high index of suspicion of major depression in any child who presents with sullenness and irritability. Guidelines for evaluating such a patient are as follows:

1. Assess suicidal ideation and ensure the patient's safety.
2. Obtain collateral information from other sources to determine the child's functioning and symptoms.
3. Obtain a thorough family history for symptoms and formal diagnoses of mood disorders.
4. Rule out bipolar disorders by assessing for symptoms of mania or hypomania.
5. Investigate primary or comorbid conditions, such as substance abuse.
6. Consider the role of life stressors in relationship to the symptoms.

Premenstrual dysphoric disorder. Both physical and mood symptoms can occur prior to a female's menstrual cycle. When the symptoms are severe, they may constitute premenstrual dysphoric disorder, the primary features of which are mood lability, irritability, dysphoria, and anxiety that appear recurrently during the premenstrual phase of a female's cycle and then resolve around the onset of menses. Delusions or hallucinations have been described but are rare. The 12-month prevalence is as high as 6% of menstruating women. Onset can be any time after menarche. Factors such as stress, a history of trauma, and seasonal changes can contribute. The DSM-5 states that the following criteria must be met:

1. In the majority of cycles, at least 4 of the following symptoms: marked affective lability (mood swings, increased sensitivity to rejection), irritability or anger, increased interpersonal conflicts, depressed mood, feelings of hopelessness or self-deprecating thoughts, anxiety, tension
2. At least 1 of the following: decreased interest in activities, difficulty concentrating, lack of energy, change in appetite, change in sleep, sense of being out of control, physical symptoms of breast tenderness, joint pain, bloating, or weight gain
3. Symptoms present during the majority of cycles over the year prior

The severity of symptoms is similar to that in other psychiatric disorders, such as major depression or generalized anxiety disorder, though the duration of symptoms is shorter. Nonetheless, symptoms do need to be severe and cause marked impairment in functioning in order to satisfy diagnostic criteria. To confirm the diagnosis, daily prospective symptom ratings are required for at least 2 cycles.

Substance-induced mood disorders. Substance-induced disorders are distinct from substance use disorders. Whereas the latter refer to the negative consequences of substance use over time, the substance-induced disorders refer to the immediate effects of substance use—**intoxication** and **withdrawal**—and to the **substance-induced mental disorders**, which include psychotic disorders, anxiety disorders, depressive disorders, bipolar and related disorders, obsessive-compulsive and related disorders, sleep disorders, sexual dysfunction, delirium, and neurocognitive disorders. The hallmark of substance-induced mental disorders is that the symptoms of the disorder are attributable to the ingestion of the substance and were not present prior to ingestion. While symptoms may abate as the pharmacologic activity of the substance abates, repeated use may lead to chronic changes in neurophysiology, and as such, behavioral effects may persist even when the substance is no longer used.

The substances specified in the DSM-5 include alcohol, caffeine, cannabis (also synthetic cannabinoids), hallucinogens (including phencyclidine and others), inhalants, opioids, sedatives/hypnotics/anxiolytics, stimulants, tobacco, and "other." Defining the symptom complex associated with each individual substance is out of the purview of this text; however, the possibility of substance use/abuse as a cause for behavioral and mood disruption is critical for all physicians to recognize. The patient interview should include time to speak with the patient individually, without a parent or other caregiver present, so as to establish rapport, to incorporate the techniques of normalizing and remaining non-judgmental, and to encourage a patient to discuss their substance use.

Adjustment disorder. Adjustment disorder is an excessive or maladaptive response to a stressor, and diagnosis is contingent upon the recognition of a particular stressor. Typical stressors for children and adolescents include separations, painful injuries, illness, hospitalization or surgery, parental divorce, change of residency, academic failure, and conflict with peers. The DSM-5 criteria for adjustment disorder are as follows:

1. The symptoms develop within 3 months of the stressor.
2. Significant social and/or academic impairment results.
3. The symptoms do not meet criteria for mood or anxiety disorder.
4. The symptoms do not represent bereavement.
5. The symptoms abate 6 months after termination of the stressor.

This disorder is further classified by the patient's symptoms, such as **depressed mood**, **anxiety**, and/or **conduct disorder**. Affected patients may be at increased risk for suicide, particularly if social and/or academic impairment are severe. If the stressor is an illness or its treatment, the morbidity of the medical condition may increase as a consequence of noncompliance. The differential diagnosis of adjustment disorder is a mood or anxiety disorder, exacerbation of a personality disorder, or post-traumatic stress disorder (PTSD).

Conditions Characterized by Extremes of Mood Lability

The **bipolar disorders** include bipolar I disorder, bipolar II disorder, and cyclothymic disorder. All are characterized by the presence of either mania or hypomania. **Mania** manifests acutely, leads to significant functional impairments, and is characterized by racing thoughts, distractibility, delusions of grandeur, and other disturbances in thinking. Problematic behaviors during a manic episode include recklessness (e.g., excessive participation in social activities, high-risk sexual activity, buying sprees), agitation, decreased sleep, and excessive talkativeness. A **manic episode** is defined as an abnormally elevated, euphoric, expansive, or irritable mood for at least 1 week unless treated. This mood disturbance is associated with at least 3 of the following symptoms or 4 if the mood is irritable:

1. Grandiosity
2. Decreased need for sleep
3. Talkativeness
4. Racing thoughts
5. Distractibility
6. Excessive goal-directed activity or psychomotor agitation
7. Reckless pursuit of pleasure

The symptoms of a **hypomanic episode** are the same, though are present for a shorter duration (i.e., 4 days or fewer), are not associated with psychotic symptoms of delusions or hallucination, and are not severe enough to cause major social or academic dysfunction. Up to 10% of patients with hypomania will eventually develop mania.

Bipolar I disorder is characterized by the presence of manic episodes. Patients may also have prior or subsequent episodes of hypomania or major depression, though these are not required. **Bipolar II disorder** is characterized by the presence of major depression episodes and hypomania. **Cyclothymic disorder** is a chronic, cyclic illness of hypomania and depressive symptoms without episodes of major depression.

Comorbid psychiatric conditions include eating disorders, ADHD, conduct disorders, panic disorders, social phobias, adjustment disorders, substance use disorders, and substance-induced disorders. The lifetime prevalence of bipolar I disorder is as high as 1.6%, and that of bipolar II disorder is 0.5%. Approximately 15% of adolescents with recurrent major depression eventually develop bipolar illnesses.

The differential diagnosis of the bipolar disorders includes schizophrenia and medical conditions that cause changes in mental status, particularly thyroid disorders, Cushing disease, and multiple sclerosis (see Table 27.3). Substance-induced mood disorders must also be considered, particularly those associated with cocaine, tricyclic antidepressants and selective serotonin reuptake inhibitors. The clinician should obtain a detailed family history as bipolar disorder frequently runs in families. Because the condition is often undiagnosed in parents, the questions should be directed toward the presence of the symptoms for bipolar disorders. The following principles should guide the evaluation of patients with symptoms of depression or mania:

1. Recognize the symptoms mania and hypomania.
2. Remember that depressed patients often have bipolar disorders.
3. Obtain a thorough family history to look for symptoms of mood disorders.
4. Consider bipolar illnesses in patients with any disruptive disorder that does not respond to treatment.
5. Assess for drug and/or alcohol use as substances may induce bipolar disorder, and substance use is frequently a comorbid condition.

Borderline personality disorder is a chronic personality disorder characterized by intense mood lability, impulsivity, identity disturbances, and unstable relationships. The diagnosis may be challenging in adolescents whose appropriate psychologic development includes the forging of identity and personality traits; however, since borderline personality disorder is associated with significant morbidity and potential mortality, it should be considered in the differential diagnosis of a patient presenting with significant mood or behavioral issues. Diagnosis requires 5 or more of the following:

1. Significant efforts to avoid real or imagined abandonment
2. Unstable and intense relationships with extremes of idolization and devaluation
3. Marked identity disturbances with unstable sense of self
4. Significant impulsivity in at least 2 areas that are potentially self-damaging: spending, sexual activity, substance abuse, reckless driving, or binge eating
5. Recurrent suicidal or self-mutilating behavior
6. Intense dysphoria, irritability, or anxiety
7. Chronic feelings of emptiness
8. Inappropriate anger
9. Transient, stress-related paranoia or dissociation

Both genetic and psychosocial factors are believed to be causative. Risk factors for borderline personality disorder include a history of abuse, neglect, or early parental loss. The median population prevalence is approximately 6% in primary care settings and is as high as 10% in outpatient mental health clinics. Females are more frequently diagnosed than males, at a ratio of 3:1.

Addressing Suicidal Thoughts and Attempts

Suicide is the second leading cause of death in adolescents, and assessing the risk of suicide is a critical component in the evaluation of any child or teen. Although depression is an important risk factor for suicide, only half of adolescents who attempt suicide have clinically diagnosable depression. In those without depression, strong predictors of suicide are impulsivity and low frustration tolerance. The approach to evaluating suicidality is complicated and includes a stepwise process of probing first for latent thoughts of suicidality (Table 27.6), then for active suicidal intent. Key to this process is assessing whether the child is considering acting on thoughts of death or suicide. To assess risk, the interviewer should focus on the **risk factors for completed suicide**, which include the following:

1. Male sex
2. Adolescence
3. Formation of a conscious plan
4. Presence of available means (e.g., medications, firearms)
5. Depression
6. Hopelessness
7. Impulsivity
8. Low frustration tolerance
9. Use of intoxicants
10. Sexual identity conflicts
11. Recent death of family member or friend
12. Previous suicide attempts

Once a patient's thoughts of suicide have escalated to suicide threats, plans, or attempts, this constitutes a medical emergency and the patient should be immediately referred to an experienced mental health professional or emergency department, and psychiatric hospitalization should strongly be considered.

CONDITIONS CHARACTERIZED BY WORRY, FEAR, AND PANIC

Conditions Characterized by Worry

Worries are primarily internal ruminations about the potential to experience negative outcomes from typically benign, everyday events. While often accompanied by somatic symptoms, such as stomach

(See *Nelson Textbook of Pediatrics,* p. 157.)

upset and headache, the hallmark of these disorders is the persistence of worry across 1 or more areas of a child's life. Conditions characterized by worry are categorized by whether they are associated with unusual behaviors (Fig. 27.3).

Worry Without Unusual Behaviors

Generalized anxiety disorder is characterized by excessive worry and concern over many issues. Chronic generalized anxiety may lead to symptoms of depression or somatic complaints, including abdominal pain, nausea, appetite loss, and headaches. Diagnostic criteria are as follows:

1. Excessive anxiety and worry about various issues for more than 6 months
2. Difficulty controlling the worry
3. Anxiety and worry are associated with 3 of the following:
   a. Restlessness
   b. Being easily fatigued
   c. Difficulty concentrating
   d. Irritability
   e. Muscle tension
   f. Sleep disturbance
4. Anxiety, worry, or physical symptoms cause significant distress or impairment

The lifetime prevalence of generalized anxiety disorder is approximately 5%, with most cases initially presenting during childhood or adolescence. The disorder is chronic and worsens during periods of stress. Comorbid diagnoses include mood disorders, other anxiety disorders, and substance use disorders.

Adjustment disorder with anxiety. The hallmark of adjustment disorders is an excessive or maladaptive response to a stressor that is out of proportion to that stressor. In **adjustment disorder with anxiety**, the maladaptive response manifests as excessive worry. Stressors that children and adolescents may encounter include social separations, parental divorce, illness, injury, moving, academic failure, and peer conflict. Of note, the stressor should not represent a perceived threat to the life of oneself or a loved one. DSM-5 diagnostic criteria are as follows:

1. Symptoms develop within 3 months of the stressor
2. Significant impairment results
3. The symptoms do not meet criteria for an alternative anxiety disorder
4. The symptoms do not represent bereavement
5. The symptoms abate 6 months after termination of the stress

Worry With Unusual Behaviors

Obsesssive-compulsive disorder (OCD) is characterized by obsessive worries that are briefly relieved by compensatory compulsive behaviors. **Obsessions** are recurrent and persistent thoughts, urges, or

TABLE 27.6 Columbia Suicide Severity Rating Scale–Screener

1. Have you wished you were dead or wished you could go to sleep and not wake up?
2. Have you actually had any thoughts about killing yourself?
   If Yes to 2, answer questions 3, 4, 5, and 6. If No to 2, go directly to question 6.
3. Have you thought about how you might do this?
4. Have you had any intention of acting on these thoughts of killing yourself, as opposed to you having the thoughts but you definitely would not act on them?
5. Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
6. Have you done anything, started to do anything, or prepared to do anything to end your life?

Response Protocol to Screening, based on last item answered YES.
Item 1 – Mental Health Referral at discharge
Item 2 – Mental Health Referral at discharge
Item 3 – Care Team Consultation (Psychiatric Nurse) and Patient Safety Monitor/Procedures
Item 4 – Psychiatric Consultation and Patient Safety Monitor/Procedures
Item 5 – Psychiatric Consultation and Patient Safety Monitor/Procedures
Item 6 – If over a year ago, Mental Health Referral at discharge
If between 1 wk and 1 yr ago, Care Team Consultation (Psychiatric Nurse) and Patient Safety Monitor
If 1 wk ago or less, Psychiatric Consultation and Patient Safety Monitor

From Posner K. *Columbia-suicide severity rating scale: screener/recent–self-report*. http://www.cssrs.columbia.edu/scales_practice_cssrs.html.

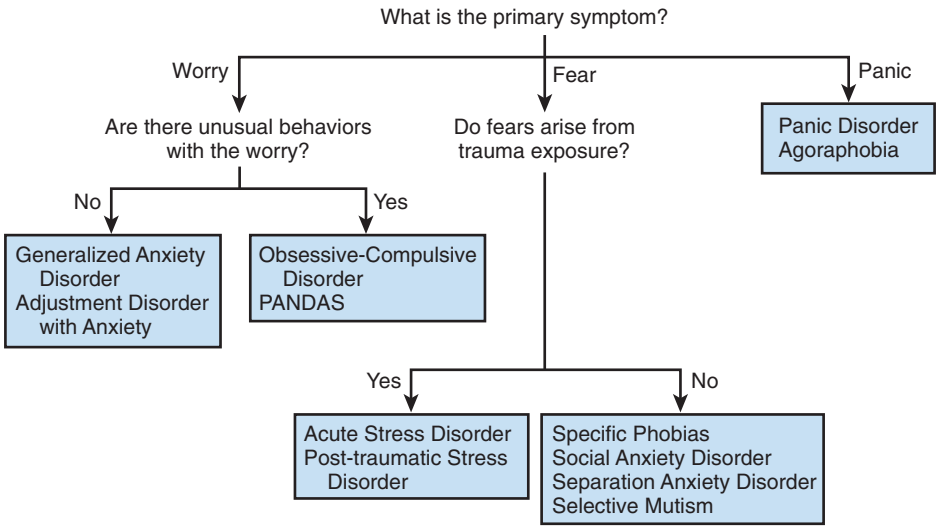


FIGURE 27.3 Evaluation of worry, fear, and panic. *PANDAS,* Pediatric Autoimmune Neuropsychiatric Dsorders Asociated with *Streptococcus pyogenes.*

(See *Nelson Textbook of Pediatrics,* p. 154.)

images that the individual attempts to ignore or suppress. Common obsessions include fear of contamination or illness, guilt regarding sexual thoughts, images of violent or horrific scenes, and urges to injure oneself or others. **Compulsions** are repetitive and excessive acts the patient performs to reduce the anxiety elicited by obsessions. Compulsions may include actions, such as repetitive hand-washing or checking locks, or mental acts, such as repeating certain words or counting internally. Some patients need to perform a particular action a specific number of times in order to satisfy the compulsion. To meet criteria for OCD, the compulsive actions must take over an hour a day or interfere with the patient's day-to-day life.

Lifetime prevalence of OCD is approximately 2.5%. While females are more frequently affected in general, males have a higher prevalence during childhood. Children generally present with vague anxiety symptoms or poor concentration before clear obsessions and compulsions are seen. In children, OCD is highly comorbid with Tourette disorder and ADHD. Other comorbidities include depression, anxiety disorders, and eating disorders.

Pediatric autoimmune neuropsychiatric disorders associated with Streptococcus pyogenes (PANDAS). *PANDAS* is the term proposed for a group of neuropsychiatric disorders (particularly OCD, tic disorder, and Tourette disorder) for which a possible relationship with group A streptococcal (GAS) infections has been hypothesized. This relationship has not been proven. It has been proposed that this subset of patients with obsessive-compulsive and tic disorders may produce autoimmune antibodies in response to a GAS infection that cross-react with brain tissue similar to the autoimmune response believed to be responsible for the manifestations of Sydenham chorea. Until carefully designed and well-controlled studies have established a causal relationship between neurobehavioral abnormalities and GAS infections, routine diagnostic laboratory testing for GAS and antistreptococcal antibodies, long-term antistreptococcal prophylaxis, or immunoregulatory therapy (e.g., intravenous immunoglobulin, plasma exchange) to treat exacerbations of this disorder clearly are not recommended. It has also been suggested that a broad spectrum of infectious agents may have the ability to trigger exacerbations in children with these neurobehavioral disorders.

Conditions Characterized by Fear

Fear is an intense emotion centered on a belief that something is dangerous or painful. Fears may be spontaneous or may arise from previous traumatic experiences. While all people experience fear as an emotion, in these disorders it causes significant functional impairment.

Fears Arising Spontaneously

Specific phobias. The hallmark of a specific phobia is intense fear upon exposure to a particular stimulus or situation, or occasionally upon thinking about or visualizing the stimulus. The fear is out of proportion to the actual danger. The fear response in children typically manifests as clinging, crying, having a tantrum, or "freezing." Common specific phobias include animals, heights, enclosed places, exposure to blood, or venipuncture. Specific phobias peak in childhood and early adulthood. Diagnostic criteria of a specific phobia are as follows:

1. Intense fear is caused by a particular stimulus.
2. The object or situation almost always provokes immediate fear or anxiety.
3. Stimuli are avoided or endured with great distress.
4. The fear is out of proportion to the actual danger.
5. The fear persists 6 months or longer.

Social anxiety disorder (social phobia). Social anxiety disorder is a specific phobia in which the stimulus is either a social or performance task. Diagnostic criteria include the following:

1. Marked fear about 1 or more social situations
2. Individual fears that he or she will act in a way that will be negatively evaluated
3. Social situations almost always provoke fear or anxiety
4. Social situations are avoided
5. Fear is out of proportion to the actual threat posed by the social situation
6. Fear or anxiety persists 6 months or longer

Social phobias most often begin in adolescence and are twice as common in boys as in girls. Children with social anxiety often refuse group play, stay close to familiar adults, and appear excessively timid in unfamiliar situations. Children may report somatic complaints, such as headaches or stomachaches, which abate when the child is allowed to remain home. Social phobia may be comorbid with panic disorder, other anxiety disorders, mood disorders, and substance abuse.

Separation anxiety disorder. The core fear in separation anxiety disorder is separation from a specific attachment figure or figures. Fear of separation is normal in infants and children aged 6-30 months but should be considered abnormal if increasing or not declining beyond this age range. Diagnosis requires the presence of symptoms for greater than 4 weeks. At least 3 of the following symptoms must be present:

1. Distress with separation
2. Worry about losing loved ones
3. Worry about an event causing separation
4. Refusal to go away from home
5. Reluctance to be alone
6. Refusal to fall asleep alone
7. Repeated nightmares of separation
8. Somatic complaints when separation occurs or is anticipated

The prevalence of separation anxiety disorder is as high as 5%, with onset typically in early childhood. Patients with separation anxiety disorder often display their worries as demands or behavioral outbursts, which may cause significant family conflict. Comorbid conditions include major depressive disorder and panic disorder with agoraphobia.

Selective mutism. Patients with selective mutism have a persistent failure to speak in specific, but not all, situations. Children with selective mutism are often shy in public but controlling at home in order to maintain proximity to parents. Diagnostic criteria include the following:

1. Consistent failure to speak in specific social situations
2. Failure to speak interferes with achievement or social communication
3. Duration of at least 1 month
4. Failure to speak is not due to lack of knowledge of the spoken language
5. Disturbance is not better explained by a communication or other psychiatric disorder

The differential diagnosis includes communication disorders, autism spectrum disorders, and social anxiety disorder. Selective mutism may be a more severe form of social anxiety disorder.

Fears Arising from Traumatic Events

A **traumatic event** is defined as an exposure to actual or threatened death, serious injury, or sexual violence. Responses to traumatic events include hyperarousal, avoidance of circumstances reminiscent of the event, or re-experiencing the event via nightmares and flashbacks. **Acute stress disorder** and **PTSD** are characterized by severe and persistent trauma responses that lead to impaired function. Symptoms are divided into 4 clusters: intrusion, avoidance, negative alteration in cognition and mood, and marked alterations in arousal and activity. **Acute stress disorder** is the persistence of at least 9 of the 14 defined

symptoms, regardless of symptom cluster designation, for 3 days to 1 month after exposure to a traumatic event. In contrast to acute stress disorder, **PTSD** must include symptoms from each of the separate symptom clusters. Exposure to the traumatic event includes directly experiencing the event, witnessing the event, learning the event occurred to a family member or close friend (caregiver for children under 6), or experiencing repeated or extreme exposure to details of a traumatic event.

1. Intrusion symptoms
   a. Distressing memories of the event
   b. Dreams in which content or effect of the dream is related to the event (in children, does not need to be related to event)
   c. Dissociative reactions in which the individual feels the event is recurring (flashbacks) (in children, may be reenactment in play)
   d. Psychologic distress at exposure to reminders of the event
   e. Marked physiologic reactions to reminders of the event
2. Avoidance
   a. Avoidance or efforts to avoid distressing memories (children may avoid places or physical reminders)
   b. Avoidance of external reminders (children may avoid people, conversations, or interpersonal relationships)
3. Negative alterations in cognition and mood
   a. Inability to remember an important aspect of the traumatic event (not a criterion for a child under 6 years of age)
   b. Persistent and exaggerated negative beliefs (not a criterion for a child under 6 years of age)
   c. Persistent, distorted thoughts about cause or consequences of trauma (not a criterion for a child under 6 years of age)
   d. Persistent negative emotional state (fear, guilt, sadness, shame)
   e. Decreased interest in activities (constriction of play in children)
   f. Feelings of detachment (socially withdrawn behavior in children)
   g. Persistent inability to experience positive emotions (express positive emotions in children)
4. Alterations in arousal
   a. Irritable behavior and angry outbursts (with little provocation)
   b. Reckless or self-destructive behaviors (not a criterion in a child under 6 years of age)
   c. Hypervigilance
   d. Exaggerated startle response
   e. Problems with concentration
   f. Sleep disturbance

While as many as 30% of children will have some symptoms of acute stress disorder following a trauma, only 10% will meet diagnostic criteria. The significance of acute stress disorder in predicting eventual development of PTSD remains unclear.

Comorbid diagnoses include panic disorder, social phobia, substance abuse, OCD, somatic symptom disorder, and major depressive disorder. In addition to PTSD, childhood trauma and other significant stressors, together known as adverse childhood experiences, have been found to predispose children to chronic medical and mental health conditions. These medical conditions include ischemic heart disease, cancer, chronic lung disease, skeletal fracture, and liver disease.

Conditions Characterized by Panic

Panic disorder. Panic attacks may be a component of many psychiatric disorders. While panic disorder is characterized by recurrent and unexpected panic attacks, the hallmark of panic disorder is persistent concern over having additional attacks, worry about the consequences of an attack, or a significant change in behavior related to the attacks. **Panic attacks** occur suddenly, peak within 10 minutes, often resolve without intervention, and consist of at least 4 of the following symptoms:

1. Palpitations or tachycardia
2. Diaphoresis
3. Trembling or shaking
4. Shortness of breath or sensation of smothering
5. Feelings of choking
6. Chest pain
7. Nausea or abdominal discomfort
8. Dizziness or feeling faint
9. Chills or heat sensation
10. Paresthesias
11. Derealization (feelings of unreality) or depersonalization
12. Fear of losing control or "going crazy"
13. Fear of dying

The 1-year prevalence rate of panic disorder is as high as 3.5%. The age of onset is bimodal, with the largest peak occurring in adolescence and a smaller one in the mid-30s. Panic disorder in prepubertal children is rare.

Patients with panic disorder have a high degree of comorbid conditions. Over half of patients may have major depressive disorder. There is a high frequency of other anxiety disorders, such as social phobia, OCD, and generalized anxiety disorder. Patients with panic disorder are also at great risk for substance abuse as a consequence of self-medicating.

Agoraphobia. Agoraphobia is characterized by intense anxiety over developing a panic attack or other incapacitating or embarrassing symptoms in a place from which the person cannot escape or in which help may not be available. Diagnosis requires that the anxiety manifest in at least 2 of the following situations:

1. Riding public transportation
2. Being in open spaces
3. Being in enclosed spaces
4. Standing in line or in a crowd
5. Being outside of the home alone

The anxiety is present nearly every time an individual is exposed to the situation they fear and may also develop when the child knows that he or she may be placed in one of these situations. While agoraphobia does present in childhood, the peak of onset is late adolescence and early adulthood. It is seen in about 1.7% of adolescents. Females are affected twice as frequently as males. Agoraphobia is typically preceded by panic disorder, phobias, and separation anxiety disorder. Other comorbidities, such as depression and substance use disorder, often follow the presentation of agoraphobia.

CONDITIONS CHARACTERIZED BY MENTAL STATUS ABNORMALITIES

The evaluation of mental status changes (Fig. 27.4) involves first determining whether the abnormality is limited—such as hallucinations unaccompanied by changes in cognition or consciousness—or pervasive (see also Chapter 31). The abnormality should then be classified by whether it is episodic or persistent. Finally, the mental status change should be classified as either acute or chronic. An example of a limited, episodic, acute change in mental status is the development of hallucinations secondary to acute anxiety. In contrast, autism represents a pervasive, persistent, and chronic alteration in mental status.

Conditions Characterized by Hallucinations

Hallucinations—the apparent perception of something that does not exist in reality—may be an indication of a medical condition, poor visual or auditory function, the ingestion of a substance, or a

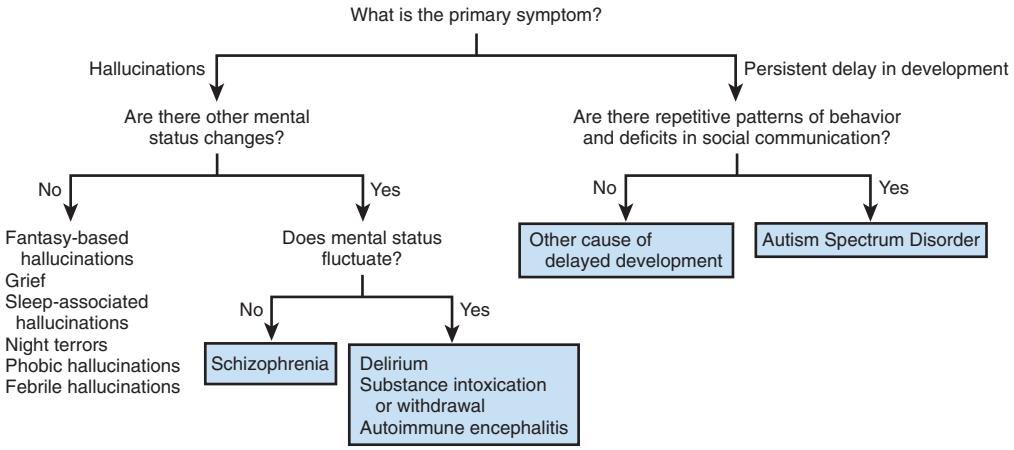


FIGURE 27.4 Evaluation of abnormal mental status findings.

psychiatric illness (see Fig. 27.4). The vast majority of hallucinations in preadolescent children do not ultimately represent a serious psychiatric or medical illness. Hallucinations occur in as many as 5% of normal children.

The first step in evaluating hallucinations is to assess the patient's mental status. Most children with hallucinations have an otherwise normal mental status. If the primary alteration in mental status is confusion, medical **delirium** should be considered (see Chapter 31). The presence of **delusions**—beliefs that are maintained despite being objectively contraindicated by reality—should prompt consideration of schizophrenia or mood disorders. Most hallucinations associated with delirium are visual, whereas those observed in psychoses are typically auditory. Auditory hallucinations may be perceived as chatter or as a voice that chastises the child. Culture can often shape the content of hallucinations and whether the sensory experiences are considered worrisome or abnormal by the patient and family. Children with an otherwise normal mental status may hallucinate in the context of fantasy, grief, sleep, acute phobia, and fever.

Fantasy-based hallucinations. To define a subjective perceptual experience as hallucinatory, the person experiencing the phenomenon has to be able to distinguish imagination from reality. As they develop, children gradually learn that imagination and reality are two separate entities. Children under 3 years of age confuse reality with imagination. By 4 years of age, children understand the concept of "pretend," and by 7 years of age, they understand imagination but act as though the fantasy is still real. They may still describe having an imaginary friend. By 8 years of age, most children are reliably able to distinguish inner thoughts from voices. Some children are involved in more fantasy than are their peers and may engage in fantasy for entertainment or comfort. On occasion, they may get carried away by their fantasies and become quite fearful. Most of these children proceed to healthy psychologic adjustment. Children who have intellectual disability or other developmental delays may, appropriately, have imaginary friends or voices into adolescence.

Grief-induced hallucinations. The grieving process following the death of a loved one may include visual hallucinations of the deceased. These hallucinations can also be auditory, in which the child hears the voice of the deceased speaking to the child. The child's and the family's reaction to these hallucinations is dependent on their cultural and religious beliefs. Some families may perceive these events as a supernatural or a religious experience. Although these experiences may be frightening to some young children, many find reassurance or comfort.

Hallucinations associated with sleep. Dreamlike hallucinations can occur during various stages of sleep. Some may be considered bizarre by the patient and may include partial preservation of consciousness. **Hypnagogic hallucinations** occur during sleep onset and **hypnopompic hallucinations** occur during awakening. The overall prevalence of hypnagogic hallucinations is as high as 37%; that of hypnopompic hallucinations is as high as 12.5%. Patients with insomnia or excessive daytime sleepiness may be more likely to experience sleep-related hallucinations. As many as 30% of patients with **narcolepsy** experience both hypnagogic and hypnopompic hallucinations. These hallucinations can also occur as part of PTSD, in which case they often take the form of a flashback or re-experiencing of the traumatic event. **Night terrors** may resemble hallucinations, though are a distinct entity of non–rapid eye movement sleep arousal. The DSM-5 defines **sleep terror disorder** as recurrent episodes of night terrors. During episodes, the child appears to arouse from sleep and cries or screams inconsolably, may speak unintelligibly, and exhibits intense fear and autonomic arousal (e.g., tachycardia, sweating). On awakening, the child has no memory of the event. Episodes of night terrors last from 1-10 minutes. Night terrors occur during stage 4 sleep and not during rapid eye movement sleep and tend to occur in the first half of the night. Over 30% of 18-month-old toddlers will experience a night terror, with the prevalence decreasing to 2.2% by adulthood. **Seizures**, especially of the temporal and frontal lobes, can produce fear and complex behavior patterns resembling night terrors, and should be considered in the differential diagnosis of night terrors.

Phobic hallucinations. Acute phobic hallucinations occur in preschool-aged children and consist of episodes of hallucinations coupled with terror. These hallucinations last from 10-60 minutes and may occur any time of the day but mostly at night. During episodes, the child may become very frightened, state that bugs are crawling over him or her and attempt to remove them, cry, or hide. Because of the acute change in mental status, this condition must be differentiated from the medical and psychotic causes of hallucinations, such as delirium. The cause of acute phobic hallucinations is unknown. Phobic hallucinations are most frequently seen in children with a personal or family history of anxiety. Symptoms usually last 1-3 days and diminish over 1-2 weeks.

Febrile hallucinations. Preschool-aged children may hallucinate during high fevers. The hallucinations are temporary and are not associated with future psychiatric disorders. The phenomenon may represent a mild form of delirium and typically requires only reassurance for management, as well as evaluation for the source of fever. Persistent hallucinations, impaired consciousness, and changes in cognition, such as not recognizing parents or difficulty completing previously accomplished tasks, suggest frank delirium and require further evaluation.

Schizophrenia. Schizophrenia is a disorder of chronic, persistent psychosis (loss of reality testing) that often presents in adolescence or young adulthood. Symptoms are divided into 4 domains: positive symptoms, negative symptoms, cognitive symptoms, and mood symptoms. **Positive symptoms** consist of psychotic symptoms (such as hallucinations), delusions (fixed false beliefs), and disorganized speech and behavior (loose associations). **Negative symptoms** consist of social withdrawal, flattening of affect, alogia (i.e., speaking in brief sentences), abulia, apathy, and avolition (i.e., lack of desire to do anything) (see Table 27.4). The flat affect may consist of a reduction in body language, lack of eye contact, and emotional unresponsiveness (see Table 27.4). **Cognitive symptoms** are characterized by deficits in executive function and an inability to appreciate and react appropriately to social cues. **Mood symptoms** often consist of depression though may also consist of context-inappropriate cheerfulness or sadness. The symptoms may fluctuate over time, and as such, schizophrenia is divided into 2 phases: prodromal and active. Diagnostic criteria for schizophrenia specify 2 or more of the following **characteristic symptoms:**

1. Delusions
2. Hallucinations
3. Disorganized speech
4. Grossly disorganized or catatonic behavior
5. Negative symptoms, such as flat affect

At least 1 symptom must be delusions, hallucinations, or disorganized speech and the symptoms must appear in the context of significant social and educational dysfunction. There must also be continuous indications of the disturbance for at least 6 months, with at least 1 month of active-phase symptoms. Medical causes and mood disorders need to be excluded (Table 27.7; see Table 27.3).

During the **prodromal phase**, the patient exhibits progressive **negative symptoms**. During this period, the patient may also have unusual beliefs that are not of the magnitude of true delusions or hallucinations. The patient may have magical thinking or may perceive that someone is talking to him or her, but no words are hallucinated.

During the **active phase** of schizophrenia, the patient has at least 2 characteristic symptoms for more than 1 month, unless the symptoms have been shortened by treatment. The most common **delusions** in this disorder are persecutory (e.g., the patient is being spied on) and referential (e.g., external events or comments are directed toward the patient). Other less common delusions may be somatic (e.g., internal organs are replaced by others), religious, or grandiose in nature. Hallucinations are most commonly auditory, but may emanate from any sensory modality.

The **disorganized speech** may be incomprehensible, and the patient may be unable to organize a logical conversation. The behavior problems consist of inappropriate dress, disheveled appearance, unprovoked aggression, and **catatonia,** decreased responsiveness to the environment. If symptoms have not been present for 6 months, the provisional diagnosis of **schizophreniform disorder** is applied. Approximately 65% of patients with schizophreniform disorder have symptoms that last longer than 6 months and are reclassified as having schizophrenia.

Schizophrenia is exceedingly rare and is often a misdiagnosis prior to 13 years of age. If diagnosed prior to this age, it is labeled as **childhood onset** or **very early onset schizophrenia**. Prevalence is approximately 2.5/100,000 in children under 13 years of age and 6/100,000 in adolescents. Forty percent of males and 23% of females with schizophrenia will have onset during adolescence. The differential diagnosis of schizophrenia consists of delirium, dementia, mood disorder, pervasive developmental disorders, and substance ingestion (Table 27.8; see Table 27.3). The prognosis of schizophrenia is guarded, with

TABLE 27.7 Features Suggesting Neurologic Disease in Patients with Psychiatric Symptoms

Atypical Psychiatric Features
- Late or very early age of onset
- Acute or subacute onset
- Lack of significant psychosocial stressors
- Catatonia
- Diminished comportment
- Cognitive decline
- Intractability despite adequate therapy
- Progressive symptoms

History of Present Illness
- New or worsening headache
- Inattention
- Somnolence
- Incontinence
- Focal neurologic complaints such as weakness, sensory changes, incoordination, or gait difficulty
- Neuroendocrine changes
- Anorexia/weight loss

Patient Medical History
- Risk factors for cerebrovascular disease or central nervous system infections
- Malignancy
- Immunocompromised status
- Significant head trauma
- Seizures
- Movement disorder
- Hepatobiliary disorders
- Abdominal crises of unknown cause
- Biologic relatives with similar diseases or complaints

Unexplained Diagnostic Abnormalities
- Screening laboratories
- Neuroimaging studies or possibly imaging of other systems
- Electroencephalogram
- Cerebrospinal fluid

From Perez DL, Murray ED, Price BH. Depression and psychosis in neurological practice. In: Daroff RB, Jankovic J, Mazziotta JC, Pomeroy SL, eds. *Bradley's Neurology in Clinical Practice.* 7th ed. Philadelphia: Elsevier; 2015.

TABLE 27.8 Potential Behavioral and Cognitive Manifestations of Substance Abuse

Depression	Impulsivity
Panic attacks	Cognitive deficits:
Anxiety	Attention
Hallucinations	Calculation
Delusions	Executive tasks
Paranoia	Memory
Mania	Fatigue
Depersonalization	Sedation
Disinhibition	

From Perez DL, Murray ED, Price BH. Depression and psychosis in neurological practice. In: Daroff RB, Jankovic J, Mazziotta JC, Pomeroy SL, eds. *Bradley's Neurology in Clinical Practice.* 7th ed. Philadelphia: Elsevier; 2015.

significant morbidity and mortality. The risk of suicide is high early in the illness. The disorder is chronic and is associated with exacerbations and remissions. Even with optimal therapy, patients with schizophrenia have significant social deficits, poor initiative, and abnormal thought processes.

Conditions Characterized by Fluctuating Mental Status

Delirium. Delirium is characterized by deficits in cognition and consciousness that develop over a short time (see Chapter 31). Diagnostic criteria include the following:

1. Disturbance in awareness and attention (i.e., reduced ability to direct, focus, sustain, and shift attention)
2. Change in cognition (e.g., memory deficit, disorientation, language disturbance, perceptual disturbance) that is not better accounted for by a preexisting, established, or evolving dementia
3. Disturbance develops over a short period of time and tends to fluctuate over time
4. There is evidence of a medical, substance-induced, or toxin-induced cause

Children with delirium may misinterpret auditory or visual stimuli or may have actual hallucinations. The hallucinations of delirium are different from those seen in psychosis in that they are more often visual and acute in onset, whereas those resulting from psychoses are usually auditory and are subacute or chronic.

Besides altered sensorium, patients often have decreased sleep or reversal of the sleep/wake cycle and may exhibit psychomotor agitation or retardation. Delirium is indicative of global cerebral dysfunction. Because causes of delirium are potentially life threatening, an expedient and comprehensive medical evaluation is needed.

Substance intoxication. Intoxication is defined as clinically significant behavioral or psychologic changes following the use of a substance. The most common signs of intoxication are changes in perception, wakefulness, attention, thinking, judgment, coordination, and interpersonal behavior. Physical findings suggest particular classes of medications and cluster into recognizable patterns of signs and symptoms termed **toxidromes** (Table 27.9). If the suspected cause of altered mental status in a patient is substance intoxication, urine and blood toxicology testing should be performed.

Patients who present with substance intoxication should be evaluated for whether the ingestion represented an attempt at self-harm or suicide. Some substance intoxications will require medical hospitalization, if severe. Patients being treated for psychiatric illnesses may be at risk of 2 particular toxidromes related to their medical therapy, **serotonin syndrome** and **neuroleptic malignant syndrome**.

TABLE 27.9 Clinically Relevant Toxidromes

Toxidrome	Clinical Findings	Example Agents
Cholinergic	Diarrhea, fecal incontinence, enuresis, miosis, tachycardia followed by bradycardia, lacrimation, sialorrhea, sweating, muscle fasciculations followed by weakness and/or paralysis, altered mental status	Organophosphate and carbamate insecticides *Amanita muscaria* Nicotine
Anticholinergic	Agitated delirium, flushing, decreased sweating, tachycardia, mydriasis, urinary retention, decreased peristalsis, hyperthermia	Atropine Benztropine Scopolamine Diphenhydramine
Sympathomimetic	Mydriasis, hyperthermia, seizures, hyperactivity, hypertension, tachycardia, diaphoresis, delusions, piloerection	Cocaine Methamphetamine MDMA
Sympatholytic	Miosis, hypotension, bradycardia or reflex tachycardia, CNS depression	Clonidine Methyldopa Oxymetazoline
Opioid	Miosis, CNS depression, respiratory depression or apnea, may have hypotension	Heroin Morphine Fentanyl Oxycodone
Serotonin syndrome	Mental status changes, autonomic hyperactivity, neuromuscular abnormalities, akathisia, tremor, clonus, muscle hypertonicity, hyperthermia	Sertraline Fluoxetine Citalopram Linezolid Trazodone Meperidine Tramadol
Neuroleptic malignant syndrome	Fever, "lead pipe" muscular rigidity, altered mental status, autonomic dysfunction (in setting of recent treatment with neuroleptics)	Haloperidol Chlorpromazine Promethazine Prochlorperazine Ziprasidone Quetiapine

CNS, central nervous system; *MDMA,* methylenedioxymethamphetamine.
From Skolnik AB, Wilcox SR. General toxicology and toxidromes. In: *Critical Care Secrets.* 5th ed. St. Louis: Mosby; 2013:545-551.

Serotonin syndrome. The triad of cognitive-behavioral changes, autonomic instability, and neuromuscular signs and symptoms are characteristic of the central serotonin syndrome. Patients frequently manifest behavior alterations that include confusion, disorientation, agitation, and irritability. Coma, anxiety, seizures, hallucinations, and hypomania are less common.

Central serotonin syndrome results from excessive central nervous system serotonin activity from dietary supplements or the use of substances that modify central nervous system serotonin levels. Most commonly, these agents are selective serotonin reuptake inhibitors or other substances that inhibit serotonin reuptake, including tricyclic antidepressants, meperidine, dextromethorphan, and 3,4-methylenedioxymethamphetamine (MDMA). Other substances, such as amphetamines, cocaine, and levodopa, increase synaptic serotonin release, while others such as lithium and lysergic acid diethylamide, are serotonin agonists. Monoamine oxidase inhibitors inhibit serotonin degradation.

Autonomic features of serotonin syndrome include hyperthermia, diaphoresis, and tachycardia. Hypertension, mydriasis, and tachypnea are less common. Neuromuscular features include myoclonus, hyperreflexia, tremor, restlessness, hyperactivity, and ataxia. **Neuroleptic malignant syndrome** is included in the differential diagnosis and is distinguished by neurologic exam since neuroleptic malignant syndrome presents with hyporeflexia and lead-pipe muscular rigidity.

Neuroleptic malignant syndrome. The hallmark of neuroleptic malignant syndrome is severe generalized rigidity, fever, and altered mental status consisting of delirium or stupor. Other findings include diaphoresis, significant creatine kinase elevation, autonomic instability, urinary incontinence, tachypnea, and pallor. While rare, as many as 0.02% of individuals treated with antipsychotics are affected and fatality rates are as high as 20% if the condition is not recognized and managed appropriately. Differentiation from serotonin syndrome is based on medication review, and the presence of significant rigidity, which serotonin syndrome lacks.

Conditions Characterized by Persistent Delay in Development

Delayed development (see Chapter 24) is a broad category of illnesses that can cause specific or global delays. The causes of general developmental delay encompass many conditions; in more than half the cases, a medical condition has caused the delay. These medical conditions include genetic disorders (5%), alterations of embryonic development (30%), perinatal or prenatal disorders (10%), and other medical illness of childhood (5%). Another 15-20% of cases are caused either by deprivation or by severe mental disorders, such as autism spectrum disorder. Specific developmental delays may be secondary to a medical condition such as cerebral palsy, learning disorders, or communication disorders.

Autism spectrum disorder. Autism spectrum disorder is characterized by severe impairment in social communication and interaction, as well as restricted, repetitive patterns of behavior, interests, or activities. In the DSM-5, the previously distinct subtypes of autism, Asperger disorder, and pervasive developmental disorder not-otherwise-specified have been incorporated into a unified diagnosis of autism spectrum disorder. Diagnosis requires the presence of the following 3 deficits in social communication:

1. Deficits in social-emotional reciprocity
2. Deficits in nonverbal communicative behaviors used for social interaction
3. Deficits in developing, maintaining, and understanding relationships

The patient also needs to demonstrate 2 of the following symptoms of repetitive patterns of behavior, interests, or activities:

1. Stereotyped or repetitive motor movements, use of objects, or speech
2. Insistence on sameness, inflexible adherence to routines, or ritualized behaviors
3. Highly restricted, fixated interests
4. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment.

Autism spectrum disorder typically is recognized during the 2nd year of life, when the lack of interest in social interaction, loss or lack of developing language skills, odd play patterns, and unusual communication patterns become more apparent. Despite potential loss of language early in life, autism is not a degenerative disorder, and developmental gains are typically seen. Intellectual disability may be seen with autism spectrum disorder and is listed as a specifier for diagnosis. However, patients with autism typically have uneven intellectual profiles, making thorough neuropsychologic testing highly recommended. Other comorbidities are common and include ADHD, anxiety disorders, developmental coordination disorder, specific learning disorders, avoidant/restrictive food intake disorder, seizures, and depressive disorders. Medical comorbidities are common and include epilepsy, sleep problems, and constipation.

CONDITIONS CHARACTERIZED BY PHYSICAL FINDINGS OR COMPLAINTS

Parents may present to the primary care provider with unexplained physical complaints on behalf of the child. These complaints may be inconsistent with the results of the medical evaluation and may fail to respond to any medical therapy. These unexplained physical complaints may be the manner in which a patient copes with a stressor. The patient may not be aware of the stressor, nor may the patient realize that these symptoms emanate from his or her effort to cope with the problem. The clinician should empathize with the patient, validate the presence of the symptoms, then state which potentially serious medical conditions are reasonably felt to be unlikely based on the patient's history, examination, and diagnostic evaluation. The clinician should highlight the notion that stress can produce or worsen symptoms and should recommend that the possibility of stress be evaluated while the clinician continues to monitor the patient for other medical illnesses. Key to the evaluation is determining whether the symptoms are more concerning primarily to the parent or to the child.

Conditions Characterized by Parental Concerns

Parental worry. Parents may worry excessively about their child's health because of a preceding life-threatening event or illness, mistrust of the medical profession, or as an expression of their own fear of having a serious condition themselves. These parents do not invent the child's symptoms but instead experience an exaggerated worry about symptoms. The evaluation of a parent's excessive concern over the child's health may be further subdivided into specific concerns versus general medical worries.

Specific medical concerns are often related to prior life-threatening events or illnesses, or previous negative experiences with the health care system. Reassurance after an appropriate and thorough medical evaluation may reduce parental anxiety. When the parent reveals the past incident that led to distrust of the reassurances of doctors, the clinician may be able to reduce the parent's worry through open discussion on the differences between past and current events.

If the parent reports that he or she worries about everything, the clinician should determine whether this is a recent development or a

chronic concern. Parents with an acute onset of general medical worries about their children may suffer from a recent stressor or may have anxiety, depression, or OCD. Reassurance alone may be insufficient under these circumstances and the parent's generalized worries may not improve until their own symptoms improve.

Factitious disorder imposed on another (formerly Munchausen syndrome by proxy) (see also Chapter 26)**.** This disorder is a condition in which the patient either feigns or produces symptoms and physical findings in their child to fulfill an underlying need to assume the sick role and receive care. There is no external reward for these symptoms, in contrast to **malingering**, in which the symptoms result in either economic gain or in avoidance of responsibilities.

Red flags include unexplained and prolonged illnesses, incongruous symptoms and signs, ineffective medical treatments, and prior episodes of sudden infant death syndrome. The offending caregiver may not seem worried about the child's medical condition. Some caregivers may form an unusually close relationship with the medical staff; however, there are many exceptions, in which the caregiver is instead neglectful, disruptive, and argumentative.

When this entity is suspected, the first step in evaluation is to ensure the child's safety, which may require hospitalization on a medical ward. With safety assured, the next step is to develop a definitive investigative plan with a multidisciplinary team consisting of mental health professionals, physicians, social services, child abuse specialists, and the legal system. This plan may include surveillance by covert video camera, with appropriate hospital legal advice and oversight, and an approved protocol.

Conditions Characterized by the Patient's Physical Complaints

Psychologic stressors may result in the development of physical symptoms. Evidence that supports a stressor as a cause of the symptom is the potential gain from the symptom and the temporal relationship of the stressor and the symptom. For example, a child may develop chronic fatigue symptoms on the anniversary of his or her mother's death, or a patient's persistent abdominal pain from inflammatory bowel disease may prevent the patient from returning to school, despite medical evidence that the disease is in remission. These symptoms seem real to the child and cause a great deal of distress. Extreme manifestations of these concerns include the somatic symptom disorders.

Illness anxiety disorder (hypochondriasis). In illness anxiety disorder, the child either fears that he or she has a serious illness or focuses on minor discomforts with a worry that he or she may have a life-threatening illness. The hallmark is not the physical symptom but the anxiety over what the symptom represents. Illness anxiety disorder is often associated with other anxiety and depressive disorders; consequently, these patients may appear sad, irritable, or fatigued and should be screened for suicidal ideation or intent, as well as evidence of other comorbid psychiatric disorders.

Somatic symptom disorder. Somatic symptom disorder requires the presence of a physical symptom that is distressing. That symptom must then lead to 1 of the following 3 behaviors:

1. Disproportionate and persistent thoughts about the seriousness of one's symptoms
2. Persistently high level of anxiety about health or the symptom
3. Excessive time and energy devoted to the health concern.

In addition, the patient must have at least 1 symptom for 6 months. This is separate from illness anxiety disorder as the patient's complaints are focused on the symptom, not anxiety about developing a life-threatening illness. It is important to note that, in contrast to conversion disorder, the symptom does not have to be medically unexplainable.

Associated comorbid conditions are major depressive disorder, panic disorder, substance abuse, borderline personality disorder, and antisocial personality disorder. This is a chronic condition that rarely remits. The psychiatric differential diagnosis is extensive and includes major depression, schizophrenia with somatic delusions, panic disorders (in which symptoms occur only during an attack), generalized anxiety disorder, and factitious disorder.

Factitious disorder. Factitious disorder consists of a patient inducing symptoms or signs to assume the role of being sick and to receive care. There is no secondary gain, such as escaping responsibilities or receiving money, as is found with malingering. The onset of this disorder usually occurs in early adulthood; it can also occur in childhood. Patients are at risk for substance use disorders (secondary to using agents to induce symptoms) as well as for complications from associated diagnostic evaluations and unnecessary surgical procedures. On confrontation, they may either change their symptoms or try to seek medical care elsewhere.

Conversion disorder (functional neurologic symptom disorder). The diagnosis of conversion disorder is based on the presence of 1 or more symptoms of altered voluntary motor or sensory function. Symptoms may take the form of weakness, paresthesias, or paroxysmal episodes of erratic movements that may be mistaken for seizure activity. The history, physical examination, and neurologic diagnostic evaluation, including the use of long-term video electroencephalogram monitoring in the case of paroxysmal movements, demonstrate incompatibility between the symptom and any medical condition. Unlike somatic symptom disorder, in which patients have excessive thoughts, feelings, or behaviors associated with the voluntary motor or sensory function, conversion disorder is an unconscious phenomenon.

Onset is usually in late adolescence or early adulthood. A typical episode is acute, follows a recent stressor, and is of relatively short duration, typically less than 4 weeks. The symptoms may solve a psychologic conflict. For example, complaints of blindness may prevent a patient from being witness to traumatic events in his or her environment. Common childhood stressors associated with conversion disorders are grief, bullying, and abuse. Major depressive disorder and anxiety disorders are associated with conversion disorders.

Conditions Characterized by Changes in Eating or Weight

Anorexia nervosa. Anorexia nervosa is an eating disorder in which the patient restricts caloric intake due to a significant fear of gaining weight and distorted body image. There are 2 subtypes, **restricting type** and **binge-eating/purging type**. Diagnostic criteria are as follows:

1. Restriction of energy intake leading to a significantly low body weight
2. Intense fear of gaining weight or becoming fat
3. Distorted perception of body size, undue influence of body weight or shape on self-evaluation, or lack of recognition of severity of low body weight.

Patients with anorexia nervosa will often go to great lengths to hide their intent and symptoms, oftentimes by wearing baggy clothes, by explaining that excessive and vigorous exercise are required for sports participation, by rationalizing food restriction as health consciousness, by complaining that allergies ruin the taste and smell of food, or by concealing purging behaviors, such as induced vomiting or diarrhea. Because of frequent concealment, the detection of these behaviors is challenging.

The prevalence of anorexia nervosa is as high as 1%; almost 90% of cases occur in females. Although this condition is associated with higher socioeconomic status, it can occur in persons from a variety of socioeconomic backgrounds and in all ethnic groups.

Besides weight loss, patients with anorexia nervosa may develop symptoms of depression or may withdraw socially secondary to the physiology of starvation. Actual loss of appetite is rare, though patients with anorexia have been found to have higher levels of leptin, which suppresses appetite. Patients with anorexia may develop obsessive-compulsive behavior regarding food, such as collecting recipes or hoarding food. These patients may also have inflexible thinking or feel the need to control their environment.

Anorexia nervosa may affect every organ system, and presenting symptoms and signs are secondary to malnutrition and purging. The symptoms of **malnutrition** are fatigue, depression, and amenorrhea. The physical findings of malnutrition are bradycardia, hypothermia, hypotension, emaciation, hair loss, yellow skin, and lanugo. If the patient controls caloric intake through **purging** via vomiting, findings may include hypertrophic salivary glands, dental erosions secondary to gastric acid irritation, and abrasions or calluses on the dorsum of the hand secondary to manual induction of vomiting. The metabolic abnormalities related to starvation and purging consist of leukopenia, anemia, hyperamylasemia from parotid gland irritation, vomiting-related metabolic alkalosis or laxative-associated metabolic acidosis, thyroid abnormalities, hypomagnesemia, hypocalcemia, hypozincemia, and electrolyte abnormalities resulting from diuretic abuse and dehydration. These patients also have regression of the hypothalamic-pituitary-gonadal axis, which results in low estrogen levels in girls and low testosterone levels in boys.

In evaluating an adolescent with unexplained weight loss, the examiner must rule out the medical causes of cachexia such as malignancy, malabsorption (celiac disease), or inflammatory bowel disease. Interview data that support a diagnosis of anorexia nervosa are a restrictive dietary history, distorted perception of body shape, and rationalization of the causative behaviors. Once the medical causes for weight loss have been ruled out, the examiner must consider the psychiatric differential diagnosis for anorexia nervosa and its associated comorbid conditions. These conditions are major depressive disorder, the abuse of stimulants, OCD, social phobia, body dysmorphic disorder, and bulimia nervosa. If the patient has symptoms of depression that fail to resolve with the correction of malnutrition, the clinician should also consider the diagnosis of major depressive disorder.

Anorexia nervosa is associated with both life-threatening psychologic conditions (i.e., suicide) and medical conditions (e.g., electrolyte abnormalities, cardiac failure, starvation). The lifelong rate of mortality secondary to anorexia nervosa in patients who require hospitalization is more than 10%. Some of the possible medical complications are osteoporosis resulting from hypocalcemia with low serum estrogen levels, cardiomyopathy, anemia, sepsis resulting from malnutrition-induced immunodeficiency, arrhythmias resulting from electrolyte abnormalities, and superior mesenteric artery syndrome. The **superior mesenteric artery syndrome**, which is characterized by postprandial vomiting and pain secondary to intermittent gastric outlet obstruction, is more common in anorexia nervosa as profound weight loss is believed to result in the loss of the intraabdominal fat pad between the duodenum and superior mesenteric artery.

Bulimia nervosa. Diagnostic criteria for bulimia nervosa are as follows:

1. Recurrent episodes of **binge eating** (eating more than what most individuals would eat in a discrete period and a sense of lack of control over eating)
2. Recurrent inappropriate **purging** (compensatory behaviors for controlling weight gain, such as induced vomiting, laxative misuse, diuretic misuse, prolonged fasting, or excessive exercise)
3. Binge eating and compensatory measures occur at least once a week for 3 months
4. Self-evaluation is unduly influenced by body shape and weight
5. Does not occur within anorexia nervosa

Bulimia nervosa is twice as common as anorexia nervosa and has a later onset, typically in late adolescence. Unlike anorexia nervosa, there is not significant food restriction or low body weight. Like anorexia nervosa, it is more common in females (90%) and can occur in any socioeconomic background. Almost 90% of patients control their weight gain by purging. Other methods for controlling weight are excessive exercise and fasting before binge eating.

Comorbid psychologic conditions are common in bulimia nervosa and include mood disorders, personality disorders, anxiety disorders, and substance use. Approximately 30% of patients who use medications to control weight also have substance use disorders, typically of alcohol or stimulants. In contrast to anorexia nervosa, significant medical complications occur less commonly in bulimia nervosa. If present, comorbid medical conditions of bulimia nervosa are associated with vomiting or medication abuse. These conditions are esophagitis and gastritis, cardiomyopathy (particularly if syrup of ipecac is used to induce vomiting), hypokalemia and nephrolithiasis from diuretic abuse, metabolic alkalosis from vomiting and metabolic acidosis from laxative abuse, and increased amylase levels.

Concealment of symptoms coupled with the lack of cachexia makes bulimia nervosa difficult to detect. Some patients may present to the clinician because of a parent's detection of binge eating and purging. Physical findings that suggest recurrent vomiting are dental erosion, parotid hypertrophy, callus abrasions on the dorsum of the hand known as **Russell sign**, and pharyngeal irritation.

Binge eating disorder. Binge eating disorder consists of recurrent binge eating episodes without compensatory behaviors to prevent weight gain. Patients with binge eating disorder may be of normal weight or overweight. DSM-5 criteria are as follows:

1. Recurrent episodes of binge eating (eating more than what most individuals would eat in a discrete period and a sense of lack of control over eating)
2. Binge-eating episodes are associated with 3 of the following:
   a. Eating much more rapidly than normal
   b. Eating until feeling uncomfortably full
   c. Eating large amounts of food when not hungry
   d. Eating alone because of embarrassment by how much one is eating
   e. Feeling disgusted, depressed, or guilty afterward
3. Marked distress regarding binge eating is present
4. Binge eating occurs, on average, at least once a week for 3 months

Binge eating disorder is distinct from obesity as most individuals with obesity do not engage in recurrent binge eating episodes. At this time, there is limited data regarding the prevalence of binge eating disorder in youths. In adults, it is roughly twice as common in females.

Avoidant/restrictive food intake disorder (ARFID). The hallmark of this condition is avoidance or restriction of food intake in infancy or early childhood that is not related to a disturbance in the way in which one's body weight or shape is experienced. The restriction in eating must be associated with 1 or more of the following:

1. Significant weight loss
2. Significant nutritional deficiency
3. Dependence on enteral feeding tubes or supplements
4. Marked interference with psychosocial functioning

Two common reasons that patients develop ARFID are an aversion to the sensory characteristics of food or a conditioned negative response to eating. Examples of sensory aversions include extreme sensitivity to appearance, color, smell, texture, or taste of food. It is separate from "picky eating" in that the restriction leads to 1 of the above outcomes. A conditioned negative response to eating could

result from an episode of choking, trauma to or traumatic investigations of the throat or upper gastrointestinal tract, or repeated vomiting. Risk factors for ARFID include anxiety disorders, autism spectrum disorder, OCD, ADHD, familial anxiety, gastroesophageal reflux disease, vomiting, and other gastrointestinal conditions.

SUMMARY AND RED FLAGS

Suicide is the second leading cause of death in adolescents. Identifying suicidal ideation and intent is crucial in the evaluation of patients presenting with changes in mood or behavior. Changes in mood or behavior carry a significant burden for patients, their family members, and society as a whole. Many psychiatric illnesses have comorbid psychiatric and medical conditions that require thoughtful and deliberate assessment, and many psychiatric symptoms may be secondary to an underlying medical condition. Red flags include risk-taking behavior, violence, poor school performance, poor attention to personal appearance and hygiene, deteriorating social interaction, reduced appetite, weight loss, reduced or excessive sleeping, delusions, and hallucinations.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

General References

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association; 2013.

Dulcan MK. *Dulcan's Textbook of Child and Adolescent Psychiatry*. Washington, DC: American Psychiatric Publishing; 2010.

Martin A, Volkmar FR, Lewis M. *Lewis's Child and Adolescent Psychiatry: A Comprehensive Textbook*. Philadelphia: Lippincott Williams & Wilkins; 2007.

History Taking

Carlat D. *The Psychiatric Interview: A Practical Guide*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2005.

Shea CA. *The Practical Art of Suicide Assessment: A Guide for Mental Health Professionals and Substance Abuse Counselors*. John Wiley & Sons, Inc.; 2002.

Disruptive Behaviors

Dulcan M. Practice parameters for assessment and treatment of children and adolescents with attention deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46:894-921.

Murphy TK, Lewin AB, Storch EA, et al. Practice parameters for assessment and treatment of children and adolescents with tic disorders. *J Am Acad Child Adolesc Psychiatry*. 2013;52:1341-1359.

Steiner H. Practice parameters for the assessment and treatment of children and adolescents with conduct disorder. *J Am Acad Child Adolesc Psychiatry*. 1997;36:1482-1485.

Mood Disorders

Birmaher B, Brent D, AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *J Am Acad Child Adolesc Psychiatry*. 2007;46:1503-1526.

Dimmock PW, Wyatt KM, Jones PW, et al. Efficacy of SSRI's in premenstrual syndrome: a systematic review. *Lancet*. 2000;356:1131-1136.

Gunderson JG. Reducing suicidal risk in borderline personality disorder. *JAMA*. 2015;314:2.

March J, Silva S, Petrycki S, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents with Depression Study (TADS) randomized controlled trial. *JAMA*. 2004;292:807-820.

McClellan J, Kowatch R, Findling RL. Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46:107-125.

Posner K. Columbia–Suicide Severity Rating Scale: Screener/Recent – Self-Report. <http://www.cssrs.columbia.edu/scales_practice_cssrs.html>.

Posner K, Brown GK, Stanley B, et al. The Columbia–Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. 2011;168:1266-1277.

Anxiety

Bryant RA. Acute stress disorder as a predictor of posttraumatic stress disorder: a systematic review. *J Clin Psychiatry*. 2011;2:233-239.

Cohen JA, Mannarino AP. Trauma-focused cognitive behavioural therapy for children and parents. *J Child Adolesc Ment Health*. 2008;4:158-162.

Cohen JA, The Work Group on Quality Issues, AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with posttraumatic stress disorder. *J Am Acad Child Adolesc Psychiatry*. 2010;49:414-430.

Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: The Adverse Childhood Experiences (ACE) study. *Am J Prev Med*. 1998;4:245-258.

Geller DA, March J. Practice parameter for the assessment and treatment of children and adolescents with obsessive-compulsive disorder. *Focus*. 2012;3:360-373.

Murphy TK, Gerardi DM, Leckman JF. Pediatric acute-onset neuropsychiatric syndrome. *Psychiatr Clin North Am*. 2014;3:353-374.

Pediatric OCD Treatment Study (POTS) Team. Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: The pediatric OCD treatment study (POTS) randomized controlled trial. *JAMA*. 2004;292:1969-1976.

Shulman ST. Group A streptococcus. In: *Nelson Textbook of Pediatrics*. Vol. 183. 20th ed. Philadelphia: Elsevier; 2016:1327-1337.

Walkup JT, Albano AM, Piacentini J, et al. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. *N Engl J Med*. 2008;359:2753-2766.

Altered Mental Status

Ballageer T, Malla A, Manchanda R, et al. Is adolescent-onset first-episode psychosis different from adult onset? *J Am Acad Child Adolesc Psychiatry*. 2005;44:782-789.

Biederman J, Petty C, Faraone SV, et al. Phenomenology of childhood psychosis. *J Nerv Ment Dis*. 2004;192:607-614.

Boeing L, Murray V, Pelosi A, et al. Adolescent-onset psychosis: prevalence, needs and service provision. *Br J Psych*. 2007;190:18-26.

Gener B, Burns JM, Griffin S, et al. Administration of ondansetron is associated with lethal outcome. *Pediatrics*. 2010;125:e1514-e1517.

Gochman P, Miller R, Rapoport JL. Childhood-onset schizophrenia: The challenge of diagnosis. *Curr Psychiatry Rep*. 2011;13:321-322.

Hatherill S, Flisher AJ. Delirium in children and adolescents: a systematic review of the literature. *J Psychosom Res*. 2010;68:337-344.

McClellan J, Werry J. Practice parameter for the assessment and treatment of children and adolescents with schizophrenia. *J Am Acad Child Adolesc Psychiatry*. 2001;40:4S-23S.

Pao M, Lohman C, Gracey D, et al. Visual, tactile, and phobic hallucinations: recognition and management in the emergency department. *Pediatr Emerg Care*. 2004;20:30-34.

Schulz S, Findling RL, Wise A, et al. Child and adolescent schizophrenia. *Psychiatr Clin North Am*. 1998;21:43-56.

Teeple RC, Caplan JP, Stern TA. Visual hallucinations: differential diagnosis and treatment. *Prim Care Companion J Clin Psychiatry*. 2009;11(1):26-32.

Ulloa RE, Birmaher B, Axelson D, et al. Psychosis in a pediatric mood and anxiety disorders clinic: phenomenology and correlates. *J Am Acad Child Adolesc Psychiatry*. 2000;39:3.

Physical Symptoms

Ford CV. Factitious disorders and malingering. In: *Current Diagnosis and Treatment – Psychiatry*. 2nd ed. New York: McGraw-Hill; 2008:411-418.

Ford CV. Somatoform disorders. In: *Current Diagnosis and Treatment – Psychiatry*. 2nd ed. New York: McGraw-Hill; 2008:395-410.

Kohn MR, Madden S, Clarke SD. Refeeding in anorexia nervosa: increased safety and efficiency through understanding the pathophysiology of protein calorie malnutrition. *Curr Opin Pediatr*. 2011;23:390-394.

Libow JA. Child and adolescent illness falsification. *Pediatrics*. 2000;105(2):336-342.

Neimark G, Caroff S, Stinnett J. Medically unexplained symptoms. *Psychiatr Ann*. 2005;35:298-305.

Shaw RJ, Spratt EG, Bernard RS, et al. Somatoform disorders. In: Shaw RJ, DeMaso DR, eds. *Textbook of Pediatric Psychosomatic Medicine*. Washington, DC: American Psychiatric Publishing; 2010.

28

Headaches

Sara M. Lauck and Sandra Gage

INTRODUCTION

Headaches are classified as primary or secondary. **Primary headaches** are benign, are not caused by underlying disease or structural problems, and include migraines, tension-type headaches, and the trigeminal autonomic cephalgias (Table 28.1). While primary headaches may cause significant pain and disability, they are not intrinsically dangerous. **Secondary headaches** are caused by an underlying disease, such as infection, tumor, intracranial hemorrhage, or a vascular disorder, and may indicate an innocuous etiology or portend a serious illness. Most headaches in children are primary headaches or harmless secondary headaches. History and physical examination guide the diagnosis of primary headache disorders, assess the degree of headache-related disability, and reveal information that may prompt evaluation for secondary headaches. Each subsequent visit allows for assessing the response to therapy and considering secondary headaches, the causes of some of which may be life threatening.

◆ History

The specific headache diagnosis is determined by the headache phenotype, which is defined in terms of laterality, location (Figs. 28.1, 28.2, and 28.3), timing, frequency, duration, quality, severity, associated symptoms, and alleviating and aggravating factors. In most cases, a single phenotypic headache is present. If the patient has more than 1 type of headache, the clinician must obtain a specific history for each type. Ideally, the history should be obtained from the child, parent, and any other caregivers, including teachers. Even a young child should be given the opportunity to describe the symptoms experienced with each headache episode and may use drawings to do this.

The laterality and location of the pain should be established (see Figs. 28.1, 28.2, and 28.3). If the pain is unilateral, it should be noted whether the pain is always on 1 side or if the side varies. The location may be fairly restricted or more widely distributed; if the location varies from 1 episode to another, this should be noted as well. The timing, frequency, and duration of headaches should be described, as the temporal patterns of headaches are useful in both creating a differential diagnosis and classifying the subtype of a particular headache diagnosis. The temporal categories of headache include acute, acute recurrent, chronic nonprogressive, and chronic progressive (Table 28.2).

The severity of a headache does not necessarily correlate with the seriousness of its etiology. Pain caused by brain tumors may initially be mild, whereas the pain of tension-type headaches may be excruciating. Pain is subjective and may be influenced by age, culture, duration, and previous encounters with medical care, leading some patients to unintentionally minimize or exaggerate their pain; as such, pain alone should not be used to narrow the differential diagnosis. An exception to this principle is the **thunderclap headache**, in which pain onsets suddenly, reaches maximum severity within seconds, and is oftentimes described by patients as the worst headache they have ever had. Such headaches may indicate subarachnoid hemorrhage, arterial dissection, or venous sinus thrombosis, among other causes (Table 28.3). Numerical scales, or visual scales for younger children, are helpful for quantifying pain and determining the efficacy of treatment. In older patients, descriptive phrases, such as *mild, moderate, severe,* and *excruciating*, may suffice.

Associated symptoms such as hemiparesis, ataxia, visual loss, diplopia, scotomas, vertigo, seizure-like activity, confusion, mood or behavioral changes, autonomic symptoms, and hemisensory occurrences may suggest neurologic dysfunction or a migraine-related aura. Any history of fevers, syncope, nausea, vomiting, and appetite changes should also be ascertained. Special note should be made if the pain awakens the patient from sleep, is present upon awakening in the morning, or worsens when recumbent; these findings may indicate increased intracranial pressure. Events associated with the onset or aggravation of headaches, such as trauma, intake of particular foods, or physical exertion, may provide insight into the etiology of headaches, as well as potential triggers to avoid. Alleviation via rest or positional changes should be noted, as should the response of the headaches to particular medications. A thorough medication history is essential for diagnosing analgesic overuse headaches and headaches caused by medication side effects. The use of over-the-counter medication and prescription medications, including medications that have not been prescribed for the patient, should be delineated, as well as any supplements or traditional remedies. Both primary and secondary headaches may respond to medications and such a response is not diagnostic of any particular headache disorder. For example, relief of an acute headache by triptans is not diagnostic of migraine, as triptans may also be effective for other causes of headache. An exception is certain trigeminal autonomic cephalgias, which respond only to indomethacin.

In patients with recurring headaches, the history may be clarified by keeping a **headache diary**, which can additionally determine headache patterns, identify triggers, aid diagnosis, and assess the efficacy of therapy (Table 28.4). A headache diary may also assist in determining the degree of disability caused by the headache. Disability evaluation

(See *Nelson Textbook of Pediatrics,* p. 2863.)

TABLE 28.1 Differential Diagnosis of Headache

Headache Type	Genetics	Epidemiology	Characteristic Features	Length	Accompanying Symptoms
Migraine headache	Complex genetics but usually a family history	More frequent in women	Unilateral, bilateral; throbbing; moderate to severe; worsens with activity	Hours to days	Photophobia, phonophobia, nausea and/or vomiting
Tension-type headache	Usually a family history	Equal frequency in men and women	Tight bandlike pain; bilateral; pain may be mild to moderate; improves with activity	Hours to days	No nausea or vomiting; small amount of light or sound sensitivity, but not both
Cluster headache	May have a family history	More frequent in men	Unilateral severe pain in the face	Minutes to hours	Ipsilateral ptosis, miosis, rhinorrhea, eyelid edema, tearing
Paroxysmal hemicrania	Usually no family history	More frequent in women	Unilateral pain in the face	Minutes	Ipsilateral ptosis, miosis, rhinorrhea, eyelid edema, tearing; responds to indomethacin
Short unilateral headache with conjunctival injection, tearing	No family history	More frequent in men	Unilateral eye pain; orbit pain	Typically 4 minutes or less	Conjunctival injection, tearing
Hemicrania continua	No family history	More frequent in women	Unilateral continuous headache with episodic stabbing pains	Continuous	Ipsilateral ptosis, miosis, rhinorrhea, eyelid edema, tearing

From Digre KB. Headaches and other head pain. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. Vol. 2. 25th ed. Philadelphia: Elsevier; 2016:2357, Table 398-2.

TABLE 28.2 Four Temporal Patterns of Childhood Headache

Acute: Single episode of pain without a history of such episodes. The "first and worst" headache, which raises concerns for aneurysmal subarachnoid hemorrhage in adults, is commonly due to a *febrile illness* related to upper respiratory tract infection in children. Regardless, more ominous causes of acute headache (hemorrhage, meningitis, tumor) must be considered.

Acute recurrent: Recurrent attacks of pain separated by symptom-free intervals. Primary headache syndromes, such as *migraine* or *tension-type headache,* usually cause this pattern. Infrequently, recurrent headaches can sometimes also be attributed to certain epilepsy syndromes (benign occipital epilepsy), substance abuse, or recurrent trauma.

Chronic progressive: Most ominous of the temporal patterns; implies a gradually increasing frequency and severity of headache. The pathologic correlate is *increasing intracranial pressure.* Causes of this pattern include pseudotumor cerebri, brain tumor, hydrocephalus, chronic meningitis, brain abscess, and subdural collections.

Chronic nonprogressive or chronic daily: Pattern of frequent or constant headache. Chronic daily headache generally is defined as >4-mo history of >15 headaches/mo, with headaches lasting >4 hr. Affected patients have normal neurologic examinations; psychologic factors and anxiety about possible underlying organic causes are common.

From Marcdante KJ, Kliegman RM. Headache and migraine. In: Marcdante KJ, ed. *Nelson Essentials of Pediatrics*. 7th ed. Elsevier; 2015:616-618.

TABLE 28.3 Main and Rare Causes of Thunderclap Headache

Main Causes	Rare Causes
Vascular Disorders	
Subarachnoid hemorrhage	Pituitary apoplexy, arteritis, angiitis
Intracerebral hemorrhage	Unruptured vascular malformation, aneurysm
Cerebral venous thrombosis	Arterial hypertension
Spontaneous intracranial hypotension	Cerebral segmental vasoconstriction
Cervical artery dissection	
Nonvascular Disorders	
	Greater occipital neuralgia
	Intermittent hydrocephalus by colloid cyst
Infections	
Meningitis, encephalitis	Erve virus
	Sinusitis
Primary Headache Disorders	
Migraine	Cluster headache
Primary thunderclap headache	Tension headache, new daily persistent headache
Primary exertional headache	
Primary cough headache	

From Linn FHH. Primary thunderclap headache. In: Aminoff MJ, ed. *Handbook of Clinical Neurology*. Vol. 97. New York: Elsevier; 2010: 473-481.

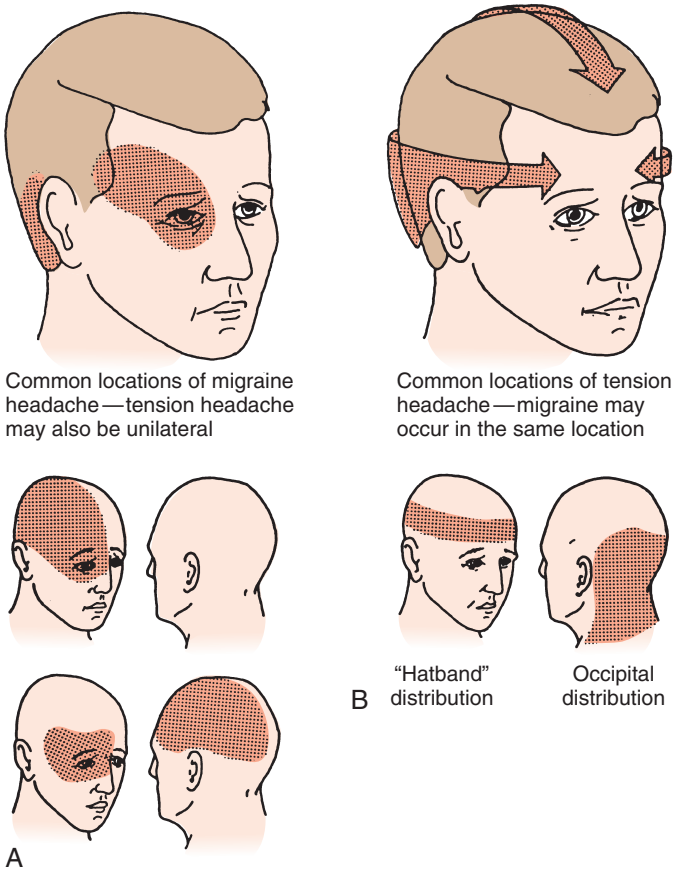


FIGURE 28.1 Common location of migraine *(A)* and tension *(B)* headaches. (From Reilly BM. *Practical Strategies in Outpatient Medicine.* 2nd ed. Philadelphia: WB Saunders; 1991.)

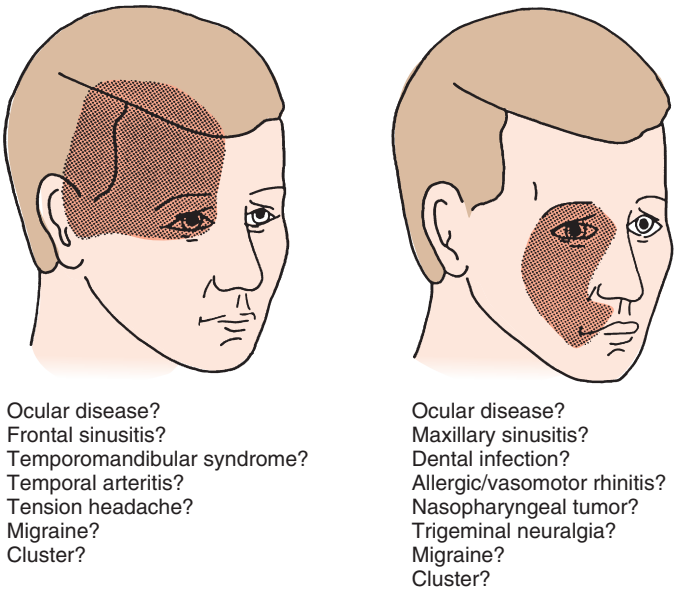


FIGURE 28.2 Periorbital headache. (From Reilly BM. *Practical Strategies in Outpatient Medicine.* 2nd ed. Philadelphia: WB Saunders; 1991.)

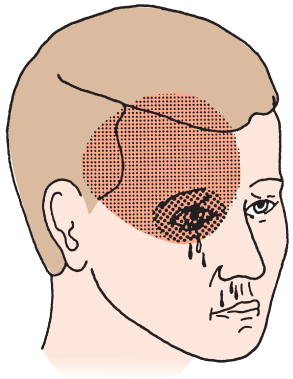


FIGURE 28.3 Cluster headache. (From Reilly BM. *Practical Strategies in Outpatient Medicine.* 2nd ed. Philadelphia: WB Saunders; 1991.)

TABLE 28.4 The Headache Diary for Recurring Headaches*

Date
Time of onset
Time of resolution
Maximum level of pain (mild, moderate, or severe *or* according to a visual or numerical pain scale)
Triggers:
Sleep
Foods
Activities
Medications
Modifiers:
Response to position changes or Valsalva maneuver
Medications used (dose, response)
Other modifiers
Additional symptoms

*If more than 1 type of headache exists, the types should be defined and labeled, and separate data should be recorded for each type.

may be augmented by school attendance and performance records. For example, headaches that improve with the onset of the summer school holiday may suggest that a child is struggling academically or is being bullied at school. In younger children, where detailed personal descriptions of pain may be more difficult to obtain and record in a diary, videos of the headache episodes may aid diagnosis.

The past medical history may reveal potentially serious causes of secondary headaches that require prompt evaluation, such as sickle cell disease, thyroid disorders, parathyroid dysfunction, malignancy, hypercoagulability, hypertension, immunodeficiency, congenital heart disease, and arteriovenous malformations. Allergic rhinitis and other

atopic disorders are also associated with headaches. Infantile colic, benign paroxysmal torticollis, cyclic vomiting syndrome, and benign paroxysmal vertigo are considered episodic syndromes that may be associated with migraine and may precede the development of typical migraine symptoms later in life. In females, a menstrual history should be obtained, including details of the cycle and the timing of headaches with respect to the menstrual cycle. A history of secondary amenorrhea could suggest pituitary or other central nervous system neoplasms.

The family history should be probed for any genetic predisposition to migraines, aneurysms, other vascular malformations, or brain neoplasms. A negative family history for primary headaches should cause the clinician to be more cautious in assigning the diagnosis of a primary headache disorder. Social history should investigate for psychosocial factors that may influence or be influenced by headaches, such as school performance, the relationships between family members, recent changes in social structure, and substance abuse in the patient or the family. The provider should also screen for indications of neglect or abuse. Detailed psychologic evaluation with screening for symptoms of depression and anxiety may be indicated.

Throughout the history, the clinician should constantly assess for warning signs of serious and sometimes life-threatening causes of secondary headache. The identification of any of these red flag symptoms should cause concern and lead promptly to further investigation (Table 28.5).

TABLE 28.5 History-Related Red Flags for Secondary Headaches

- Quality:
  - "Thunderclap" headache or the "worst headache of my life"
  - Recent worsening in severity or frequency
  - Change in quality
  - New-onset symptoms consistent with cluster headache
- Location:
  - Unilateral without alteration of sides
  - Chronic or recurrent occipital headache
- Timing:
  - Awakens from sleep
  - Occurs in morning or causes morning vomiting
  - Chronic progressive pattern
- Positional or activity-related variations:
  - Worsened in the recumbent position
  - Headache experienced with cough or the Valsalva maneuver
- Associated neurologic history:
  - Altered sensorium during headache
  - Sensory deficits or changes in vision, gait, or coordination
  - Other focal neurologic deficits
  - Seizures or syncope
  - Mental status changes (e.g., confusion or disorientation)
  - Regression in fine or gross motor developmental skills
  - Decline in cognition or school performance
  - Change in behavior or personality
- Associated general history:
  - Vomiting without nausea
  - Polyuria or polydipsia
  - Preschool or younger age
  - History of head trauma
  - Medical comorbidities
  - Negative family history of primary headache disorders

◆ Physical Examination

Abnormalities in the examination may provide clues to the underlying etiology of secondary headaches, and red flags may identify specific diagnoses of concern (Table 28.6). Vital signs assessment may reveal elevated blood pressure, which may be the cause of headache, signal increased intracranial pressure, or herald an underlying renal abnormality. Fever may be a sign of an infectious or inflammatory process. Growth parameters, including height, weight, body mass index, and head circumference should be obtained. Poor weight gain may indicate an underlying chronic illness associated with headaches, such as celiac disease, respiratory disorders, neurofibromatosis type 1, or neglect. Obesity should alert the clinician to assess for symptoms of obstructive sleep apnea or pseudotumor cerebri. Enlarged head circumference associated with signs of headache or other evidence of increased intracranial pressure warrants alarm.

The general examination starts with assessment of mental status and overall level of distress. The head and neck examination should assess specifically for nasal congestion, sinus tenderness, and signs of allergic rhinitis, such as boggy nasal turbinates. Frontal bone tenderness could be an early sign of Pott puffy tumor, a complication of frontal sinusitis. Tenderness over the mandibular condyle in children with dental malocclusion, or jaw crepitus in patients with arthritis, may indicate temporomandibular joint dysfunction as a cause of headache. Thorough lymphatic, respiratory, cardiac, and abdominal examinations should also be completed. Genitourinary examination should include pubertal stage, as headaches may be associated with

TABLE 28.6 Physical Examination Red Flags for Secondary Headaches

- Hypertension
- Growth failure
- Increased head circumference or bulging fontanel
- Meningeal signs with or without fever
- Evidence of cranial trauma
- Cranial bruit
- Frontal bony tenderness
- Abnormal ophthalmologic findings:
  - Papilledema
  - Abnormal ocular movements
  - Squinting
  - Pathologic pupillary response
  - Visual field defects
- Abnormal neurologic findings:
  - Impaired mental status
  - Cranial nerve palsy
  - Ataxia
  - Abnormal gait
  - Abnormal coordination
  - Abnormal reflexes
  - Asymmetric motor or sensory examination
  - Hemiparesis
  - Developmental regression
- Precocious, delayed, or arrested puberty
- Skin findings:
  - Café-au-lait or ash leaf macules
  - Petechiae or purpura
  - Facial hemangioma
  - Malar rash

TABLE 28.7 Headache Disorders Associated with Neurologic Signs

Headache	Pain Profile	Neurologic Sign
Complicated migraine	AR	Hemiparesis, aphasia, paresthesia, hemianopsia
Migraine with brainstem aura	AR	Dysarthria, vertigo, tinnitus, hypoacusis, diplopia, ataxia, decreased level of consciousness
Acute confusional migraine	AR	Alteration in migraine sensorium, stupor, agitation, fugue state
Vasculitis	CP, AR	Seizure, changes in sensorium
Brain neoplasm or mass	CP	Papilledema, focal deficit
Hydrocephalus	CP, AR	Papilledema, bilateral sixth nerve palsies, increased motor tone, impaired upward gaze and Parinaud syndrome
Pseudotumor cerebri	CP	Papilledema, constricted visual fields, enlarged blind spot
Subarachnoid hemorrhage, ruptured aneurysm	A	Changes in sensorium, focal neurologic signs, meningismus
Subdural or epidural hemorrhage	CP	Focal neurologic signs, papilledema, changes in sensorium
Sagittal sinus thrombosis	A	Papilledema, focal neurologic deficits, changes in sensorium, seizures
Meningitis, encephalitis	A	Papilledema, focal neurologic deficits, changes in sensorium, seizures
Optic neuritis	A	Papillitis, decreased visual acuity, afferent pupillary defect

A, acute; AR, acute recurrent; CP, chronic progressive.

endocrine disorders. Skin should be evaluated for petechiae, atopic findings, and lesions associated with neurocutaneous syndromes such as neurofibromatosis or tuberous sclerosis. Signs of trauma should be noted. Neurologic examination should be detailed and include assessments of mental status, cranial nerves, auditory function, sensation, motor strength, reflexes, gait, coordination, and speech. Whenever possible, a thorough ophthalmologic examination should be undertaken, including visual acuity testing and a funduscopic evaluation for papilledema. In a young child, much of the neurologic examination is completed through observation or engaging the child in play to elicit findings. A complete ophthalmologic evaluation may be limited by lack of cooperation or comprehension. If the clinician is unable to complete or interpret the neurologic and ophthalmologic assessments, the support of a neurologist and ophthalmologist may be required. If the results of either examination suggest a structural brain lesion or increased intracranial pressure, neuroimaging is warranted (Table 28.7). However, many causes of headache, including some serious diseases early in their course, do not present with abnormal findings on physical examination or have fluctuating abnormal findings (Table 28.8). A single normal physical examination does not exclude pathology; thus, periodic reassessments are essential if headache persists.

◆ Neuroimaging

Most children do not require neuroimaging for headaches, particularly children with recurrent headaches and normal neurologic examinations. Neuroimaging in the assessment of headaches in children is indicated under the following circumstances: (1) abnormal neurologic findings, (2) headaches occurring early in the morning or waking the child from sleep, (3) associated confusion, disorientation, or signs of increased intracranial pressure, (4) presence of a ventricular shunt, (5) recent trauma, and (6) age less than 3 years. Additional indications for neuroimaging include recent onset of severe headache, incompatibility of headache with a primary headache disorder diagnosis, change in the pattern or severity of a previously stable headache, and a history of neurologic dysfunction beyond typical aura symptoms (Table 28.9). In specific cases, neuroimaging may be considered when there is history of a brain tumor in the family, fear by the patient or the parents of underlying pathology, or an inability to obtain an accurate physical examination due to lack of patient cooperativity.

TABLE 28.8 Headache Disorders with No Neurologic Signs

Headache Disorder	Pain Profile
Tension-type headache	CN, AR
Migraine without aura	AR, CN
Cluster headache	AR
Hypertension, uncomplicated	AR, CN
Fever	A
Anoxia	A
Medication overuse	CN
Caffeine withdrawal	A, AR
Early hydrocephalus or brain mass	CP
Cough headache, uncomplicated	AR
Meningitis, uncomplicated	A
Sinusitis, dental or pharyngeal abscess	AR
Temporomandibular joint syndrome	CN
Postconcussive syndrome	CN
Conversion disorder	CN

A, acute; AR, acute recurrent; CN, chronic nonprogressive; CP, chronic progressive.

Magnetic resonance imaging (MRI) and computed tomography (CT) are the 2 neuroimaging modalities to consider (Table 28.10). CT remains the most sensitive and rapid method for detecting acute intracranial bleeding, and is preferred in emergency situations or when MRI is contraindicated or unavailable. *MRI is otherwise the preferred imaging modality,* offering superior visualization of soft-tissue contrast and gray-to-white matter differentiation without exposing the patient to the ionizing radiation associated with CT scanning. While gadolinium contrast for MRI is considered safe, it is not usually necessary. MRI may involve the need for sedation, particularly in younger children. Normal neuroimaging and a single normal neurologic examination should not give complete reassurance. Follow-up assessment of ongoing symptoms or for changes in the physical examination remains necessary.

TABLE 28.9 Reasons to Obtain Neuroimaging in a Child with Headache

- Abnormal neurologic findings (including papilledema)
- Associated confusion, disorientation, or signs of increased intracranial pressure
- Change in pattern or severity of previously stable headache
- Cough headache
- Headache consistent with trigeminal autonomic cephalgia
- Headache occurring in the morning or waking the child from sleep
- Headache with known concerning underlying disorder or insult
- History of neurologic dysfunction (outside of typical aura symptoms)
- Incompatibility of headache with primary headache disorder or unusual headache in a child
- Meningeal signs without fever
- Recent onset of severe headache
- Recent trauma
- Seizures
- "Thunderclap" headache or "worst headache of my life"
- Ventriculoperitoneal shunt
- Young age (less than 6 yr) or inability to describe headache

TABLE 28.10 Neuroimaging Modalities

Advantages of Magnetic Resonance Imaging

- Most vascular malformations are detected
- Accurate detection of tumors in temporal lobes and posterior fossa, and small tumors that obstruct CSF flow (quadrigeminal plate and third ventricular)
- Paranasal sinuses usually included in the examination without special request
- More sensitive for detecting transependymal CSF in cases of borderline hydrocephalus
- Diagnostic for Chiari malformations
- Magnetic resonance angiography can detect many aneurysms
- Magnetic resonance venography can detect cortical vein and dural sinus thrombosis

Advantages of Computed Tomography

- Can rapidly diagnose intracranial bleed
- Shorter imaging time, important in evaluating ill patients
- May be used in patients with pacemakers, metal implants (surgical clips), and cosmetic tattoos (MRI may turn off pacemakers and dislodge the clips; tattoos distort the image)
- Less expensive and easier access than MRI

CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

◆ Laboratory Investigations

Routine blood work is not indicated when history suggests a primary headache disorder and physical and neurologic examinations are normal. Findings in the history, physical examination, or neuroimaging that dictate directed laboratory evaluation are listed in Table 28.11.

CLASSIFICATION OF HEADACHES

Headaches are classified broadly as primary or secondary. The acuity or chronicity of the headache helps to guide the development of the differential diagnosis (Fig. 28.4).

TABLE 28.11 Potentially Useful Laboratory Tests in Children with Headaches

Laboratory Test	Possible Cause of Headache
Complete blood count	Infection (elevated white blood cell count); bleeding diathesis (thrombocytopenia); anemia
CSF examination with opening pressure	Infection, vasculitis, pseudotumor cerebri, subarachnoid hemorrhage after CT is normal
Toxicology assays	Substance abuse, possible toxin exposure, carbon monoxide
Hypercoagulation panel	Unexplained venous sinus thrombosis
ESR, ANA, ANCA	Vasculitis
Genetic tests	Familial hemiplegic migraine, MELAS
EEG	Seizure disorder
Electrolytes, ECG, UA	Hypertension
VP shunt radiographic series	Malfunctioning VP shunt
Blood glucose	Hypoglycemia or hyperglycemia
Serum calcium	Hyperparathyroidism

ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; CSF, cerebrospinal fluid; CT, computed tomography; ECG, electroencephalography; EEG, electroencephalogram; ESR, erythrocyte sedimentation rate; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; UA, urinalysis; VP, ventriculoperitoneal.

Primary Headaches

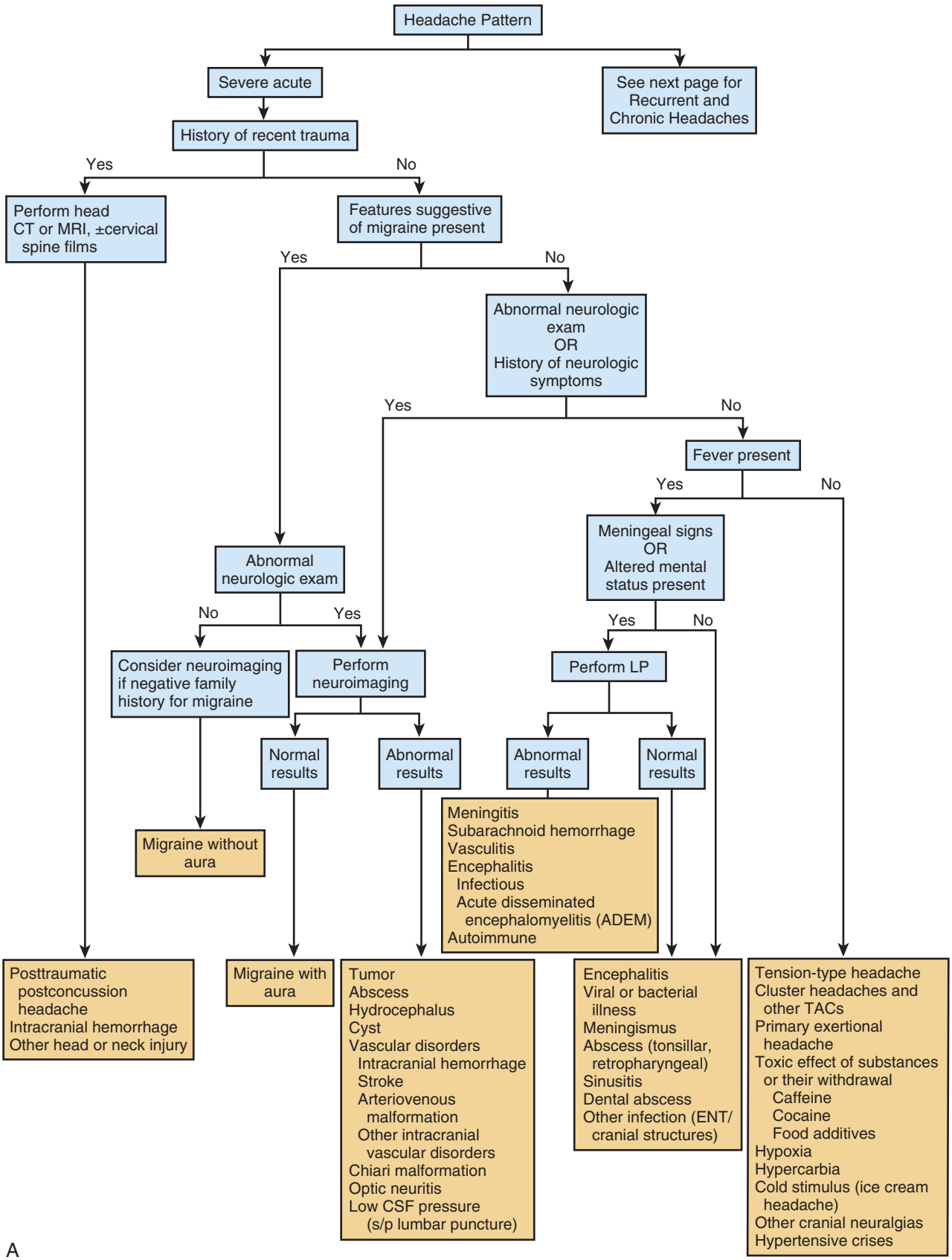
There are 3 categories of primary headaches: tension-type headache, migraine headache, and the trigeminal autonomic cephalgias. Tension-type headache and migraine are the most common headache types in children and adolescents.

Tension-Type Headaches

Tension-type headache (TTH) occurs in up to 15% of older children. Prevalence increases with age such that TTH is the most frequent headache type in children between 8-12 years of age. Younger children also experience both episodic and chronic TTH, usually with mild to moderate symptoms.

These headaches have a typical pattern. Patients awaken feeling well, with pain beginning gradually and escalating throughout the day. Pain is constant, squeezing, nonpulsatile, and located in a band extending from the front of the head, across the temples, and toward the occiput or neck. Photophobia and phonophobia may accompany these headaches but are not a constant feature; patients with tension-type headache typically do not experience both photophobia and phonophobia in the context of a single episode. Unlike migraine headaches, routine physical activity does not tend to influence the severity of the headache. In patients with long-standing pain, the headaches may assume characteristics of migraines; indeed, tension-type headaches often accompany other headache disorders.

Tension-type headaches are classified as either episodic or chronic. Both episodic and chronic TTH are further classified as having associated pericranial tenderness or as lacking such tenderness. This tenderness is typically present between headaches and increases during episodes. **Episodic tension-type headache** is categorized as either infrequent or frequent. Infrequent episodic TTH is defined as 10 or more episodes total, occurring less than once per month on average. Frequent episodic TTH is defined as 10 or more episodes total, occurring on 1-14 days per month on average for over 3 months. Individual



A

FIGURE 28.4 Decision-making algorithm in the assessment of headache. The temporal pattern of the headache must be clarified. Each pattern (acute, recurrent episodic or acute recurrent, chronic progressive, chronic nonprogressive) has its own differential diagnosis. CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; ENT, ear, nose, and throat; LP; lumbar puncture; MRI, magnetic resonance imaging; s/p, status post; TAC, trigeminal autonomic cephalgias. (From Pomeranz AJ, Sabnis S, Busy SL, Kliegman RM. *Pediatric Decision-Making Strategies*. 2nd ed. Philadelphia: Elsevier; 2016:185-186.)

Continued

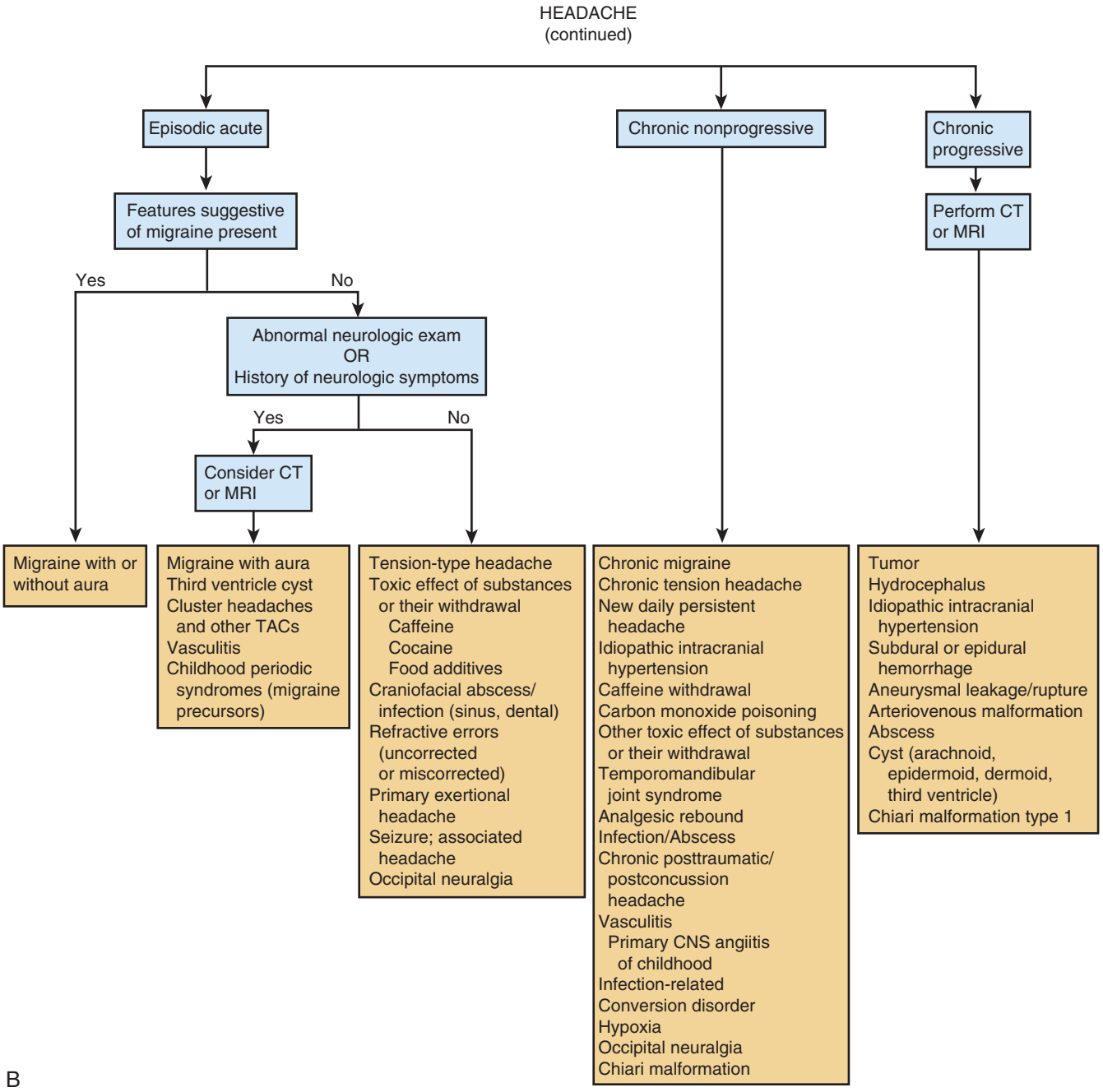


FIGURE 28.4, cont'd

episodes of either may last from 30 minutes to as long as a week and have at least 2 of the following features: (1) bilateral location, (2) pressing or tightening (nonpulsating) quality, (3) mild or moderate intensity, (4) not aggravated by routine physical activity such as walking or climbing stairs. Nausea or vomiting must be absent; if present, migraine should be considered. Either photophobia or phonophobia may be present; if both are present simultaneously, migraine should be considered. **Chronic tension-type headaches** are defined as headaches occurring at least 15 days a month for over 3 months, with features otherwise similar to episodic TTH.

Psychosocial history may uncover the cause of the headache. Adjustment disorders and depression may be either the underlying causes or reactions to chronic pain. Sleep disturbances, school absences, and chronic analgesic use are common. However, some patients with chronic TTH may have negative psychosocial histories. In some highly motivated and successful children, the headaches may be a reaction to the stress associated with achievement. In this instance, school attendance is usually perfect and the patient continues to achieve in all realms.

Patients with tension-type headaches have normal neurologic and physical findings, except for possible tenderness along the affected muscles. These muscles often feel tight, and palpation may trigger the pain. Laboratory tests are not required in the evaluation of tension-type headaches.

Migraine Headaches

The diagnosis of migraine headache is typically based on the historical description of episodes. Childhood migraines are similar to those in adults; however, several features distinguish migraine in children from adult migraine. In children, the headaches are less frequent, are shorter in duration, and respond better to treatment. Vomiting and abdominal pain are more common in children than in adults. Pain is more frequently bilateral in children, though tends to become unilateral after the onset of puberty. The pain may be frontal or facial, instead of the more typical temporal location. Prevalence is higher in boys prior to puberty, though prevalence is higher in girls following the onset of puberty. In the adult population, 18% of females and 6% of males have migraines. A family history of migraines is common, with up to 90% of children having a 1st- or 2nd-degree relative with recurrent headaches.

By 15 years of age, at least 10% of children will have had a migraine headache. Migraine and migraine variants occur in early childhood but with an unknown prevalence, as diagnostic criteria for migraine are often insufficient in young children and infants, in whom the headaches tend to be shorter or have less typical features. While the diagnosis of migraine is typically made later in childhood, a careful retrospective history of infancy and early childhood events may reveal early episodic symptoms consistent with migraine, including pallor, vomiting, photophobia, phonophobia, fussiness, and sleepiness occurring outside the context of concurrent illnesses. Furthermore, benign paroxysmal torticollis, cyclic vomiting syndrome, and benign paroxysmal vertigo are episodic syndromes that may be associated with the diagnosis of migraines later in life.

The pattern of migraines is variable. Without prophylactic treatment, most patients have between 1-4 migraines a month. There is often no temporal pattern, although in postmenarchal females, migraines may cluster around particular phases of the menstrual cycle. Unless the migraines tend to cluster, patients rarely have migraines more than twice a week. Mild or moderate headaches often occur between more severe migraine attacks.

Certain exposures trigger migraine attacks in susceptible patients. The most common migraine precipitants are specific foods and food additives, such as chocolate, hard cheeses, onions, yeast, and beans. Other precipitants include menstruation, caffeine withdrawal, hunger, estrogen exposure (typically via oral contraceptives), sleep deprivation, stress, heat, and exertion.

Migraines are categorized based on the presence or absence of an associated aura. Migraine without aura is the most common migraine phenotype in pediatric patients.

Migraine without aura. Criteria assist in the diagnosis of **migraine without aura** and are based on the number and duration of episodes, as well as symptoms and associated findings (Table 28.12). It has been recognized that children may have shorter-duration headaches, so an allowance has been made to reduce the duration to 2-72 hours or 1-72 hours with diary confirmation. The pain typically onsets gradually and is dull and constant. At times, though, the pain of an episode may be sudden and severe, prompting concern for a thunderclap headache. More typically, pain increases in severity over the course of an individual episode and becomes throbbing. As the headache proceeds, the pain may generalize to the entire cranium. Intense nausea often accompanies migraines, with occasional vomiting. Skin pallor is a common finding. Nasal congestion and tearing may be present. Because most patients are sensitive to motion, light, and noise during a migraine attack, they search for a dark and quiet place to sleep. The patient usually awakens within hours feeling fatigued but pain free.

TABLE 28.12 Migraine Without Aura

A. At least 5 attacks fulfilling criteria B-D
B. Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)
C. Headache has at least 2 of the following 4 characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least 1 of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

ICHD-3, International Classification of Headache Disorders, 3rd edition. From Hersey AD, Kabbouche MA, O'Brien HL. Headaches. In: Kliegman RM, ed. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:2866.

TABLE 28.13 Migraine with Typical Aura

A. At least 2 attacks fulfilling criteria B and C
B. Aura consisting of visual, sensory, and/or speech/language symptoms, each fully reversible, but no motor, brainstem, or retinal symptoms
C. At least 2 of the following 4 characteristics:
   1. At least 1 aura symptom spreads gradually over 5 or more min, and/or 2 or more symptoms occur in succession
   2. Each individual aura symptom lasts 5-60 min
   3. At least 1 aura symptom is unilateral
   4. The aura is accompanied, or followed within 60 min, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded

ICHD-3, International Classification of Headache Disorders, 3rd edition. From Hersey AD, Kabbouche MA, O'Brien HL. Headaches. In: Kliegman RM, ed. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:2866.

Migraine with aura. In migraine with aura, the headache is preceded by sensory signs or symptoms termed an **aura**, which is caused by vasoconstriction and diminished blood flow to the affected region of the brain. In **migraine with typical aura** (Table 28.13), the aura is visual and may consist of blurred vision, spreading scintillating scotomas, flashing lights, zigzag lines, and hemianopsia. These features typically last less than 60 minutes. Sensory auras are less common than visual auras and may consist of numbness or tingling. Further types of migraine with aura are classified by the specific aura symptoms.

Migraine with brainstem aura (Table 28.14), previously known as *basilar artery migraine*, has aura limited to brainstem symptoms such as dysarthria and ataxia. In some patients, the headache may be a minor component of the syndrome. Visual changes may also occur and may include vivid visual images. Vertigo and tinnitus are less common symptoms. Diplopia, vertigo, and vomiting should prompt evaluation for a posterior fossa abnormality, such as a mass or a vascular malformation.

Hemiplegic migraine has an aura that consists of unilateral motor weakness and visual, sensory, and/or speech/language symptoms that are fully reversible. Both familial and sporadic forms have been described. The familial hemiplegic migraine is an autosomal dominant disorder with mutations described in 3 separate genes: (1) *CACNA1A*, (2) *ATP1A2*, and (3) *SCN1A*.

(See *Nelson Textbook of Pediatrics,* p. 2866.)

TABLE 28.14 Migraine with Brainstem Aura

A. At least 2 attacks fulfilling criteria B-D
B. Aura consisting of visual, sensory, and/or speech/language symptoms, each fully reversible, but no motor or retinal symptoms
C. At least 2 of the following brainstem symptoms:
   1. Dysarthria
   2. Vertigo
   3. Tinnitus
   4. Hypacusis
   5. Diplopia
   6. Ataxia
   7. Decreased level of consciousness
D. At least 2 of the following 4 characteristics:
   1. At least 1 aura symptom spreads gradually over 5 or more min, and/or 2 or more symptoms occur in succession
   2. Each individual aura symptom lasts 5-60 min
   3. At least 1 aura symptom is unilateral
   4. The aura is accompanied, or followed within 60 min, by headache
E. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded

ICHD-3, International Classification of Headache Disorders, 3rd edition. From Hersey AD, Kabbouche MA, O'Brien HL. Headaches. In: Kliegman RM, ed. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:2866.

TABLE 28.15 Cluster Headache

A. At least 5 attacks fulfilling criteria B-D
B. Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15-180 min (when untreated)*
C. Either or both of the following:
   1. At least 1 of the following symptoms or signs, ipsilateral to the headache:
      a) Conjunctival injection and/or lacrimation
      b) Nasal congestion and/or rhinorrhea
      c) Eyelid edema
      d) Forehead and facial sweating
      e) Forehead and facial flushing
      f) Sensation of fullness in the ear
      g) Miosis and/or ptosis
   2. A sense of restlessness or agitation
D. Attacks have a frequency between 1 every other day and 8 per day for more than half of the time when the disorder is active
E. Not better accounted for by another ICHD-3 diagnosis

*During part (but less than half) of the time course of cluster headaches, attacks may be less severe and/or of shorter or longer duration.
ICHD-3, International Classification of Headache Disorders, 3rd edition. From Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders. 3rd ed. (beta version). *Cephalalgia*. 2013;33:629-808.

Retinal migraine involves monocular visual disturbance. This migraine subtype is extremely rare, and other causes of the vision disturbance should be investigated prior to designating this diagnosis.

The **childhood periodic syndromes**, or episodic syndromes that may be associated with migraine, are a group of potentially related symptoms that occur with increased frequency in children with migraine. The hallmark of these symptoms is the recurrent episodic nature of the events. Some of these have included gastrointestinal-related symptoms (motion sickness, recurrent abdominal pain, recurrent vomiting including cyclic vomiting, and abdominal migraine), sleep disorders (sleepwalking, sleeptalking, and night terrors), unexplained recurrent fevers, and even seizures.

Confusional migraine and **Alice in Wonderland syndrome** are rare migraine with aura variants that occur primarily in children. Confusional migraine begins after 5 years of age and usually converts to typical migraine as the patient gets older. Episodes begin with an alteration in consciousness, which may include varying degrees of lethargy, agitation, and stupor. A fuguelike state has also been described with these migraines. Attacks last a few hours, with the child eventually falling asleep. The child awakens without memory of the incident. The aura of Alice in Wonderland syndrome is characterized by perceptual disturbances in which the sense of proportion or distance, particularly with respect to the body, is distorted.

Complications of migraine. Some patients have an aura that lasts longer than 1 week. This duration is uncommon and the aura is typically bilateral in these cases. Patients with migraine may have neurologic deficits that persist during and after the headache. These deficits include hemisensory symptoms, hemiparesis, aphasia, visual loss, and alteration in consciousness. In most cases, the neurologic deficit precedes the headache. These symptoms usually last for the duration of the headache but may remain for days following headache abatement. Permanent neurologic deficits are rare but may occur if the vasoconstriction is severe and causes infarction.

Status migrainosus is defined as a migraine headache that lasts over 72 hours. This prolonged headache is usually associated with protracted vomiting and dehydration. Diagnosis is based on a propensity for previous prolonged migraine attacks.

Some disorders that feature migraine with aura episodes have an identified genetic etiology. **Autosomal dominant familial hemiplegic migraine** and **episodic ataxia type 2** are caused by mutations in genes encoding transmembrane ion channels and ATPases. Patients may present with hemiplegic migraine, episodic ataxia, or both. **MELAS** (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes) is a mitochondrially inherited disorder with a high frequency of hemiplegic migrainous attacks. Recovery from attacks is variable. This diagnosis must be considered in children with coexisting epilepsy, mental retardation or regression, and myopathy. A DNA test for the most common mitochondrial mutation is available. Migraines are also common in a variety of other mitochondrial disorders.

Trigeminal Autonomic Cephalgias

Trigeminal autonomic cephalgia (TAC) is rare in children under 7 years of age, but has been reported in a child as young as 3 months. Onset typically occurs during adolescence or adulthood. Cluster headaches and paroxysmal hemicranias are types of TAC.

Cluster headache. **Cluster headaches** are characterized by episodes of pain interspersed between long periods of remission (Table 28.15). Pain is unilateral and localized to the eye and temple but may spread to other parts of the head. The pain begins suddenly and rapidly increases to an excruciating level. These headaches usually occur at a particular time of day, most often at night. Cluster headaches may be as short as 15 minutes or may last as long as 3 hours. Lacrimation, rhinorrhea, sweating, and nasal stuffiness usually accompany the headache. Patients find it impossible to rest, and they become agitated and restless during an attack. They may yell, scream, pace around, or bang their head against the wall. This is in sharp contrast to a migraine, in which the patient is quiet and withdraws to a dark cool room for sleep.

Cluster headache is categorized as either episodic or chronic. Episodic cluster headaches occur in a series that may last for weeks or months, separated by remission periods of months to years, whereas chronic cluster headaches are defined as occurring for more than 1 year without such a remission period, or with remission periods that last less than 1 month. Cluster headaches are more common in individuals who smoke tobacco.

Paroxysmal Hemicrania

Paroxysmal hemicrania is characterized by shorter attacks (2-30 minutes) and absolute prevention with and response to indomethacin. Chronic paroxysmal hemicrania consists of frequent and intense unilateral headaches. This disorder is much more common in women than in men. Although it usually begins in adulthood, chronic paroxysmal hemicrania may affect older children and adolescents. The average headache lasts about 10 minutes. Patients have at least 20 attacks a day, and the pain may awaken the patient from sleep. Sudden head movement may also precipitate an attack. This headache responds dramatically to indomethacin therapy. Relief of symptoms occurs within a few days of beginning the medication. Other nonsteroidal anti-inflammatory drugs (NSAIDs) are of no benefit. Because the symptoms of chronic paroxysmal hemicrania are similar to those of vascular malformations of the brain, a neuroimaging study should be performed to rule out malformation before the diagnosis of chronic paroxysmal hemicrania is made.

Secondary Headaches

Headache Associated with Trauma

Acute headache. If a child presents with a headache after trauma and has abnormal neurologic signs or symptoms, noncontrast CT of the head should be obtained emergently to assess for subarachnoid, subdural, or epidural intracranial bleed. Cervical spine radiographs should be obtained if cervical injury is suspected. If the child has focal neurologic deficits indicating possible vascular injury, MRI is indicated, potentially with MR angiography.

Persistent headache. Headaches may occur as part of the postconcussive or post-traumatic syndrome. The headache is generally constant and may have qualities of both chronic tension-type and migraine headaches. For example, some patients may have nausea, vomiting, and visual auras. Other features of this syndrome are fatigue, dizziness, vertigo, poor memory, decreased reaction times, and inability to concentrate. The neurologic findings are usually normal. Symptoms begin within 1-7 days of the head injury and may persist for years. About 70% of patients recover within a year, but 15% are still symptomatic after 3 years. Post-traumatic headache is considered acute if duration is less than 3 months and chronic if over 3 months. The pathophysiology of this syndrome is unknown.

Even though postconcussive syndrome is more common in persons with a history of psychologic or psychosomatic illness, a neuroimaging study may be necessary to exclude the rare possibility of a chronic subdural hematoma. Patient education is the most important element of treatment. Some patients may also benefit from psychotherapy. Amitriptyline, NSAIDs, and propranolol may be helpful, but opioids should be avoided because of their addictive potential in the treatment of chronic headaches. Trauma may also lead to the development of primary headaches such as migraines.

Headaches Associated with Vascular Disorders

Acute ischemic stroke. Headache is a feature of up to one-third of acute ischemic strokes. More commonly experienced symptoms are focal neurologic deficits such as weakness of the limbs and face or speech abnormalities; as such, every child presenting with a focal neurologic deficit must undergo evaluation for stroke. The headache in acute ischemic stroke is typically of moderate intensity, and otherwise lacks consistent features, though may occasionally present as a thunderclap headache. Similar headaches may also accompany transient ischemic attacks.

Aneurysms and Arteriovenous Malformations

Arterial aneurysms may be congenital (berry) or caused by an infectious process (mycotic). Rupture of an arterial aneurysm is rare in children. The rupture produces an excruciating headache, known as a thunderclap headache. Patients will often describe the pain as the worst headache of their lives. The pain is acute in onset and associated with nuchal rigidity, emesis, and changes in sensorium. The neurologic examination findings may be nonfocal. CT scan reveals blood in the cisterns and meninges in 85% of cases. If the CT scan shows no pathologic process, a lumbar puncture (LP) is necessary in all patients thought to have a ruptured aneurysm. The spinal fluid in a ruptured aneurysm is bloody, xanthochromic, or both. In half of the cases, patients report having previous headaches before having the headache associated with the rupture. These earlier headaches may be caused by leakage of blood from the aneurysm. If the clinician suspects a leaking or ruptured aneurysm, rapid neurologic and neurosurgical care is mandatory. Arteriovenous malformations may produce similar manifestations.

Arteritis, Cerebral Venous Thrombosis, and Vascular Dissection

Vascular dissection may present with a headache that precedes ischemic symptom development by hours to days. These headaches are typically persistent, nonthrobbing, and unilateral but may be throbbing, thunderclap, and steadily worsening. Infection, coughing, vomiting, and connective tissue disorders such as Ehlers-Danlos disease are risk factors. MRI with angiography of the head and neck is required for diagnosis.

Vasculitis

Vasculitis is an important cause of headaches in adults; however, in children, headache is rarely the presenting manifestation of this disorder and is instead a less frequent associated finding. Because of the increased risk of systemic hypertension in patients with vasculitis, it is important to include a blood pressure measurement as part of the complete history and physical examination. When systemic lupus erythematosus and mixed connective tissue disorders affect the central nervous system, children may present with seizures and mental status changes. These symptoms may occur with or without headaches.

Genetic Vasculopathies

Genetic vasculopathies also cause headaches. **Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes (MELAS)** may present with recurrent, oftentimes migrainous headaches and is associated with short stature, hearing deficits, ophthalmologic problems, learning disabilities, hemiparesis, cardiac problems, and diabetes. **Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)** is a mitochondrial disorder that may present with headaches and should be considered in children with subcortical infarcts, migraines, and multifocal T2/FLAIR hyperintensities in the deep white matter. CADASIL is inherited in an autosomal dominant fashion and may lead to early stroke and/or dementia, so a suggestive family history should increase suspicion.

Headaches Associated With Nonvascular Intracranial Disorders

This category includes headaches due to a variety of causes including increased cerebrospinal fluid (CSF) pressure, decreased CSF pressure,

(See *Nelson Textbook of Pediatrics,* p. 2871.)

noninfectious inflammation, neoplasms, intrathecal injection, seizures, and Chiari type I malformations.

Disorders Associated with Increased CSF Pressure

Pseudotumor cerebri is characterized by increased intracranial pressure (ICP) in the absence of a tumor, and is a disorder associated with significant morbidity. Headache in pseudotumor cerebri may be intermittent or constant and may resemble a migraine. Papilledema is usually present at the time of presentation. The characteristic findings are chronic progressive or nonprogressive headaches, papilledema, normal neuroimaging, and raised ICP.

Pseudotumor cerebri may be either primary or secondary to a variety of medical conditions. In **idiopathic intracranial hypertension**, a subset of primary pseudotumor cerebri, the typical patient is postpubertal, obese, and female. Pseudotumor cerebri may also be due to obstructive, toxic, metabolic, or hormonal causes that may often be revealed through a thorough history and physical examination (Table 28.16).

In addition to headache and papilledema, signs and symptoms may include sixth and seventh cranial nerve palsies and visual field changes. In severe cases, the retinal blind spot may enlarge, and the visual fields may become constricted. Physical examination otherwise is usually normal. Diagnosis in most cases is based on the historical presentation and the demonstration of an elevated cerebrospinal fluid opening pressure on a lumbar puncture obtained in the lateral position. Cerebrospinal fluid opening pressure values of 280 mm H_2O or greater are considered elevated in sedated or obese children; values of 250 mm H_2O are considered elevated in nonobese, nonsedated children. The CSF profile is typically normal. If papilledema is present, neuroimaging should be obtained prior to lumbar puncture to evaluate for other causes of papilledema, such as a tumor or hydrocephalus (see Table 28.9). MRI with venography should be considered in patients who are at risk for venous thrombosis or in those whose presentation does not fit the typical idiopathic intracranial hypertension profile (e.g., males, young children, and nonobese females), in order to assess for dural sinus thrombosis.

Pseudotumor cerebri may be diagnosed in the absence of papilledema if a sixth cranial nerve palsy is present and the patient has a normal neurologic examination, normal neuroimaging (including venography if indicated), an elevated CSF opening pressure, and a normal CSF profile. If the patient does not have a sixth cranial nerve palsy, then the diagnosis may be suggested (but not confirmed) if 3 of the following imaging requirements are met: empty sella, flattening of the posterior aspect of the globe, distention of the perioptic subarachnoid space with or without a tortuous optic nerve, and transverse venous sinus stenosis. Ongoing observation with recurrent exams, imaging, and studies is indicated to confirm the diagnosis.

All patients with pseudotumor cerebri should be monitored closely with special attention to ocular findings, as they are at risk for development of permanent visual impairment.

TABLE 28.16 Conditions Associated with Pseudotumor Cerebri

Intracranial Venous Drainage Obstruction
Mastoiditis and lateral (sigmoid) sinus obstruction
Extracerebral mass lesions
Congenital atresia or stenosis of the venous sinuses
Head trauma
Cryofibrinogenemia
Polycythemia vera
Paranasal sinus and pharyngeal infections

Cervical or Thoracic Venous Drainage Obstruction
Intrathoracic mass lesions and postoperative obstruction of venous return

Endocrine Dysfunction
Pregnancy
Menarche
Marked menstrual irregularities
Oral contraceptives
Obesity
Withdrawal of corticosteroid therapy
Addison disease
Hypoparathyroidism
"Catch-up" growth after deprivation, treatment of cystic fibrosis, correction of heart anomaly
Initiation of thyroxine treatment for hypothyroidism
Adrenal hyperplasia
Adrenal adenoma

Hematologic Disorders
Acute iron deficiency anemia
Pernicious anemia
Thrombocytopenia
Wiskott-Aldrich syndrome

Vitamin Metabolism
Chronic hypervitaminosis A
Acute hypervitaminosis A
Hypovitaminosis A
Cystic fibrosis and hypovitaminosis A
Vitamin D deficiency rickets

Drug Reaction
Tetracyclines
Perhexiline maleate
Nalidixic acid
Sulfamethoxazole
L-Asparaginase
Indomethacin
Penicillin
Prophylactic antisera

Miscellaneous
Galactosemia
Galactokinase deficiency
Lyme disease
Sydenham chorea
Sarcoidosis
Roseola
Hypophosphatasia
Paget disease
Maple syrup urine disease
Turner syndrome

Modified from Burg FD, Ingelfinger JR, Wald ER, eds. *Gellis and Kagan's Current Pediatric Therapy*. 14th ed. Philadelphia: WB Saunders; 1993:67.

Hydrocephalus usually causes a generalized headache. Slowly developing hydrocephalus initially causes mild pain, whereas rapidly developing hydrocephalus causes severe pain. Most patients with hydrocephalus have morning headaches that lessen after they arise, though pain may also be constant. Physical examination reveals signs of increased intracranial pressure, such as papilledema or tenderness of the neck. Papilledema is usually absent in children with an open fontanel. Macrocephaly is present in young children with unfused cranial sutures and in those with long-standing hydrocephalus. Other signs of hydrocephalus are a bulging fontanel and widened cranial sutures. The head growth chart is especially important in the evaluation of children with hydrocephalus. Head growth is abnormal if the plot of sequential head circumferences crosses percentile lines.

Cough headaches are intermittent headaches caused by transient increases in ICP resulting from activities that elevate intrathoracic pressure, such as exertion, coughing, or bending. The pain is maximum and severe at the onset of the activity and then resolves in seconds. Patients are usually asymptomatic between events. Cough headaches, which are much shorter than are exercise-induced vascular headaches, may be caused by both benign and life-threatening conditions. Structural causes of cough headache include brain tumors, cysts, and Chiari malformations. The results of the physical examination are usually normal, even when structural lesions cause this syndrome. Patients with cough headaches should undergo MRI.

Disorders Associated with Decreased CSF Pressure

Intracranial hypotension may occur from a tear in the dura caused by trauma, surgery, or lumbar puncture. The etiology of the headache is due to traction on the dura and vessels at the base of the brain. The headache associated with intracranial hypotension typically improves while the patient is recumbent and worsens upon sitting or standing.

The most common cause of a headache from intracranial hypotension is a persistent cerebrospinal fluid leak following lumbar puncture. Risk factors for post–lumbar puncture headache include the use of large-bore spinal needles and multiple attempts at obtaining CSF. Patients describe a severe headache within seconds after assuming an upright position. The headache disappears soon after the patient lies down. Other causes of low-pressure headaches include CSF leaks from fractures or tumors at the base of the skull.

Intracranial Masses

Brain neoplasms are the second most common type of childhood malignancy, though the overall incidence is low. As such, tumor is an infrequent cause of headache in children. The mechanisms by which tumors produce headaches include obstruction of CSF flow leading to hydrocephalus, or direct traction on dural or vascular structures. Headaches caused by hydrocephalus may develop rapidly, whereas traction on dural or vascular structures from tumor growth causes a slow and progressive headache. At the time of presentation, most patients with tumors or hydrocephalus have chronic and progressive headaches, with a history of increasing frequency and severity of pain over time.

Headache secondary to a tumor may or may not be localized to the tumor site. For example, patients with posterior fossa tumors usually have occipital pain, but if hydrocephalus is also present, the pain may be generalized. Headache secondary to tumor typically demonstrates a slow increase in the severity and frequency of painful episodes; initially, pain may be mild, and over-the-counter analgesics provide adequate pain relief. However, it is important to note that many patients with brain tumors have no particular pattern to their headaches. Patients with brain tumors near the optic chiasm may have visual disturbances, endocrine deficiencies, or galactorrhea. Diplopia may be present if the third or sixth cranial nerve is compressed; ptosis may also be present. Other historical features concerning for intracranial neoplasm include changes in school performance, reported motor or balance disturbances, personality or behavior changes, or seizures.

Physical examination often reveals abnormal findings, including papilledema and neurologic deficits. Focal neurologic findings may include eye movement abnormalities, anisocoria, facial weakness, ptosis, swallowing difficulties, hemiparesis, sensory deficits, cranial nerve deficits, altered mental status, and ataxia. Papilledema may be absent in children with posterior fossa tumors (with or without hydrocephalus) or in children with open fontanels. Nonlateralizing signs include increased motor tone as well as third and sixth nerve palsies. Increased motor tone may not be a constant finding and may manifest as transient shivering.

The **Parinaud syndrome** is the triad of upward-gaze paresis, poor pupillary reaction to light, and retraction nystagmus on convergence. This constellation of physical findings is seen in patients with hydrocephalus or tumors in the pineal region. The presence of Parinaud syndrome always warrants neuroimaging.

Increased intracranial pressure secondary to hydrocephalus and/or a brain tumor should be suspected in any child with chronic progressive headaches, abnormal neurologic examination findings, nuchal rigidity, or abnormal head growth. Patients with these signs and symptoms should undergo neuroimaging (see Table 28.9).

Intracranial cysts are classified as arachnoid, epidermoid, or dermoid. Slow-growing cysts often produce headache patterns similar to those of neoplasms. Epidermoid and dermoid cysts may have sinus tracts that communicate with the skin. If these cysts become infected, their clinical manifestations resemble that of a brain abscess.

A **colloid cyst of the third ventricle** is a potentially life-threatening cause of headache. With changes in position, this cyst functions as a ball valve and intermittently impedes the flow of CSF. This obstruction causes transient increases in intracranial pressure. During some episodes of obstruction, the patient may be asymptomatic. At other times, symptoms may be severe and include debilitating thunderclap headaches, neurologic posturing, coma, and even death. The ICP returns to normal when position is changed or when the increased CSF pressure overcomes the obstruction. Physical findings are normal between events. MRI confirms diagnosis. Treatment consists of CSF diversion or removal of the cyst.

Headaches Associated with Epileptic Seizures

Headache may be a preictal phenomenon in patients with focal epilepsy syndromes, or a consequence of an epileptic seizure. Postictal headaches tend to remit within hours of the cessation of seizure activity, but may last as long as 72 hours. Headache occurring as an ictal phenomenon in partial seizures remits with or soon after the cessation of seizure activity.

Chiari I Malformations

Chiari I malformation may present with headaches that worsen with cough and Valsalva maneuvers, and may be associated with radicular extremity pain. Patients presenting with this pattern of findings require neuroimaging.

Headaches Related to a Substance

Carbon monoxide poisoning should be suspected in any child with chronic headaches, as mild exposure may cause headache and nausea. The diagnosis is difficult to confirm with an arterial hemoglobin carbon monoxide (HbCO) level because the half-life of HbCO in room air is only 4 hours. Hence, the level may be normal only a few hours after exposure. One way of diagnosing and treating this condition is

by removing the cause of the exposure. Sources of carbon monoxide exposure include heavy urban traffic in which the patient is a car passenger, methylene dichloride paint strippers, kerosene space heaters, a gasoline engine running in an attached garage, cigarette smoking, and faulty home furnaces. Typically co-inhabitants have similar symptoms. Patients exposed to carbon monoxide may have behavioral and neurologic findings days to months later.

Other substance exposures may also lead to headaches. Ingestion of alcohol may lead to headache either during or after consumption. Use of cocaine causes headaches through various mechanisms, including hypertension, vasoconstriction, hypersensitivity vasculitis, and subarachnoid hemorrhage. Elevations in serum lead levels may cause headache (lead encephalopathy).

Medication-Overuse Headaches

A thorough medication history is essential as many analgesics may be associated with overuse headaches. All classes of headache medications can paradoxically cause headaches that may be worse on waking and exacerbated by activity. Stopping the medication improves the situation.

Caffeine Withdrawal Headaches

The threshold for withdrawal for each person is variable, but when caffeine is ingested in sufficient quantities for prolonged periods, sudden withdrawal may lead to vascular headaches. In the most common scenario, consumption occurs on weekdays, and because of schedule differences, the caffeinated beverage is not consumed on the weekend. This syndrome is easily diagnosed by history or by the use of a headache diary.

Intracranial and Systemic Infections

Infectious causes of headache are common and are typically benign, with the most common etiology being a viral upper respiratory tract infection. However, serious and life-threatening infections may present with headache. **Meningitis** and **meningoencephalitis** may present with a headache that is acute in onset and generalized. Fever, nuchal rigidity, alteration in sensorium, and abnormal neurologic findings may be present as well. Children presenting with this constellation of findings require an emergent lumbar puncture with cell counts and differential, glucose and protein quantification with a simultaneous determination of serum glucose, Gram stain, bacterial culture, and any indicated viral studies based on history, physical findings, or local epidemiology.

The child with a **brain abscess** may present with progressive neurologic dysfunction and may deteriorate quickly. Brain abscess should be considered in any child with a right-to-left cardiac shunt, chronic mucosal surface infections (sinus, otitis, dental), endocarditis, and a recent onset of persistent, chronic headaches. These patients may present with focal neurologic findings and signs of increased intracranial pressure rather than fever and nuchal rigidity. Neuroimaging should be considered prior to lumbar puncture, due to risk of herniation with space-occupying lesions.

Headache may accompany infections of the eye and orbit. The signs and symptoms of **periorbital cellulitis** are periorbital redness and tenderness, whereas in **orbital cellulitis**, the patient may also have chemosis, proptosis, ophthalmoplegia, and visual loss. Inflammation of the eye and orbit usually causes localized pain.

Children affected by **Lyme disease** commonly have headache in conjunction with other systemic symptoms. Lyme disease can cause an indolent lymphocytic meningitis, or may cause an isolated increased intracranial pressure in the absence of other findings that, if left untreated, may lead to permanent vision loss.

Disorders Affecting Homeostasis

Anoxia and **hypoxia** (<70 mm Hg) may produce headaches through dilatation of cerebral arteries, which in turn causes an increase in cerebral blood flow. Headaches are typically bifrontal, throbbing, and worsen with exertion, straining, or supine positioning. In children with illnesses that predispose them to hypoxia (chronic lung disease, obstructive sleep apnea), treatment should be directed at alleviating the source of the hypoxia. High altitudes may also lead to an acute hypoxic state. Hypercapnia (levels >50 mm Hg) may also cause throbbing headaches. For nocturnal or morning headaches, in addition to neuroimaging, polysomnography should be considered to assess for obstructive sleep apnea.

Systemic hypertension, both acute and chronic, may be associated with headaches. The pain is related to altered regulation of cerebral blood flow. Acute hypertension typically occurs in a child with underlying renal disease due to poststreptococcal glomerulonephritis, renal failure, or collagen vascular disease. Although hypertension is an uncommon cause of headaches in children, the diagnosis of hypertension is straightforward, and treatment of the hypertension alleviates the headaches. Headaches may be part of **malignant hypertension syndrome**, in which retinal exudates and microscopic hematuria are usually present. Severe hypertension may also cause intracerebral hemorrhage.

Headaches triggered by **fasting** may occur in individuals with and without primary headache disorders. Children may fast due to dieting or irregular schedules. These headaches may occur within 1 hour but generally take 12 hours to develop. A thorough diet history will reveal prolonged fasting as the etiology of the headache.

Headaches and/or Facial Pain Related to Dysfunction of Head and Neck Structures (Table 28.17)

Asthenopia or eye strain may be a cause of headache and mild, dull, aching discomfort of the eyes. Because it is due to muscle strain that occurs while trying to correct visual acuity, it is not present on awakening and worsens with prolonged visual duties. Referral to an ophthalmologist should be made if asthenopia is suspected. Physical examination is otherwise normal. Abnormal extraocular movements should prompt neuroimaging to evaluate for possible intracranial lesions.

A **corneal abrasion** should be suspected in the irritable infant and in the patient with excruciating eye pain. Diagnosis is made by fluorescein examination of the cornea. Corneal irritation, keratoconjunctivitis sicca, and recurrent erosion syndrome may present with recurrent eye pain that must be differentiated from cluster headaches.

Optic neuritis (inflammation of the optic nerve) often causes ipsilateral retro-orbital pain. Optic neuritis may occur as a single entity, or it may be part of the manifestation of multiple sclerosis. This disorder is rare in children but common in adolescents. The ophthalmologic examination reveals papillitis, an afferent pupillary defect, and decreased visual acuity. Often, the findings are normal except for decreased visual acuity. A neuroimaging study should be performed to fully evaluate the orbit and optic nerve and to rule out multiple sclerosis.

The headache associated with **sinusitis** may be acute or chronic. When the frontal or maxillary sinuses are involved, pain is frontal or orbital in location. When the ethmoid or sphenoid sinuses are infected, the headache may be frontal or occipital. Signs and symptoms of sinusitis include purulent rhinorrhea, halitosis, cough, tenderness to palpation over the sinuses or teeth, and fever. A prior history of allergic rhinitis or sinusitis may be present. The diagnosis of sinusitis in

TABLE 28.17 Chronic Facial Pain: Differential Diagnosis

Orbital Pain
Ocular disease
Migraine
Cluster headache
Sinusitis
Orbital cellulitis
Tolosa-Hunt syndrome
Intracranial aneurysm
Cavernous sinus disease
Giant cell arteritis
Neoplasm
Graves disease
Neoplasm, frontal lobe
Trigeminal neuralgia
Postherpetic neuralgia
Zoster

Ear/Periauricular Pain
Chronic external otitis
Relapsing polychondritis
Cholesteatoma
TMJ syndrome
Migraine
Carotidynia
Glossopharyngeal neuralgia
Thyroiditis
Muscle contraction
Carotid aneurysm
Cervical spine disease
Neoplasm
Zoster

Nasal/Cheek Pain
Sinusitis
Facial cellulitis
Neoplasm (nasopharynx, sinus)
Vasomotor rhinitis
Allergic rhinitis
Trigeminal neuralgia
Midline granuloma
Wegener granulomatosis
TMJ syndrome
Dental disease
Postherpetic neuralgia
Atypical odontalgia
Cluster headache

Poorly Localized/Vague
Sinus disease
TMJ syndrome
Depression
Conversion reaction
Neoplasm
Muscle contraction

Dental/Jaw Pain
Toothache
TMJ syndrome
Sinusitis
Neoplasm
Trigeminal neuralgia
Parotid disease
Atypical odontalgia
Postherpetic neuralgia

TMJ, temporomandibular joint.
Modified from Reilly BM. *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991:106.

pediatric patients may be made if symptoms of nasal discharge or daytime cough persist without improvement for more than 10 days, clinical course worsens after symptoms improve or stabilize, fever develops following a period of symptom stabilization or abatement of initial fever, or symptoms are severe at onset, defined as fever of or above 39°C with purulent nasal discharge for at least 3 days. Imaging studies are not required to confirm a diagnosis of sinusitis.

Dental abscesses may produce headaches that are aching or stabbing, and may occur as a complication of dental caries, tooth extractions, or root canal procedures. Physical examination may be normal or may reveal gingival swelling, redness, or pain. Palpating each tooth individually with a tongue blade may reveal the source of pain.

Malocclusion of the temporomandibular joint (TMJ) may cause chronic headaches. The pain is localized to the side of the affected joint. Some patients report constant pain, whereas others have pain only with jaw movement. An identifying "click" occurs when the patient opens the mouth. Full depression of the mandible may be limited in range. Not every person with a click has **TMJ syndrome,** and not everyone with TMJ syndrome has headaches. Gum chewing may exacerbate the pain associated with TMJ syndrome. In patients without TMJ syndrome, gum chewing may cause headaches through overuse of the temporalis muscles. Patients with symptomatic TMJ syndrome often find relief with the use of an occlusal splint worn during sleep.

Psychologic Factors

There is a high rate of comorbid psychiatric diagnoses in children with headaches, of which anxiety and depression are the most common. Primary headaches are more commonly seen in children with a history of psychiatric disorders. Consequently, screening for mental health symptoms should occur in conjunction with the medical history. History should also aim to determine child coping skills, family relationships, and parental reactions to pain.

Conversion disorder may manifest as headaches. Headaches associated with conversion disorder are very difficult to diagnose and treat appropriately. The frequency and severity of these headaches increase without lasting relief from any pharmacologic or physical therapy. Some patients appear as if they are in pain, whereas others look perfectly normal despite claiming to be in considerable pain. Secondary tension-type headache pain may occur, which further complicates the diagnosis. The neurologic findings in conversion disorder are normal.

The 2 problems in approaching conversion disorder headaches are (1) to convince the family that there is no physical cause for these headaches, and (2) to uncover the origin of the conversion disorder. The physician with a pre-established rapport with the family is clearly at an advantage in convincing the family that no physical cause exists for the headaches. The origins of a conversion disorder are difficult to uncover and require the finesse of an experienced therapist. Psychologic intervention is mandatory, not only to identify the source of the problem but also to offer appropriate counseling.

SUMMARY AND RED FLAGS

Headaches are a common cause of morbidity and health care utilization in children. Most children who present with headaches will have a benign secondary headache or the primary headache disorders of tension-type headache or migraine. However, the clinician must always consider conditions associated with significant morbidity or mortality in the evaluation of each patient with a headache. A thorough history and physical examination are the best tools to aid the clinician in determining which patients have a serious and life-threatening cause for their headaches. Certain symptoms should be considered red flags and prompt further evaluation (see Tables 28.5 and 28.6). Indications for neuroimaging are shown in Table 28.9. In the evaluation of the patient with headache, a single normal neurologic examination or 1 normal neuroimaging study should not provide complete reassurance. If headache persists, children require continued follow-up and ongoing physical examination assessments. Maintenance of a headache diary for patients with frequent or chronic headaches may be invaluable in determining the diagnosis and assessing the response to therapy. Assessment of headaches requires a strong patient-physician relationship in order to provide continued review of associated symptoms, ongoing assessments, appropriate evaluation, consideration of psychosocial factors, and reassurance when indicated.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Abend N, Younkin D, Lewis D. Secondary headaches in children and adolescents. *Semin Pediatr Neurol*. 2010;17:123-133.

Abu-Arafeh I, Howells R. Primary headaches in children under the age of 7 years. *Curr Pain Headache Rep*. 2014;18:401.

Alexiou GA, Argyropoulou MI. Neuroimaging in childhood headache: a systemic review. *Pediatr Radiol*. 2013;43:777-784.

Annequin D, Tourniaire B, Massiou H. Migraine and headache in childhood and adolescence. *Pediatr Clin North Am*. 2000;47:617-631.

Anttila P, Metsahonkala L, Sillanpaa M. Long-term trends in the incidence of headache in Finnish schoolchildren. *Pediatrics*. 2006;117(6):e1197-e1201.

Appleton R, Farrell K, Buncic JR, et al. Amaurosis fugax in teenagers. *Am J Dis Child*. 1988;142:331-333.

Avery RA, Frank G, Glutting JJ, et al. Prediction of Lyme meningitis in children from a Lyme disease-endemic region: A logistic-regression model using history, physical, and laboratory findings. *Pediatrics*. 2006;117:e1-e7.

Caviness V, Ebinger F. Headache in pediatric practice. In: *Handbook of Clinical Neurology*. Vol. 112 (3rd series) *Pediatric Neurology.* Part II. 2013; Chapter 86:827-838.

Dahlof CGH, Hargreaves RJ. Pathophysiology and pharmacology of migraine. Is there a place for antiemetics in future treatment strategies? *Cephalalgia*. 1998;18:593-604.

Dalessio DJ. Relief of cluster headache and cranial neuralgias. Promising prophylactic and symptomatic treatments. *Postgrad Med*. 2001;109:69-72.

Digre KB. Not so benign intracranial hypertension. *BMJ*. 2003;326:613-614.

Dodick DW, Rozen TD, Goadsby PJ, et al. Cluster headache. *Cephalalgia*. 2000;20:787-803.

Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. *Neurology*. 2013;81:1159-1165.

Gerber MA, Shapiro ED, Burke GS, et al. Lyme disease in children in southeastern Connecticut. Pediatric Lyme Disease Study Group. *N Engl J Med*. 1996;335:1270-1274.

Green MW. A spectrum of exertional headaches. *Med Clin North Am*. 2001;85:1085-1092.

Guidetti V, Galli F. Recent development in paediatric headache. *Curr Opin Neurol*. 2001;14:335-340.

Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition (beta version). *Cephalalgia*. 2013;33(9):629-808.

Hershey AD, Kabbouche MA, O'Brien HL. Headaches. In: Kliegman RM, ed. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Saunders Elsevier; 2016:2863-2874.

Hirano M, Pavlakis A. Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS): current concepts. *J Child Neurol*. 1994;9:4-13.

How CH, Chan WSD. Headaches in children. *Singapore Med J*. 2014;55(3):128-131.

Jensen VK, Rothner AD. Chronic nonprogressive headaches in children and adolescents. *Semin Pediatr Neurol*. 1995;2:151-154.

Jones JS, Nevai J, Freeman MP, et al. Emergency department presentation of idiopathic intracranial hypertension. *Am J Emerg Med*. 1999;17:517-521.

Joutel A, Bousser MG, Biousse V, et al. A gene for familial hemiplegic migraine maps to chromosome 19. *Nat Genet*. 1993;5:40-45.

Kaniecki R. Headache assessment and management. *JAMA*. 2003;289:1430-1433.

Kirton A, deVeber GA. Pediatric stroke. In: Kliegman RM, ed. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Saunders Elsevier; 2016:2925-2933.

Kosmorsky G. Pseudotumor cerebri. *Neurosurg Clin N Am*. 2001;12:775-797.

Lessell S. Pediatric pseudotumor cerebri (idiopathic intracranial hypertension). *Surv Ophthalmol*. 1992;37:155-166.

Lewis DW. Headaches in children and adolescents. *Am Fam Physician*. 2002;65:625-632.

Lewis DW, Ashwal S, Dahl G, et al. Practice parameter: Evaluation of children and adolescents with recurrent headaches: report of the quality standards subcommittee of the American Academy of Neurology and the practice committee of the Child Neurology Society. *Neurology*. 2002;59:490-498.

Lewis DW, Qureshi F. Acute headache in children and adolescents presenting to the emergency department. *Headache*. 2000;40(3):200-203.

Linder SL, Winner P. Pediatric headache. *Med Clin North Am*. 2001;85:1037-1053.

Lipton RB, Stewart WF, Stone AM, et al. Stratified care vs step care strategies for migraine. The Disability in Strategies of Care (DISC) study: a randomized trial. *JAMA*. 2000;284:2599-2605.

Lipton RB, Stewart WF, Von Korff M. Burden of migraine: societal costs and therapeutic opportunities. *Neurology*. 1997;48:S4-S9.

Marcdante KJ, Kliegman RM. Headache and migraine. In: Marcdante KJ, ed. *Nelson Essentials of Pediatrics*. 7th ed. Philadelphia: Elsevier; 2015:616-618.

Mark AS, Casselman J, Brown D, et al. Ophthalmoplegic migraine; reversible enhancement and thickening of the cisternal segment of the oculomotor nerve on contrast-enhanced MR images. *AJNR Am J Neuroradiol*. 1998;19:1887-1891.

Maytal J, Lipton RB, Solomon S, et al. Childhood onset cluster headaches. *Headache*. 1992;32:275-279.

Ozge A, Termine C, Antonaci F, et al. Overview of diagnosis and management of paediatric headache. Part I: diagnosis. *J Headache Pain*. 2011;12:13-23.

Papetti L, Capuano A. Headache as an emergency in children and adolescents. *Curr Pain Headache Rep*. 2015;19:3.

Practice parameter: The utility of neuroimaging in the evaluation of headache in patients with normal neurologic examinations (summary statement). Report of the quality standard subcommittee of the American Academy of Neurology. *Neurology*. 1994;44:1353-1354.

Romanello S, Spiri D, Marcuzzi E, et al. Association between childhood migraine and history of infantile colic. *JAMA*. 2013;309:1607-1612.

Roser T, Bonfert M, Ebinger F, et al. Primary versus secondary headache in children: a frequent diagnostic challenge in clinical routine. *Neuropediatrics*. 2013;44:34-39.

Rothner AD. Headaches in children and adolescents. *Child Adolesc Psychiatr Clin N Am*. 1999;8:727-745.

Rothner AD. Evaluation of headache. In: Winner P, Rothner AD, eds. *Headache in Children and Adolescents*. Hamilton, Ontario: BC Decker; 2001.

Senior K. New understanding into the mechanics of migraine. *Lancet*. 2002;359:500.

Silbert PL, Mokri B, Schievink WI. Headache and neck pain in spontaneous internal carotid and vertebral artery dissections. *Neurology*. 2005;45:1517-1522.

Sillanpaa M, Piekkala P, Kero P. Prevalence of headache at pre-school age in an unselected child population. *Cephalalgia*. 1991;11:239-242.

Singhi S, Jacobs H, Gladstein J. Pediatric headache: where have we been and where do we need to be? *Headache*. 2014;54:817-829.

Soler D, Cox T, Bullock P, et al. Diagnosis and management of benign intracranial hypertension. *Arch Dis Child*. 1998;78:89-94.

Stafstrom C, Rostasy K, Minster A. The usefulness of children's drawings in the diagnosis of headache. *Pediatrics*. 2002;109(3):460-472.

Steiner TJ, Fontebasso M. Headache. *BMJ*. 2002;325:881-886.

Vaz I. Probable trigeminal autonomic cephalgia in 3-month-old infant. *Dev Med Child Neurol*. 2009;52(4):400-440.

Winner P. Triptans in childhood and adolescence. *Semin Pediatr Neurol*. 2001;8:22-26.

29

Hypotonia, Weakness, and Stroke

Chamindra Konersman

MUSCLE WEAKNESS AND HYPOTONIA

Hypotonia, or abnormally diminished muscle tone, is defined as decreased resistance to passive movement of a limb through its range of motion. Hypotonia affects children of all ages and may be acute or chronic, progressive or static, isolated or part of a complex clinical situation, and may or may not be associated with weakness. The evaluation of children with hypotonia can be simplified by a thoughtful, analytic approach to the differential clues that are useful in identifying an underlying cause starting with detailed general and neurologic examinations (Table 29.1 and Fig. 29.1). Localizing the lesion based on examination in conjunction with laboratory, genetic, and imaging studies is key to arriving at a diagnosis (Table 29.2).

The assessment of muscle tone can be made by several observations, including:

- Evaluation of spontaneous posture
- Extent of mobility of joints
- Response to flapping of distal extremities
- Response to postural changes

The method of evaluating muscle tone and strength depends on the age of the patient.

Muscle tone is defined as the resistance experienced by the examiner to movement of limbs about joints. Muscle tone is divided into postural and phasic. **Postural tone** is that experienced by the steady flexion or extension of a joint and is caused by the resultant uniform resistance of muscle to passive movement. Antigravity posture of muscle is caused by postural tone. **Phasic tone** is the catch experienced when an extremity is rapidly flexed or extended. The anatomic structures responsible for muscle tone are contained in a closed circuit formed by the muscle spindle, which is connected to the spinal cord by sensory afferent pathways. The sensory afferent fibers synapse directly or indirectly with anterior horn α and γ motor neurons. The α motor neurons end at the neuromuscular junction (NMJ), and the γ motor neurons end at the muscle spindle, completing the closed circuit (Fig. 29.2). It is the level of activity of the γ motor neurons and its influence on the muscle spindle that sets the level of resting muscle tone. This lower motor neuron pathway is closely monitored and influenced by descending pathways from the cerebral cortex, basal ganglia, brainstem, and cerebellum. These descending pathways constitute the upper motor neuron pathways that influence resting muscle tone.

The maintenance of normal muscle tone requires the integrity of the entire central and peripheral nervous systems from the cerebral cortex, cortical white matter pathways, basal ganglia, cerebellum, brainstem, spinal cord, peripheral nerve, NMJ, and muscle. Diseases that affect the function of the nervous system at any level may result in abnormal muscle tone (Table 29.3; see Table 29.2). Broadly categorizing hypotonia into central versus peripheral nervous system causes based on history and examination is a useful initial diagnostic step (Table 29.4). An estimated 80-90% of infantile hypotonia is central in origin, with the remaining 10-20% being peripheral.

Most cases of acute *lateralized* body weakness result from abnormalities of the blood supply to a portion of the central nervous system (CNS). **Stroke** serves as a term to denote the sudden onset of symptoms attributable to such an interruption of cerebral or spinal perfusion. The clinical presentations and causes of stroke are best considered with respect to each of three age groups: neonates, children between 1 and 13 years of age, and adolescents, and are discussed later in this chapter.

HYPOTONIC INFANT

◆ Clinical Evaluation

In an infant, historical information must include a complete obstetric history as well as accurate data about perinatal events, diet, toxic exposure, and family diseases. The muscle strength, passive tone, joint extensibility, and postural reflexes including responses to traction, axillary suspension, and ventral suspension of the hypotonic infant should be compared to that of the normal infant (Fig. 29.3).

Muscle Strength

Muscle strength cannot be measured directly in infants (Table 29.5), but numerous clinical clues allow the careful observer to identify weakness. The most important of these is the spontaneous posture. The weak infant has diminished or no spontaneous movement, often in striking contrast to the usual vigorous and plentiful movements of the infant with normal strength. The lower extremities are abducted, and the lateral surfaces of the thighs lie against the examination table, whereas the upper extremities lie extended alongside the body or flexed in a flaccid position beside the head (Figs. 29.4 and 29.5*A*). With marked weakness, there are no movements that overcome the pull of gravity. The immobility of the weak infant results in flattening of the occipital bone, which is often associated with occipital hair loss. When placed in a sitting posture, the infant droops forward, the shoulders droop, the head falls forward, and the arms hang limply.

Passive Tone

Passive tone can be assessed by evaluating the resistance to movement of the limbs through a range of motion at the joints. Evaluation of the shoulders, elbows, wrists, hips, knees, and ankles is especially helpful. The examiner senses a "looseness" of the limbs as the limbs are moved.

In addition, grasping the midportion of the infant's limb and passively flapping the extremity allow the examiner to evaluate the degree of limpness of the distal extremity. In the hypotonic infant, the hands and feet wave limply; in the normal infant, the ankle and wrist are maintained fairly rigidly in line with the rest of the extremity.

Even in normal infants, there is a wide variation of muscle tone. Passive muscle tone varies and is particularly diminished after feeding

(See *Nelson Textbook of Pediatrics*, p. 3397.)

TABLE 29.1 Causes of Hypotonia and Weakness

Systemic	Connective Tissue	Cerebral	Spinal Cord	Anterior Horn Cell	Peripheral Nerve	Neuromuscular Junction	Muscle
Common							
Sepsis Heart failure Acidosis Hypoxia Renal failure Hypoglycemia Down syndrome Prader–Willi syndrome Fragile X syndrome Hypothyroidism Other chromosomal disorders Maternal-fetal drug effects	Stickler syndrome Marfan syndrome Achondroplasia	Hypoxic-ischemic brain injury Intracranial hemorrhage Brain malformation* Intrauterine infection Postnatal brain injury	Myelodysplasia Spinal cord tumor Epidural abscess Transverse myelitis Trauma (transection or compression) Syringomyelia	Spinal muscular atrophy	Postinfectious polyneuropathy (Guillain–Barré syndrome) Toxic neuropathies (isoniazid, vincristine, platinum-based antineoplastic medications, nitrofurantoin)	Botulism Infantile myasthenia Transient acquired neonatal myasthenia	Duchenne muscular dystrophy Becker muscular dystrophy Myotonic dystrophy Dermatomyositis
Uncommon							
Disorders of amino acid metabolism Urea cycle disorders Peroxisomal disorders Scurvy Rickets Sotos syndrome Angelman syndrome Rett syndrome Smith–Lemli–Opitz syndrome	Ehlers–Danlos syndrome Osteogenesis imperfecta Velocardiofacial syndrome	Progressive encephalopathies Mitochondrial disease	Neonatal spinal cord transection Hypoxic-ischemic myelopathy Arteriovenous malformation	Möbius syndrome	Chronic inflammatory demyelinating polyneuropathy Charcot–Marie–Tooth disease Hereditary sensory and autonomic neuropathies	Toxic (organophosphate poisoning, aminoglycosides, magnesium) Postneuromuscular blocking agents (vecuronium)	Pompe disease
Rare							
Lowe syndrome Zellweger syndrome Neonatal adrenoleukodystrophy Mucolipidosis type IV Tay–Sachs disease Gangliosidosis Mannosidosis Infantile neuroaxonal dystrophy		Miller–Dieker syndrome Congenital muscular dystrophy Metachromatic leukodystrophy Krabbe disease		Poliomyelitis Incontinentia pigmenti Fazio–Londe disease Brown–Vialetto–Van Laere syndrome	Refsum disease Giant axonal neuropathy Metachromatic leukodystrophy Krabbe disease	Congenital myasthenic syndromes	Other muscular dystrophies Congenital myopathies Metabolic myopathies Mitochondrial myopathies

*Examples of brain malformations include agenesis of the corpus callosum, lissencephaly, Joubert syndrome, and Dandy-Walker malformations.

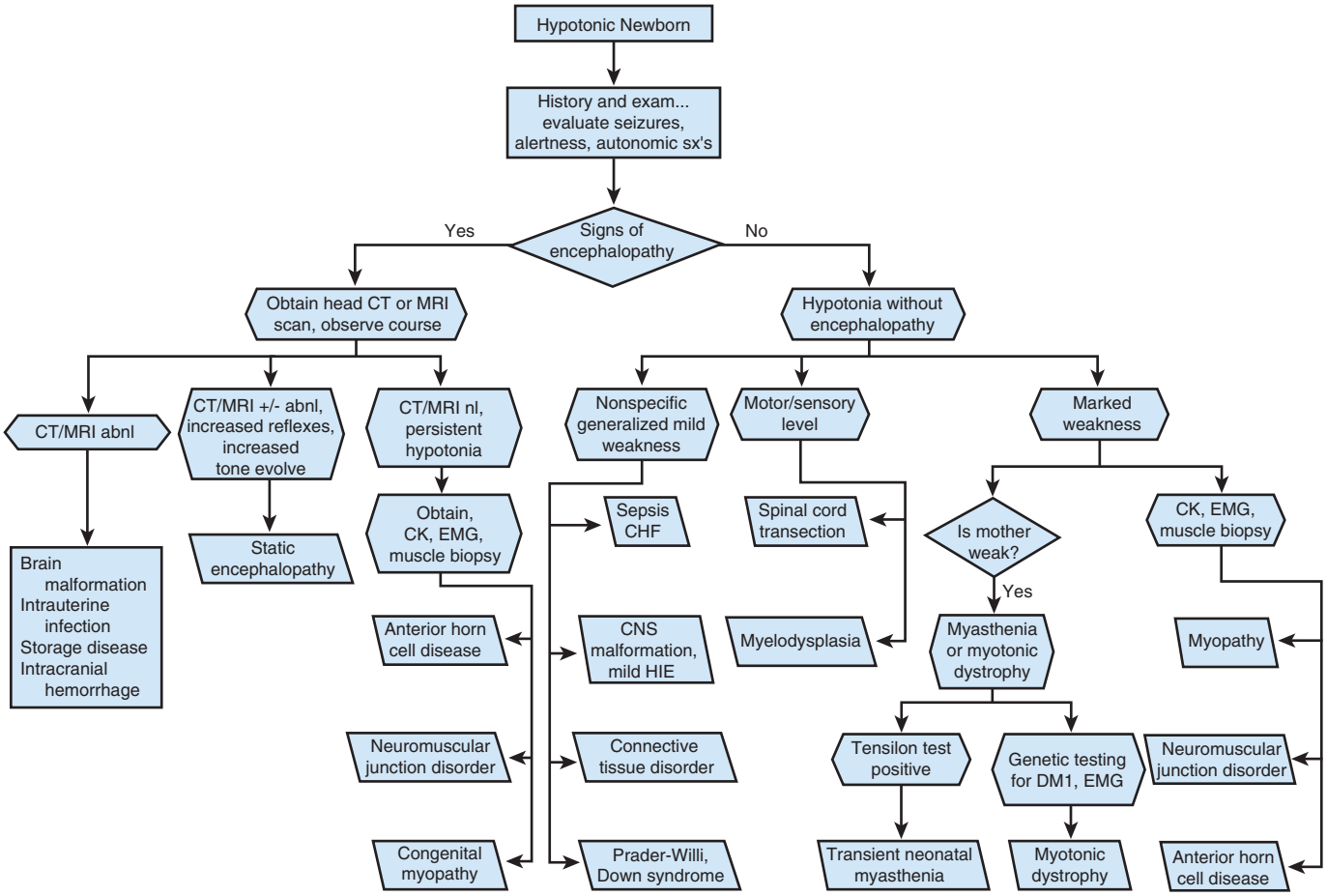


FIGURE 29.1 Approach to the hypotonic newborn. abnl, abnormal; CHF, congestive heart failure; CNS, central nervous system; CK, creatine kinase; CT, computed tomography; EMG, electromyography; HIE, hypoxic-ischemic encephalopathy; MRI, magnetic resonance imaging; DM1, myotonic dystrophy type 1; nl, normal; sx, signs.

and before sleep. There is profound hypotonia in all infants during sleep. Tone can also be affected by the position of the head. The child whose head is turned to one side may be manifesting an **asymmetric tonic neck response**, with increased extensor tone on the side of the body to which the head is turned and increased flexor tone on the contralateral side. This asymmetry of tone may be elicited even in the child who does not exhibit the typical "fencer's" posture (Fig. 29.6). Therefore, examination of an infant should always be conducted while the infant's head is at the midline; the same is true for eliciting muscle stretch reflexes. Hypotonia can also be associated with heart failure, sepsis, acidosis, failure to thrive, and other systemic conditions (see Table 29.1).

Joint Extensibility

The extent to which the joints may be extensible provides an indirect clue to the presence of hypotonia. Examination of **mobility** at the elbows, wrists, hips, and knees is helpful. The hypotonic infant may assume unusual postures in the presence of joint hyperextensibility. The "scarf sign" is a useful sign of hyperextensibility in the young infant. With the infant in a semireclining position, the hand is pulled across the chest toward the opposite shoulder and the position of the elbow is noted (see Fig. 29.3*A*). If the elbow passes the midline, then there is hypotonia.

Postural Reflexes

Traction response (pull-to-sit). The traction response is the most useful and most sensitive of the postural reflexes in infants. With the infant lying supine, the infant's hands are grasped, and the infant is pulled up to a sitting position. Once the sitting posture is attained, the head is held erect in the midline. During the maneuver, the examiner notes the infant's attempt to counter the traction by flexion of the arms (see Fig. 29.3*B*).

In an infant younger than 3 months, the **plantar grasp** should also be evident. In addition, there should be flexion at the elbow, knee, and ankle in response to the maneuver. The degree to which the head and neck pull up along with the trunk depends on the child's age.

In infants younger than 33 weeks' gestation, there is no traction response. From 33 weeks to term, the infant has head lag but responds to the traction maneuver by flexing the neck flexors in an attempt to lift the head. The full-term infant exhibits a traction response with minimal head lag, and when the sitting posture is attained, the head may be held erect momentarily and then falls forward.

By age 3 months, there should be no head lag, and the head should be aligned with the plane of the back as the child is pulled to sitting. The absence of flexion of the limbs in response to the examiner's pull

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TABLE 29.2 Differentiating the Causes of Infantile Hypotonia

Localization	Cause	History and Exam Findings	Investigation to Aid in Diagnosis
Central nervous system	HIE Intracerebral hemorrhage	Prematurity, difficult delivery	Brain MRI
	Brain malformations	Cranial nerve abnormalities, Babinski sign, gradual development of hypertonia (especially axial), respiratory or feeding difficulties, global delay	Cerebral ultrasound Brain MRI
	Intrauterine infection	Fever, altered mental status	Microbial cultures/evaluations, CSF evaluation
	Postnatal birth injury	Seizures, focal neurologic deficits	Brain MRI, EEG
	Progressive encephalopathies (leukodystrophies, progressive myoclonic epilepsies, Lennox–Gastaut syndrome, infantile spasms)	Seizures, developmental regression, ataxia, focal neurologic deficits, visual loss	Brain MRI, EEG, EMG/NCS (useful in adrenoleukodystrophy, Krabbe disease and metachromatic leukodystrophy), specific genetic testing
	Mitochondrial disease	Seizures, focal neurologic deficits, global delay, visual loss, hyper- or hyporeflexia	Brain MRI, muscle biopsy, mitochondrial DNA sequencing and deletion on muscle or affected tissue, elevated lactic acid, elevated CK, EMG/NCS
Spinal cord	Spinal cord tumor Syringomyelia HIE Trauma AVM	Spinal level on exam, weakness below a defined spinal level, absent reflexes (acutely) or hyperreflexia (chronically) below the level, may have Babinski sign, history of trauma	Brain MRI, complete spinal MRI
Anterior horn cell	Spinal muscular atrophy	Absence of antigravity movements, tongue fasciculations, absent reflexes to hyporeflexia, normal cognition, breathing/feeding difficulties; weakness in legs more than arms in SMA types II–III	*SMN* deletion analysis
	Poliomyelitis	Neck stiffness, muscle spasms, areflexia, asymmetric flaccid paralysis of a limb, respiratory distress, muscle atrophy, normal sensation	Isolate poliovirus from stool, confirm using RT-PCR or genomic sequencing, acute and convalescent serology showing 4-fold increase in titer, EMG/NCS showing pure motor neuronopathy
	Incontinentia pigmenti	Skin blistering, wartlike skin lesions, hyperpigmented streaks, pale/hairless atrophic linear streaks that respect Blaschko lines, dental abnormalities, intellectual delay	DNA analysis, EMG/NCS showing pure motor neuronopathy
	Fazio-Londe disease Brown–Vialetto–Van Laere syndrome (BVVL)	Bulbar palsy, facial weakness, hearing loss (BVVL only), respiratory compromise, muscle weakness	DNA analysis
Peripheral nerve	Guillain–Barré syndrome (GBS) Chronic inflammatory demyelinating polyneuropathy (CIDP)	Sensory ataxia with walking difficulties, rapidly (GBS) or slowly (CIDP) progressive weakness, absent reflexes or hyporeflexia, autonomic dysfunction, antecedent gastrointestinal/respiratory illness in GBS	EMG/NCS with absent or prolonged F-waves, prolonged distal latencies, conduction block, demyelinating nerve conduction velocities, CSF showing cytoalbuminologic dissociation, MRI with edematous enhancing nerve roots
	Toxic neuropathies	History and temporal correlation with exposure to a neurotoxic drug, distal then proximal muscle weakness, absent reflexes or hyporeflexia, sensory ataxia with walking difficulties	EMG/NCS showing mixed axonal/demyelinating features, plasma drug levels
	Charcot–Marie–Tooth disease	Family history of similar disease, pes cavus and hammer toe foot deformities, ataxic gait, foot drop, absent reflexes or hyporeflexia	EMG/NCS to determine if axonal or demyelinating subtypes, DNA analysis

TABLE 29.2 Differentiating the Causes of Infantile Hypotonia—cont'd

Localization	Cause	History and Exam Findings	Investigation to Aid in Diagnosis
Peripheral nerve (cont'd)	Hereditary sensory and autonomic neuropathies	Sensory loss in a stocking/glove distribution, chronic skin ulceration and poor wound healing, distal muscle weakness with foot deformity, absent reflexes or hyporeflexia, variable anhidrosis	EMG/NCS showing normal or mildly abnormal motor responses and abnormal sensory responses, nerve biopsy showing reduced myelinated and unmyelinated fibers, DNA analysis
	Refsum disease	Autosomal recessive inheritance, stocking/glove distribution of sensory and motor weakness, anosmia, hearing loss, ataxia, ichthyosis, short metacarpals and metatarsals, cardiac arrhythmia, and cardiomyopathy	Elevated plasma phytanic acid concentration, DNA analysis
	Giant axonal neuropathy	Stocking/glove distribution of sensory loss and motor weakness, cerebellar ataxia, absent reflexes or hyporeflexia, kinky hair (tightly curled), nystagmus, dysarthria, pyramidal tract signs, optic neuropathy, seizures	Brain MRI with white matter abnormalities, axonal sensorimotor polyneuropathy on EMG/NCS, nerve biopsy showing giant axons (axonal swelling) and disorganized neurofilaments, DNA analysis
	Metachromatic leukodystrophy Krabbe disease Adrenoleukodystrophy	Developmental regression, absent reflexes or hyporeflexia, Babinski signs	EMG/NCS showing demyelinating neuropathy, brain MRI showing white matter disease, DNA analysis
Neuromuscular junction	Botulism	Sudden poor feeding, constipation, weak cry, gradual muscle weakness, dilated poorly reactive pupils, exposure to soil/dust with bacterium or honey consumption	Presence of toxin in stool/serum, culture bacterium from stool, EMG/NCS showing low-amplitude motor responses or decrement on repetitive nerve stimulation in a weak muscle
	Transient acquired neonatal myasthenia	Ptosis, feeding and respiratory difficulties, aspiration, mother with signs or symptoms of autoimmune myasthenia	Maternal history of myasthenia, EMG/NCS showing decrement on repetitive nerve stimulation in a weak muscle, good response to acetylcholinesterase inhibitors
	Infantile (autoimmune) myasthenia	Ptosis, episodic weakness, recurrent feeding and respiratory difficulties, easy fatigability	EMG/NCS showing decrement on repetitive nerve stimulation in a weak muscle, good response to acetylcholinesterase inhibitors, antiacetylcholine receptor antibody serology
	Congenital myasthenic syndrome	Ptosis, episodic weakness, recurrent feeding and respiratory difficulties, easy fatigability	EMG/NCS showing decrement on repetitive nerve stimulation in a weak muscle, DNA analysis, negative anti-acetylcholine receptor antibody serology
Muscle	Duchenne/Becker muscular dystrophy	X-linked recessive pattern of inheritance, enlarged calves, proximal muscle weakness with a Gower maneuver	Markedly elevated CK, DNA analysis
	Congenital myotonic dystrophy	Autosomal dominant pattern of inheritance, frog-leg position, open down-turned mouth, minimal antigravity movements in infants, distal > proximal weakness in children, impaired relaxation of grip, dysarthria, myopathic facies with temporal wasting	Test mother (then father) for clinical myotonia or electrical myotonic discharges, EMG/NCS with myopathy in newborn period and myotonic discharges in older children, normal to mildly elevated CK, *DPMK* gene CTG repeat analysis
	Dermatomyositis	Subacute proximal muscle weakness, rash (Gottron papules, heliotrope rash), cutaneous calcinosis	Normal to mildly elevated CK, muscle biopsy showing perimysial and perivascular inflammation, and MAC deposition on microvasculature
	Pompe disease	Absence of antigravity movements, severe cardiomegaly, feeding/respiratory difficulties, hepatomegaly	GAA enzyme activity in dried blood spot, lymphocytes or fibroblasts, *GAA* gene analysis to confirm

Continued

TABLE 29.2 Differentiating the Causes of Infantile Hypotonia—cont'd

Localization	Cause	History and Exam Findings	Investigation to Aid in Diagnosis
Muscle (cont'd)	Congenital muscular dystrophy	Family history, proximal > distal muscle weakness, feeding and respiratory difficulties, early-onset contractures in specific subtypes, keloids/hyperkeratosis pilaris in specific subtypes, CNS dysfunction in specific subtypes	Brain MRI, mild to markedly elevated CK, muscle biopsy showing dystrophic changes, muscle MRI, EMG/NCS to assess for demyelinating neuropathy component and myopathy, DNA analysis
	Congenital myopathies	Family history, proximal > distal muscle weakness, feeding and respiratory difficulties, ptosis and ophthalmoparesis in specific subtypes	Normal to mildly elevated CK, muscle biopsy showing specific changes (nemaline rods, cores, centrally-placed nuclei), DNA analysis
	Metabolic myopathies	Family history, proximal muscle weakness, history of rhabdomyolysis or myoglobinuria, 2nd-wind phenomenon in some subtypes	Normal to markedly elevated CK, EMG/NCS usually myopathic, muscle biopsy, DNA analysis
	Mitochondrial myopathies	Maternal inheritance pattern, proximal > distal weakness, ptosis, ophthalmoparesis, short stature, variable cardiac and CNS involvement, recurrent rhabdomyolysis	Normal to moderately elevated CK, EMG/NCS showing myopathy and variable neuropathy, muscle biopsy with ragged red fibers, mitochondrial DNA analysis

AVM, arteriovenous malformation; CK, creatine kinase; CNS, central nervous system; CSF, cerebrospinal fluid; CTG, cytosine-thymine-guanine; GAA, α-glucosidase; HIE, hypoxic-ischemic encephalopathy; EEG, electroencephalogram; EMG/NCS, electromyography/nerve conduction study; GI, gastrointestinal; MAC, membrane attack complex; MRI, magnetic resonance imaging; RT-PCR, reverse transcription polymerase chain reaction; SMA, spinal motor atrophy.
Modified from Sparks SE. Neonatal hypotonia. *Clin Perinatol*. 2015;42:363-371.

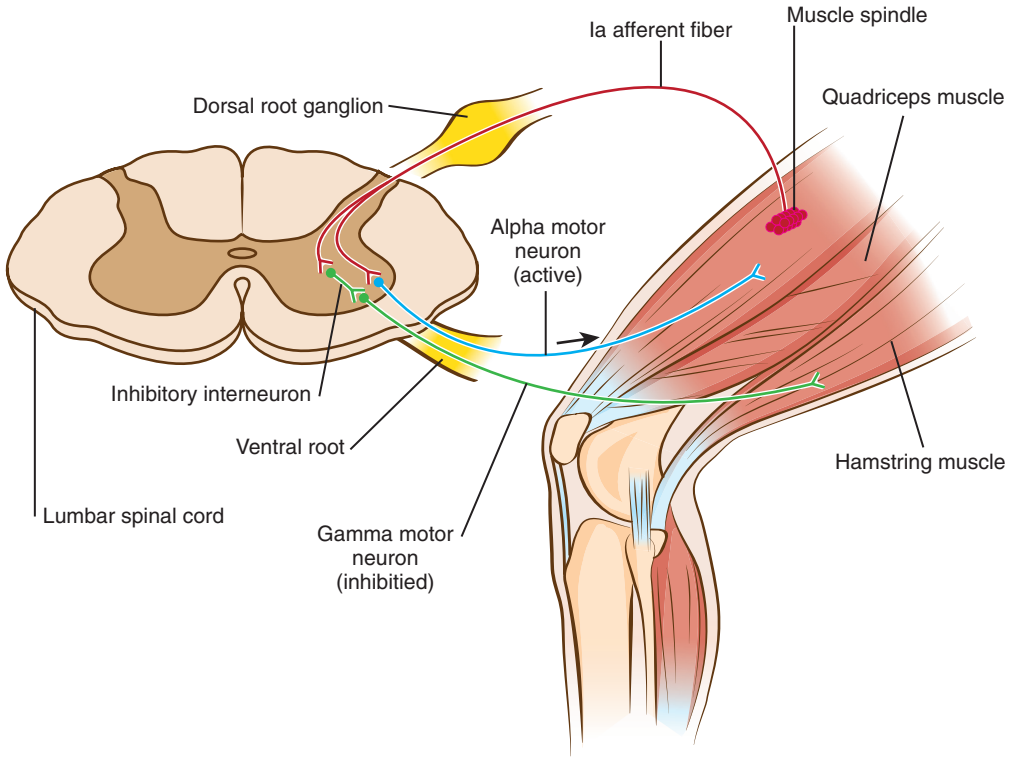

FIGURE 29.2 Lower motor neuron pathway influencing resting muscle tone. Stretching of the quadriceps muscle (agonist) will result in relaxation or inhibition of the hamstring muscle (antagonist).

TABLE 29.3 Localization of Symptoms to Neural Axis

	UPPER MOTOR UNIT		LOWER MOTOR UNIT			
	Brain	Spinal Cord	Alpha Motor Neuron	Peripheral Nerve	Neuromuscular Junction	Muscle
Level of consciousness	↓	Normal	Normal	Normal	Normal	Normal
Strength	Mild to moderate ↓	Mild to moderate ↓	Marked ↓	Marked ↓	Marked ↓	Marked ↓
Tone	Spastic (hypotonia at onset possible)	↓Acutely; ↑	↓, flaccid	↓	↓	↓
DTR	Normal to ↑	↓Acutely; ↑	↓ to absent	↓ to absent (lost early)	Normal	Normal to ↓ to absent
Babinski	Present	Present usually	Absent	Absent	Absent	Absent
Fasciculations	Absent	Absent	Present	Rarely	Absent	Absent
Atrophy	Mild to moderate	Mild to moderate	Present	Present	Absent	Present Pseudohypertrophy
Sensation	Normal	Absent below level of lesion	Normal	Abnormal in defined peripheral nerve distribution or glove/stocking	Normal	Normal
CK	Normal	Normal	Normal to moderately elevated (several 1000s IU/L)	Normal or mildly elevated (100s IU/L)	Normal	Normal to severely elevated
Overall pattern	Hemibody deficits	Spinal level present	Proximal weakness in SMA; asymmetric weakness in other diseases	Distal, length-dependent usually, defined nerve territory	Symmetric, painless weakness of tonically active muscles	Proximal > distal weakness
Other	Seizures Developmental delay Regression Cortical signs (e.g., language)	Radicular back pain, bowel/bladder dysfunction			Fluctuating diurnal variation	Myalgia, Gower sign

CK, creatine kinase; DTR, deep tendon reflexes; SMA, spinal muscular atrophy.

TABLE 29.4 Exam and Historical Findings to Distinguish Central from Peripheral Hypotonia

Finding	Central	Peripheral
Seizures	Present	Absent
Altered mental status	Present	Absent
Delayed cognitive milestones	Present	Absent
Deep tendon reflexes	Normal or increased	Absent or decreased usually
Babinski sign	Present	Absent
Infantile reflexes	Persistent	Not persistent
Pull-to-sit	Minor head lag	Marked head lag
Tongue fasciculations without other cranial nerve deficits	Unlikely	Very likely
Ophthalmoparesis	Present in brainstem disease	Present in some myopathic diseases
Ptosis	Present in some brainstem diseases	Present in some myopathic and neuromuscular junction diseases
Weakness	Mild to moderate	Severe
Antigravity movements	Present	Absent usually
Arthrogryposis	Less common	More common
Muscle atrophy	None to mild	Moderate to severe

FIGURE 29.3 Normal postural responses in a 5-month-old infant showing that the elbow does not extend beyond the midline on joint extensibility testing *(A),* the head and body in the same plane (no head lag) on pull-to-sit with resistance resulting in flexed elbows and knees *(B),* and lack of a slip-through feeling with resistance against the examiner's hands, good maintenance of head control, and extension of the head and legs with the steppage reflex *(D).* An infant with hypoxic-ischemic encephalopathy who was initially hypotonic at the time of delivery was noted to be hypertonic at 8 months with a normal ventral suspension response as evidenced by the ability to keep the head above horizontal *(C).*

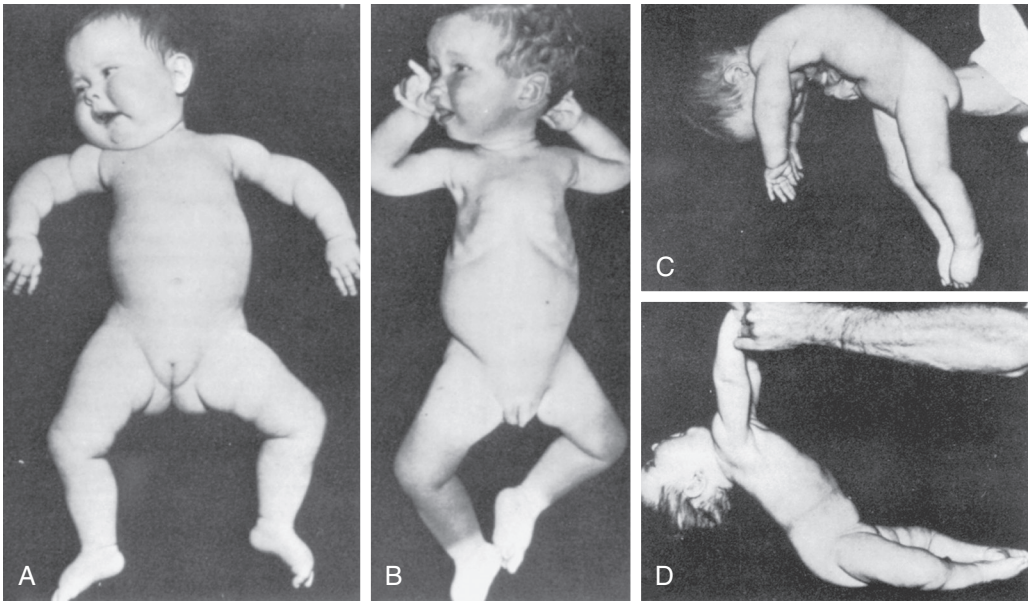

FIGURE 29.4 Spinal muscular atrophy I (Werdnig-Hoffman disease): characteristic postures. *A,* A 6-week-old infant with severe weakness and hypotonia from birth. Note the frog-leg posture of the lower limbs and internal rotation ("jug-handle") at the shoulders. *B,* A 1-year-old infant with frog-leg posture, external rotation at shoulders, intercostal recession, and normal facial expressions. A 6-week old infant with marked weakness of the limbs and trunk giving the characteristic inverted "U" appearance on ventral suspension *(C)* and pull-to-sit *(D).* (Modified from Volpe JJ, ed. *Neurology of the Newborn.* 5th ed. Philadelphia: Saunders; 2008: 770-771.)

and the presence of head lag inappropriate for age suggests hypotonia (see Figs. 29.4*D* and 29.5*C*).

Axillary suspension. The response to axillary suspension allows assessment of generalized and shoulder girdle tone. The infant is held under the arms, lifted, and suspended from the axillae without the thorax being grasped. In infants with normal tone and strength, the shoulder girdle muscles exert enough strength to allow the infant to be suspended without slipping through the examiner's grasp. In addition, the infant's head is held midline and the legs are held with some flexion at the hips, knees, and ankles (see Fig. 29.3*D*). The hypotonic infant droops with legs extended and head falling forward, and the absence of resistance of the muscles of the shoulder girdle allows the infant to slip through the grasp of the examiner as the baby's arms fling upward (see Fig. 29.5*B*).

TABLE 29.5 Grading Muscle Strength

0: No contraction
1: Minimal contraction only
2: Moves in horizontal plane but not against gravity
3: Moves against gravity but not against resistance
4: Moves against gravity and minimal resistance
5: Moves against gravity and full resistance

Ventral suspension. The response to ventral suspension allows assessment of tone of the trunk, neck, and extremities. The examiner holds the infant, who is lying prone. The infant is supported only by the examiner's hand on the abdomen. A normal infant holds the head erect and the back straight and holds the extremities with some flexion at the elbows, hips, knees, and ankles (see Fig. 29.3*C*). A full-term neonate makes intermittent attempts to hold the head straight, maintains the back straight, and can flex the limbs. The hypotonic infant droops in the examiner's palm, as if in the shape of an inverted "U," with the head and legs dangling limply (see Fig. 29.4*C*).

FIGURE 29.5 An 18-month-old infant, with an undiagnosed pure motor neuron disorder with severe axial more than appendicular weakness, delays in motor milestones, and respiratory insufficiency, has internal rotation of upper arm and frog-leg position *(A),* a slip-through appearance on axillary suspension *(B),* and a prominent head lag on pull-to-sit traction testing *(C).*

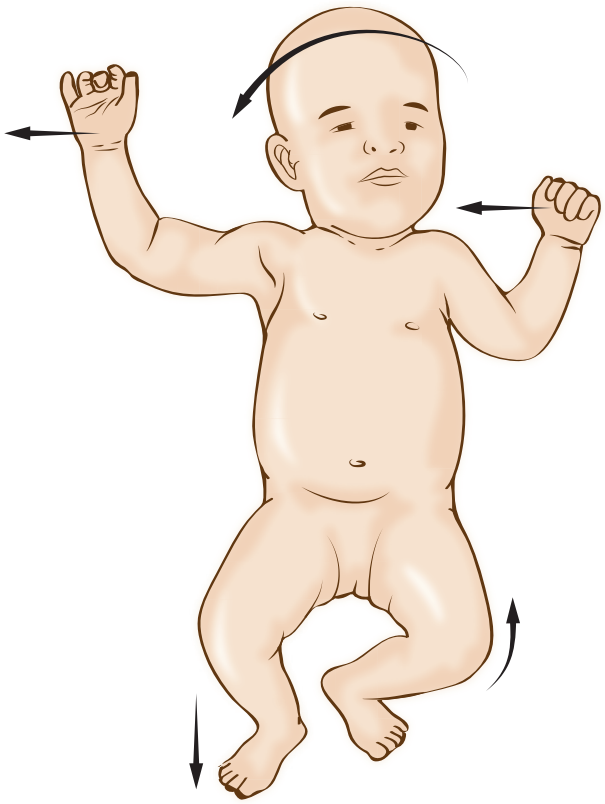

FIGURE 29.6 Asymmetric tonic neck reflex. Normally present from birth to 2 months. Turning head to 1 side when supine elicits extension of arms and leg ipsilateral to side that head is turned and flexion of opposite arm and leg. Persistence beyond 2 months might suggest abnormal development of contralateral motor cortex.

◆ Diagnostic Approach

A careful perinatal history is obtained to identify possible features suggestive of perinatal **hypoxic-ischemic brain injury**. The infant who has a neurologic dysfunction attributable to perinatal asphyxia should have demonstrated evidence of an acute encephalopathy during the neonatal period (disturbance of consciousness, poor feeding, seizures, autonomic dysfunction).

A computed tomographic (CT) study or magnetic resonance imaging (MRI) of the head is helpful to identify evidence of brain malformation, intrauterine infection, hypoxic brain injury, intracranial hemorrhage, or hydrocephalus. If the history suggests seizures, an electroencephalogram (EEG) should be obtained.

An **ophthalmologic evaluation** may detect evidence of ocular malformation (cataracts, microphthalmia, optic hypoplasia), evidence of intrauterine infection (chorioretinitis), or retinal/macular abnormality (retinitis pigmentosa, cherry-red spot) (see Chapter 32).

In some cases, requesting a hearing evaluation or brainstem auditory evoked response may be appropriate. A lumbar puncture is necessary only if acute or chronic (intrauterine) meningitis is suspected.

Fig. 29.1 summarizes the approach to the hypotonic newborn. After a thorough history and careful physical examination, it should be determined whether the infant has signs of encephalopathy. A CT scan or MRI of the head is obtained to detect any anatomic abnormalities. If the scan does not reveal an abnormality and if the neonate exhibits increased reflexes and tone over time, a diagnosis of static encephalopathy can be made. If hypotonia persists, anterior horn cell disease, congenital myopathy, or NMJ disease should be considered (see Tables 29.1 and 29.3).

If the baby is not encephalopathic, the practitioner should determine whether a syndrome (Prader–Willi or Down) is present. Is the motor-sensory level consistent with myelodysplasia or spinal cord injury? In addition, causes of **arthrogryposis multiplex congenita** must be considered (Table 29.6).

If the baby is markedly weak, the examiner should check to see whether the mother is also weak (proximal muscle weakness, ptosis, ophthalmoparesis) or whether she displays myotonia (on hand grip or to percussion). If either is true, then transplacental-derived **transient neonatal myasthenia gravis** or **myotonic dystrophy**, respectively, is a possibility (Table 29.7). If neither is the case, then myopathy (Table 29.8), congenital (genetic) myasthenia, infant botulism (Table 29.9), or anterior horn cell disease must be considered (see Table 29.2).

Common Disorders

Hypoxic-ischemic encephalopathy. Brain injury resulting from asphyxia, hypoxia, or ischemia is an important cause of neonatal neurologic morbidity. Tissue oxygen deficiency is presumed to underlie the neurologic injury caused by hypoxic-ischemic insults. An oxygen deficit may be incurred by either hypoxemia or ischemia. **Hypoxemia** is defined as diminished oxygen content of blood. **Ischemia** is characterized by reduced blood perfusion in a particular tissue bed. Hypoxemia and ischemia often occur simultaneously or in sequence. Ischemia is likely to be the more important of these 2 insults.

Asphyxia denotes an impairment in gas exchange, which results not only in a deficit of oxygen in blood but also in an excess of carbon dioxide and thereby acidosis. Furthermore, sustained asphyxia usually results in hypotension and ischemia, which is consistent with the likely predominant importance of ischemia as the final common pathway to brain injury. Asphyxia is the most common clinical insult resulting in brain injury during the perinatal period.

Evidence of hypoxic-ischemic injury to the neonatal nervous system is reflected by a constellation of signs noticed early after birth. The asphyxiating event or events may occur at any point in the antepartum, intrapartum, or postpartum periods. On the basis of admittedly imprecise historical data, it has been concluded that insults sustained by the fetus during the antepartum period account for approximately 20% of cases of hypoxic-ischemic encephalopathy (HIE). Maternal cardiac arrest or hemorrhage leading to transplacental and fetal hypotension represents such prenatal insults. Intrapartum events, such as placental abruption, uterine rupture, and traumatic delivery, may account for 35% of cases of HIE. In an additional 35% of infants displaying signs of HIE, markers of intrapartum fetal distress and antepartum risk, such as maternal diabetes, intrauterine growth restriction, or maternal infection, are found. Postpartum difficulties, such as cardiovascular compromise, persistent fetal circulation, and recurrent apnea, account for approximately 10% of HIE cases. Postpartum difficulties are found more commonly in premature than in full-term infants. Therefore, for at least 65% of cases of neonatal HIE, difficulties of the intrapartum period alone do not explain the encephalopathy.

Recognition of neonatal HIE requires careful observation and examination of the newborn in the context of a detailed history of pregnancy, labor, and delivery. Newborns who have sustained hypoxic-ischemic insults severe enough to cause permanent neurologic injury usually demonstrate abnormalities on neurologic examination. Indeed, a combination of low Apgar scores, fetal acidosis or distress, and abnormal neurologic examination findings help define HIE. Nonetheless, if the hypoxic-ischemic damage has occurred well in advance of parturition, it may be asymptomatic in the neonate.

Mild HIE (stage 1) may be characterized by hyperalertness or by mild depression of the level of consciousness, which may be

TABLE 29.6 Major Causes of Arthrogryposis Multiplex Congenita

Site of Major Pathologic Findings	Disorder
Cerebrum, brainstem, cerebellum	• Microcephaly • Cortical migrational disorders: lissencephaly-pachygyria (e.g., Zellweger syndrome), polymicrogyria, agenesis of the corpus callosum, schizencephaly • Pontocerebellar hypoplasia (type 1) • Dentato-olivary dysplasia • Cytomegalovirus infection • Leptomeningeal angiomatosis • Encephaloclastic processes: porencephalies, hydranencephaly, multicystic encephalomalacia • Hydrocephalus
Spinal cord	• Cervical spinal atrophy • Lumbosacral meningomyelocele • Sacral agenesis
Anterior horn cell	• Spinal muscular atrophy type 1 • Spinal muscular atrophy with respiratory distress type 1
Peripheral nerve	• Charcot–Marie–Tooth disease
Neuromuscular junction	• Congenital myasthenic syndromes • Maternal autoimmune myasthenia (rare)
Muscle	• Congenital myotonic dystrophy • Congenital muscular dystrophies • Congenital myopathies (nemaline myopathy, myotubular myopathy, core myopathy) • Distal arthrogryposis syndromes (types 1–10)
Intrauterine/maternal factors	• Amyoplasia (vascular compromise to fetus or placenta during embryogenesis) • Lack of space: multiple pregnancies, uterine abnormality (bicornuate uterus, uterine fibroid) • Fetal alcohol syndrome with contractures • Intrauterine tumors • Amniotic fluid leakage • Disruption (bands) • Maternal illnesses: infections, untreated SLE, metabolic imbalances • Maternal medications (curare, muscle relaxants) • Maternal injuries in the 1st trimester
Joint and connective tissue abnormalities	• Chondrodysplasia • Congenital contractural arachnodactyly • Marfan syndrome

SLE, systemic lupus erythematosus.
Modified from Volpe JJ, ed. *Neurology of the Newborn*. 5th ed. Philadelphia: Saunders; 2008:760.

accompanied by uninhibited Moro and brisk deep tendon reflexes, signs of sympathetic activity (dilated pupils), and a normal or only slightly abnormal EEG. Typically, these symptoms last less than 24 hours. **Moderate HIE (stage 2)** may be marked by obtundation, hypotonia, diminished number of spontaneous movements, and seizures.

TABLE 29.7 Clinical Features of Congenital Myotonic Dystrophy

Clinical Feature	% of Cases Exhibiting Feature
Hypotonia	100
Muscle atrophy	100
Transmission via mother	100
Intellectual disability in survivors	100
Facial diplegia	100
Feeding difficulties	92
Respiratory distress	88
Hyporeflexia or areflexia	87
Arthrogryposis	82
Polyhydramnios	80
Reduced fetal movements	68
Edema	54
Premature birth (<36 wk)	52
Elevated right hemidiaphragm	49
Neonatal mortality	41
Infant death in siblings	28

From Volpe JJ, ed. *Neurology of the Newborn*. 5th ed. Philadelphia: Saunders; 2008:802.

Infants with **severe HIE (stage 3)** are ill for more than 24 hours and are comatose. In addition, they are markedly hypotonic and display bulbar and autonomic dysfunction. The EEG is abnormal and may demonstrate a burst-suppression pattern or seizures, or it may be isoelectric.

Neonates with moderate or severe HIE may show variation in level of consciousness during the 1st days after birth. Initially, depression of level of alertness may appear to improve after the first 12-24 hours after birth. However, specific signs of improving alertness such as visual fixation or following are lacking. In addition, other persistent or progressive neurologic deficits, as well as functional deterioration of other extraneural systems, are inconsistent with a true improvement in neurologic state. Coma may persist, supervene, or even progress to brain death by 72 hours of life. If the infant survives 72 hours without losing all cerebral function, a variable amount of improvement may be observed.

Diffuse hypotonia accompanied by a lack of movement constitutes the most frequently observed motor deficit found early in the course of neonatal HIE. By the end of the 1st day, patterns of weakness that reflect the distribution of cerebral injury from a generalized hypoxic-ischemic insult may emerge. Affected full-term infants may demonstrate quadriparesis with predominant proximal limb weakness. This pattern of weakness derives from ischemia in the watershed or parasagittal region of the brain, which corresponds to the border zones of circulation between the anterior and the middle cerebral arteries and the middle and the posterior cerebral arteries. Affected premature infants may have weakness primarily in the lower extremities because of perinatal ischemic injury of motor fibers serving the legs. These fibers lie dorsal and lateral to the external angles of the lateral ventricles. Focal injury resulting from focal ischemia (stroke) may result in focal deficits reflective of the vascular territory in which the injury has occurred. These patterns are relatively subtle. As many as 70% of infants with moderate or severe HIE experiences seizures by the end of the 1st day of life.

(See *Nelson Textbook of Pediatrics,* p. 2980.)

TABLE 29.8 Specific Congenital Myopathies: Distinguishing Clinical Features

Subcategory	Distinguishing Clinical Features	Associated Genes:
Central core disease	• Facial weakness mostly with *RYR1* • Ophthalmoparesis and ptosis with *RYR1* • High incidence of malignant hyperthermia with *RYR1* • Severe axial/respiratory weakness out of proportion to limb weakness with *SEPN1* • Prominent early fixed kyphoscoliosis with *RYR1* • Rigid spine in older childhood with *SEPN1* • High incidence of club feet, pes cavus, foot drop, and distal hand/foot muscle atrophy with *RYR1*	*RYR1, SEPN1, TTN, MYH7, CCDC78*
Nemaline myopathy	• Prominent facial weakness • Severe bulbar weakness, feeding difficulties, and respiratory compromise in neonatal period or early infancy in some	*ACTA1, NEB, TPM3, TPM2, TNNT1, CFL2, KBTBD13, KLHL40, KLHL41, LMOD3*
Centronuclear myopathy	• Prominent facial weakness • Prominent ophthalmoparesis and ptosis (in infancy) • Prominent bilateral ptosis • Severe bulbar weakness, feeding difficulties, and respiratory compromise in neonatal period or early infancy • Infant that is long for age with elongated hands/feet • High incidence of neonatal/infantile death with *MTM1* • High incidence of club feet, pes cavus, foot drop, and distal hand/foot muscle atrophy with *DMN2*	*MTM1* (causes myotubular myopathy), *DNM2, BIN1, RYR1*
Congenital fiber type disproportion	• Severe axial/respiratory weakness out of proportion to limb with *SEPN1* • Rigid spine in older childhood with *SEPN1*	*TPM3, RYR1, TPM2, SEPN1, ACTA1*

RYR1, ryanodine receptor 1; *SEPN1*, selenoprotein N 1; *TTN*, titin; *MYH7*, myosin heavy chain 7; *CCDC78*, coiled-coil domain-containing protein 78; *ACTA1*, alpha-actin-1; *NEB*, nebulin; *TPM3*, tropomyosin 3; *TPM2*, tropomyosin 2; *TNNT1*, troponin T1; *CFL2*, cofilin 2; *KBTBD13*, Kelch repeat and BTB/POZ domains-containing protein 13; *KLHL40*, Kelch-like 40; *KLHL41*, Kelch-like 41; *MTM1*, myotubularin; *DNM2*, dynamin 2; *BIN1*, bridging integrator 1; *LMOD3*, leiomodin 3.

TABLE 29.9 Infantile Botulism Versus "Congenital Myasthenia"*

	Infantile Botulism	"Congenital Myasthenia"
Sudden onset in a previously healthy infant	+	–
Generalized hypotonia and weakness	+	+
Facial weakness, ptosis	+	+
Dilated, poorly reactive pupils	+	–
Constipation	+	–
Response to anticholinesterases	–	+
3 Hz (low frequency) RNS^	Decremental response	Decremental response
High-frequency RNS^	Incremental response in mild cases	Decremental response
Family history	–	+/–

*Congenital myasthenia includes congenital myasthenic syndromes, infantile (autoimmune) myasthenia, and transient acquired neonatal myasthenia; +, present; –, absent; +/–, variable; RNS^, repetitive nerve stimulation.

Modified from Volpe JJ, ed. *Neurology of the Newborn.* 5th ed. Philadelphia: Saunders; 2008:791.

Focal and multifocal ischemic brain injury may occur during the perinatal period. Such injury, most often infarction, occurs in a vascular distribution. Prenatal cerebral infarctions have been identified by intrauterine ultrasonography. In one autopsy study of neonates, 32 of 592 (5%) infants had cerebral infarctions. Among neonates surviving only a few hours after birth, several had infarctions with subacute or chronic histologic characteristics, indicating that the ischemic insult occurred before parturition. Focal seizures are the heralding sign of neonatal stroke. Although clinical signs corresponding to the area of infarction are expected, they may be absent. Neonatal strokes may follow uneventful deliveries and may occur in otherwise normal-appearing infants. Stroke may also accompany asphyxia, coagulopathy, polycythemia, and sepsis. A predilection for these ischemic lesions to occur in the territory of the middle cerebral artery, especially the left, has been noted and remains unexplained.

A direct relationship between motor and cognitive deficits at 1 year of age and the severity of acidosis observed at birth in asphyxiated and symptomatic neonates has been described. The extent of these sequelae is dependent not only on the occurrence of asphyxia but also on its duration. The 3 stages of HIE also correlate with outcome at 1 year of age. Those neonates with mild (stage 1) HIE or those who demonstrate moderate (stage 2) HIE for less than 5 days usually develop normally. Persistence of moderate encephalopathy or appearance of severe (stage 3) HIE is associated with seizures and motor and cognitive delay during follow-up. Children with mild HIE as neonates tend to be free of handicap in motor, cognitive, and school performance. Greater impairment of performance in each of these developmental spheres is found among children who exhibited moderate or severe neonatal HIE.

The likelihood of long-term neurologic sequelae after HIE is increased by the presence of neonatal seizures. The EEG may provide valuable prognostic information after the occurrence of seizure. Interictal background abnormalities, such as a burst-suppression pattern, persistently low voltage, and electrocerebral inactivity, are highly correlated with poor outcome. Conversely, infants with normal EEGs or those revealing only maturational delay have much more favorable prognoses.

Neuroimaging is useful in determination of prognosis. Head ultrasonography has shown that severe periventricular intraparenchymal echodensities followed by evidence of tissue injury (cyst formation) are correlated with later motor and cognitive deficits in premature infants. MRI performed early in the neonatal course of hypoxic-ischemic brain injury provides useful prognostic information. Most infants with MRI evidence of basal ganglia "hemorrhage," periventricular leukomalacia, or multicystic encephalomalacia after asphyxia ultimately demonstrate neurodevelopmental abnormalities. Diffusion-weighted imaging (DWI) reveals evidence of neonatal brain injury earlier than T1 and T2 weighted pulse sequences. Indeed, DWI reveals focal injury when standard MRI and CT are normal (Fig. 29.7).

Brain malformations. Brain malformation can arise as a result of a chromosomal disorder, as a component of a multiple malformation syndrome, or as an isolated abnormality. When associated with a chromosomal disorder or multiple malformation syndromes, the other associated features are the primary clues to diagnosis. In isolated brain malformation, the primary features are microcephaly (in most cases) and cognitive and motor developmental impairment. The MRI scan can detect abnormalities of development of the hemispheric structures (agenesis of the corpus callosum, holoprosencephaly), abnormalities of cortical cellular migration (lissencephaly, pachygyria), and cerebral heterotopias as well as brainstem and cerebellar malformations (e.g., Joubert syndrome).

Uncommon Disorders

Progressive encephalopathies of infancy. Progressive encephalopathies of infancy account for a small number of children with persistent hypotonia (see Chapter 24). These disorders are recognizable by a progressive deterioration of neurologic function and by diagnostically specific clues. The infant's development is normal for some time and then plateaus; this is followed by developmental regression with loss of previously acquired skills. Hypotonia is a feature of many of these disorders, at least at some point during the course of the illness. Some disorders feature hypotonia as the result of the combination of CNS injury and an associated polyneuropathy (Krabbe disease and metachromatic leukodystrophy). Progressive disorders that may be associated with hypotonia include neonatal adrenoleukodystrophy, mannosidosis, fucosidosis, Gaucher disease types 2 and 3, GM_1 gangliosidosis, infantile neuroaxonal dystrophy, infantile Refsum disease, Krabbe disease, metachromatic leukodystrophy, mucolipidosis type IV, and Tay–Sachs disease. The diagnosis of these disorders is based on recognition of clinically suggestive clues and on results of specialized biochemical and molecular genetic testing. If such a disorder is

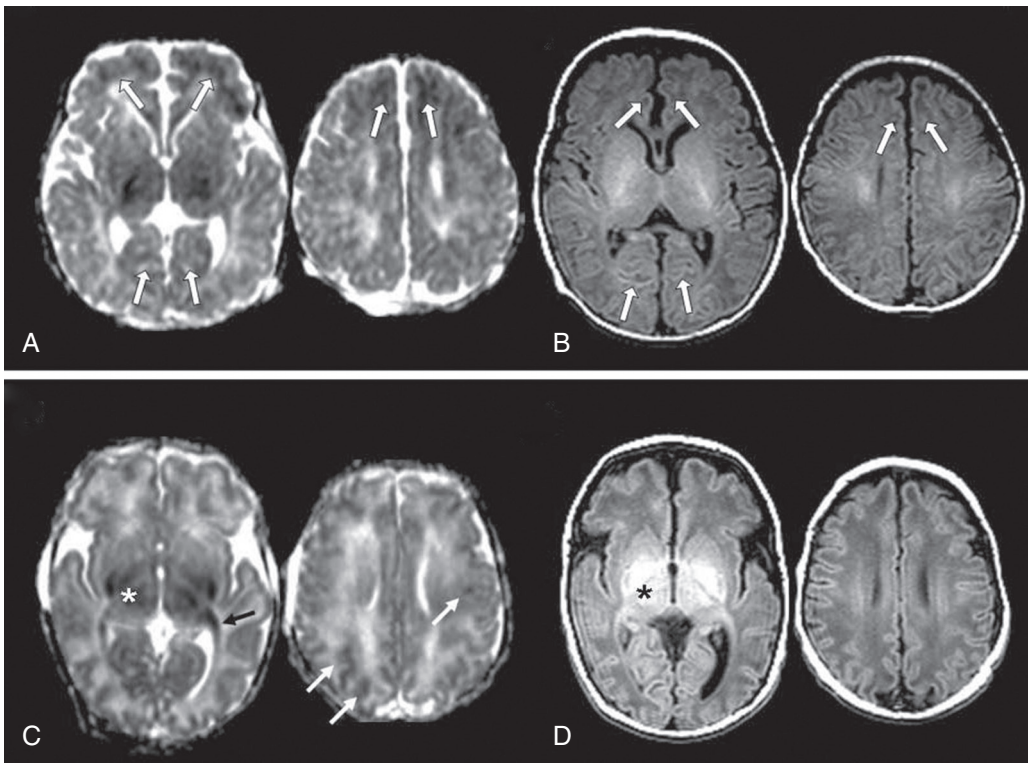

FIGURE 29.7 *A* and *C,* Predominant patterns of brain injury in newborns with hypoxic-ischemic brain injury. These apparent diffusion coefficient maps performed on day 3 of life and (*B* and *D*) T1 weighted images performed on day 10 of life are typical of the 2 major predominant patterns of brain injury seen in term newborns with hypoxic-ischemic encephalopathy. *A,* In the "watershed" pattern, areas of restricted diffusion are seen in the parasagittal regions *(arrows). B,* One week later, very subtle hyperintensities can be seen in the same areas on the T1 weighted images *(arrows). C,* In the "basal nuclei" predominant pattern, the areas that show restricted diffusion are the thalami and basal ganglia *(white star)* bilaterally. In this example, part of the optic radiation is also affected *(black arrow). D,* On day 10, the injury in the thalami and basal ganglia *(black star)* appears as T1 hyperintensities bilaterally.

suspected, the infant should be referred to appropriate genetic and neurologic specialists.

Mitochondrial diseases. Mitochondrial diseases often affect both the brain and muscle and clinically manifest as hypotonia, probably as a combination of both cerebral dysfunction and myopathy (Tables 29.10 and 29.11). The diagnosis is based on recognition of clinical symptoms, presence of lactic acidosis, presence of ragged red fibers on muscle histologic examination, and mitochondrial abnormalities identifiable on a muscle electron microscopic examination (Fig. 29.8). The diagnosis of many mitochondrial diseases is possible by specific mitochondrial DNA testing. Other inborn errors of metabolism may produce hypotonia by central mechanisms (organic acidurias, hyperammonemia) or by interfering with muscle metabolism (Table 29.12).

Brain malformation syndromes. **Miller–Dieker syndrome** is characterized by severe **lissencephaly** ("smooth brain" with agyria), severe developmental impairment, hypotonia early in life, and hypertonia with age. The facial changes include bitemporal hollowing, upturned nares, thin vermilion border, and small jaw. Fluorescence in situ hybridization–detectable microdeletions of 17p13.3 in the *PAFAH1B1* and *YWHAE* genes cause 80% of de novo mutations, whereas the remaining 20% are inherited from a parent with a balanced chromosomal rearrangement.

Muscle-eye-brain diseases (MEB) are an expanding category of congenital muscular dystrophies with eye abnormalities and an assortment of brain malformations including cobblestone lissencephaly type II, focal pachygyria, polymicrogyria, pontocerebellar hypoplasia, and occipital encephalocele. These diseases are characterized by hypotonia in infancy due to a concomitant muscular dystrophy and CNS disease and variable degrees of intellectual disability. **Walker–Warburg syndrome** is the most severe form of MEB, usually resulting with early demise. Genes associated with MEB are increasing rapidly: *POMT1*, *POMT2*, *POMGnT1*, *FKTN*, *FKRP*, *LARGE*, *ISPD*, *GTDC2*, *B3GALNT2*, *B3GNT1*, *TMEM5*, *POMK*, *DPM1*, *DPM2*, *DPM3*, *DOLK*, *GMPPB*, and *DAG1*.

TABLE 29.10 Clinical Spectrum of Mitochondrial Disease

Nervous System
- Hypotonia
- Failure to thrive
- Motor regression
- Stroke (nonvascular)
- Dementia
- Episodic encephalopathy (elevated cerebrospinal fluid lactate)
- Intellectual disability
- Neuropathy (axonal, demyelinating, or sensory ganglionopathy)
- Ophthalmoparesis (slowly progressive)
- Ptosis (slowly progressive; little diurnal variation; asymmetric at onset)
- Optic atrophy
- Retinitis pigmentosa (perimacular; vision usually spared)
- Ataxia
- Central apnea
- Epilepsy (focal or multifocal myoclonus; status epilepticus; triggered by sodium valproate)
- Migraines
- Sensorineural hearing loss (asymmetric; young onset; partial recovery possible)

Heart
- Cardiomyopathy
- Conduction block or arrhythmia

Skeletal Muscle
- Myopathy (proximal, symmetric weakness; myalgia)
- Exercise intolerance
- Episodic rhabdomyolysis

Other
- Lactic acidosis
- Recurrent bowel obstruction (pseudoobstruction)
- Short stature
- Diabetes (young onset; nonobese)

Modified from Amato A, Russell J. *Neuromuscular Disorders.* 1st ed. New York: McGraw-Hill; 2008; Liang C, Ahmad K, Sue CM. The broadening spectrum of mitochondrial disease: shifts in the diagnostic paradigm. *Biochim Biophys Acta.* 2014;1840:1360-1367.

HYPOTONIC OLDER CHILD

◆ Clinical Evaluation

Posture and Strength

Observation of the child's spontaneous posture may suggest the presence of weakness. Muscle strength can be observed as the child performs functional tasks, including pulling to sit spontaneously from a prone position, arising to stand from a sitting or lying position, standing on 1 leg independently, hopping, walking, running, and climbing stairs. The **wheelbarrow maneuver** can be used to functionally assess strength in the upper extremities. In the child older than 5 years, manual muscle testing can be performed if the child is cooperative (see Table 29.5). The examiner evaluates each muscle group independently, comparing the child's muscle strength in resistance to the examiner's strength. The child with muscle weakness has difficulty performing motor tasks and may exhibit unusual postures (lordosis) or toe walking, and on manual muscle testing, may be easily overcome by the examiner's strength.

Passive Tone

Passive muscle tone is more consistent during the waking hours in the child than in the infant. The major joints should be moved through their range of motion and the extent of resistance noted. Flapping the distal extremities provides a useful clue. Briskly lifting the lower extremity at the knee while the patient lies supine is a useful test of muscle tone. In the normal child, the foot briefly drags along the examination table and then rises with the leg. In the hypertonic child, the leg remains extended stiffly at the knee. In the hypotonic child, the lower leg hangs limply and the foot drags as the knee is raised.

Joint Extensibility

The hypotonic child demonstrates hyperextensibility of joints, especially at the elbows, wrists, knees, and ankles. Examination of the small muscles of the fingers may also be helpful (Fig. 29.9).

◆ Diagnostic Approach

The diagnosis of a particular neurologic disorder depends on the location of the lesion (i.e., which part of the nervous system is impaired or abnormal), the patient's age, and whether the condition is progressive or static (see Tables 29.1 to 29.3). Fig. 29.10 outlines an algorithm for determining the cause of muscle weakness in a child.

Anatomic Localization

The initial approach is to identify the location of dysfunction along the axis of the nervous system. Disorders of the cerebral cortex

TABLE 29.11 Select Mitochondrial Disorders with Hypotonia Classified by Clinical Phenotype and Genotype

Clinical Phenotype	Associated Mutations	Mode of Inheritance	Common Clinical Features
MELAS syndrome (mitochondrial encephalopathy, lactic acidosis, and strokelike episodes)	tRNA point mutations: • m.3243A>G in $tRNA^{Leu}$ (~80% of cases) • m.3217T>C in $tRNA^{Leu}$ (~7.5% of cases) • m.13513G>A encoding NADH-ubiquinone (<15% of cases) • m.3252A>G in $tRNA^{Leu}$ (<5% of cases) • Multiple other mtDNA point mutations	Maternal	• Cardinal—strokelike episodes, intermittent encephalopathy, T2/FLAIR abnormalities on brain MRI that do not respect vascular territory, lactic acidosis • Other—hearing loss, diabetes, short stature, gastrointestinal issues
MERRF syndrome (myoclonic epilepsy with ragged red fibers)	tRNA point mutations: • m.8344A>G in $tRNA^{Lys}$ (>80% of cases) • m.8356T>C in $tRNA^{Lys}$ • m.8363G>A in $tRNA^{Lys}$ • m.8361G>A in $tRNA^{Lys}$ • Multiple other mtDNA point mutations	Maternal	• Cardinal—myoclonus, proximal weakness, generalized epilepsy, ataxia • Other—multiple lipomatosis, hearing loss, cognitive impairment, neuropathy
KSS (Kearns–Sayre syndrome)	Single large mtDNA deletion (1.1-10-kb) • m.8470_13446del4977 (deletion of 4977 base pairs; most common) • Multiple other mtDNA deletions	Sporadic	• Cardinal—multisystemic disease with progressive external ophthalmoplegia, pigmentary retinopathy, cardiomyopathy before age 20 yr • Other—short stature, proximal muscle weakness, hearing loss, dementia, ataxia, multiple endocrinopathies (diabetes, hypothyroidism, hypoparathyroidism, hypogonadism
CPEO (chronic progressive external ophthalmoplegia)	Single large mtDNA deletion (1.1-10 kb) • m.3243A>G in $tRNA^{Leu}$ (most common; same as MELAS) • Multiple other mtDNA point mutations • Multiple mtDNA deletions caused by mutations in the following nuclear genes: *SLC25A4* encoding ANT1, *C10orf2* encoding twinkle, *POLG1* encoding mtDNA polymerase, *POLG2, OPA1*	Sporadic Maternal Autosomal dominant	• Cardinal—skeletal muscle disorder with ptosis, ophthalmoparesis, +/– proximal muscle weakness
Leigh syndrome (subacute necrotizing encephalomyelopathy)	mtDNA mutations: • m.8993T>G or m.8993T>C in *MT-ATP6* (~10% of cases) • Multiple other mtDNA point mutations • m.8470_13446del4977 (deletion of 4977 base pairs; also seen in KSS) Nuclear gene mutations resulting in respiratory chain complex deficiencies: • Complex I: *NDUFV1, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS7, NDUFS8, NDUFA1, NDUFA2, NDUFA10, NDUFA9, NDUFA12, NDUFAF2, NDUFAF5, NDUFAF6, FOXRED1* • Complex II: *SDHA, SDHAF1* • Complex III: *BCS1L, UQCRQ, TTC19* • Complex IV: *SURF1, COX10, COX15, SCO2, NDUFA4, PET100, LRPPRC*	Maternal Sporadic Autosomal recessive	• Hypotonia, spasticity, movement disorders (chorea), cerebellar ataxia, neuropathy, bilateral basal ganglia lesions, seizures, lactic acidosis, psychomotor retardation/regression especially with illness between 3-12 mo of age • Hypertrophic cardiomyopathy
NARP (neurogenic muscle weakness, ataxia, retinitis pigmentosa)	• m.8993T>G or m.8993T>C in *MT-ATP6* (50% of cases)	Maternal	• Proximal neurogenic muscle weakness, sensory neuropathy, seizures, ataxia, pigmentary retinopathy, learning difficulties, dementia with onset usually in childhood
Mitochondrial DNA depletion syndrome	• Homozygous or compound heterozygous mutations in *TK2* (thymidine kinase 2), a mitochondrial deoxyribonuclease, resulting in mitochondrial depletion	Autosomal recessive	• Hypotonia, proximal muscle weakness, axial weakness, respiratory insufficiency, marked clinical variability with death in infancy to early adulthood due to respiratory insufficiency

FLAIR, fluid-attenuated inversion recovery; GI, gastrointestinal; MRI, magnetic resonance imaging; mtDNA, mitochondrial DNA; NADH, nicotinamide adenine dinucleotide, reduced form; tRNA, transfer RNA.

Data from DiMauro S, Hirano M. *MERRF*. 2003 Jun 3. Seattle (WA): University of Washington: GeneReviews (Internet); DiMauro S, Hirano M. *MELAS*. 2001 Feb 27. Seattle (WA): University of Washington: GeneReviews (Internet); Thorburn DR, Rahman S. *Mitochondrial DNA-Associated Leigh Syndrome and NARP*. 2003 Oct 30. Seattle (WA): University of Washington: GeneReviews (Internet); Liang C, Ahmad K, Sue CM. The broadening spectrum of mitochondrial disease: shifts in the diagnostic paradigm. *Biochim Biophys Acta*. 2014;1840:1360-1367.

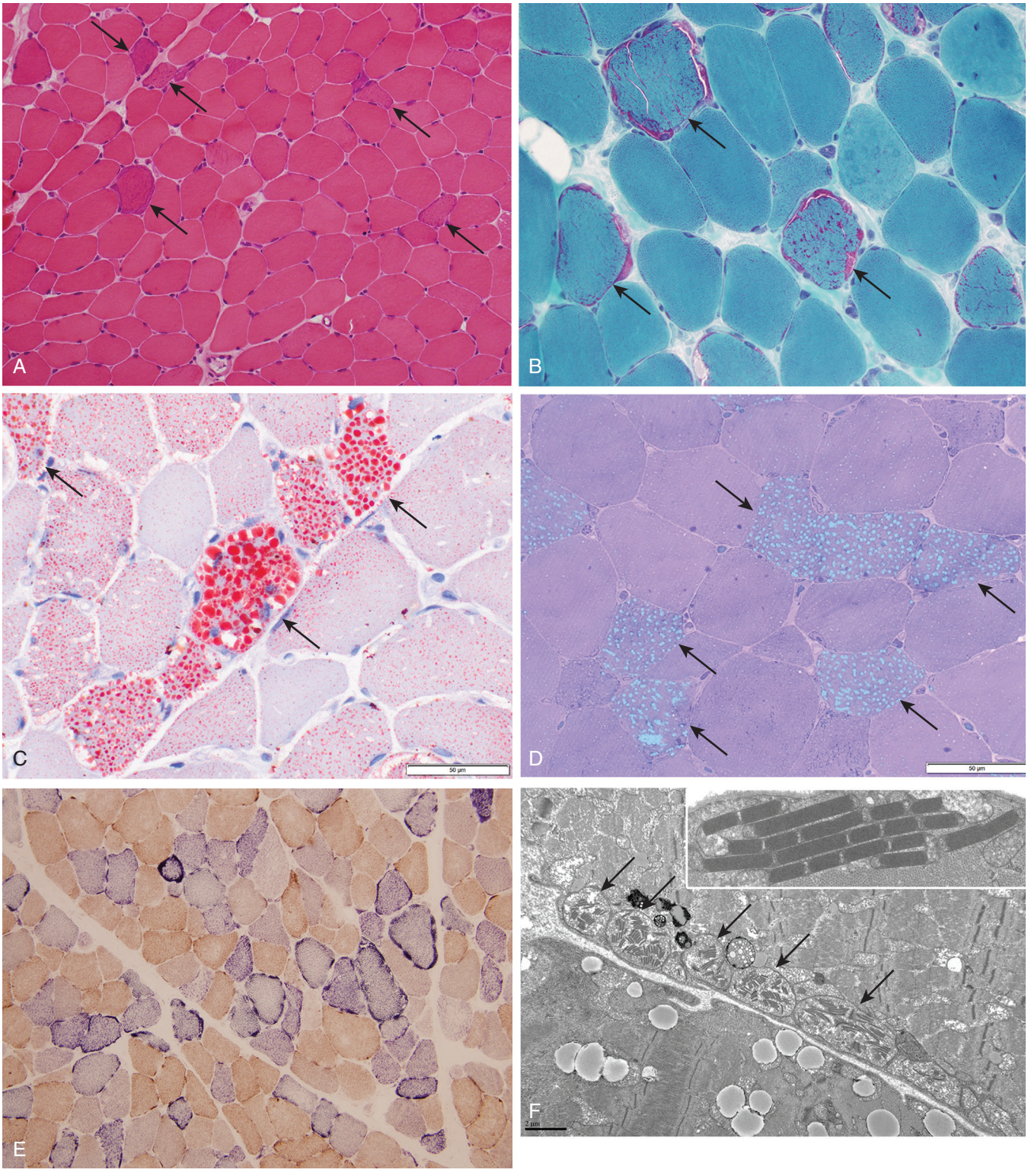

FIGURE 29.8 Pathologic changes seen in mitochondrial myopathy. Hematoxylin and eosin stain *(A)* demonstrating increased fiber size variation and subsarcolemmal basophilic deposits *(arrows)* correlating with ragged red fibers *(arrows)* on Gomori trichrome *(B)* oil red O *(C)* and toluidine *(D)* staining showing increased lipid deposition in the fibers *(arrows)* indicative of marked mitochondrial dysfunction due to defects in β-oxidation. *(E)* COX (brown stain) with SDH counterstain (blue stain) showing many COX-negative fibers (blue staining fibers) indicative of mitochondrial dysfunction since the COX enzyme is partly encoded within mitochondrial DNA. *(F)* Electron microscopy showing classic paracrystalline "parking lot" inclusions within the mitochondria located immediately underneath the sarcolemma that correlate highly with mitochondrial dysfunction *(arrows*; inset with higher magnification) and increased lipid deposition *(arrowheads)*. (*A,* Courtesy Michael Lawlor, MD, PhD, Medical College of Wisconsin, Milwaukee, WI; *C, D,* and *F* courtesy Karra Jones, MD, PhD, UC San Diego, San Diego, CA; *B, E,* courtesy Chamindra Konersman, MD, Medical College of Wisconsin, Milwaukee, WI.)

TABLE 29.12 Metabolic Diseases That Affect Muscle

Name(s)	Enzyme Deficiency	Clinical Features	Diagnostic Testing
Glycogen storage disease type II (Pompe disease)	α-1,4-Glucosidase (GAA enzyme)	• Infantile-onset Pompe—poor feeding, motor delay and hypotonia with weakness, respiratory difficulties, cardiac issues (short P-R interval with wide QRS complex, cardiomegaly, LV outflow obstruction, cardiomyopathy) • Late-onset Pompe—limb-girdle pattern of weakness, respiratory insufficiency without clinical heart disease • GAA enzyme replacement therapy available	• Measure α-glucosidase (GAA) enzyme activity on dried blood spot to screen • Confirm via *GAA* gene sequencing demonstrating biallelic mutations for definitive diagnosis • Baseline elevated CK (~10× normal) in infantile-onset form; baseline CK may be normal in adult-onset form • Muscle biopsy may show vacuoles (lysosomes) and glycogen accumulation with positively staining PAS; 20–30% of patients with adult-onset form may not show specific changes on biopsy
Glycogen storage disease type IIIa (Debrancher deficiency, Cori disease, Forbes disease)	Amylo-1,6-glucosidase	• Ketotic hypoglycemia, hepatomegaly, hyperlipidemia, elevated liver enzymes, cardiomyopathy in childhood, limb-girdle pattern of weakness in 20s–30s	• Baseline elevated CK (2–20× normal) • Triglycerides, cholesterol, and liver enzymes are elevated • *AGL* gene sequencing demonstrating biallelic mutations for definitive diagnosis
Glycogen storage disease type IV (Brancher deficiency, Andersen disease)	Glycogen branching enzyme (GBE)	• Fatal perinatal neuromuscular subtype—fetal akinesia, polyhydramnios, fetal hydrops • Congenital neuromuscular subtype—hypotonic newborn, respiratory distress, dilated cardiomyopathy, death in infancy • Childhood neuromuscular subtype—chronic progressive myopathy, dilated cardiomyopathy	• Demonstrate deficiency of GBE in the liver, muscle, or skin fibroblasts • *GBE1* gene sequencing demonstrating biallelic mutations for definitive diagnosis
Glycogen storage disease type V (McArdle disease)	Myophosphorylase	• Exercise-induced muscle cramps and pain, especially early in exercise, that improve with rest or lower intensity ("2nd-wind phenomenon") • Recurrent myoglobinuria +/– rhabdomyolysis	• Baseline elevated CK (>5× normal) • *PYGM* gene sequencing demonstrating biallelic mutations for definitive diagnosis • Quantitative or qualitative (stain) on muscle biopsy shows virtual absence of enzyme activity • Subsarcolemmal glycogen accumulation on muscle biopsy on LM (either PAS-positive or vacuoles on H&E) and EM
Glycogen storage disease type VII (Tarui disease)	Phosphofructokinase	• Classical form—muscle aching, cramping, exercise intolerance, myoglobinuria, nausea/vomiting after intense exercise, starting in childhood; hemolytic anemia • Late-onset form—cramps, myalgia, mild proximal weakness in adulthood • Infantile form—hypotonia, arthrogryposis, intellectual disability, fatal in infancy	• Baseline elevated CK • *PFK* gene sequencing demonstrating biallelic mutations for definitive diagnosis
Glycogen storage disease VIII (phosphorylase kinase [PhK] deficiency)	Phosphorylase b kinase Phosphorylase a1 kinase	• Exercise intolerance, cramps, myoglobinuria, progressive muscle weakness in childhood to adulthood • Hepatomegaly, growth retardation, fasting ketosis and hypoglycemia • Same as above but X-linked and very rare	• Baseline elevated CK • PhK enzyme activity reduced in muscle • *PHKA1* gene sequencing or/and *PHKB* gene sequencing demonstrating biallelic mutations for definitive diagnosis
Glycogen storage disease IX (phosphoglycerate kinase deficiency)	Phosphoglycerate kinase	• Myopathic form—muscle weakness, pain, cramping, especially with exercise with myoglobinuria +/– rhabdomyolysis	• Baseline mildly elevated CK • *PGK1* gene sequencing demonstrating biallelic mutations for definitive diagnosis
Glycogen storage disease X (Phosphoglycerate mutase deficiency)	Phosphoglycerate mutase	• Strenuous exercise intolerance, cramps, myoglobinuria	• Baseline mildly elevated CK • *PGAM2* gene sequencing demonstrating biallelic mutations for definitive diagnosis
Glycogen storage disease XI (lactate dehydrogenase deficiency)	Lactate dehydrogenase	• Exercise intolerance, cramping, recurrent myoglobinuria	• Normal CK between attacks • *LDHA* gene sequencing demonstrating biallelic mutations for definitive diagnosis

Continued

TABLE 29.12 Metabolic Diseases That Affect Muscle—cont'd

Name(s)	Enzyme Deficiency	Clinical Features	Diagnostic Testing
Systemic primary carnitine deficiency	Solute carrier family 22 (sodium-dependent carnitine transporter)	• Childhood myopathic form—hypotonia, dilated cardiomyopathy that could result in death, proximal muscle weakness in early childhood (2–4 yr) • Adult form—fatigability	• Baseline CK elevated • Reduced plasma carnitine levels • Increased lipid deposition on muscle biopsy • *SLC22A5* gene sequencing demonstrating biallelic mutations for definitive diagnosis
Carnitine palmitoyltransferase II deficiency	Carnitine palmitoyltransferase II (CPT II)	• Myopathic form—recurrent myalgia and myoglobinuria after prolonged exercise, cold, or fasting; weakness during attacks; onset from childhood to adulthood • Severe infantile form—liver failure, cardiomyopathy, seizures, hypoketotic hypoglycemia, myopathy before 1 yr of age (rare)	• Normal CK between attacks • CPT II gene sequencing demonstrating biallelic mutations for definitive diagnosis • Muscle biopsy can be normal

CK, creatine kinase; EM, electron microscopy; H&E, hematoxylin and eosin; LM, light microscopy; LV, left ventricular; PAS, periodic acid–Schiff.

FIGURE 29.9 Hyperlaxity at the distal interphalangeal joints in a 9-year-old girl with a congenital myopathy.

commonly cause hypotonia in infants and children. Some progressive neurologic disorders affect both the brain and peripheral nerves (metachromatic, Krabbe disease, adrenoleukodystrophies, and some mitochondrial disorders). Other progressive disorders may affect both brain and muscle (MEB, neonatal myotonic dystrophy, and some mitochondrial disorders).

Sometimes disturbance of function at one site conveys a predilection for injury to another site in the nervous system. Children with congenital muscle weakness (congenital myopathy) are likely to have had severe respiratory impairment at birth that resulted in secondary anoxic injury to the brain. Because hypotonia is nonspecific with regard to localizing the site of nervous system dysfunction, the evaluation of the child with hypotonia must begin with a search for other clues that might identify the location of the abnormality.

Is the Problem a Systemic Disorder?

Systemic disorders are a common cause of generalized hypotonia in infants and even in toddlers and children (see Table 29.1). Hypotonia is commonly seen in association with sepsis and other infections, heart failure, failure to thrive, hypercalcemia, renal failure, hypothyroidism, acidosis, hypoxia, hyperammonemia, hypoglycemia, rickets, scurvy, amino and organic acid disorders, severe malnutrition, and other chronic disorders. This observation warrants a careful search for a systemic or metabolic abnormality in children with hypotonia, particularly (but not exclusively) when the onset of hypotonia is acute (Fig. 29.11). Most of these disorders cause hypotonia by causing a disturbance of cerebral cortex function.

Frequently overlooked causes of hypotonia are those that are not traditionally considered neurologic disorders. **Connective tissue disorders** often produce a clinical picture similar to those of neurologic causes of hypotonia in infancy and early childhood, with associated delay of developmental milestones with joint hyperextensibility disproportionate to the extent of weakness and in the absence of other neurologic abnormalities or microcephaly (velocardiofacial syndrome, achondroplasia, Marfan syndrome, Ehlers–Danlos syndrome). In several congenital disorders, hypotonia is a regular feature as a result of a combination of abnormalities of neurologic, muscle, and connective tissue function, including Sotos syndrome, Prader-Willi syndrome, Angelman syndrome, Noonan syndrome, Rett syndrome, and Smith–Lemli–Opitz syndrome.

Diagnostic Considerations

Any child with hypotonia and weakness should be evaluated for a systemic disorder. Laboratory evaluation, such as electrolyte measurements, renal function tests, thyroid function tests, and acid-base balance assessment, should be considered. Laboratory evaluation should also be considered for uncommon metabolic disorders in children with chronic hypotonia, especially those with other neurologic findings and those with recurrent bouts of lethargy, episodic severe hypotonia, vomiting, or acidosis. Appropriate metabolic screening tests include plasma and urine amino acid quantification, urine organic acid quantification, and measurements of blood ammonia, blood lactate, and pyruvate.

Karyotyping and a chromosomal microarray should be done for any hypotonic child who additionally demonstrates microcephaly,

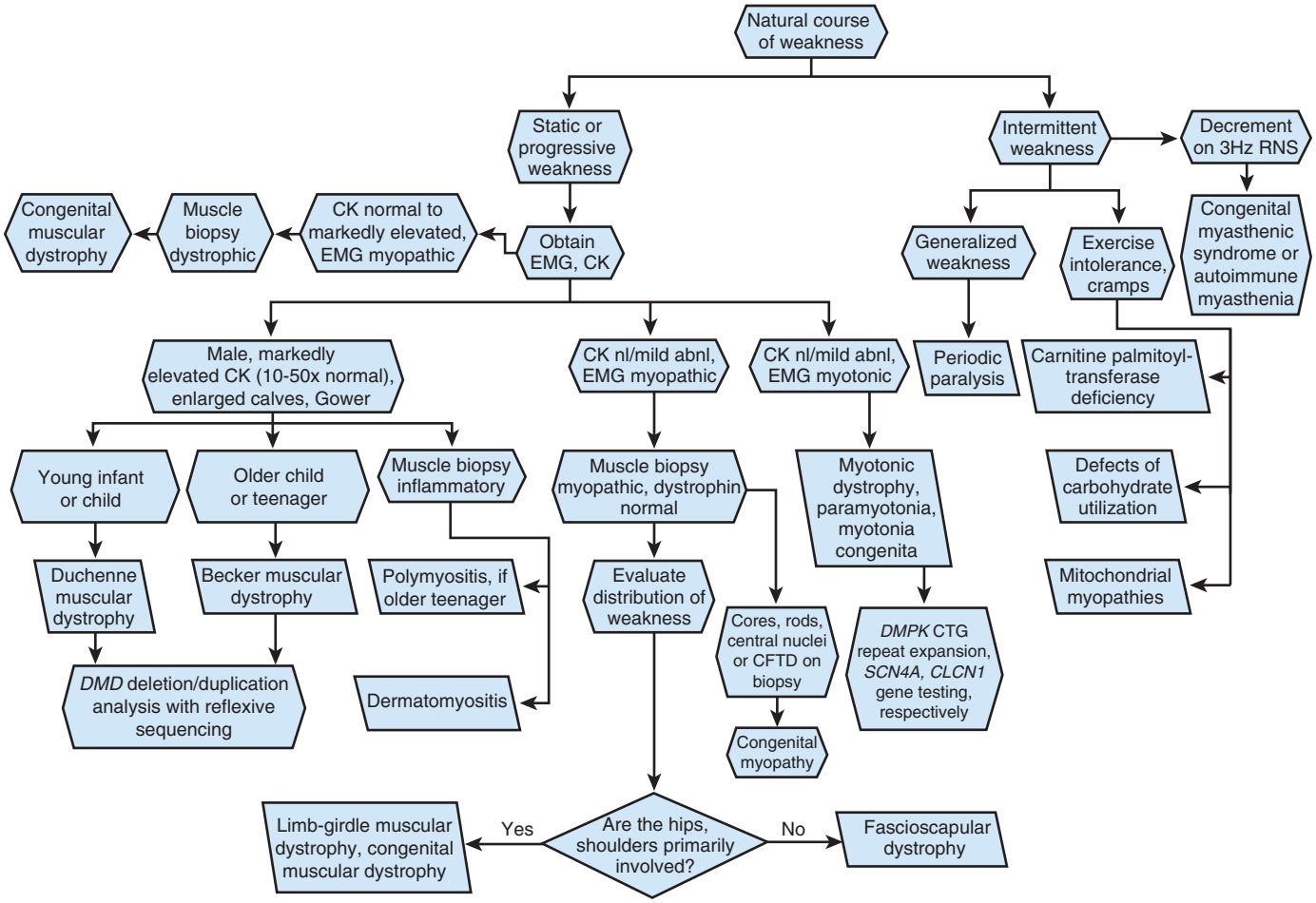

FIGURE 29.10 Diagnostic approach to the child with muscle disease. abnl, abnormal; CFTD, congenital fiber type disproportion; CK, creatine kinase; CTG, cytosine-thymine-guanine; DMD, Duchenne muscular dystrophy; EMG, electromyography; nl, normal; RNS, repetitive nerve stimulation.

growth retardation, congenital malformations, dysmorphism, global developmental delay, or features of specific disorders (Down or Prader–Willi syndromes).

If unusual neurologic or dysmorphic features are present, specific disorders, such as Rett syndrome, Angelman syndrome, Prader–Willi syndrome, Noonan syndrome, Sotos syndrome, and fragile X syndrome, must be considered.

Common Disorders

Down syndrome. The child with Down syndrome generally has recognizable features, including microcephaly, up-slanted palpebral fissures, epicanthal folds, flat nasal bridge, protuberant tongue, excess posterior nuchal skin, and simian palmar creases (see Chapter 25). Hypotonia and associated weakness are almost constant findings. As the child grows, the muscle strength generally improves, but the hypotonia persists.

The diagnosis is established by karyotype analysis showing trisomy 21.

Prader–Willi syndrome. Prader–Willi syndrome manifests in early infancy with marked hypotonia and virtually no other identifiable symptoms. As the child grows, the phenotypic features become more apparent, including microbrachycephaly, almond-shaped palpebrae, short stature, and small hands and feet. At 3-6 years of age, the child has a disorder of appetite that results in ravenous food-seeking behaviors, impaired satiety, and eventual marked obesity. Weakness associated with the disorder is most prominent in the neonate and older infant and gradually lessens, whereas the hypotonia persists.

DNA methylation analysis (detects >99% of cases) is the only technique that accounts for paternal deletion, maternal uniparental disomy, and imprinting defect. Seventy to 75% of affected children have deletion of chromosome 15q11-q13 of paternal origin, and 20-25% have maternal disomy. Because the clinical findings are nonspecific during the early months, such testing should be performed in any neonate or infant with hypotonia of unknown cause.

Uncommon Disorders

Metabolic disorders. Metabolic disorders that are associated with hypotonia include the following (see Tables 29.1, 29.11, and 29.12):

- Amino acid and organic acid disorders
- Lowe syndrome
- Peroxisomal disorders (infantile Refsum syndrome, infantile adrenoleukodystrophy, Zellweger syndrome)
- Acyl coenzyme A dehydrogenase deficiencies
- Storage disorders (mannosidosis, Krabbe disease, sialuria, mucolipidosis type IV, Tay–Sachs disease)

Neurologic disorders. Neurologic disorders associated with hypotonia are often recognizable by unusual neurologic features:

- Angelman syndrome: awkward gait, inappropriate laughter, and seizures. DNA methylation analysis reveals that ~80% have abnormal methylation in the maternally inherited 15q11.2-q13 locus, the same chromosome that is affected in Prader–Willi syndrome.

(See *Nelson Textbook of Pediatrics*, p. 610.)

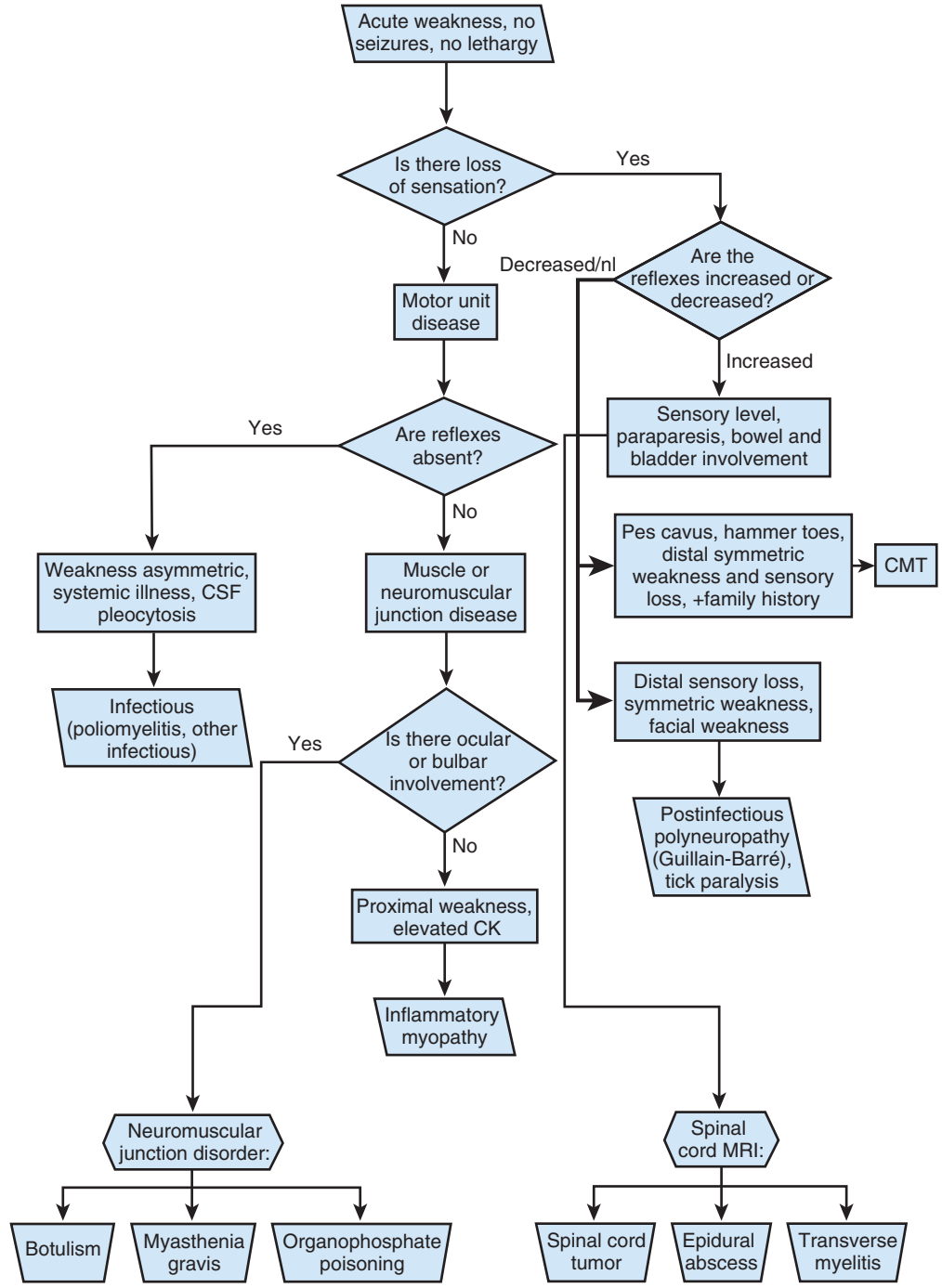

FIGURE 29.11 Diagnostic approach to the child with acute weakness. CSF, cerebrospinal fluid; CK, creatine kinase; MRI, magnetic resonance imaging; nl, normal; CMT, Charcot–Marie–Tooth disease.

- Rett syndrome: autism, loss of hand use, characteristic wringing hand movements

Congenital malformation syndromes. Congenital malformation syndromes are recognizable by their characteristic features:

- Sotos syndrome: macrocephaly, macrosomia, down-slanted palpebrae, mild ventriculomegaly
- Noonan syndrome: short stature, down-slanted palpebrae, ear abnormalities, congenital heart disease, wide-spaced nipples and shield chest, pectus deformities
- Lowe syndrome: cataracts, aminoaciduria, hypotonia

Connective tissue disorders. Connective tissue disorders associated with hypotonia, and particularly with joint hyperextensibility, can also generally be recognized by their associated symptoms:

- Stickler syndrome: micrognathia, Pierre Robin cleft palate
- Velocardiofacial syndrome: congenital heart disease, micrognathia, hypocalcemia, T cell disorders, cleft palate
- Achondroplasia: disproportionate short stature, risk of brainstem compression
- Ehlers–Danlos syndrome: skin bruising and scarring, skin hyperelasticity, smooth skin, joint hypermobility

- Marfan syndrome: tall stature, long, thin arms and fingers, ectopic lens, blue sclera, aortic dissection, mitral valve prolapse
- Osteogenesis imperfecta: fractures

Is the Problem in the Cerebrum or Cerebellum?

Several clues suggest that hypotonia is caused by an abnormality of cerebral function. The presence of associated symptoms attributable to dysfunction of the cerebral cortex is the most useful:

- Acute impairment of consciousness
- Acute or chronic impairment of cognitive abilities (mental status examination or poor school grades, respectively)
- Seizures

Delayed language and social development are typical of chronic problems. The presence of microcephaly or macrocephaly is also an important clue. The presence of brisk reflexes, clonus, an asymmetric tonic neck response, and the Babinski sign suggests possible cerebral cortical dysfunction. The presence of dysmorphism or of congenital malformations suggests the possibility of a cerebral malformation. Congenital ocular malformations (e.g., microphthalmia or optic hypoplasia) are frequently associated with congenital brain malformation.

The presence of hypertonia mixed with signs of hypotonia strongly suggests a cerebral origin. This may seem paradoxical, but it is often overlooked that many children with cerebral causes of hypotonia have signs of hypertonia as well. This may occur as an evolutionary phenomenon in the development of spasticity; cerebral palsy is often characterized by hypotonia in infancy with later development of spasticity. In some children with cerebral dysfunction, the coexistence of hypotonia and hypertonia is persistent. Thus, an infant with hypotonia of the neck and trunk musculature who also exhibits scissoring of the lower extremities or persistent fisting of the hands (typical signs of hypertonia) can be presumed to have cerebral dysfunction.

Signs of cerebellar dysfunction (ataxia, nystagmus, titubation, dysmetria, and impairment of coordination) are often useful diagnostic clues. The cerebellum helps maintain normal muscle tone, and diseases of the cerebellum typically are associated with some degree of hypotonia.

Is the Problem in the Spinal Cord?

Classically, spinal cord dysfunction produces spastic weakness of all 4 extremities or paraparesis of the lower extremities (Tables 29.13 to 29.15). However, particularly after acute injury to the spinal cord and in some chronic disorders of the spinal cord, hypotonia may be the prominent motor sign. The typical associated findings of hyperreflexia, clonus, Babinski signs, and sensory loss (with a sensory level) are important clues, as is the disparity between the weakness and sensory impairment of the extremities in contrast to the normal strength and function of the head and neck.

Spinal cord injury resulting from birth trauma is frequently overlooked as a cause of hypotonia in the newborn. A history of a lengthy or difficult (breech or vertex) delivery should suggest spinal cord injury, and care should be taken not to falsely attribute motor dysfunction in these infants to anoxic brain injury. The bones of the cervical spine are *normal*, but MRI demonstrates the cord lesion. This diagnosis should never be missed because neurosurgical intervention is often required. To make matters more confusing, many neonates with spinal cord injuries also have anoxic encephalopathy because of the traumatic nature of the delivery.

Finally, the extent to which the hypotonia of neonatal hypoxic-ischemic injury is caused by hypoxic injury to the spinal cord has not yet been fully elucidated. Any child with suspected spinal cord injury should undergo MRI.

Common Disorders

Meningomyelocele. Meningomyelocele is a congenital malformation of the spine, spinal cord, and overlying meninges, that affects 1 in 500 to 1 in 2000 liveborn infants, with some degree of geographic variation of incidence. The spinal defect is obvious at birth, except in milder abnormalities that are covered by skin. The degree to which the lower extremities are hypotonic and flaccid depends on the location of the spinal defect. The presence of an Arnold-Chiari malformation and associated hydrocephalus must be sought in every affected patient.

TABLE 29.13 Spinal Cord Syndromes

Site	Mechanism	Manifestation
Complete—upper cord (above T10)	Space-occupying lesion Trauma	Flaccid symmetric weakness, paralysis, loss of sensation below lesion, areflexia (in spinal shock), reflexes return and are ↑ after recovery from spinal shock, distended bladder, positive Babinski sign, positive Beevor sign*
Conus medullaris (T10–L2)	Space-occupying lesion Trauma	Symmetric weakness, paralysis, ↑ knee deep tendon reflexes, ↑ ankle deep tendon reflexes, positive Babinski sign, spastic bladder and sphincter disturbance
Cauda equina (below L2)	Space-occupying lesion Tethered cord (?) Trauma	Asymmetric weakness, loss of lower extremity deep tendon reflexes, sensory saddle perineum sensory loss, no Babinski sign, distended atonic bladder with urinary retention and overflow incontinence and decreased rectal tone
Anterior cord	Flexion-rotation force from anterior dislocation or compression fracture of vertebral body (+/– ischemia of anterior spinal artery)	Weakness and reduced pain and temperature sensation
Central cord	Hyperextension injury; tumor, hemorrhage, syringomyelia	Flaccid weakness of arms (lower motor neuron lesion) with strong and spastic lower extremities (upper motor neuron lesion) Sacral sensation with bowel and bladder partially affected
Posterior cord	Hyperextension (fractures of posterior vertebra)	Significant ataxia (loss of proprioception); strength and pain and temperature sensations may be spared or less affected
Brown-Séquard syndrome	Laceration (stabs), lateral space-occupying lesions: hemisection	Strength, position, and vibration sensations are affected on the side of the lesion; pain and temperature sensation are affected on the contralateral side

*Beevor sign, superior displacement of umbilicus in paraplegia during attempts to lift shoulders off an examining table.

TABLE 29.14 Spinal Paraplegia

Congenital Malformations
1. Arachnoid cyst
2. Arteriovenous malformations
3. Atlantoaxial dislocation
4. Caudal regression syndrome
5. Dysraphic states
   a. Chiari malformations
   b. Myelomeningocele
   c. Tethered spinal cord
6. Syringomyelia

Familial Spastic Paraplegia
1. Autosomal dominant
2. Autosomal recessive
3. X-linked recessive

Infections—Inflammatory
1. Diskitis
2. Epidural abscess
4. Herpes zoster myelitis
5. Polyradiculoneuropathy
6. Tuberculous osteomyelitis

Neonatal Cord Infarction

Transverse Myelitis
1. Devic disease
2. Encephalomyelitis
3. Idiopathic

Trauma
1. Concussion
2. Epidural hematoma
3. Fracture-dislocation
4. Neonatal cord trauma

Tumors
1. Astrocytoma
2. Ependymoma
3. Neuroblastoma
4. Other

Modified from Piña-Garza. *Fenichel's Clinical Pediatric Neurology: A Signs and Symptoms Approach*. 7th ed. Philadelphia: Saunders; 2013.

Patients with meningomyelocele have elevated amniotic fluid α-fetoprotein, and antenatal diagnosis is possible.

Transverse myelitis. Transverse myelitis is a common cause of acute hypotonia and weakness. As with any spinal cord lesion, the localization is suggested by an identifiable motor-sensory level and by impairment of bowel and bladder function. Reflexes are characteristically depressed at the onset of the disease and then become exaggerated with clonus and Babinski signs. The diagnosis is made with MRI and lumbar puncture; signal intensity of the cord segment involved is abnormal on MRI, and mild pleocytosis and elevated cerebrospinal fluid protein levels are present.

Uncommon Disorders

An **epidural spinal abscess** may manifest in a manner similar to transverse myelitis, except with more back pain and local tenderness. **Spinal cord tumor** (primary or metastatic) usually manifests with subacute onset of spastic weakness of the extremities but occasionally manifests as hypotonia (see Table 29.13). Rapid diagnosis with MRI and medical or neurosurgical intervention is essential.

TABLE 29.15 Motor Involvement in Spinal Cord Lesions

Affected Cord Segment	Motor Involvement
C1–C4	Paralysis of neck, diaphragm, intercostal muscles, and all 4 extremities
C5	Spastic paralysis of trunk, arms, and legs; partial shoulder control
C6–C7	Spastic paralysis of trunk and legs; upper arm control; partial lower arm control
C8	Spastic paralysis of trunk and legs; hand weakness only
T1–T10	Spastic paralysis of trunk and legs
T11–T12	Spastic paralysis of legs
L1–S1	Flaccid paralysis of legs
S2–S5	Flaccid paralysis of lower legs; bowel, bladder, and sexual function affected

From Swartz MH. *Textbook of Physical Diagnosis: History and Examination*. 2nd ed. Philadelphia: WB Saunders; 1994:496; modified from Fenichel GM. *Clinical Pediatric Neurology: A Signs and Symptoms Approach*. 2nd ed. Philadelphia: WB Saunders; 1993:262.

Is the Problem in the Motor Unit?

The functional unit of the anterior horn cell, peripheral nerve, NMJ, and muscle fiber makes up the motor unit. Disorders that affect the motor unit produce a common clinical picture characterized by preservation of cognitive function and alertness, absence of seizures, characteristically diminished or absent muscle stretch reflexes, and hypotonia. **Muscle atrophy** is frequently associated with motor unit disorders, but it can also occur in cerebral causes of hypotonia.

It is not always easy to determine which component of the motor unit is abnormal (anterior horn cell, peripheral nerve, NMJ, or muscle), but the following guidelines are useful.

Anterior horn cell disease is suggested by hypotonia, weakness, absence of reflexes, and fasciculations. The presence of **fasciculations** of muscle usually cannot be appreciated in infants because of the presence of subcutaneous fat. Fasciculations might be seen on the tongue, but they must be distinguished from normal quivering movements. Muscle enzymes are usually normal but can sometimes be mildly to moderately elevated, and nerve conduction studies are usually normal (Table 29.16). The electromyogram (EMG) may demonstrate fibrillations and large motor unit potentials that are reduced in number.

Diagnostic Considerations

The patient is examined for distribution of weakness, reflexes, and the presence of tongue fasciculations. Creatine kinase (CK) levels and an EMG are obtained, and a lumbar puncture is performed when an acute infectious polyradiculoneuritis is suspected.

Common Disorders

Anterior horn cell disease. Spinal muscular atrophy (SMA) is characterized by degeneration of anterior horn cells in the spinal cord (Table 29.17). SMA type I (Werdnig–Hoffman disease) is the prototype for the spinal muscular atrophies and is inherited as an autosomal recessive trait. Manifestations begin early in life and even occasionally

TABLE 29.16 Typical Electrophysiologic Features of Nerve and Muscle Diseases

	Motor Nerve Conductions	Sensory Nerve Conductions	F Response	H Reflex	Needle Electromyography
Myopathy (dystrophic, inflammatory)	Normal	Normal	Normal	Normal	• Spontaneous activity: fibrillation potentials and positive sharp waves (muscle membrane irritability) • Volitional activity: small-amplitude myopathic units
Myopathic (mitochondrial, congenital myopathy)	Normal	Normal	Normal	Normal	• Spontaneous activity: usually none • Volitional activity: small-amplitude, short-duration units with rapid recruitment
Axonal neuropathy	• ↓ Amplitude • Normal or mildly slow conduction velocities	↓ Amplitude	Normal	Normal	• Spontaneous activity: fibrillation potentials and positive sharp waves (muscle membrane irritability) especially in distal muscles • Volitional activity: large-amplitude, long-duration units with reduced recruitment
Demyelinating neuropathy	• Markedly slow conduction velocities • Prolonged latencies • ↓ or normal amplitude	• Prolonged latencies • ↓ Amplitude or no response	Delayed or absent	Delayed or absent	• Spontaneous activity: usually none • Volitional activity: large-amplitude, long-duration units with reduced recruitment
Radiculopathy	Normal or ↓ amplitude	Normal	Delayed or absent	Delayed or absent if S1 is involved	• Spontaneous activity: fibrillation potentials and positive sharp waves (muscle membrane irritability); fasciculations • Volitional activity: large-amplitude, long-duration units with reduced recruitment
Motor neuron disease	Normal or ↓ amplitude	Normal	Normal	Normal	• Spontaneous activity: fibrillation potentials and positive sharp waves (muscle membrane irritability); fasciculations • Volitional activity: large-amplitude, long-duration units with reduced recruitment

in the prenatal period (e.g., decreased fetal movements, congenital contractures, polyhydramnios caused by poor swallowing, poor respiratory effort at birth). Neonates and young infants experience progressive weakness and hypotonia, which result in poor head and body control and a flaccid, motionless, extended posture with alert facies (see Fig. 29.4). Fasciculations may be noted in the tongue, over muscles with little subcutaneous fat, and as a fine tremor of the outstretched fingers. Bilateral paralysis of the diaphragm may be present before loss of deep tendon reflexes or detection of muscle weakness.

Genetic analysis shows that 95-98% of individuals have a homozygous deletion of survival motor neuron 1 (*SMN1*) gene, but 2-5% are compound heterozygotes for a deletion coupled with a point mutation in *SMN1*. If *SMN1* mutations are confirmed, then a reflexive *SMN2* copy number analysis should be performed to help prognosticate since more copies of *SMN2* gene confer a milder phenotype (see Table 29.17). The *SMN2* gene differs from *SMN1* by 1 nucleotide base pair in exon 7 and 90% of the time expresses a nonviable gene product but 10% of the time accidentally expresses a functional *SMN1* protein. If genetic test results are positive, no further evaluation is necessary. If mutation tests are negative, a more traditional evaluation—including serum CK levels, EMG, muscle and brain MRI, and muscle biopsy—is pursued.

Neuropathies. Neuropathies are characterized by hypotonia, weakness, and diminished or absent reflexes (Tables 29.18 and 29.19). Neuropathies may be primarily motor or sensory, and the child's symptoms may be either acute or chronic weakness or discomfort caused by paresthesias and dysesthesias. The pattern of weakness in most neuropathies is in a **distal-to-proximal gradient** with foot deformity and atrophy resulting in pes cavus and hammer toe deformities. **Pes planus** may be a common feature in a neuropathy during infancy or early childhood due to low tone with high-arched feet developing as the patient ages. In chronic sensory neuropathies, the child may sustain injuries (e.g., burns or even fractures) that are unnoticed. Autonomic symptoms associated with some neuropathies include orthostatic hypotension, gastrointestinal dysmotility, and abnormalities of sweating. In general, the reflexes in neuropathies are diminished disproportionately to the extent of muscle weakness; that is, the reflexes

TABLE 29.17 Spinal Muscular Atrophy (SMA): Clinical and Genetic Characteristics

Phenotype	Age of Onset	Natural Age of Death	Highest Motor Milestones	Other Findings	*SMN2* Copy Number
SMA 0	Prenatal	2–6 mo	None achieved	• Arthrogryposis • Facial diplegia • Decreased fetal movements • Polyhydramnios • Breech presentation • Respiratory failure in early infancy	
SMA I (Werdnig–Hoffman)	<6 mo	Usually ≤2 yr, but may survive longer	Sitting with support	• Prominent tongue fasciculations • Mild joint contractures • Facial weakness • Poor suck and swallow • Small bell-shaped chest • Paradoxical breathing	1-2
SMA II	6–18 mo	70% alive at age 25 yr	Independent sitting when placed	• Legs more affected than arms, with failure to sit alone by 9–12 mo and stand by 1 yr • Postural hand/finger tremor • Lose ability to sit independently by mid-teens	2; sometimes 3
SMA III (Kugelberg–Welander)	>12 mo	Normal	Independent ambulation	• Legs more affected than arms, manifesting as difficulty walking • Distal then proximal contractures	≥3
SMA IV	2nd or 3rd decade	Normal	Walking during adulthood	• May lose ambulation with time	3-4

may be markedly reduced or absent, whereas the muscle strength is only mildly diminished. Nerve conduction studies (NCS) and EMGs demonstrate slowing of nerve conduction velocities and features that suggest either primary axonal involvement (fibrillations, normal or mildly slow nerve conduction velocity) or demyelination (marked slowing of nerve conduction velocity) (see Table 29.16).

Guillain–Barré syndrome (GBS) is an acute demyelinating polyneuropathy that frequently follows an upper respiratory tract infection or an illness with diarrhea, especially those caused by *Campylobacter*. The disorder is characterized by ascending motor weakness and areflexia. The weakness is usually symmetric, ascends and progresses over various periods (usually 1–2 weeks), and may cause serious respiratory compromise by producing weakness of the respiratory muscles. Therefore, all patients must be tested for respiratory function (negative inspiratory forces and vital capacity). Children complain of difficulty walking, rising from the floor, climbing stairs, and become irritable and refuse to bear weight. More commonly than adults, children present with acute-onset ataxia with multiple falls and poor balance stemming from sensory disturbance with milder weakness. Children often have more paresthesias and discomfort than their adult counterparts with neck, back, leg, and buttock pain in at least 50% of cases, presumably mimicking a radiculopathy due to nerve root inflammation. The triad of **ophthalmoplegia, areflexia, and ataxia** without overt weakness characterizes **Miller–Fisher syndrome (MFS)**, a variant of GBS. Autonomic nervous system involvement may produce hypotension or hypertension and bradyarrhythmias or tachyarrhythmias. Therefore, due to the risk of respiratory and autonomic dysfunction, all patients suspected of having GBS should be monitored in the intensive care unit or other telemetry setting with high-frequency nursing care. In addition to an abnormal nerve conduction velocity, the cerebrospinal fluid protein level is usually elevated out of proportion to the white cell count (**cytoalbuminologic dissociation**) after the 1st week of illness, indicative of an inflammatory process occurring within the CSF space. Postgadolinium enhancement of edematous nerve roots and peripheral nerves as seen on MRI in the cervical and lumbosacral regions can be seen in ~95% of children with GBS and is suggestive, although not specific for, the disease.

Dejerine-Sottas syndrome (DSS) is an umbrella term for severe, infantile-onset Charcot–Marie–Tooth (CMT) disease regardless of inheritance pattern manifesting with hypotonia. Patients exhibit moderate-to-severe motor delays, foot deformities with pes cavus and hammer toes, claw-hand deformities, respiratory insufficiency, and early-onset scoliosis that may need surgical correction. Nerve biopsy shows axons without evidence of myelination and onion-bulb formation. Nerve dysfunction may be axonal or demyelinating and inheritance may be autosomal recessive or autosomal dominant. Mutations in the following genes are associated with the DSS phenotype: *MPZ*, *EGR2*, *PMP22*, *PRX*, *NEFL*, *MFN2*, and *GDAP1*.

Muscle and neuromuscular junction disorders. NMJ disorders must be differentiated from muscle diseases. Both are characterized by hypotonia and weakness; however, reflexes may be impaired in myopathies but are usually preserved in NMJ disorders. In myopathies, the degree of muscle weakness is usually more pronounced than the extent of loss of reflexes, just the reverse of the case observed in neuropathies. Disorders of the NMJ are identifiable by a history of diurnal fluctuations (worse symptoms later in the day) and acute episodes of worsening. In NMJ disorders and most myopathies, weakness is most prominent in the proximal muscles and the sensory examination is normal. Laboratory testing and studies performed show a normal CK level and normal motor and sensory nerve conduction velocities, but a decrementing response to 3-Hz repetitive nerve stimulation in NMJ disorders (Fig. 29.12). The needle EMG may be normal or appear myopathic if the NMJ disorder is severe, resulting in static weakness.

Myopathies. **Duchenne and Becker muscular dystrophy** (**DMD** and **BMD**) are X-linked recessive disorders caused by mutations in the *DMD* gene encoding dystrophin. DMD is characterized by the absence of dystrophin in muscle, whereas BMD has a partially functional protein product. The genetic difference between the 2 phenotypes is

TABLE 29.18 Mnemonic for Peripheral Neuropathy: CHANCE-IT

***C*ollagen Vascular Diseases**	***H*ereditary**	***A*utoimmune**	***N*utrition**	***C*ancer**	***E*ndocrine**	***I*nfectious**	***T*oxin or *T*rauma**
Polyarteritis nodosa	CMT	GBS	Vitamin deficiencies (B_1, B_6, B_{12}, E)	Lambert–Eaton	Diabetes mellitus	*Campylobacter* (GBS)	Tick toxin
SLE	HSAN	Immunizations			Hypothyroidism	Diphtheria	INH
Vasculitis	Metabolic (porphyria)	Chronic inflammatory demyelinating polyneuropathy			Acromegaly (entrapment)	Lyme (cranial)	DDI
Angiitis	Refsum disease					Leprosy	DDC
Granulomatous (sarcoidosis)	Leukodystrophies (e.g., Krabbe disease, adrenoleuko-dystrophy, metachromatic)					HIV	Organophosphates
Wegener granulomatosis						Herpes-zoster	Lead
Henoch–Schönlein purpura	Amyloid (familial)					Rabies	Mercury
Mononeuritis multiplex	Congenital abetalipoproteinemia						Thallium
	Fabry disease						Arsenic
	Tangier disease						Vincristine
							Uremia
							Nitrofurantoin
							Chloramphenicol
							Acrylamide
							Cyanide
							N-Hexane
							Glue sniffing
							Buckthorn toxin
							Carbon monoxide
							Entrapment
							Obstetric trauma

CMT, Charcot-Marie-Tooth disease; DDC, dideoxycytidine; DDI, dideoxyinosine; GBS, Guillain–Barré syndrome; HIV, human immunodeficiency virus; HSAN, hereditary sensory-autonomic neuropathy–Riley-Day syndrome (dysautonomia); INH, isoniazid; SLE, systemic lupus erythematosus.

TABLE 29.19 Polyneuropathies with Onset in Infancy

AXONAL NEUROPATHIES

Salient Clinical Feature	Clinical Phenotype	Gene	Mode of Inheritance
Pes cavus with foot drop	CMT2E	*NEFL*	AD, AR
Optic atrophy	CMT2A	*MFN2*	AD, AR
	CMT4A	*GDAP1*	AR
	IOSCA	*C10orf2*	AR
	Infantile neuroaxonal dystrophy	*PLA2G6*	AR
Ophthalmoparesis	Mitochondrial disorders	*SCO2*	AR
		C10orf2	
		TK2	
Skeletal abnormalities	CMT2C, SPSMA, congenital dSMA	*TRPV4*	AD
Arthrogryposis	Congenital dSMA	*TRPV4*	AD
	SMARD1	*IGHMBP2*	AR
	X-linked SMA	*UBE1*	X-linked
	Pontocerebellar hypoplasia type 1	*EXOSC3, VRK1, TSEN54, RARS2*	AR
	SMA with congenital fractures	Unknown	Unknown, presumed AR
Congenital fractures	X-linked SMA	*UBE1*	X-linked
	SMA with congenital fractures	Unknown	Unknown, presumed AR
Vocal cord paresis	CMT2A	*MFN2*	AD, AR
	CMT2C, SPSMA, congenital dSMA	*TRPV4*	AD
	CMT4A	*GDAP1*	AR
	BVVL/Fazio–Londe disease	*SLC52A3*	AR
Early infantile respiratory failure	SMA1	*SMN1*	AR
	SMARD1	*IGHMBP2*	AR
	X-linked SMA	*UBE1*	X-linked
	Pontocerebellar hypoplasia type 1	*EXOSC3, VRK1, TSEN54, RARS2*	AR
	SMA with congenital fractures	Unknown	Unknown, presumed AR
	Lethal neonatal AR axonal sensorimotor polyneuropathy	Unknown	AR
	Congenital axonal neuropathy with encephalopathy	Unknown	Unknown, presumed AR
Predominant motor involvement	Congenital dSMA, SPSMA	*TRPV4*	AD
	SMA1	*SMN1*	AR
	X-linked SMA	*UBE1*	X-linked
	Pontocerebellar hypoplasia type 1	*EXOSC3, VRK1, TSEN54, RARS2*	AR
	SMA with congenital fractures	Unknown	Unknown, presumed AR
	Mitochondrial disorders	*SCO2, TK2*	AR
Kinky hair hepatopathy	Giant axonal neuropathy	*GAN*	AR
	Mitochondrial disorders	*DGUOK*	AR
		C10orf2	
	MTP/LCHAD deficiency	*HADHA/HADHB*	AR
Cardiomyopathy	Mitochondrial disorders	*SCO2*	AR
		TK2	AR
		DGUOK	AR
	MTP/LCHAD deficiency	*HADHA/HADHB*	AR
CNS involvement	Pontocerebellar hypoplasia type 1	*EXOSC3, VRK1, TSEN54, RARS2*	AR
	Giant axonal neuropathy	*GAN*	AR
	Infantile neuroaxonal dystrophy	*PLA2G6*	AR
	HMSN/ACC	*KCC3*	AR
	IOSCA	*C10orf2*	AR
	CMTX1	*GJB1*	X-linked
	Mitochondrial disorders	*SCO2*	AR
		TK2	AR
		DGUOK	AR
	Adrenoleukodystrophy	*ABCD1*	X-linked

TABLE 29.19 Polyneuropathies with Onset in Infancy—cont'd

Salient Clinical Feature	Clinical Phenotype	Gene	Mode of Inheritance
AXONAL NEUROPATHIES			
Developmental regression	Adrenoleukodystrophy	*ABCD1*	X-linked
Dysautonomia, chronic skin ulceration	HSAN III (Riley–Day syndrome)	*IKBKAP*	AR
DEMYELINATING NEUROPATHIES			
Acute sensory ataxia, walking difficulties in a previously well child	GBS		
Slowly progressive weakness, ataxia in a previously well child; responsive to steroids	CIDP		
Developmental regression	MLD Krabbe disease	*ARSA* *GALC*	AR AR
Irritable, stiff, crying infant; occasional unexplained fevers	Krabbe disease	*GALC*	AR
Pes cavus with foot drop, marked difficulties walking	CMT1A CMT1B CMT1F CMT4C CMT4E CMT4F CMT4H	*PMP22* point mutations or duplication *MPZ* *NEFL* *SH3TC2* *EGR2* *PRX* *FGD4*	De novo (AD), AR De novo (AD) AD, AR AR AR, AD AR AR
Early respiratory insufficiency	CMT1A CMT1B CMT4C CMT4E	*PMP22* point mutations or duplication *MPZ* *SH3TC2* *EGR2*	De novo (AD), AR De novo (AD) AR AR, AD
Severe scoliosis requiring surgery in infancy	CMT1B CMT4C	*MPZ* *SH3TC2*	De novo (AD) AR
Facial weakness	CMT4B1 CMT4B2 CMT4C	*MTMR2* *SBF2* *SH3TC2*	AR AR AR
Sensorineural hearing loss	CMT1A CMT4C CMT4F	*PMP22* point mutations or duplication *SH3TC2* *PRX*	De novo (AD), AR AR AR
Congenital nystagmus	CMT1B CMT4C	*MPZ* *SH3TC2*	De novo (AD) AR

AD, autosomal dominant; AR, autosomal recessive; BVVL, Brown–Vialetto–Van Laere syndrome; CMT, Charcot–Marie–Tooth disease; CIDP, chronic inflammatory demyelinating polyneuropathy; CNS, central nervous system; dSMA, distal spinal muscular atrophy; GBS, Guillain-Barré syndrome HMSN/ACC, hereditary motor and sensory neuropathy with agenesis of the corpus callosum; HSAN, hereditary sensory and autonomic neuropathy; IOSCA, infantile-onset spinocerebellar ataxia; MLD, metachromatic leukodystrophy; MTP/LCHAD, mitochondrial trifunctional protein/long-chain 3-hydroxyacyl-CoA dehydrogenase; SMA, spinal muscular atrophy; SMARD, spinal muscular atrophy with respiratory distress type 1; SPSMA, scapuloperoneal spinal muscular atrophy.

based on the concept of the "reading frame rule," in which mutations that cause DMD are "out-of-frame" resulting in a premature termination of translation with subsequent degradation, while mutations that cause BMD are "in-frame" due to a partly functional, albeit truncated, protein. The distribution of DMD mutations is described in Table 29.20. Using Fig. 29.13, one can easily determine if a deletion or duplication results in an in-frame or out-of-frame mutation.

Some boys have mild delays in their motor and/or cognitive milestones, but most have normal early milestones and do not come to clinical attention until 2-5 years of age when they are noted to be

TABLE 29.20 Distribution of DMD Mutations

Deletions	65%
Duplications	7%
Single-point mutations	20%
Small insertions/deletions	7%
Splice site or intronic mutations	<1%

DMD, Duchenne muscular dystrophy.

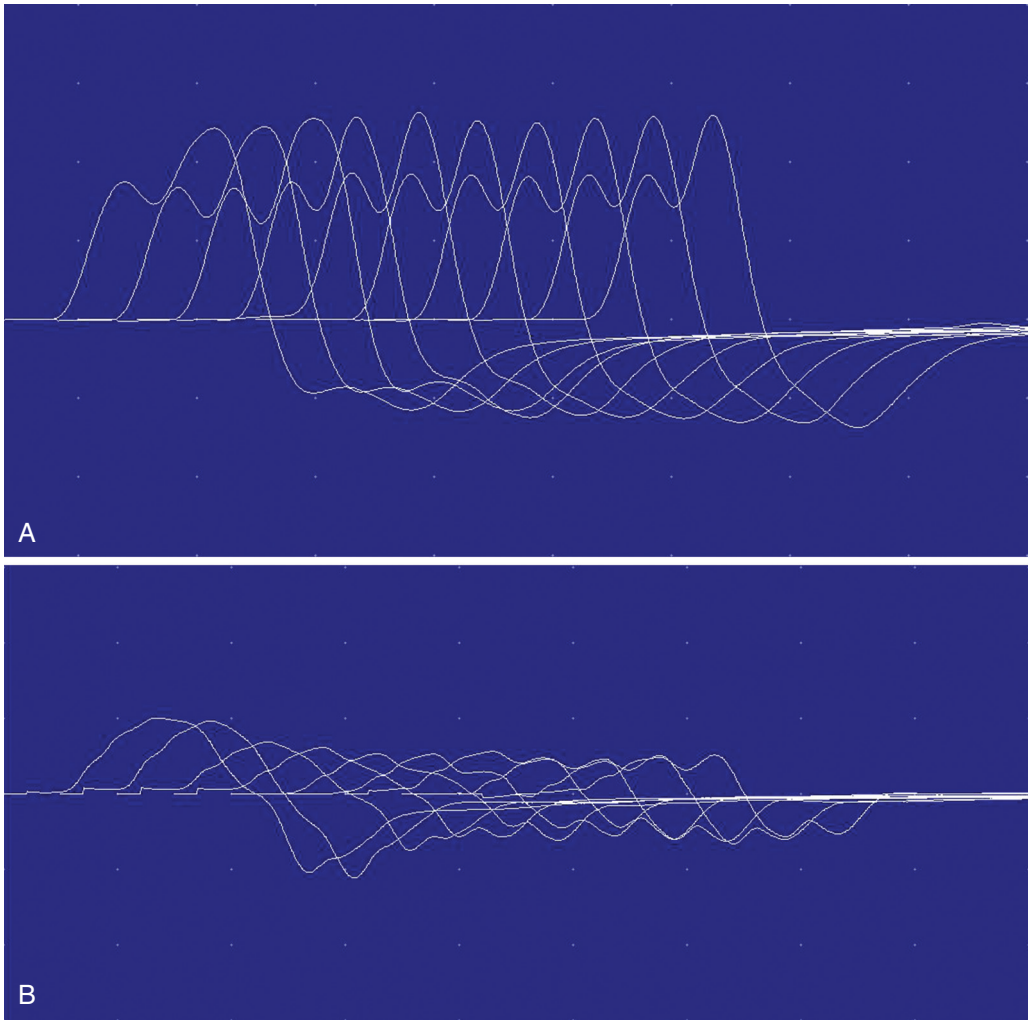

FIGURE 29.12 Repetitive nerve stimulation (RNS) at a rate of 3 Hz in a 15-year-old female with ptosis and generalized weakness diagnosed with seropositive myasthenia. RNS of a clinically strong muscle, the abductor digiti minimi, shows no decremental response *(A);* however, when performed on a clinically weak muscle, the trapezius, a decremental response of 44% between the 1st and 5th responses *(B)* is seen.

slower in walking or running, rising from the floor, or climbing stairs compared to their peers. The classic maneuver employed to rise from the floor is a **Gower sign**, indicative of proximal hip extensor weakness and is typically seen by 3 years of age (Fig. 29.14). The characteristic toe-walk with Trendelenburg gait (waddling) in a hyperlordotic boy with enlarged calves is usually seen by 5-6 years of age. Early in the disease, there is usually **calf pseudohypertrophy** because of a proliferation of fat and collagen and even some muscle hypertrophy giving a herculean appearance in a small subset of patients. However, atrophy of all muscles occurs with age. Language and cognitive abnormalities are seen in many patients.

With time, proximal muscle weakness makes ambulation difficult, and the patient requires a wheelchair. With the standard use of steroids, the age of wheelchair dependence ranges between 9-14 years. Respiratory muscle failure develops by late adolescence. The pulmonary insufficiency may be aggravated by thoracic kyphoscoliosis. Another possible complication is cardiomyopathy. Most affected patients die by 25-35 years of age.

BMD has marked clinical heterogeneity with a variable age of onset ranging from childhood to adulthood. These patients also have calf pseudohypertrophy and eventually exhibit a Gower maneuver with variable degrees of proximal muscle weakness. Other phenotypes in BMD include isolated quadriceps weakness, childhood cramps-myalgia syndrome, exercise-induced myoglobinuria, and asymptomatic elevated CK levels (rare). Childhood-onset weakness typically results in loss of ambulation in the 3rd or 4th decade. Cognition is usually normal but cardiomyopathy occurs frequently in this population and rarely may be the heralding symptom.

The diagnoses of DMD and BMD is suspected from the history (including the family history), physical examination findings, and an elevated serum CK (often 10,000-30,000 IU/L). Genetic testing via *DMD* deletion/duplication with reflexive sequencing analysis confirms the diagnosis. Although muscle biopsy is no longer necessary in DMD, it may still be useful in certain cases of BMD (Fig. 29.15).

Myotonic dystrophy is a common muscle disorder of childhood that is distinct in that it causes primarily a distal distribution of muscle weakness and is associated with myotonia, a phenomenon characterized by persistent muscular contraction with apparent delay in relaxation of muscles. A child with **myotonia** has difficulty releasing a ball after gripping it tightly or letting go of a doorknob. Myotonia usually is present by age 10 years, but significant distal muscle weakness is not usually evident until the end of the 2nd decade. In **congenital myotonic dystrophy**, the newborn infant has severe generalized

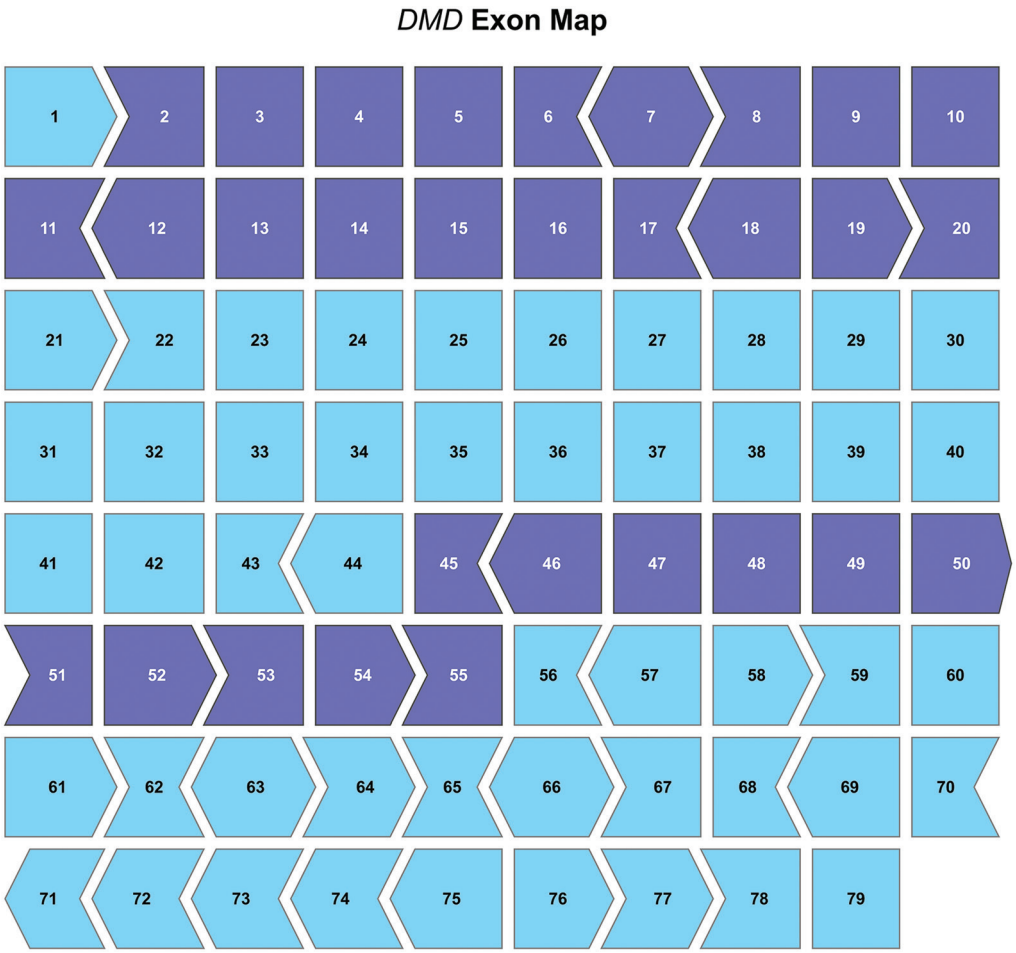

FIGURE 29.13 An exon schematic diagram of the *DMD* gene used to determine the impact of deletions or duplications on the reading frame. The *DMD* gene has 79 exons. Exons colored in purple represent regions of "hot spots" in which a high frequency of mutations occurs across the general population. The primary hot spot is exons 45-55 and the secondary is 2-20. If all 3 base pairs of a codon end within an exon, then a vertical border is used to depict the exon. If either 1 or 2 base pairs of a codon are located in the next exon, then an angled border is drawn. Therefore, a deletion/duplication of a particular exon or exons may result in alteration of the reading frame. For example, deletion of exon 50 results in an out-of-frame mutation because the right-sided "edge" of exon 49 does not align the left-sided "edge" of 51, whereas a deletion of both exons 50 and 51 results in an in-frame mutation because the right "edge" of exon 49 aligns the left "edge" of 52.

hypotonia and weakness, often with swallowing and sucking difficulty, facial diplegia, a down-turned tented mouth, moderate-to-severe intellectual disability, and congenital joint contractures (talipes equinovarus, arthrogryposis) (Fig. 29.16). Usually there is a history of polyhydramnios and reduced fetal movements in utero.

This is a slowly progressive disorder with multisystemic involvement, including the development of cataracts, premature male-pattern baldness, facial muscle atrophy resulting in a "hatchet face" appearance, cervical kyphosis, cardiac arrhythmias, diabetes, pilomatrixomata, increased risk of thyroid cancer, thyroid dysfunction, gastrointestinal dysmotility, and testicular atrophy. EMGs in children reveal the characteristic myotonic discharge ("dive bomber") but an EMG in the neonatal period may not show this characteristic finding. Gene testing demonstrating the cytosine-thymine-guanine (CTG) trinucleotide repeat expansion in the *DMPK* gene of chromosome 19q13.3 establishes the diagnosis.

Congenital myopathies are a genetically and clinically heterogeneous category of myopathies (see Table 29.8). This category of myopathy has characteristic muscle biopsy findings that may guide in narrowing the genetic differential diagnosis. Specific muscle pathologic features are distinguished by the presence of cores, nemaline rods, central nuclei, or congenital fiber type disproportion (CFTD) (Fig. 29.17). **Centrally placed nuclei** are usually large in relation to the myofiber, present in a disproportionate number of fibers, and may be centrally placed along the length of the fiber. **Cores** are areas devoid of oxidative enzyme activity, best seen on oxidative stains such as nicotinamide adenine dinucleotide or ATPase. **Nemaline rods** are red, purple, or blue inclusions best seen on Gomori trichrome stain and vary per fiber, by fiber type, and in their distribution within the myofiber. **CFTD** refers to the relative atrophy of type 1 fibers by 35-40% compared to type 2 fibers in the absence of other structural changes such as rods, cores, and central nucleation.

Neuromuscular junction disorders. Myasthenia gravis is caused by the presence of antiacetylcholine receptor antibodies that produce a neuromuscular blockade at the level of the NMJ.

Transient neonatal myasthenia is caused by transplacental transfer of antiacetylcholine receptor antibodies in infants born to mothers with this disease. These patients usually demonstrate generalized

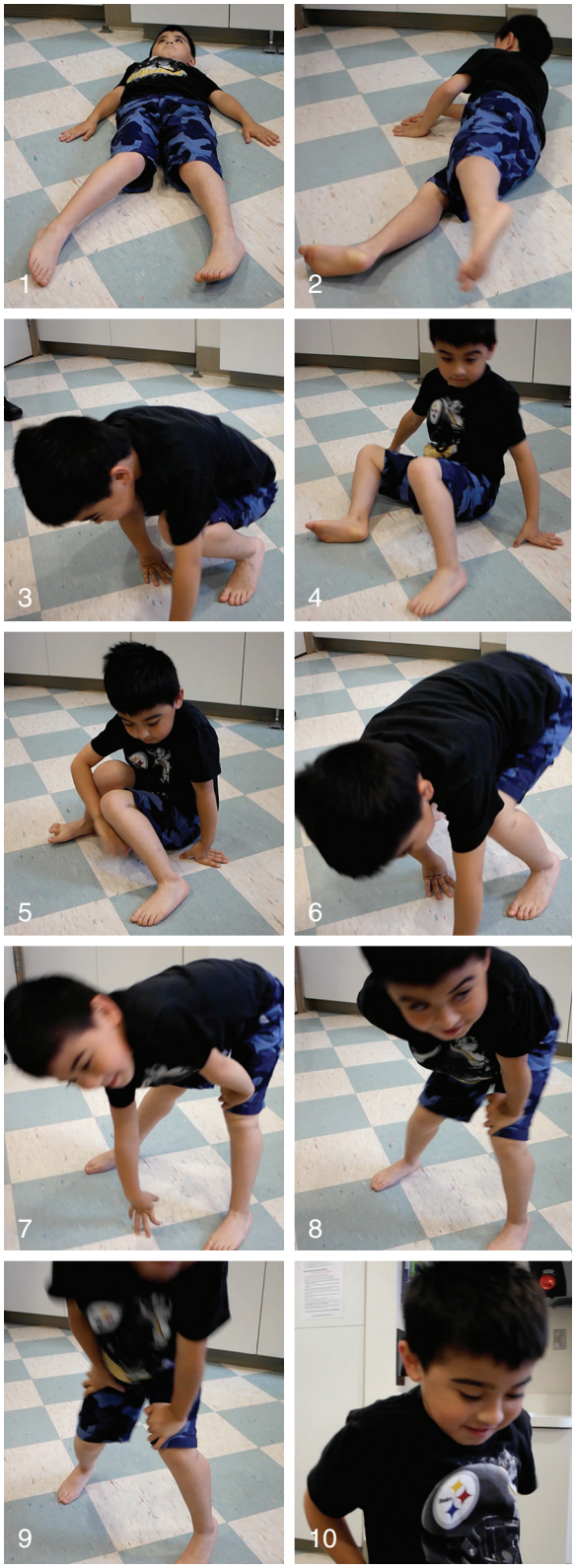

FIGURE 29.14 The Gower maneuver in a 7-year-old boy with Duchenne muscular dystrophy: the sequence of postures used in getting up from the ground. *1,* Lying prone. *2-4,* Getting onto the hands and knees. *5-6,* Legs and arms extended and legs brought as close as possible to the arms. *7,* Hand placed on the knee. *8,* Both hands on the knees, knees extended. *9,* Hands moving alternately up the thighs, "climbing up himself." *10,* Erect posture.

hypotonia and difficulty feeding a few hours after birth. Otherwise, they are alert, and pupils are reactive. Complete recovery in 4-6 weeks is the rule. Anticholinesterase therapy may be needed for a few days to a few weeks after birth.

Infantile (autoimmune) myasthenia is less common than transient neonatal myasthenia. Symptoms include acute-onset ophthalmoparesis, ptosis, and respiratory and feeding difficulties in a previously healthy infant with worsening symptoms later in the day. Demonstrating a decrementing response on repetitive nerve stimulation and a good response to a short course of steroids makes the diagnosis. Childhood autoimmune myasthenia has a high rate of seronegativity (36-50%), higher rates of pure ocular form, higher remission rates, and affects males and females equally. Distinguishing between autoimmune and genetic forms of myasthenia can be challenging in the infant. Treatment includes long-acting cholinesterase inhibitors such as pyridostigmine. Prednisone is useful because of the autoimmune nature of the disease.

Congenital myasthenic syndrome is a rare set of disorders stemming from many genetic defects causing either defective release of acetylcholine (presynaptic), lack of acetylcholinesterase or abnormal clustering of acetylcholine receptors (synaptic), or abnormal acetylcholine receptor response (postsynaptic). Clinically, all congenital myasthenic syndromes are seronegative for acetylcholine receptor antibodies and can manifest ophthalmoparesis, ptosis, and feeding and respiratory difficulties, making them indistinguishable from the autoimmune variety (Fig. 29.18).

Infantile botulism is caused by the germination of *Clostridium botulinum* organisms in the infant's gastrointestinal tract with local endogenous toxin production. Toxin is absorbed into the circulation and eventually inhibits the release of neuronal acetylcholine in the peripheral nervous system.

Infantile botulism is common between the ages of 2 and 6 months of life; many affected infants are breast-fed and may have a prior history of constipation. The sources of *C. botulinum* include honey, corn syrup, soil, and dust. Manifestations include lack of fever, poor feeding (poor sucking and swallowing), constipation, a weak cry and smile, hypotonia, ptosis, mydriasis, ileus, bladder atony, and hypotonia (see Table 29.9). Respiratory arrest and inappropriate antidiuretic hormone secretion may ensue. There is a descending paralysis, as symptoms are usually first noted in the face and bulbar region.

Food-borne botulism is manifested after ingestion of preformed toxin in poorly canned foods. Affected children have nausea and vomiting with dilated pupils, diplopia, dysphagia, dysarthria, dry mouth, and hypotonia.

The diagnosis of infant botulism is confirmed by recovery of the organism or the toxin from stool, blood, or food.

STROKE IN CHILDHOOD

Stroke is among the top 10 causes of death in childhood. The sequelae are not trivial. In addition to lasting lateralized weakness, learning disabilities, disturbances of language, visual deficits, and seizures may persist.

Brain injury resulting from stroke occurs in 1 of 2 general forms:

1. **Ischemia** consists of inadequate brain or spinal cord perfusion with consequent lack of oxygen or other blood-delivered substances necessary for normal metabolic function.
2. **Hemorrhage** occurs when blood is released into the extravascular cranial space. In this circumstance, focal injury of brain or spinal tissue occurs as a result of pressure exerted by the space-occupying mass of blood.

(See *Nelson Textbook of Pediatrics*, p. 2925.)

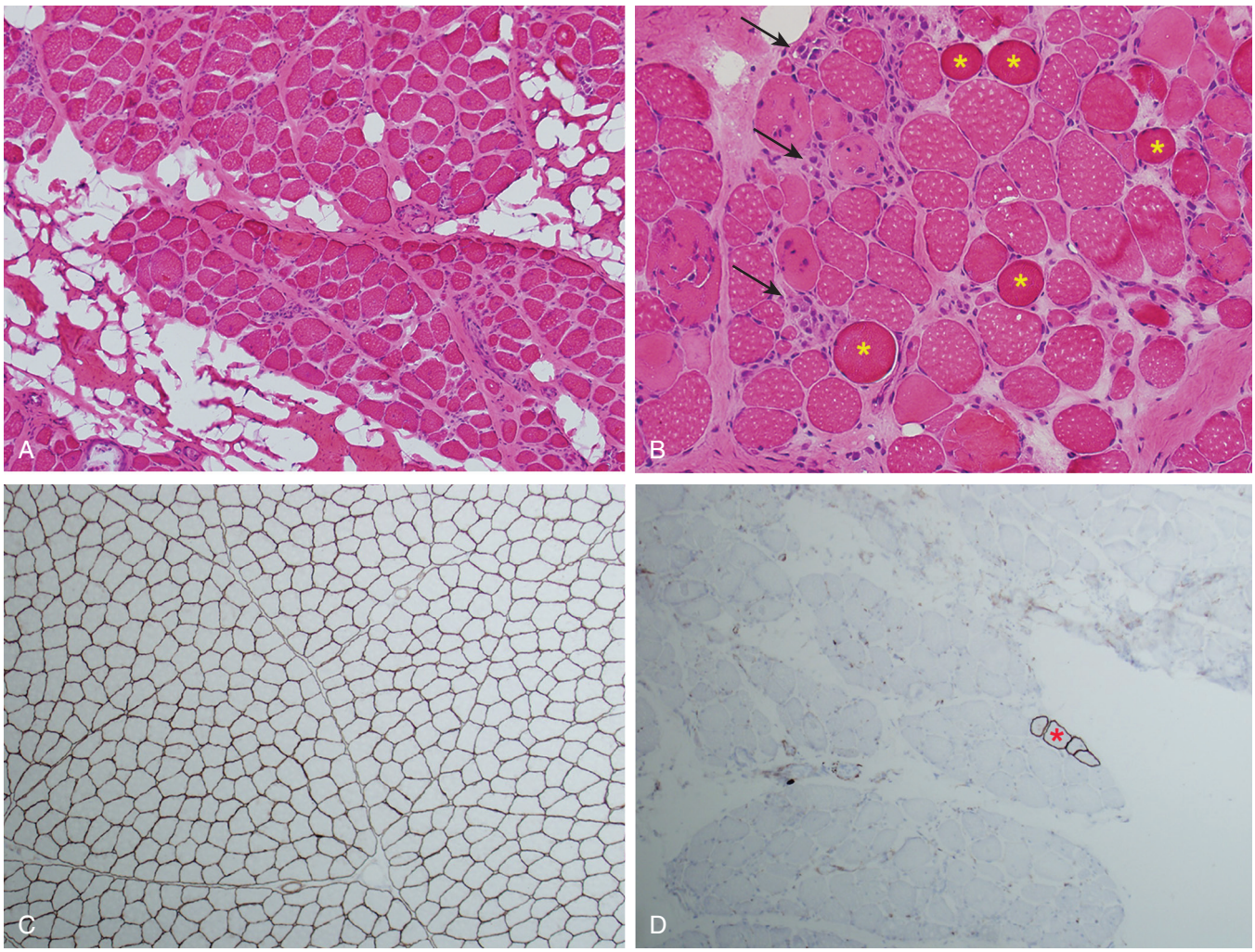

FIGURE 29.15 Muscle biopsy in Duchenne muscular dystrophy (DMD) showing prominent dystrophic changes consisting of fiber size variation, thick endomysial (around each myofiber) and perimysial connective tissue, increased internal nucleation, and fatty replacement of muscle tissue on hematoxylin and eosin (H&E) *(A)*. Higher magnification on H&E *(B)* shows mild inflammation consisting of myophagocytes consuming degenerating muscle fibers *(arrows)* and hypercontracted fibers *(yellow asterisks)*. Dystrophin immunohistochemistry demonstrates the normal staining pattern outlining the sarcolemma *(C)* in normal muscle, whereas the absence of staining in nearly all the fibers is seen in a DMD patient *(D)*. A few fibers within the muscle, called "revertant fibers" may have their reading frame spontaneously restored, thus enabling them to express dystrophin *(red asterisk)*. (Courtesy Michael Lawlor, MD, PhD, Medical College of Wisconsin, Milwaukee, WI.)

Ischemic injury of the brain occurs as a result of 1 of the 3 mechanisms: embolism, thrombosis, or global cerebral hypoperfusion.

Embolic damage to the brain occurs when material formed at a site in the vascular system proximal to the brain lodges in a blood vessel, thus blocking cerebral perfusion. Emboli originate most commonly from the heart, arising from a thrombus on cardiac chamber walls or from vegetation on valve leaflets. Artery-to-artery emboli are composed of clot or platelet aggregates that originate in vessels proximal to the brain but ultimately come to rest and occlude flow in vessels critical for cerebral perfusion. Systemic vein-to-cerebral artery emboli (paradoxical emboli) are possible in the presence of right-to-left shunts with cyanotic congenital heart disease or a patent foramen ovale.

Thrombosis denotes vascular occlusion caused by a localized process within a blood vessel or vessels. Although atherosclerosis underlies most thrombotic processes affecting adults, it is not common in children. Localized luminal clot formation occurs in polycythemia or in a hypercoagulable state. Alternatively, anatomic abnormalities may lead to clot formation or mechanical obstruction as is found in fibromuscular dysplasia, arteritis (vasculitis), or arterial dissection.

Global cerebral hypoperfusion due to cardiac pump failure (resulting from congenital heart disease or its surgical repair) and systemic hypotension resulting from hypovolemia represent common causes of hypotensive cerebral ischemic injury. With diminished cerebral perfusion, brain injury is more diffuse than the more focal injuries characteristic of thrombotic and embolic cerebral events.

Intracranial hemorrhage arises in 1 of 2 neuropathologic patterns:

1. **Subarachnoid hemorrhage (SAH)** occurs when blood flows from the intracranial vascular bed and onto the surface of the brain to mix with cerebrospinal fluid in the subarachnoid space. The most

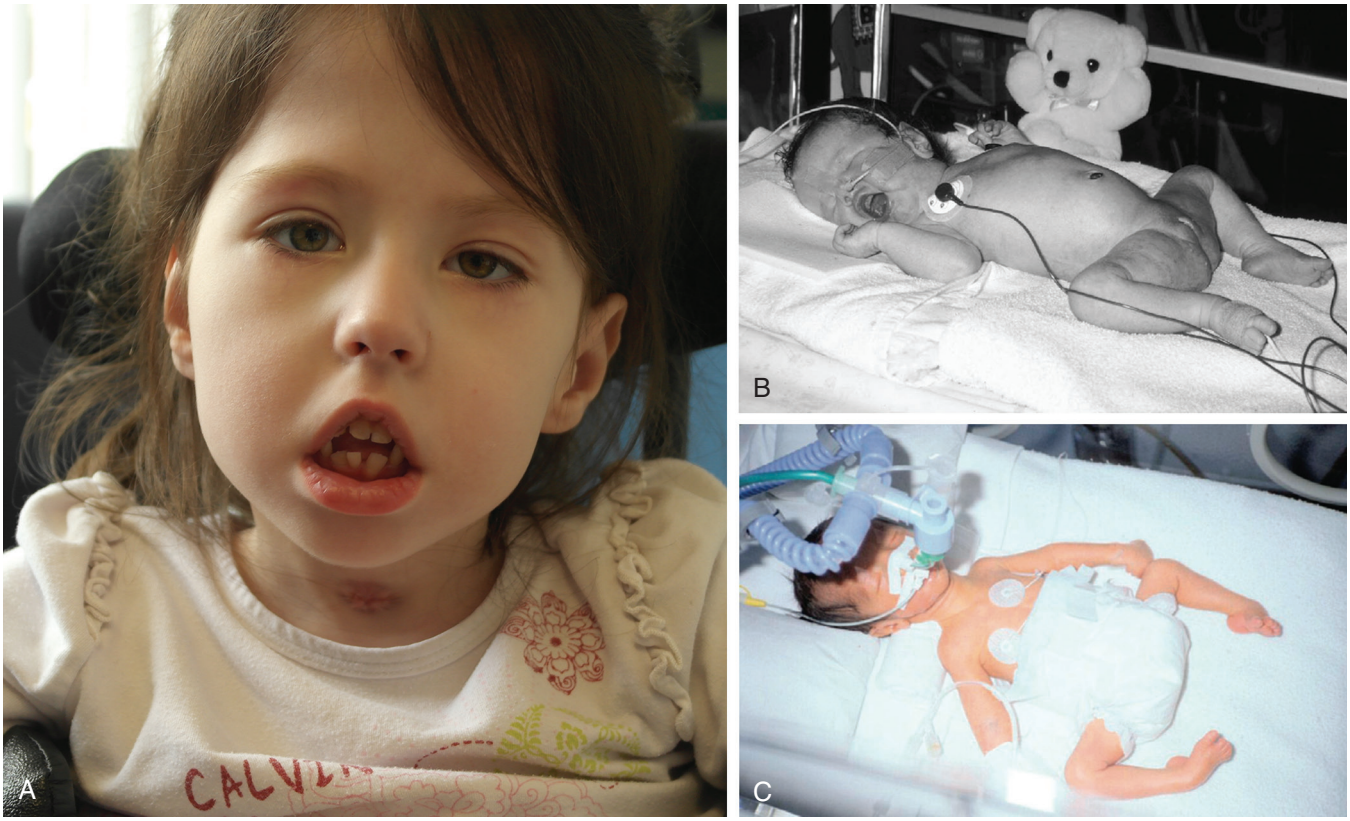

FIGURE 29.16 A 6-year-old with congenital myotonic dystrophy with 1975 cytosine-thymine-guanine (CTG) repeats in the *DMPK* gene showing the characteristic elongated facies, left ptosis, and an open, down-turned (tented) mouth with dental malocclusion *(A)*. The tracheostomy scar is evidence of the severe respiratory distress requiring intubation at time of birth. Neonate with congenital myotonic dystrophy *(B)* also with an open, down-turned mouth and frog-leg position of lower extremities. A neonate with congenital myotonic dystrophy with severe respiratory distress and arthrogryposis *(C)*. (*B,* From Johnston H. The floppy weak infant revisited. *Brain Dev.* 2003;25:155-158; *C,* from Echenne B, Bassez G. Congenital and infantile myotonic dystrophy. *Handb Clin Neurol.* 2013;113:1387-1393.)

common source of such intracranial bleeding in early childhood is an **arteriovenous malformation (AVM)**. Ruptured **intracranial aneurysms** also cause subarachnoid hemorrhage, especially in older children.

2. **Intracerebral hemorrhage** denotes bleeding into the parenchyma of the brain. Severity and region of deficits caused by intraparenchymal hemorrhage are determined by the extent and location of bleeding in the brain.

The location, or focality, of the resultant deficit after a stroke depends on whether the event occurred in the cortex, the subcortical areas, the brainstem, or the cerebellum. Although alterations of blood flow result in permanent deficits, some cause only temporary ones. **Transient ischemic attacks (TIAs)** are brief episodes of focal, nonconvulsive neurologic deficit attributable to interruption of cerebral perfusion. As in stroke, the onset is abrupt. By definition, a TIA must last less than 24 hours and in reality lasts only a few minutes, and recovery must be complete.

Progression of symptoms characterizes stroke when the underlying process, either ischemia or hemorrhage, widens its CNS domain with resultant expansion of symptoms and signs. Whether short-lived or permanent, deficits are commonly motor. Loss of strength may occur as a lateralized weakness involving one-half of the body (**hemiparesis**) or as complete loss of strength (**hemiplegia**). Diparesis, or diplegia, involves weakness of the legs and is found primarily in premature infants who have suffered bilateral hypoxic-ischemic brain injury, in full-term neonates after intracranial hemorrhage that has led to posthemorrhagic hydrocephalus, and in children suffering spinal cord injury below the neck. Involvement of the cerebellum often manifests as gait ataxia or impairment of fine motor coordination. Stroke occurring in the brainstem is reflected by cranial nerve dysfunction in the distribution of the vascular event. If long sensory or motor tracts running between the brain and spinal cord are involved, dysfunction of these systems may be involved.

Distinction among the 3 processes underlying stroke—embolism, thrombosis, and hemorrhage—is possible according to clinical features (Table 29.21). **Thrombotic strokes** are usually abrupt and on occasion may be heralded by TIAs. This type of stroke may bear a stepwise tempo, and neurologic symptoms may appear haltingly. The cerebrospinal profile is normal. **Embolic strokes** are infrequently preceded by TIAs. Onset of the episode is abrupt, and neurologic symptoms are manifested immediately. A mild-to-moderate headache may accompany neurologic symptoms. Lumbar puncture yields normal cerebrospinal fluid. **Intracerebral hemorrhage** is frequently marked by headache. Severe headache of sudden onset marks SAH, in particular. Prodromal symptoms generally do not occur. However, previous seizures may suggest the existence of an AVM, whereas previous episodes of headache may be attributable to leaks from intracranial aneurysms. Consciousness is often lost, although it may be regained after a short while. Cerebrospinal fluid is bloody if SAH has occurred or if intraparenchymal bleeding reaches the ventricular system.

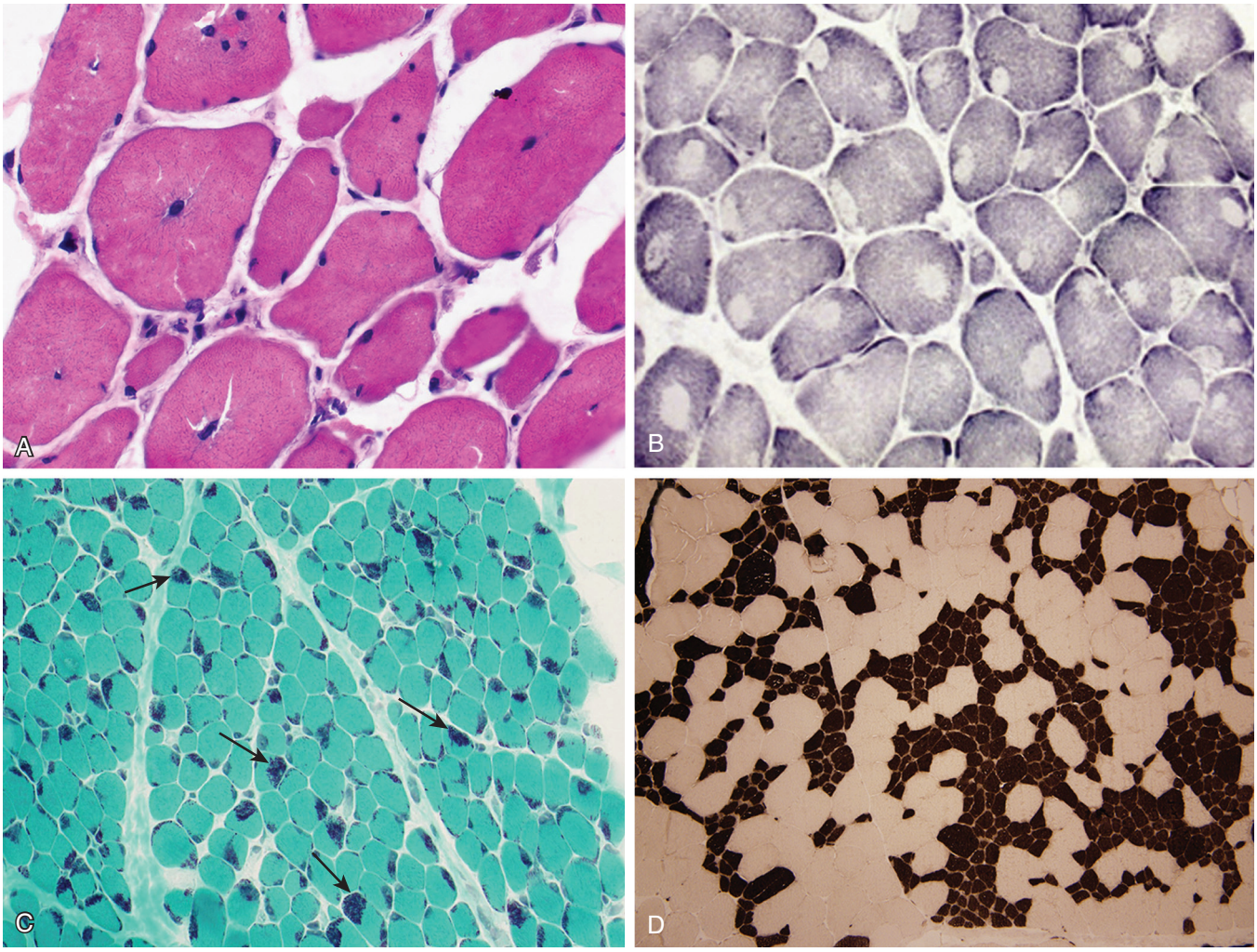

FIGURE 29.17 Characteristic Pathologic Changes Seen on Muscle Biopsy in Congenital Myopathies. Centronuclear myopathy is classified based on a centrally placed nucleus *(A)* seen in a disproportionate number of myofibers, on the background of fiber size variability shown here on hematoxylin and eosin (H&E) staining. Core myopathy has well-demarcated centrally or eccentrically placed cores, best visualized on oxidative stains such as SDH *(B)*. Nemaline rods are purple-blue staining rods (few are labeled by *arrows*) best visualized on Gomori trichrome located in a subsarcolemmal position *(C)*. Congenital fiber-type disproportion showing small, dark-staining type 1 fibers (average diameter, 20-40 μm) on ATPase at pH 4.3 relative to the larger, pale-staining type 2 fibers (average diameter, 80–100 μm) *(D)*. SDH, succinate dehydrogenase. (*A,* Courtesy Karra Jones, MD, PhD, University of California, San Diego, San Diego, CA; *B,* from North KN, Wang CH, Clarke N et al. Approach to the diagnosis of congenital myopathies. *Neuromuscular Disord.* 2014;24:97-116, with permission; *C,* courtesy Michael Lawlor, MD, PhD, Medical College of Wisconsin, Milwaukee, WI; *D,* courtesy Chamindra Konersman, MD, Medical College of Wisconsin, Milwaukee, WI.)

The signs of stroke found on physical examination often reflect interruption of the motor pathways extending from cortical upper motor neurons to the spinal cord lower motor neuron, the anterior horn cell. Upper motor neuron motor deficits seen in stroke patients may result from events occurring at any of several levels in the CNS: cerebral cortex, subcortical white matter, brainstem, or spinal cord. Despite the vast neurologic terrain in which stroke may occur, characteristics common to its occurrence at each of these locations can be found. A group of muscles is always involved. Never are individual muscles affected in isolation. The group of muscles affected may initially be flaccid and powerless, but the paralysis is rarely permanently complete.

Spasticity serves as the chronic functional manifestation of upper motor neuron injury caused by stroke. The antigravity muscles, consisting of arm flexors and leg extensors, are most commonly affected. As a result, the arms assume a position of flexion and pronation, whereas legs become extended and adducted. Testing for spasticity involves rapidly moving the relaxed affected extremity in the range of motion of the joint and assessing for freedom of movement. The extremity should then be stretched at higher velocity at which point increased tone is encountered in spasticity and classically referred to as *clasp-knife phenomenon*. Enhancement of deep tendon reflex response has been attributed to the interruption of descending inhibitory pathways as well as to increased activity of the γ neuron reflex loop.

Clonus, repetitive muscle contraction in response to tendon percussion or stretch, further reflects the enhanced response of tendon reflexes resulting from upper motor neuron injury in stroke. Reflex

FIGURE 29.18 Congenital Myasthenia. This child was referred at 4 years of age with a history of swallowing difficulty. By 2 years, his walking had not progressed further, and he was unable to run or climb stairs. His parents had also noted some ptosis in the 1st year. On examination, he had obvious ptosis, limited ocular movement, associated weakness of facial movement, an expressionless face, open mouth, and an inability to close the eyes tightly *(A)*. There was general hypotonia with joint laxity. The child got up from the floor with a Gower sign and could not stand on 1 leg or run. A diagnosis of myasthenia was confirmed by demonstrating a response decrement to repeated ulnar nerve stimulation. A definite improvement in the ptosis and his ability to get up from the floor was noted after intravenous edrophonium chloride (Tensilon). He was treated with pyridostigmine and showed a definite improvement, but with time, he needed an increased dosage and frequency. His performance improved after each dose and tended to wane as the next dose became due. He still had a Gower sign on rising from the floor, marked ptosis, external ophthalmoplegia, and facial weakness *(B-D)*. His parents are 1st cousins, and so this is probably a case of autosomal recessive infantile (congenital) myasthenia. (From Dubowitz V. *Muscle Disorders in Childhood*. 2nd ed. London: WB Saunders; 1995:414.)

TABLE 29.21 Stroke in Children: Characteristics of Stroke by Mechanism

Mechanism	Onset	Pace of Deficit Onset	Location	TIAs	Neck Pain	Headache	Impaired Consciousness
Embolism	Sudden	Abrupt	Remote site of origin	Rare	None	Yes	Rare unless infarction is large or involves ARAS or bilateral thalami
Thrombosis	Sudden; may occur during sleep or systemic hypotension	Abrupt; may be stepwise	In situ	Yes	None*	Rare	Unusual
Hemorrhage	Rapid	Abrupt or rapid in progression	In subarachnoid space or in brain parenchyma	None	Yes	Yes	Frequent in SAH and large parenchymal hemorrhages

*Except in carotid dissection with intimal tearing.
ARAS, ascending reticular activating system; SAH, subarachnoid hemorrhage; TIAs, transient ischemic attacks.

elicitation at 1 point, such as at the biceps muscle, may provoke reflex responses in adjacent muscle groups, such as brachioradialis or finger reflexes. Such spread of reflex responsiveness is commonly seen in patients whose upper motor neuron pathways have been injured by stroke.

Children with stroke present similarly to adults with focal neurologic deficits but diffuse features occur more commonly, although not in isolation (Table 29.22). Stroke in children is commonly caused by or related to congenital heart disease, infection, metabolic disorders, hematologic and coagulation diatheses, and collagen vascular disease (Table 29.23). Nonetheless, despite the most thorough evaluation, the cause escapes detection in 25-33% of patients. A pediatric stroke classification system originally proposed by Wraige et al. in 2005 demonstrated that stenoocclusive arteriopathy is the most common cause of arterial ischemic strokes (AISs) (Table 29.24), whereas AVMs were the most common cause of hemorrhagic strokes (Table 29.25). The evaluation of stroke should proceed in a stepwise fashion, with determination of whether the stroke is ischemic or hemorrhagic via cranial CT or MRI. Subsequent diagnostic testing may include cerebral vessel imaging, echocardiography, and laboratory work-up for prothrombotic and inflammatory states based on history (Fig. 29.19).

The outcome of stroke varies considerably due to differences in etiology, age, management, population studied, and functional outcome measures studied. In general, 5-10% of affected children die, and more than half of the survivors incur a functional or cognitive neurologic deficit.

The clinical presentations and causes of stroke are best considered with respect to each of 3 age groups: neonates, children between 1 and 13 years of age, and adolescents.

NEONATES

Perinatal Ischemic Stroke

The National Institute of Neurologic Disorders and Stroke defines ischemic perinatal stroke as a "focal disruption of cerebral flow secondary to arterial or cerebral thrombosis or embolization between 20

TABLE 29.22 Symptoms of Strokes in Children Based on Etiology

	ARTERIAL ISCHEMIC STROKES[1]	HEMORRHAGIC STROKES[1]	CEREBRAL VENOUS THROMBOSIS[2]	
Symptoms/Signs	**%**	**%**	**Symptoms/Signs**	**%**
Hemiparesis	70-80	35	Headache	75
Facial weakness	40-60	35	Altered consciousness	55
Speech disturbance	30-40	10	Focal deficits	40–50
Visual changes	5-15	20	Seizures	25
Limb ataxia	20-25	5		
Focal numbness	20	<5		
Vomiting	10-20	55		
Headache	25-45	75		
Decreased level of consciousness	20-40	50		
Seizures	15-30	20		
Vertigo	10	nda[3]		
Diplopia	3	nda		
Papilledema	1	nda		
No lateralizing symptoms	35	65		
No neurologic signs	10	60		
GCS[4] ≥14	85	60		
GCS 9–13	15	20		
GCS ≤8	0	20		

[1]The Approximate percentage of patients having each symptom based on pooled data from 1-4.

1. Mallick AA, Ganesan V, Kirkham FJ, et al. Childhood arterial ischaemic stroke incidence, presenting features, and risk factors: a prospective population-based study. *Lancet Neuro.* 2014;13:35-43.
2. Yock-Corrales A, Mackay MT, Mosley I, Maixner W, Babl FE. Acute childhood arterial ischemic and hemorrhagic stroke in the emergency department. *Ann Emerg Med.* 2011;58:156-63.
3. Wintermark M, Hills NK, deVeber GA, et al. Arteriopathy diagnosis in childhood arterial ischemic stroke: results of the vascular effects of infection in pediatric stroke study. *Stroke.* 2014;45:3597-605.
4. Lynch J, Hirtz DG, DeVeber G, Nelson KB. Report of the National Institute of Neurological Disorders and Stroke Workshop on Perinatal and Childhood Stroke. *Pediatrics.* 2002;109:116-123.

[2]Ichord RN, Benedict SL, Chan AK, Kirkham FJ, Nowak-Gottl U, International Paediatric Stroke Study G. Paediatric cerebral sinovenous thrombosis: findings of the International Paediatric Stroke Study. *Arch Dis Child.* 2015;100:174-9.

[3]Nda, no data available.

[4]GCS, Glasgow Coma Scale.

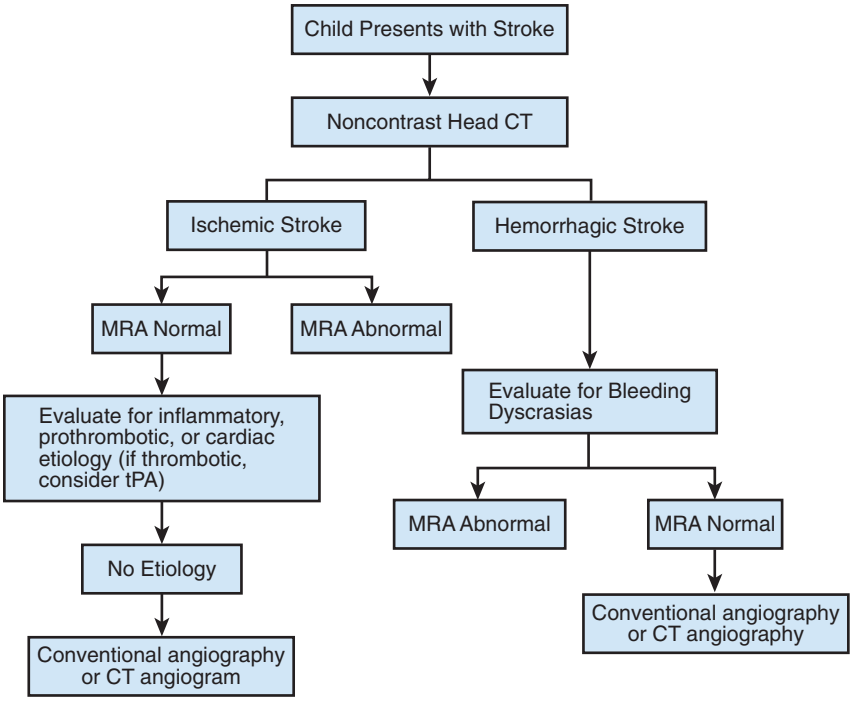

FIGURE 29.19 Algorithm for evaluation of child presenting with stroke. CT, computed tomography; MRA, magnetic resonance angiography; tPA, tissue plasminogen activator. (Modified from Gumer LB, Del Vecchio M, Aronoff S. Strokes in children. *Pediatr Emerg Care.* 2014;30:660-664.)

TABLE 29.23 Causes of Stroke in Children

Cardiovascular Disease
Congenital
- Aortic stenosis
- Mitral stenosis
- Ventricular septal defects
- Patent ductus arteriosus
- Cyanotic congenital heart disease involving right-to-left shunt
- PHACE syndrome

Acquired
- Endocarditis
- Kawasaki disease
- Cardiomyopathy
- Atrial myxoma
- Arrhythmia
- Paradoxical emboli through patent foramen ovale
- Rheumatic fever
- Prosthetic heart valve

Hematologic Abnormalities
Hemoglobinopathies
Polycythemia
Leukemia/lymphoma
Thrombocytopenia
Disorders of coagulation
- Protein C deficiency
- Protein S deficiency
- Factor V (Leiden) resistance to activated protein C
- Antithrombin III deficiency
- Lupus anticoagulant
- Oral contraceptive pill
- Pregnancy and the postpartum state
- Disseminated intravascular coagulation
- Paroxysmal nocturnal hemoglobinuria
- Inflammatory bowel disease (thrombosis)
- L-Asparaginase
- Prothrombin 20210A mutations
- Methylenetetrahydrofolate reductase (MTHFR) deficiency
- Hyperhomocysteinemia

Systemic Disorders
Meningitis
- Viral
- Bacterial
- Tuberculosis

Systemic infection
- Viremia
- Bacteremia
- Local head and neck infections
- Postvaricella (and other viruses)

Drug-induced inflammation/vasoconstriction
- Amphetamine
- Cocaine
- Ergots

Autoimmune disease
- Systemic lupus erythematosus
- Juvenile idiopathic arthritis
- Takayasu arteritis
- Mixed connective tissue disease
- Polyarteritis nodosa
- Primary CNS vasculitis

Trisomy 21

Metabolic Diseases
Homocystinuria/elevated homocysteine levels
Pseudoxanthoma elasticum
Fabry disease
Sulfite oxidase deficiency

Mitochondrial Disorders
MELAS
Leigh syndrome

Intracerebral Vascular Processes
Ruptured aneurysm
Arteriovenous malformation
Fibromuscular dysplasia
Moyamoya disease
Migraine headache
Postsubarachnoid hemorrhage vasospasm
Hereditary hemorrhagic telangiectasia
Sturge–Weber syndrome
Carotid or vertebral artery dissection
Neurofibromatosis type 1
CADASIL

Trauma and Other External Causes
Child abuse
Head trauma/neck trauma
Oral trauma
Placental embolism
ECMO therapy
Lollipop stroke (pharyngeal trauma)

CNS, central nervous system; ECMO, extracorporeal membrane oxygenation; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke; PHACE, posterior fossa brain malformations, facial hemangiomas, arterial anomalies (cerebrovascular hypoplasia, aneurysms, stenosis, aberrancy), coarctation of the aorta, cardiac and eye defects; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukomalacia.

TABLE 29.24 Pediatric Stroke Classification and Etiologic Prevalence

	Subtype	Definition/Examples	% of cases
Arterial	Sickle cell disease	• Homozygous HbSS, HbS thalassemia, HbSC (not HbSA) with proximal occlusion/stenosis or normal • If moyamoya syndrome or arterial dissection, categorize under multiple probable etiologies	5
	Cardioembolic	Congenital heart disease	6
	Moyamoya syndrome	Terminal ICA or proximal MCA/ACA stenosis or occlusion with lenticulostriate collaterals; include unilateral cases, primary and secondary cases • Categorize as multiple probable if another etiology is found	11
	Cervical arterial dissection	MRI or angiography showing intramural hematoma, dissection flap, increased vascular diameter, and/or cerebral angiogram with string sign, pseudoaneuryms, or dissection flap • Exclude other probable etiologies	9
	Stenoocclusive cerebral arteriopathy	• Irregularity, stenosis, or occlusion of large intracranial artery (not moyamoya or dissection; include if history of clinical varicella infection within previous 1 yr) • Exclude other probable causes	24
	Other determined etiology	• Isolated cerebral angiitis • Fibromuscular dysplasia • CNS vasculitis • Migrainous infarction • Radiotherapy (unless patient has moyamoya disease as a complication of this) • Large artery atherosclerosis	6
	Multiple probable/possible etiologies	• Classify into this if other etiologies have not been excluded or if only some criteria for a specific etiology are fulfilled • Prothrombotic states (elevated anticardiolipin IgG, IgM on ≥2 occasions at least 6 wk apart, MTHFR mutation, FVL mutation, prothrombin mutation, protein C/S deficiency, antithrombin III deficiency, hyperhomocysteinemia) • Bacterial meningitis • Hypertension	12
	Undetermined etiology		26
Venous	Sinovenous thrombosis		1

HbSS, hemoglobin S; HbSC, hemoglobin SC; HbSA, hemoglobin SA; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; CNS, central nervous system; Ig, immunoglobulin; MTHFR, methylenetetrahydrofolate reductase deficiency; FVL, factor V Leiden deficiency

Data from Gumer LB, Del Vecchio M, Aronoff S. Strokes in children. *Pediatr Emerg Care*. 2014;30:660-664; Wraige E, Pohl KRE, Ganesan V. A proposed classification for subtypes of arterial ischemic stroke in children. *Dev Med Child Neurol*. 2005;47:252-256.

TABLE 29.25 Prevalence of the Causes of Hemorrhagic Stroke in Children

Etiology	% of Cases
Vascular malformations	54
AVM	30
Cavernous hemangioma	12
Aneurysm	10
Venous malformation	0.5
SAH	2
Medical etiologies	9
Brain tumors	2.5
Trauma/dissection	1
Undetermined	33

AVM, arteriovenous malformations; SAH, subarachnoid hemorrhage.

weeks of fetal life through 28th postnatal day" as confirmed by neuroimaging, fetal imaging methods, or neuropathologic studies. Perinatal stroke can be subclassified into fetal (diagnosed before birth), neonatal (diagnosed after birth but before the 28th postnatal day), or presumed perinatal (diagnosed after the 28th postnatal day) ischemic stroke. The causes of stroke in neonates are similar to those in children (Table 29.26).

The incidence of neonatal arterial ischemic stroke (AIS) in term infants is reportedly 1 in 2300 to 1 in 5000 live births. Neonatal AIS occurs more frequently in preterm newborns with an incidence of 7 in 1000 infants born at or before 34 weeks of gestation.

Newborns who incur AIS present 58-68% of the time in the newborn period. Focal seizures are the most common presenting symptom of neonatal AIS, occurring in 69-90% of term newborns (Table 29.27). Onset of seizures after 12 hours of life and focal motor seizures predict an association with stroke compared to HIE. Furthermore, most seizures associated with AIS occur within the 1st 3 days of life. Even though lateralized findings on neurologic examination may

TABLE 29.26 Causes of Stroke in Neonates

Hypoxic-ischemic encephalopathy
Cerebral venous thrombosis
Thrombophilias
Maternal idiopathic thrombocytopenic purpura
Intracranial hemorrhage
Intraventricular hemorrhage
Polycythemia
Familial porencephaly
Organic acidemias
Methylmalonic acidemia
Propionic acidemia
Isovaleric acidemia
Unknown presumed emboli (placental, patent ductus arteriosus) of in utero onset

TABLE 29.27 Symptoms Associated with Perinatal Arterial Ischemic Strokes (AIS)

Symptom	% of cases
Neonatal AIS in Term Infants	
Seizures (usually focal motor)	69–90
Hemiparesis	~30
Impaired level of consciousness	39
Abnormal tone	38–46
Respiratory difficulties	26
Feeding difficulties	24
Neonatal AIS in Preterm Infants	
Respiratory distress or apnea	83
Seizures	30
Abnormal feeding	26
Abnormal tone	22
Presumed Perinatal AIS	
Early hand preference (<2 yr of age) Hand fisting	81–86
Seizures	14–15
Gaze preference	5

From Lehman LL, Rivkin MJ. Perinatal arterial ischemic stroke: presentation, risk factors, evaluation, and outcome. *Pediatr Neurol.* 2014;51:760-768.

TABLE 29.28 Risk Factors for Perinatal Arterial Ischemic Stroke (AIS)

Type of Risk Factor	Risk Factors
Term Infants with Neonatal AIS	
Maternal	Thrombophilia Infertility Prolonged rupture of membranes Preeclampsia or gestational hypertension Smoking Intrauterine growth restriction Infection Maternal fever during delivery Smoking
Fetal	Thrombophilia (MTHFR mutation, FVL, prothrombin gene mutation, protein C/S deficiency) Congenital heart disease Arteriopathy Hypoglycemia Perinatal asphyxia Infection (sepsis/meningitis) Need for resuscitation Apgar score of <7 at 5 min
Placental	Chorioamnionitis Placental infarcts Distal villous immaturity Placenta weighing <10th percentile
Preterm Infants with Neonatal AIS	
Maternal	Infection Gestational bleeding Maternal smoking Maternal drug use
Fetal	Twin-twin transfusion Abnormal fetal heart rate Hypoglycemia Thrombophilia (MTHFR mutation, FVL)
Presumed Perinatal AIS	
Maternal	Preeclampsia Infection Gestational bleeding Gestational diabetes Thrombophilia
Fetal	Congenital heart disease

MTHFR, methylenetetrahydrofolate reductase deficiency; FVL, factor V Leiden deficiency.
Modified from Lehman LL, Rivkin MJ. Perinatal arterial ischemic stroke: presentation, risk factors, evaluation, and outcome. *Pediatr Neurol.* 2014;51:760-768.

be found, they need not be present as hallmarks of cerebral infarction. Furthermore, diminished movement of extremities on the side of the focal seizure may represent a postictal Todd paralysis rather than paresis from upper motor neuron injury caused by cerebral infarction. Initially, other neurologic signs may be absent. However, as the child grows, motor or cognitive impairment may become progressively more apparent during the 1st 1-3 years of life. Preterm neonates with AIS are commonly asymptomatic and are diagnosed on cerebral ultrasound, whereas the most common presentation of presumed perinatal AIS is early hand preference (see Table 29.27).

The cause of the cerebral infarction frequently escapes detection among neonates who have not been subjected to prenatal asphyxia. Data analyzing risk factors for perinatal AIS are limited and sometimes conflicting, but can be broadly categorized into maternal, fetal, and placental factors (Table 29.28). For unknown reasons, a left hemispheric location (53-64% with an isolated unilateral lesion) has been noted to be the most common area involved in perinatal AIS and exclusive involvement of the middle cerebral artery (MCA) territory is seen in 75-90% of perinatal AIS cases. The location of strokes varies based on age of gestation (Table 29.29). Emboli from the placenta may lodge in cerebral vessels and result in stroke. In addition, congenital

heart defects involving right-to-left shunts through septal defects or through a patent ductus arteriosus serve as settings for embolic stroke in neonates. Coagulopathies caused by congenital defects of coagulation (factor VIII, protein C or S, or antithrombin III deficiency and others) or by sepsis-induced disseminated intravascular coagulation may underlie neonatal embolic stroke. Fetal head trauma during labor and delivery that results in endothelial damage to cerebral vessels occasionally leads to thrombosis and resultant focal ischemia of the brain. Polycythemia and hypotension can each lead to intravascular stasis and abnormalities in flow, resulting in cerebrovascular thrombosis in neonates. Meningitis and encephalitis cause diffuse or localized thrombosis as a result of vascular inflammation, leading to hemostasis and thrombosis.

Evidence of localized dysfunction of brain found on EEG consists of focal, persistent voltage reduction or of marked focal slowing and sharp wave activity. In some instances, EEG evidence of clinically observed seizures may be found. Each of these findings may exist while the EEG remains relatively normal over other regions of the brain. The areas of electrical abnormality should correspond to the affected areas of brain revealed by neuroimaging. Cranial CT demonstrates a low-density region that eventually evolves into atrophy (Fig. 29.20). MRI demonstrates low or isointense signal intensity on T1 weighted images and high signal intensity on T2 weighted images as a result of increased water content in the infarcted region of the brain. DWI reveals the local area of edema before any other neuroimaging procedure and must be performed if the CT and MRI are normal (Figs. 29.21 to 29.24).

TABLE 29.29 Location of Arterial Strokes in Perinatal Arterial Ischemic Stroke Based on Gestational Age

Gestational Age	Location of Arterial Stroke	% of Cases
Full-term neonate	Cortical branch strokes	59
Preterm neonate (overall) <28–32 wk of gestation 32–36 wk of gestation	Lenticulostriate (overall) Lenticulostriate Cortical branch infarcts	39

The mortality rate for neonatal AIS is low at 0.16 per 100,000 live births. Stroke recurrence occurs in only 2% of neonates, most of whom have thrombophilia, congenital heart disease, or an arteriopathy. Chronic motor deficits occur in 48-59% of neonates with AIS with MRI evidence of infarction in the basal ganglia, cerebral cortex, and posterior limb of internal capsule in term neonates correlating with long-term hemiparesis. Other long-term sequelae in neonatal AIS include behavioral disorders (attention and/or hyperactivity) (11%) and language delay (21%). About 38-46% of neonates with AIS develop epilepsy as a result of their stroke. Patients with presumed perinatal AIS fare poorer than their neonatal AIS counterparts: Approximately 95% have hemiparesis, 41% require limb casting/splinting, 50% have cognitive/behavioral difficulties, and 38% have epilepsy.

Polycythemia

Neonates are much more commonly polycythemic (central venous hematocrit >65%) than are older children. Polycythemia has been estimated to be present in 1.5% of newborns. It is most commonly encountered in neonates who are born at high altitude, those who are small for gestational age, infants of diabetic mothers, or recipients in twin-twin transfusion syndrome; it may also be seen in neonatal hyperthyroidism or adrenogenital syndrome. Clinical signs of the elevated hematocrit are present in some but not all affected infants and include plethora, acrocyanosis, impaired renal function, poor feeding, apnea, tachypnea, hypoglycemia, and indirect hyperbilirubinemia. Neurologic symptoms include jitteriness, irritability, lethargy, seizures, and focal motor deficits.

Most cases of polycythemia are idiopathic or secondary to acquired abnormalities of fetal oxygen delivery. Nonetheless, other polycythemias bearing autosomal dominant or recessive inheritance patterns have been described. These familial polycythemias are associated with mutant hemoglobins that create abnormalities of oxygen delivery.

Polycythemia and its resultant hyperviscosity may contribute to stroke in neonates. Inadequate cerebral perfusion and cerebrovascular thrombosis cause cerebral ischemia. Although most of the systemic complications of polycythemia resolve with adequate treatment, neurologic signs frequently do not. Cerebral infarction resulting from polycythemia-related ischemia causes deficits that resolve either slowly

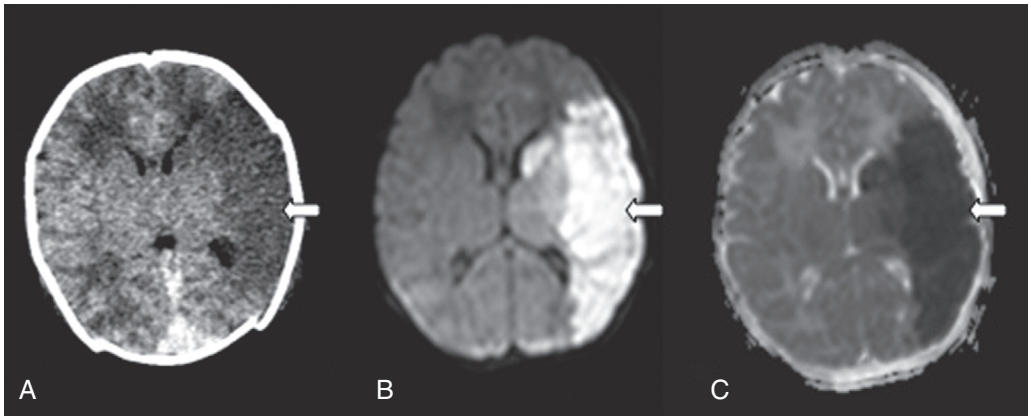

FIGURE 29.20 Neonatal Arterial Ischemic Stroke. Computed tomography (CT) and magnetic resonance imaging (MRI) demonstrate an arterial ischemic stroke in a 1-day-old term infant who presented with a right focal seizure. *A,* An axial CT image reveals hypodensity *(white arrow)* in the left middle cerebral artery (MCA) territory consistent with acute infarction. *B,* Axial MRI diffusion-weighted trace image of the same patient reveals a clearly demarcated area of infarct as a region of hyperintensity *(white arrow)* in the left MCA territory. *C,* Apparent diffusion coefficient map reveals region of signal hypointensity and restricted diffusion *(white arrow)* to match area of signal hyperintensity observed in *(B).* (With permission from Lehman LL, Rivkin MJ. Perinatal arterial ischemic stroke: Presentation, risk factors, evaluation and outcome. *Pediatric Neurol.* 2014;51:760-768.)

(See *Nelson Textbook of Pediatrics*, p. 2360.)

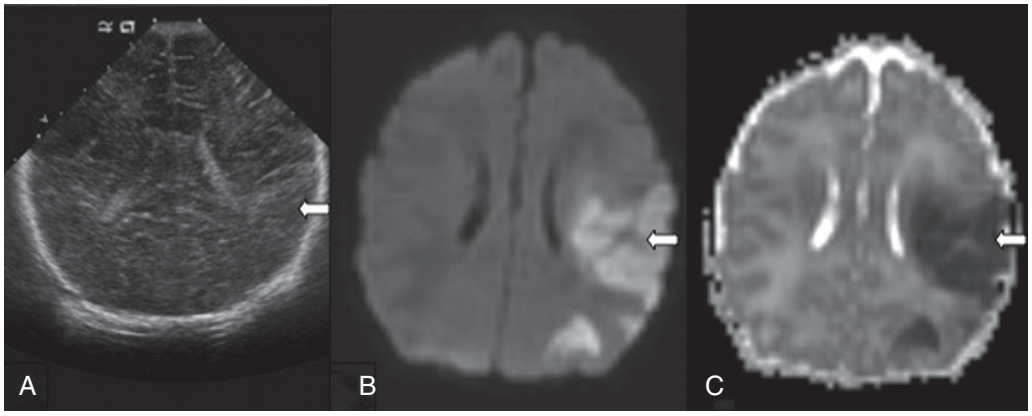

FIGURE 29.21 Neonatal Arterial Ischemic Stroke. Ultrasound (US) and magnetic resonance imaging (MRI) of neonatal arterial ischemic stroke in a 1-day-old term infant who presented with a right focal seizure. *A,* US reveals hyperechogenicity in the left cerebral hemisphere (indicated by *white arrow),* concerning for ischemic injury. *B,* Axial MRI diffusion-weighted trace image of the same patient reveals well-defined hyperintensity (indicated by *white arrow)* in the left middle cerebral artery (MCA) territory. *C,* Apparent diffusion coefficient map of the matching slice observed in *(B)* reveals corresponding hypointensity (indicated by *white arrow)* in the left MCA territory. (With permission from Lehman LL, Rivkin MJ. Perinatal arterial ischemic stroke: Presentation, risk factors, evaluation, and outcome. *Pediatr Neurol*. 2014;51:760-768.)

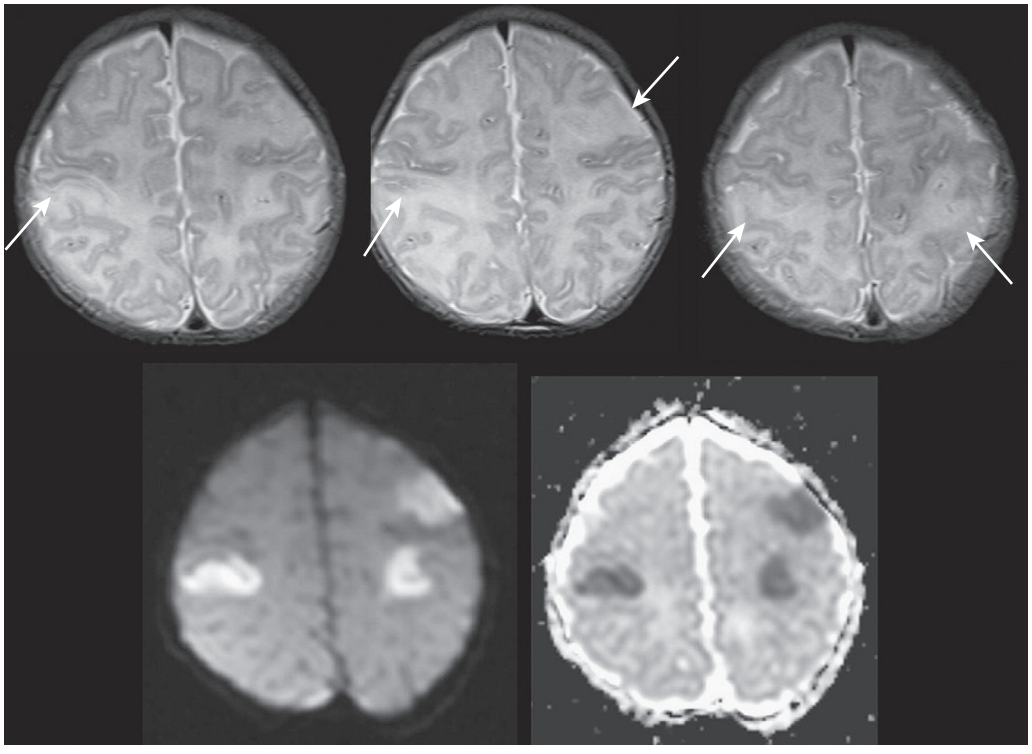

FIGURE 29.22 MR axial T2 weighted images *(top row),* a diffusion-weighted image, and calculated apparent diffusion coefficient (ADC) map *(bottom row)* of a term baby boy who presented with right-sided seizures. MR imaging on day 3 of life showed bilateral multiple acute cortical branch MCA territory infarcts. Note the cortical and white matter signal hyperintensity on T2 weighted images with loss of the normal cortical ribbon in some regions *(arrows in top row).* The diffusion-weighted imaging increases the conspicuity of the lesions; these show restricted diffusion with signal hyperintensity on the diffusion-weighted image *(bottom left)* matched by the low signal on the ADC map *(bottom right).* (With permission from Gunny RS, Lin D. Imaging of perinatal stroke. *Magn Reson Imaging Clin North Am*. 2012;20:1-33.)

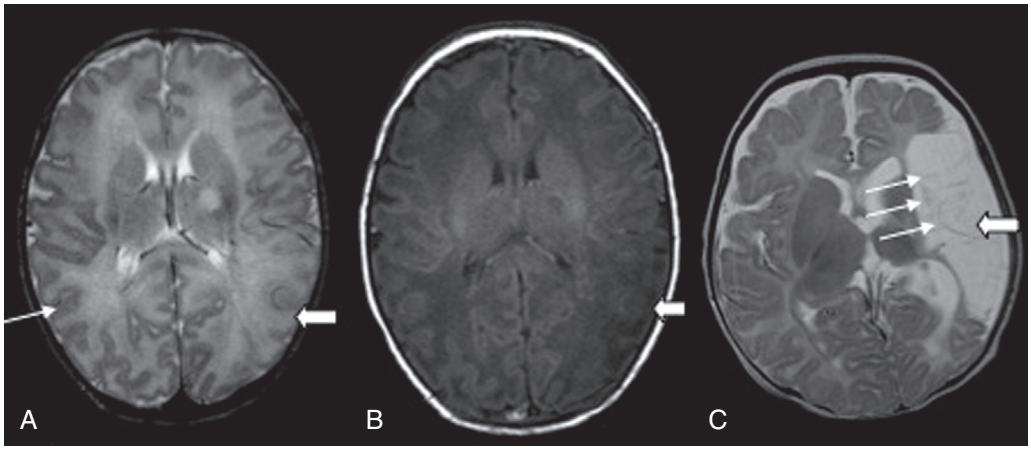

FIGURE 29.23 Presumed Perinatal Arterial Ischemic Stroke (AIS). Comparison of magnetic resonance imaging (MRI) appearance of a patient with acute neonatal AIS compared with MRI of a patient with presumed perinatal AIS. *A,* T2 weighted (T2W) axial image obtained in a 1-day-old term infant who presented with seizure reveals hyperintensity *(thick arrow)* in gray matter cortex and underlying white matter with loss of gray and/or white matter differentiation in the left middle cerebral artery territory *(thick arrow)* consistent with acute infarction compared with the normal right side with dark cortex *(thin arrow)* and normal differentiation of the white and gray matter. *B,* T1 weighted axial image, obtained in the same patient at the same time as the image in *(A),* reveals signal hypointensity in cortical gray matter *(white arrow)* matching the area of hyperintensity observed in *(A)* consistent with a diagnosis of acute neonatal AIS. *C,* T2W image obtained in a 3-month-old infant with an unremarkable neonatal history who presented at 3 months of age with a prematurely appearing right-hand preference reveals an area of hyperintensity and cystic change *(thick arrow)* with cystic septations *(thin arrows)* typical of chronic infarction. (With permission from Lehman LL, Rivkin MJ. Perinatal arterial ischemic stroke: Presentation, risk factors, evaluation, and outcome. *Pediatr Neurol.* 2014;51:760-768.)

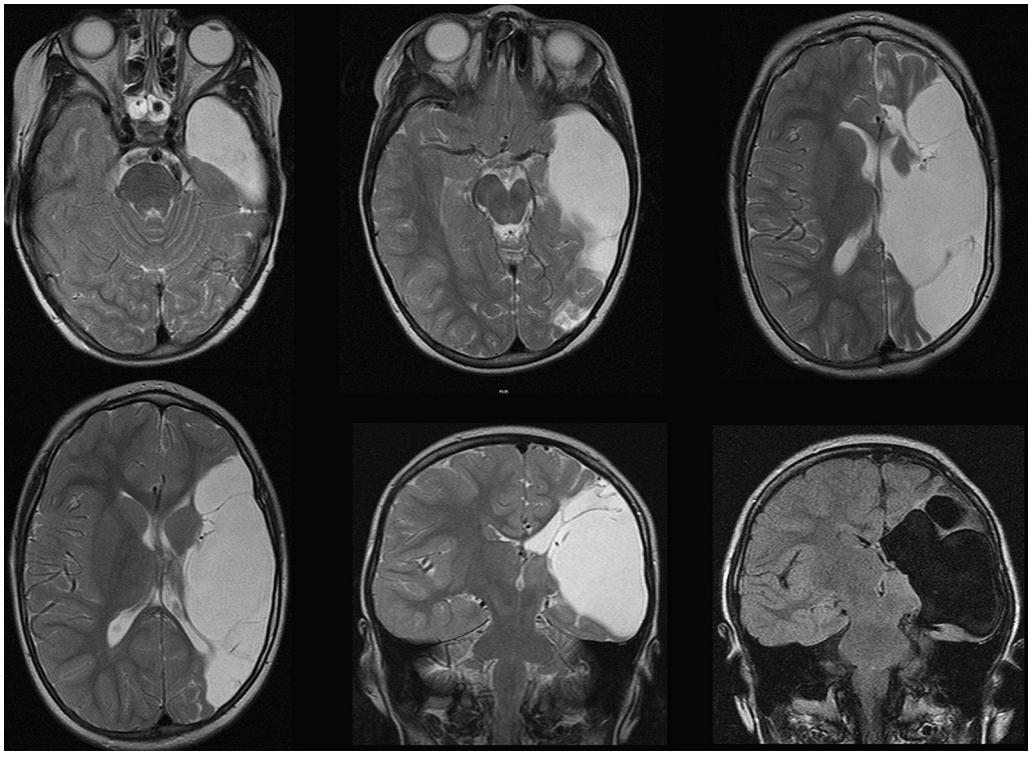

FIGURE 29.24 Presumed Perinatal Arterial Ischemic Stroke (AIS). Magnetic Resonance Imaging of a 5-year-old girl with long-standing right hemiplegia and intractable epilepsy secondary to a left-sided infarct. Note the large area of cystic cavitation in the left temporal (*top left* and *middle* images), frontal (*top right* image), and parietal lobes (*top right* and *bottom left* images) in the extended left middle cerebral artery territory (with some additional anterior choroidal involvement, and atrophy of the left thalamus; *bottom left* image). The left hemicranium is smaller, and there is some expansion of the left calvarial diploic space. There is 3-site involvement of the basal ganglia, superficial cortex, and posterior limb of the internal capsule (*bottom row* images). There is imaging evidence of Wallerian degeneration with atrophy, and signal hyperintensity suggestive of gliosis in the ventral midbrain and pons (*bottom middle* and *right* images). (Modified with permission from Gunny RS, Lin D. Imaging of perinatal stroke. *Magn Reson Imaging Clin North Am.* 2012;20:1-33.)

or not at all. Neurologic sequelae may be present in up to 35% of neonates with symptomatic polycythemia.

If signs of polycythemia are found in a neonate, further evaluation should be undertaken. Venous or arterial hematocrit, rather than capillary hematocrit, should be measured. If the family history and physical examination findings suggest a hereditary polycythemia, hemoglobin electrophoresis should be undertaken. Routine hemoglobin electrophoresis does not elucidate high oxygen-affinity hemoglobinopathies in all cases. If clinical suspicion is high, the heat instability test for unstable hemoglobins and oxygen dissociation assays can be utilized. Neuroimaging should be used to assess for cerebral infarction.

Neonatal Cerebral Sinovenous Thrombosis (CSVT)

Full-term neonates are the most frequently affected age group in the pediatric population for CSVT with an estimated incidence of 40.7 per 100,000 live births per year. Thrombosis may occur in cerebral veins that conduct deoxygenated blood from the parenchyma to the dural sinus system. These sinuses—the sagittal, straight, transverse, cavernous, and petrous—then convey the blood to the jugular veins. Occlusion of flow anywhere in these venous conduits leads to ischemia, infarction, and even hemorrhage.

Pathophysiology of CSVT is similar to perinatal AIS with the inherited thrombophilias being just as likely to cause venous infarctions as they do arterial (Table 29.30). Infection, dehydration, polycythemia, congenital heart disease, and extracorporeal membrane oxygenation (ECMO) have also been implicated. Five percent of all infants on ECMO have evidence of CSVT. The lesions associated with cerebral venous thrombosis include thrombosis in the deep or superficial veins, venous infarction, and hemorrhage. The hemorrhage that typically accompanies CSVT is a result of the increased venous/capillary hydrostatic pressure due to the presence of the clot causing extravasation of fluid and red blood cells.

The only signs may be lethargy and focal or generalized seizures. Other common symptoms include apnea and poor feeding (see Table 29.22). The features of slowly developing focal motor deficits, headache, and cranial nerve dysfunction found in older children with cerebral venous thrombosis are seldom observed.

Neuroimaging reveals the venous stasis best if magnetic resonance phase imaging, which detects blood flow, or magnetic resonance venography is performed, as well as conventional T1 and T2 weighted imaging (Fig. 29.25). An unenhanced CT may show a hyperdense, expanded "dense triangle" or "cord sign." An enhanced CT venogram may aid in the detection of the "empty delta" sign indicating a nonenhancing thrombus within the lumen of the vein (Fig. 29.26). Outcomes of CSVT include severe neurologic deficits in 19-38% of cases including death, but 45% have normal development.

TABLE 29.30 Risk Factors for Neonatal Cerebral Sinovenous Thrombosis

Type of Risk Factor	Risk Factors (Estimated % of Cases)
Maternal	Preeclampsia Diabetes
Fetal	Acute neonatal illness (61–84%) Infection Meningitis Dehydration Congenital heart disease Thrombophilia (same as in arterial; 15–20%) ECMO Complicated delivery Polycythemia

ECMO, extracorporeal membrane oxygenation.

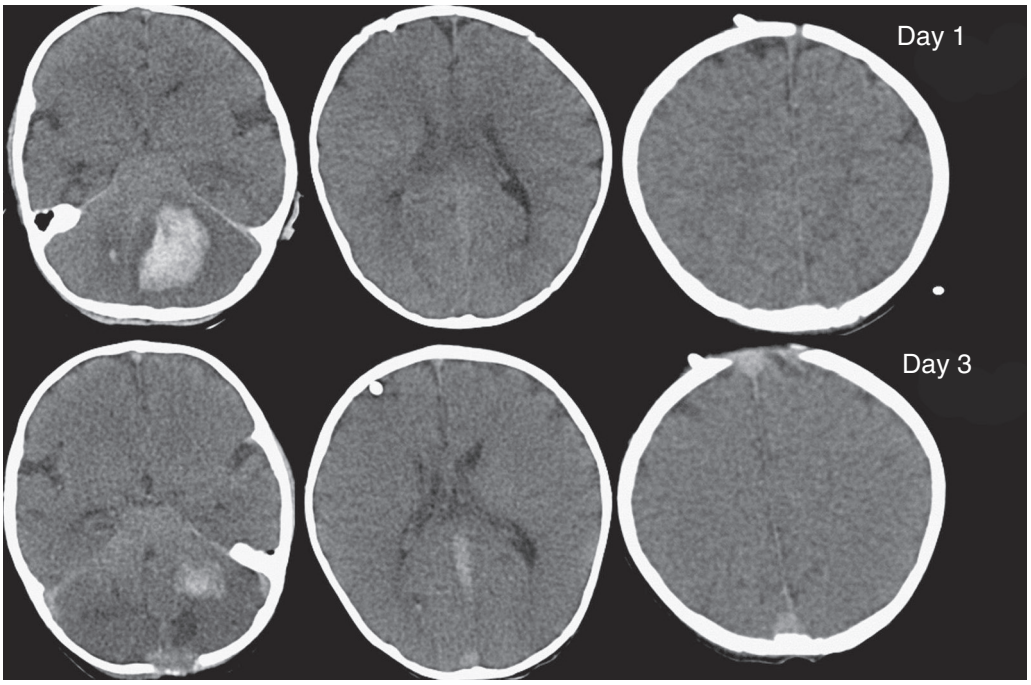

FIGURE 29.25 Neonatal Cerebral Sinovenous Thrombosis. Computed tomography (CT) scan *(top row)* in a 6-week-old infant with acute cerebellar hemorrhages causing marked cerebellar swelling presumed to be secondary to idiopathic thrombocytopenic purpura. A CT scan the day after the posterior fossa hematoma resection *(botttom row)* shows there is new acute thrombus in the straight sinus, torcular, and superior sagittal sinus. (With permission from Gunny RS, Lin D. Imaging of perinatal stroke. *Magn Reson Imaging Clin North Am.* 2012;20:1-33.)

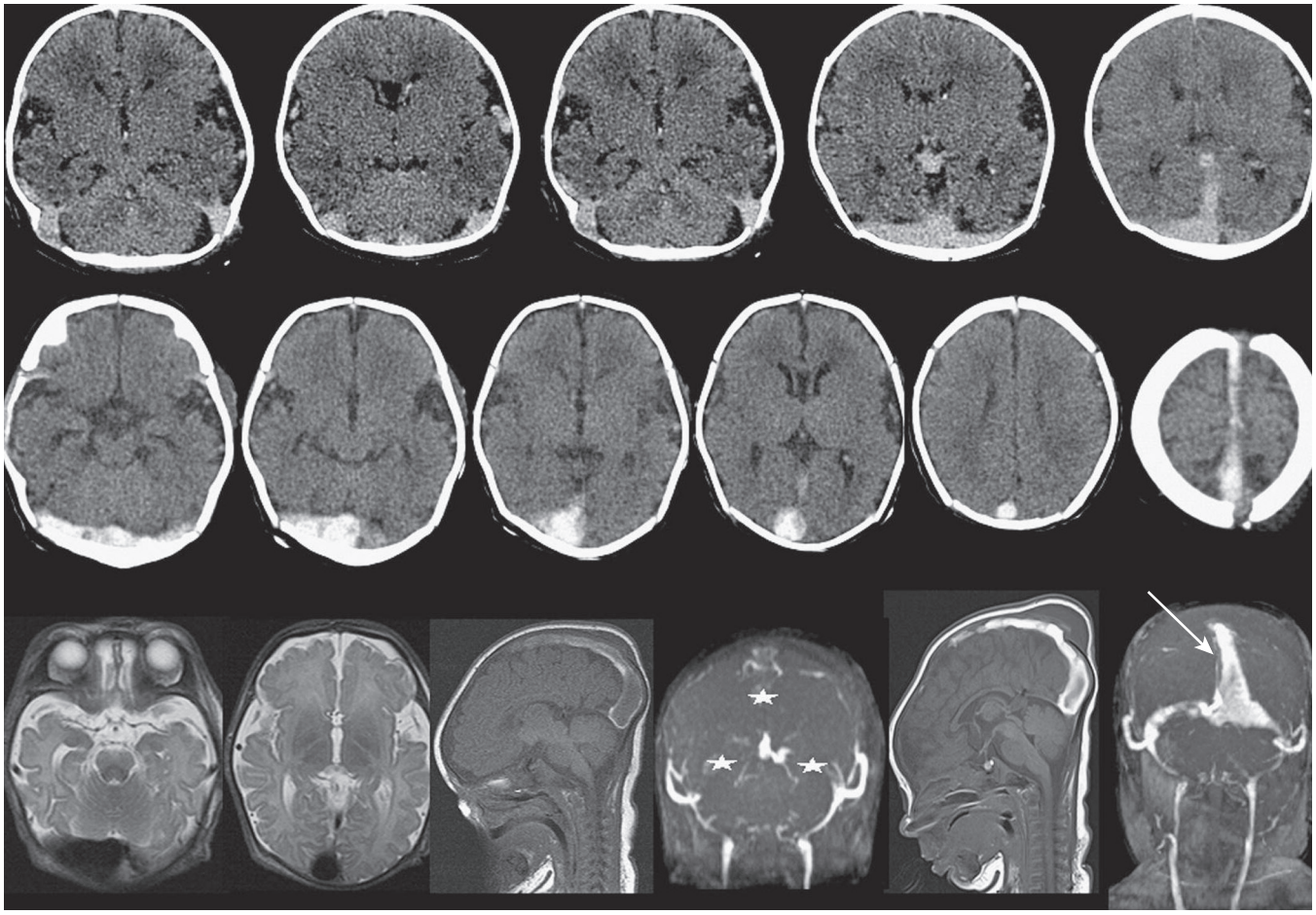

FIGURE 29.26 Neonatal Cerebral Sinovenous Thrombosis. A term male neonate was hypotonic at birth with poor respiratory effort requiring resuscitation. Initial computed tomography (CT) *(top row)* on day 2 of life shows diffuse brain edema with expanded and hyperdense transverse and sagittal sinuses, torcula, and internal cerebral veins as well as the cerebral cortical veins. CT performed on day 9 *(middle row)* shows resolution of the cerebral edema, increased density of the thrombus within the transverse sinus, torcula, and superior sagittal sinus. Magnetic resonance (MR) imaging on day 9 *(bottom left,* images 1–4) shows mild diffuse cerebral atrophy but no focal venous infarcts, with a persistent thrombus and no flow on the MR venography (*stars*). Follow-up MR imaging on day 15 (*bottom right*, images 5 and 6) shows the evolution of thrombus signal intensity to methemoglobin. Note the effect of T1 shortening within the thrombosed sagittal and transverse sinuses and torcula, mimicking flow within the sinuses *(arrow)*. (With permission from Gunny RS, Lin D. Imaging of peinatal stroke. *Magn Reson Imaging Clin North Am.* 2012;20:1-33.)

Intracranial Hemorrhage in the Neonate

Intracranial hemorrhage occurs in neonates in 1 of 4 different neuroanatomic distributions: subdural (SDH), subarachnoid (SAH), intraparenchymal (IPH), or intraventricular (IVH).Whereas SDH occurs more commonly in full-term infants, the other 3 types of hemorrhage are more common in premature infants.

Subdural Hemorrhage

SDH in neonates usually results from head trauma during birth. Thus, factors of labor and delivery promoting the application of increased force on the fetal head are liable to promote SDH. Cephalopelvic disproportion, rigidity of the bony pelvis, prolonged duration of labor, unusual presentations, or the need for prolonged manipulation or forceps application may each generate increased forces on the fetal head and cause SDH. As a result, shearing forces may create tears in the vein of Galen or tears of superficial cerebral veins. If forces are extreme, tears at the junction of falx and tentorium can generate large subdural blood collections in the relatively small posterior fossa, culminating in compression of the brainstem and cerebellar tonsillar herniation. The incidence of SDH has steadily declined as a result of improved obstetric practice.

Clinical features of SDH depend on the location and size of the hemorrhage. Tentorial laceration (Fig. 29.27) can cause stupor or even coma. Pupillary and extraocular movement abnormalities are common. Dystonic postures such as retrocollis or opisthotonos are seen. Finally, abnormalities of respiratory pattern regulation such as apneustic or ataxic respirations are seen and signify imminent respiratory arrest. Less severe SDHs in the posterior fossa evolve more slowly and cause less severe brainstem dysfunction. Subdural collections of blood over the cerebral surfaces that result from tears of superficial cerebral veins may be asymptomatic, or may present with subtle symptoms such as irritability. With time the blood may liquefy and draw water into the area by osmotic forces, thus expanding the size of the lesion. If the collection is sufficiently large, seizures occur. Greater pressure may cause oculomotor dysfunction accompanied by pupillary dilation and ablated pupillary light responses.

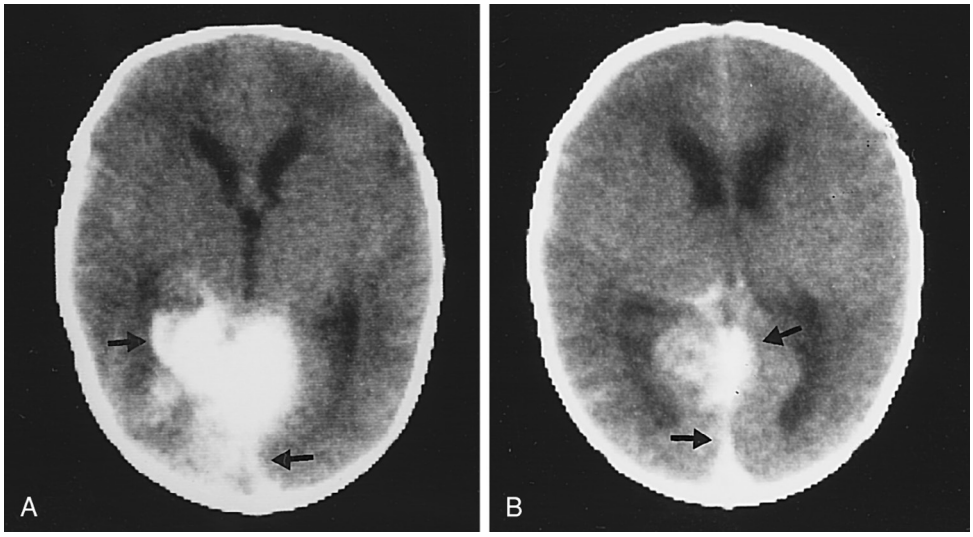

FIGURE 29.27 *A* and *B,* Generalized tonic seizures, lethargy progressing to coma, and an irregular respiratory pattern were observed in a 1-day-old full-term infant. Computed tomography scan demonstrates a hyperdense lesion emanating from the falx and tentorium *(arrows)* caused by a traumatic tear of the tentorium, which resulted in hemorrhage from the straight sinus.

SDH may escape diagnosis in the 1st few weeks of life and appear later as a chronic subdural effusion; in this situation, the clinician must consider child abuse (see Chapter 26). Such an occurrence is marked by a rapidly enlarging head circumference. There may also be a combination of acute and chronic SDH in cases of child abuse.

Subarachnoid Hemorrhage

Blood can occupy the subarachnoid space in 1 of 2 ways. First, blood may reach the subarachnoid space after hemorrhage has occurred in the cerebral parenchyma or in the periventricular region. Second, SAH may result from disruption of the superficial leptomeningeal arteries or of the fragile vessels bridging the subarachnoid space; disruption of either vascular structure leads to direct bleeding into the subarachnoid space, so-called primary SAH. Primary SAH commonly occurs after hypoxic-ischemic brain insults and after fetal head trauma.

Mild SAH is clinically the most common type, occurring as an occult phenomenon with few if any manifestations. Greater amounts of blood collecting over the convexities may result in focal motor deficits and seizures. Large SAH accumulating over the convexities has been associated not only with seizures but with infarction of underlying cerebral cortex. The presence of accompanying infarction is indicated by the occurrence of focal seizures. A history of difficult labor and delivery may be associated with large SAH. Cerebral infarction in the setting of SAH has been observed more commonly in full-term infants than in premature infants.

When SAH is mild, the neurologic outcome can be good. Even in cases of SAH accompanied by an infrequent seizure or cerebral infarction, the prognosis is often favorable. Adverse consequences appear to be more dependent on the severity of any underlying intrapartum trauma or hypoxic-ischemic brain injury.

Intraparenchymal and Intraventricular Hemorrhage

IPH of the brain occurs in both full-term and preterm infants. **Cerebral hemorrhage** in the absence of IVH occurs most commonly in full-term infants. Hemorrhage into the parenchyma of the cerebral hemispheres can be caused by head trauma, vascular malformation (Fig. 29.28), coagulopathy, thrombocytopenia, tumor, or infarction. A common cause of prenatal, intrapartum, and postnatal hemorrhage is alloimmune thrombocytopenia, caused by acquired antiplatelet antibodies when a mother becomes sensitized to paternal antigens on fetal platelets. Maternal immune thrombocytopenia may also affect the fetus, producing thrombocytopenia in utero. However, the incidence of neonatal cerebral hemorrhage is much lower in immune thrombocytopenia than in alloimmune thrombocytopenia. Vitamin K deficiency should be considered for breast-fed full-term neonates who present with intracranial hemorrhage. In the absence of recognized coagulation or anatomic abnormalities, cerebral hemispheric IPH has been attributed to hemorrhagic infarction. In premature infants, parenchymal hemorrhage most often occurs in conjunction with severe IVH (Fig. 29.29). Hemorrhage from the friable, unsupported germinal matrix leads to accumulation of intraventricular blood, and often ventricular distention. These events, in turn, cause impairment of blood flow in the medullary veins located in the periventricular white matter, preventing blood drainage into the greater cerebral venous system. Eventually, the periventricular venous congestion leads to ischemia and a resultant venous infarction.

Developmental outcome in full-term infants with IPH depends on the location and extent of the underlying cause. The occurrence of posthemorrhagic hydrocephalus or of moderate-to-severe asphyxia is predictive of abnormal outcomes, including motor impairment or cognitive delay. In premature infants, the simultaneous occurrence of IVH with IPH carries high risk for major motor deficits and marked cognitive impairment.

Evaluation of Stroke in Infants

Head ultrasonography detects areas of increased echogenicity in the cerebral cortex. In especially severe cases of ischemia, increased echogenicity of injured subcortical structures such as the thalamus and basal ganglia can be appreciated. Ischemic cortical injury involving the territory of the middle cerebral artery (frontal and parietal lobe regions surrounding the central sulcus) is better revealed by ultrasonography than are other vascular territories. The principal advantages of cranial ultrasonography are its easy portability to the patient's bedside and its lack of radiation exposure to the infant.

CT of the brain is particularly useful for evaluation of full-term infants after a suspected cerebral insult. Diffuse injury appears as abnormal generalized attenuation throughout the cerebral parenchyma with a loss of the distinction between gray and white matter;

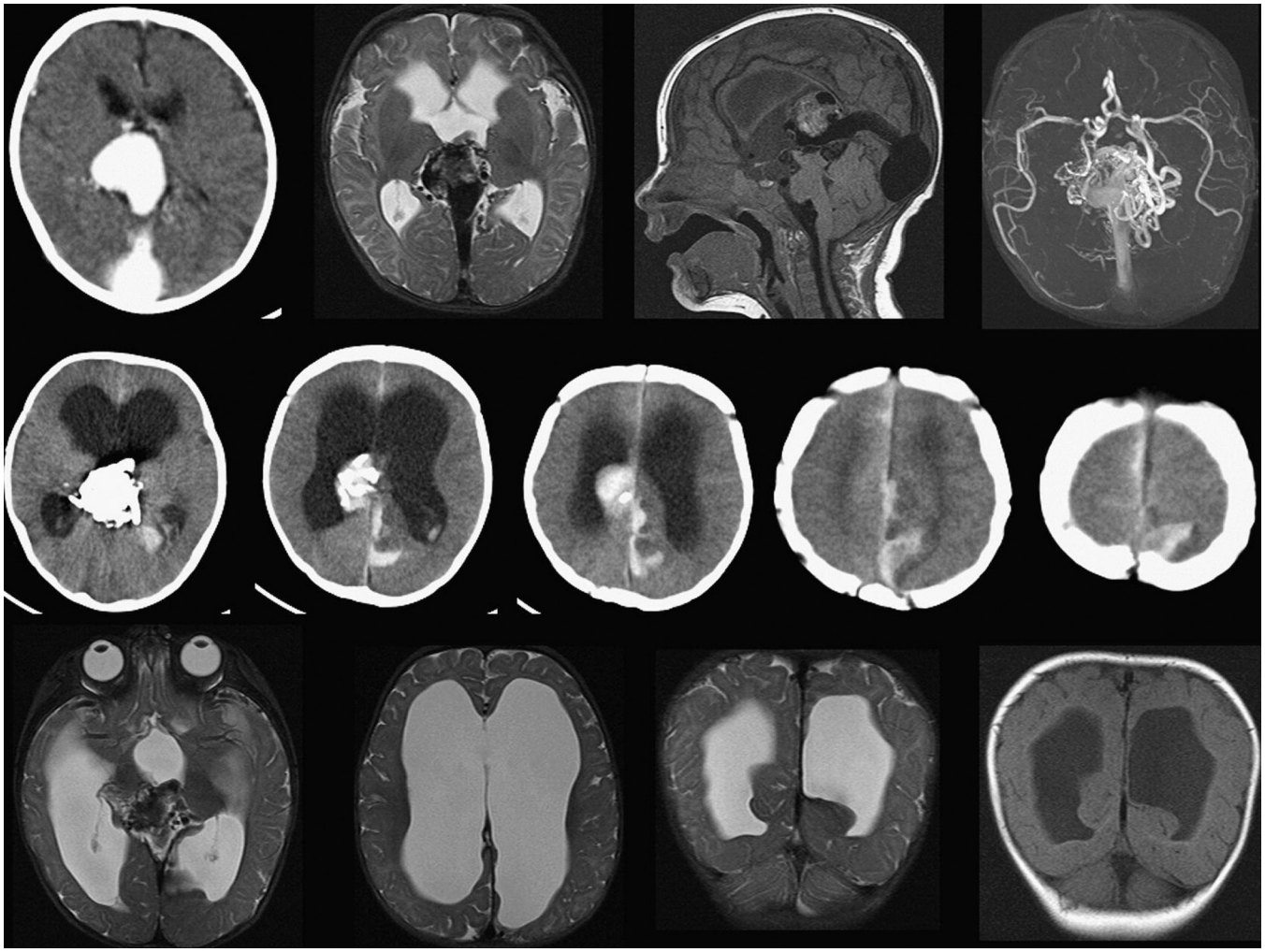

FIGURE 29.28 Neonatal Vein of Galen Malformation and Intraventricular Hemorrhage. A 5-day-old female born at 38 weeks was noted to be drowsy with poor feeding. She had signs of cardiac failure. A computed tomography (CT) scan *(top left)* demonstrates vein of Galen aneurysmal malformation, which was partly treated by transarterial glue embolization without complication but with significant residual arteriovenous shunting (MR images, *top row*). Following a 2nd embolization procedure, there was acute clinical deterioration with signs of raised intracranial pressure *(middle row)*. CT shows acute intraventricular hemorrhage and hydrocephalus, and a left parieto-occipital lobe low-density lesion (*middle*, images 1-3) with adjacent subarachnoid and subdural hematoma (*middle*, images 4-5). Some linear hyperdensity was believed to be due to thrombus within the persistent falcine sinus (*middle*, images 4-5). Follow-up imaging shows maturation of the focal left parieto-occipital lesion in keeping with an infarct *(bottom row)*, which is probably venous in origin. (With permission from Gunny RS, Lin D. Imaging of pediatric stroke. *Magn Reson Imaging Clin North Am.* 2012;20:1-33.)

this abnormality may represent cerebral edema. Focal and multifocal brain injury is readily detected by cranial CT.

MRI scans obtained within the first 4 days of life in full-term infants with signs of severe HIE reveal white matter abnormalities and indistinct gray matter–white matter junctions on T2 weighted images. **DWI** can identify areas of recent infarct even earlier than conventional T1 and T2 weighted images. Subsequent images can show chronic changes such as cerebral atrophy, paucity of white matter, delayed myelination, and ventriculomegaly. MRI has proved useful in documenting delay of myelination, a sequela to perinatal ischemic white matter injury not readily discerned with CT. This additional capability has provided a potential explanation for subtle motor deficits found in children who have ischemic brain injury in the perinatal period. MRI also detects neonatal hypoxic-ischemic injuries of basal ganglia not well detected by either head ultrasonography or CT. Moreover, MRI with venography is the procedure of choice in the neonatal period for identification of venous thrombosis.

Laboratory testing for the wide variety of etiologic factors underlying stroke should be conducted. The causes include infection, liver dysfunction, coagulopathy, prothrombotic states, organic and amino acid inborn errors of metabolism, urea cycle disorders, and mitochondrial abnormalities.

CHILDREN AGED 1-13 YEARS

When stroke occurs in children, focal symptoms are reported and corresponding localized deficits are noted on the neurologic examination, which correlate anatomically with the involved region of the CNS (see Table 29.22). Lateralized weakness often signifies injury to the contralateral hemisphere, including the regions governing movement. Such

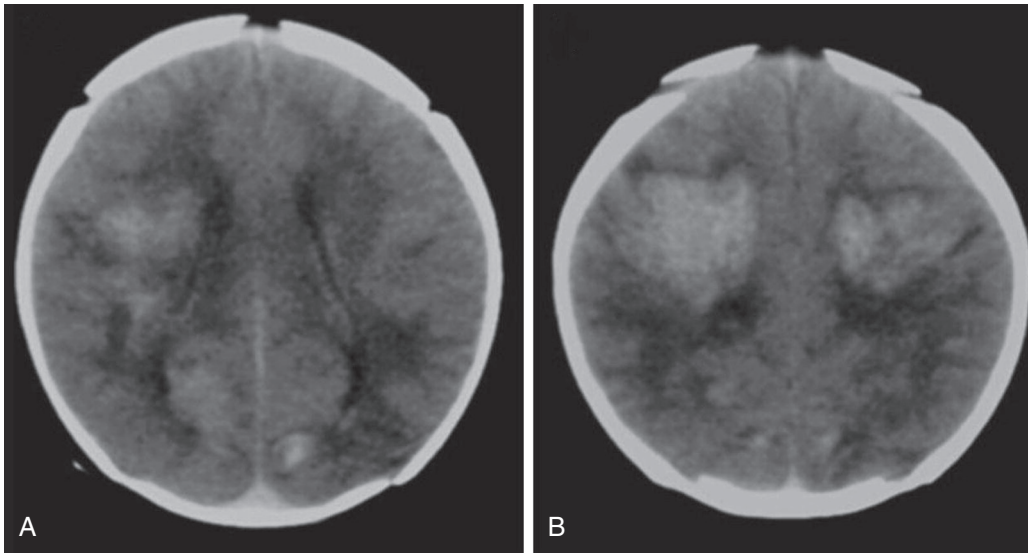

FIGURE 29.29 Neonatal Intraventricular and Intraparenchymal Hemorrhages. A term baby delivered by Cesarean section for thick meconium and late decelerations, Apgar scores of 1, 6, and 8 (at 1, 5, and 10 minutes), presented with neonatal seizures on the 1st day of life. *A* and *B,* Axial head computed tomography images show bilateral frontal, parietal, and scattered occipital hemorrhages in the periventricular and subcortical white matter, the largest in the frontal centrum semiovale. (With permission from Gunny RS, Lin D. Imaging of perinatal stroke. *Magn Reson Imaging Clin North Am.* 2012;20:1-33.)

motor impairment accompanied by cranial nerve dysfunction on the side of the head opposite to the side of extremity weakness suggests brainstem infarction at a location above the pyramidal decussation. Findings of the sensory examination also may be helpful. Preservation of primary sensory modalities provides assessment of spinothalamic axis (pain and temperature) and posterior column (proprioception) integrity. Loss of pain and temperature sensation on one side of the body combined with motor weakness and the presence of proprioceptive deficits on the other side indicate that the cerebrovascular event is in the spinal cord. If the same distribution of motor and sensory disturbances occurs but is accompanied by cranial nerve dysfunction, a brainstem site of injury is likely. Finally, impairment of cortically based sensations such as graphesthesia and stereognosis on one side of the body implies a contralateral hemispheric cause of the observed cortical sensory deficit.

Analysis of language function in the older child may provide help in localizing the region of the cerebrovascular event. Unilateral lesions of the dominant hemisphere involving the frontal lobe immediately anterior to the motor strip supplying the face result in characteristic speech disturbance, Broca aphasia. Broca (nonfluent) aphasia consists of the patient's inability to utter or to write the words or phrases that he or she wishes to express. Although the patient knows the thoughts that he or she wishes to express, the volitional motor function for written or oral expression cannot be mustered. Infarction in the more posterior superior temporal lobe results in an aphasia of a different type, Wernicke aphasia, characterized by marked impairment of auditory comprehension. Comprehension of written matter may be impaired as well. Although the patient remains fluent in speech, language is peppered with unintelligible utterances that are meaningless (neologisms) or are similar but incorrect versions of the intended word (paraphasias). The larger the injury to this region, the more severe is the impairment of language. Speech in most right-handed people and in 50% of left-handed people is governed by the left hemisphere (so-called left hemispheric dominance). The remaining minority share right hemispheric dominance.

The causes of stroke in 1- to 13-year-old children may be considered in 2 general groups: (1) ischemic stroke and (2) intracranial hemorrhage. The ischemic category comprises embolic, thrombotic, and hypotensive causes of stroke. The category of intracranial hemorrhage includes both IPH and SAH.

Ischemic Stroke in Children

Congenital Heart Disease

Congenital heart disease remains the most common diagnosable cause of stroke in childhood. Children with cyanotic congenital heart disease (right-to-left shunts or mixing lesions) face the greatest risk. An embolic stroke constitutes the most common cerebrovascular event. Cardiac defects involving right-to-left shunts allow emboli originating in peripheral venous circulation to bypass their filtration and removal by the pulmonary vascular bed. Thus, emboli entering the heart via venous return may be shunted to the peripheral arterial circulation, only to lodge in the cerebrovascular tree (Fig. 29.30).

Patent foramen ovale contributes significantly to the occurrence of stroke in children. Echocardiographic evaluation of patients who have had stroke reveals patent foramen ovale or evidence of right-to-left shunting in many. Transesophageal echocardiography conducted with Valsalva bubble studies for evidence of direct right-to-left flow is the most useful diagnostic test.

Valvular defects can cause stroke. Mitral valve prolapse may contribute to the occurrence of embolic stroke. Small emboli are dislodged from the abnormal valve leaflets. Mitral valve prolapse has been estimated to underlie 20-30% of strokes in patients younger than 30 years. Echocardiography in both 2-dimensional and M modes proves most helpful in discerning the cardiac valvular abnormality. Rheumatic valvular disease (mitral, aortic), once a common cause of embolic stroke, has become an infrequent cause of childhood stroke. Infected valves in bacterial endocarditis pose a considerable risk for the occurrence of embolic stroke (native, prosthetic, rheumatic, or congenitally abnormal valve). Mitral and aortic valvular vegetations may dislodge and travel distally to occlude cerebral arteries. The most common

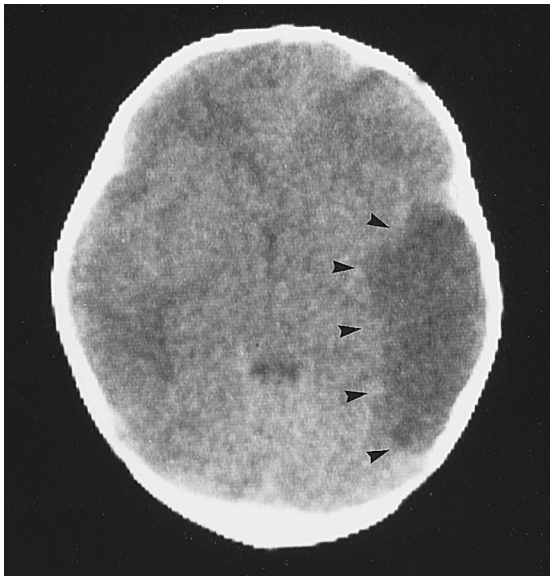

FIGURE 29.30 Computed tomography scan of a 3-month-old boy with trisomy 21 and tetralogy of Fallot who, after cardiac catheterization, had focal seizures involving the right side of the face and right arm. Region of hypodensity in the left hemisphere *(arrowheads)* reflects infarction of the left middle cerebral artery territory, most likely caused by embolic occlusion of that vessel.

organisms found are streptococci and staphylococci (see Chapter 8). Even after vegetations have been successfully sterilized, they may embolize and cause stroke. Emboli from infected valvular vegetations may embolize, travel to the cerebral vasculature, and seed the adventitia of the cerebral vessel. The resultant infection and inflammation result in weakening of the vessel and development of a mycotic aneurysm. Aneurysms may lie dormant for some time before their rupture leads to SAH or IPH and resultant neurologic signs.

Procoagulopathies

Several disorders of coagulation can lead to embolic or thrombotic stroke (see Table 29.23). Adverse consequences of antiphospholipid antibodies have been identified in all age groups. Children, adolescents, and young adults experience the cerebrovascular consequences of these antibodies most often. Antiphospholipid antibodies, including the lupus anticoagulant (LAC), are polyclonal antibodies found in serum that are able to bind to both neutral and negatively charged phospholipids (see Chapter 38). LAC and anticardiolipin antibodies were 1st associated with thrombotic or embolic cerebrovascular events in patients with systemic lupus erythematosus (SLE). Subsequently, patients suffering stroke with no evidence of underlying immune-mediated illness other than the LAC or anticardiolipin antibody were found. The antibody prolongs the partial thromboplastin time (PTT) in vitro but acts as a procoagulant in vivo. A common finding associated with coagulation testing among children with AIS is the presence of anticardiolipin antibody. The presence of these antibodies in a patient who concurrently smokes cigarettes, has findings positive for antinuclear antibodies, or suffers from hyperlipidemia may impart a higher risk for stroke than if the patient carries the antibody alone. The antibody's presence is indicated by a prolonged PTT and a falsely positive serum Venereal Disease Research Laboratory (VDRL) result. The antibody's presence can be conclusively demonstrated functionally and immunologically. Although cerebral infarction and TIAs constitute the most frequently observed neurologic manifestations related to the presence of these antibodies, migraine headache, seizures, and monocular visual disturbances are also associated.

TABLE 29.31 Autoimmune Disorders Associated with Central Nervous System (CNS) Involvement

Disorder	CNS Manifestations
Systemic lupus erythematosus	Migraine headache, seizures, stroke, cerebellar dysfunction, transverse myelopathy, aseptic meningitis, psychosis
Mixed connective tissue disease	Seizures, stroke, cerebellar dysfunction, trigeminal neuropathy
Polyarteritis nodosa	Migraine headache, stroke, subarachnoid hemorrhage, seizures
Granulomatosis with polyangiitis	Migraine headache, subarachnoid hemorrhage, stroke
Takayasu arteritis	Seizure, stroke
Henoch–Schönlein purpura	Headache, stroke, seizures, chorea
Primary CNS vasculitis	Headache, stroke, seizure

Absence of specific serum proteins that act as inhibitors of coagulation may lead to stroke. Two of these proteins, protein S and protein C, have been associated with thrombotic or embolic cerebrovascular disease. Protein C and its cofactor protein S act as anticoagulants and synergistically attenuate coagulation by deactivating the activated forms of factors V and VIII. Absence of (or resistance to) either of these proteins disrupts the balance of coagulation toward increased spontaneous clotting and can result in stroke. In addition, antithrombin III opposes the action of the activated forms of factors II, IX, X, XI, and XII through the irreversible formation of inactivating complexes with these factors. Deficiencies of proteins S and C as well as of antithrombin III may cause arterial thrombotic or embolic stroke or venous infarction. Although their deficiencies are often congenital, they may be acquired through liver disease or nephrotic syndrome. Factor V Leiden, prothrombin 20210A, and lipoprotein A are all important factors that may contribute to the pathogenesis of AIS. Elevated lipoprotein A, protein C deficiency, and sickle cell anemia increase the risk of recurrent strokes. A screening battery of tests, including prothrombin time, PTT, and specific immunologic and functional testing for the proteins suspected of being deficient is essential for diagnosis. Cranial radiation therapy may induce an occlusive vasculopathy, leading to focal cerebral ischemia.

Autoimmune Disorders

Autoimmune disorders may cause neurologic disturbance and cerebrovascular involvement (Table 29.31). Symptoms of abrupt onset with accompanying deficits referable to the CNS have long been associated with SLE. A CNS vasculitis had been presumed to underlie the CNS manifestations of SLE; however, an autopsy study of patients who suffered from SLE revealed a virtual absence of cerebrovascular inflammation. Rather, small areas of infarction relate to proliferative changes in cerebral arterioles that lead to luminal occlusion. Large areas of infarction are more probably related to LAC-derived thromboembolism or to embolism from the sterile cardiac valve leaflet vegetations associated with SLE (Libman–Sacks endocarditis). Additional causes of CNS illness include thrombocytopenic hemorrhage, steroid-induced pseudotumor or psychosis, and CNS infection.

True **cerebral arterial vasculitis** may be an isolated disease or seen in association with recognizable systemic autoimmune disorders. Isolated angiitis of the CNS may affect small, medium-sized, or large vessels. Multiple regions of infarction are often found on MRI.

Neuropathologic evidence of polymorphonuclear leukocyte or monocyte infiltration leading to intimal proliferation and vessel wall necrosis is found. The inflammation affects blood flow and predisposes to thrombosis.

Stroke may occur in the course of **polyarteritis nodosa**. Involvement of the CNS is found in 20-40% of such patients.

Granulomatosis with polyangiitis (formally known as Wegener granulomatosis), a necrotizing vasculitis of the upper pulmonary system, rarely affects the CNS; stroke is uncommon. When the CNS is affected, extension of sinus or nasal inflammation into the basilar skull frequently has occurred.

Mixed connective tissue disease, which clinically overlaps with polymyositis, SLE, and progressive systemic sclerosis, can involve the CNS. Cranial neuropathy, most commonly trigeminal nerve dysfunction, has been the most frequently cited deficit. Stroke manifesting as sudden-onset hemiparesis and aphasia has been reported in children afflicted with mixed connective tissue disease.

Takayasu arteritis, involving the aorta and its principal branches, has been associated with thrombotic stroke. Inflammation-induced luminal constriction leading to thrombosis is thought to cause cerebral ischemia in children.

Necrotizing arteritis with inflammatory infiltrate has been found in both meningeal and cerebral vessels of children suffering from Henoch–Schönlein purpura. Both fixed and transient deficits may occur in this disorder.

Inflammation of cerebral vessels may also occur in the course of bacterial meningitis. The subarachnoid arteries become immersed in exudate. The vessel wall is affected by the inflammatory process. If this condition proceeds long enough, thrombophlebitis ensues. Vascular occlusion results, with consequent features of stroke.

Metabolic Disorders Causing Stroke

Homocystinuria, a disorder of homocysteine metabolism, can cause thrombotic stroke in children. Abnormal homocysteine metabolism results from 1 of 3 inheritable enzymatic defects. The most striking phenotype results from deficiency of cystathionine synthetase, the enzyme that facilitates the catabolism of homocysteine to cystathionine. This leads to accumulation of not only homocysteine but also methionine. Children affected by this autosomal recessive disorder (Table 29.32) have marfanoid habitus, global developmental delay, lens dislocation, and thromboembolism. Thromboemboli may travel to cerebrovascular beds, causing stroke. Serum hyperhomocystinuria injures the vascular endothelium. The denuded vessel wall then becomes a site for thrombosis. The resulting thrombus may remain at its site of origin or it may embolize to a distal locus. Therefore, stroke may have thrombotic or embolic characteristics. Both arterial and venous infarctions may result. Some patients without homocystinuria but with elevated homocysteine levels may be at risk for vascular morbid conditions, including stroke.

Sulfite oxidase deficiency, another autosomal recessive disorder, results in the accumulation of serum sulfite. The associated phenotype may result from deficiency of either the enzyme or its associated and essential pterin-containing molybdenum cofactor. Intellectual disability, seizures, lens displacement, and acute hemiplegia result. The mechanism of the strokelike episodes has not been fully elucidated. It is possible that ischemic mechanisms are not involved and that direct metabolic neurotoxicity accounts for the sudden onset of deficits resembling those of stroke. Sulfites and S-sulfocysteine accumulate in urine.

Fabry disease, a lipid storage disease attributable to ceramide trihexosidase deficiency, results in accumulation of the sphingolipid trihexoside in the kidneys, vascular endothelium, and corneas. Symptoms become apparent in childhood or adolescence. Angiokeratomas and painful paresthesia often constitute the 1st symptoms. Renal failure follows. However, because of endothelial accumulation of sphingolipid in vessel walls, cerebrovascular occlusion results in stroke. Recurrent stroke is common in this rare X-linked disorder.

The manifestations of **mitochondrial disorders** include recurrent and sometimes catastrophic stroke. The syndrome of mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS) manifests in childhood and results from a mutation of mitochondrial DNA. The most common biochemical finding is a deficiency of complex I of the electron transport chain. An elevated serum or cerebrospinal fluid lactate level serves as its chemical signature, and molecular confirmation of the diagnosis can be secured from blood. Although some features of MELAS are shared by other mitochondrial syndromes, hemiparesis of abrupt onset is fairly specific for this syndrome. An excruciating headache resembling migraine may precede the strokelike episodes. Seizures and sensorineural hearing loss are almost always present at some point in the course of the illness. Neuropathologic study of brains from patients with MELAS has shown cystic cavities and necrosis of cortex with relative sparing of white matter.

Other metabolic disorders have been associated with stroke in childhood. Urea cycle defects, especially ornithine transcarbamylase deficiency manifesting in girls, can cause stroke. Deficiency of arginase, another important enzyme of the urea cycle, has been observed in association with hemiparesis and diparesis of subacute onset. Finally, familial lipoprotein disorders, especially those featuring a dearth of high-density lipoprotein or an abundance of triglycerides, have been associated with stroke in children. In most cases, a family history of hyperlipidemia is found.

TABLE 29.32 Genetic Causes of Stroke

Thrombotic/Embolic Stroke

Homocystinuria or elevated homocysteine levels
Fabry disease
Fibromuscular dysplasia
Procoagulopathies (protein C/S deficiency; antithrombin III; factor V Leiden; prothrombin 20210A mutation; methylenetetrahydrofolate reductase mutations)
Sickle cell anemia

Hemorrhage

Factor VIII deficiency
Factor IX deficiency
Factor XI deficiency
Familial intracranial aneurysm
Sickle cell disease
Familial cavernous angioma
Glanzmann thrombasthenia
X-linked thrombocytopenia

Unknown Mechanism

Familial porencephaly
Organic acidemia
Mitochondrial disorders

Rare Monogenic Disorders

APP, CST3, BRI genes (autosomal dominant amyloid angiopathies)
NOTCH3 gene (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL])
KRITI gene (cavernous angiomas)

Moyamoya Disease

Moyamoya disease commonly affects children younger than 15 years and manifests with TIAs or sudden-onset fixed motor deficits. Progressive narrowing and occlusion of the intracranial portion of the internal carotid arteries are characteristic. Endothelial proliferation, fibrosis, and intimal thickening characterize the vascular disease. Resultant proliferation of collateral vessels from the basilar skull circulation creates an intricate latticework of compensatory blood flow. The appearance on angiography is characteristic and consists of a fine vascular network located at the base of the brain. Moyamoya means "hazy" or "puff of smoke" as seen on conventional angiography (Fig. 29.31).

Children usually present with acute hemiplegia as a result of uncompensated occlusion of the internal carotid artery. Because the anatomic abnormality is often bilateral, the hemiplegia may alternate. Disturbance of fine motor function has been observed. Chorea has been reported in association with moyamoya disease. The designation moyamoya syndrome is given when the progressive distal internal carotid artery occlusion occurs as a sequela to a primary disorder such as sickle cell disease, neurofibromatosis, trisomy 21, tuberculous meningitis, and fibromuscular dysplasia. Evidence suggesting a hereditary origin in some cases has been reported in Japan.

Sickle Cell Disease

Acute hemiplegia may be found in children with sickle cell disease (see Chapter 37). Strokes are designated as overt, meaning clinically symptomatic, or silent, in which no symptoms occur but changes are seen on brain imaging. The incidence of overt strokes is 11% in children with HbSS by 20 years and silent strokes occur in up to 37% of children. It may be an isolated event, or it may occur in the setting of a sickle crisis. Sickle cell disease–related cerebral vasculopathy encompasses stroke, TIA, SAH, and moyamoya syndrome. Neurologic signs include hemiparesis, aphasia, and visual disturbances. Neuroimaging studies, particularly MRI, reveal that stroke occurs in watershed distributions between 2 cerebrovascular territories, affecting both the gray and white matter of the cortex. Children with sickle cell disease who have silent infarctions may demonstrate school dysfunction as the only manifestation of neurologic involvement of the disease. These children can demonstrate twice the rate of school difficulties found in children with sickle cell disease without infarctions. Recurrences are common.

The proposed pathophysiologic mechanisms encompass both sickling and progressive stenosis in cerebral vessels. Sickled red blood cells (RBCs) through arteries and capillaries alter the rheology and activate endothelial proliferation in large vessels, ultimately leading to stenosis. Angiography demonstrates large-vessel vasculopathy in the internal carotid arteries and middle cerebral arteries, which on microscopic analysis reveal endothelial proliferation, disruption of the elastic lamina, and microthrombi. Furthermore, there is increased RBC adhesion, endothelial activation, inflammation, and coagulation dysregulation. Cerebral hyperemia thought to be caused by vasodilation has been suggested as a mechanism contributing to the occurrence of watershed infarctions in patients with sickle cell disease.

SAH also occurs among children with sickle cell disease. The frequency of SAH is less than that of infarction, occurring in fewer than 2%. The clinical findings of SAH differ from those of infarction in patients with sickle cell disease. Severe headache, vomiting, and alteration in mental state characterize SAH in children with sickle cell disease. Meningeal signs and focal neurologic deficits may be found on examination. Angiography should be performed on all patients to detect any surgically correctable vascular lesion underlying the hemorrhage.

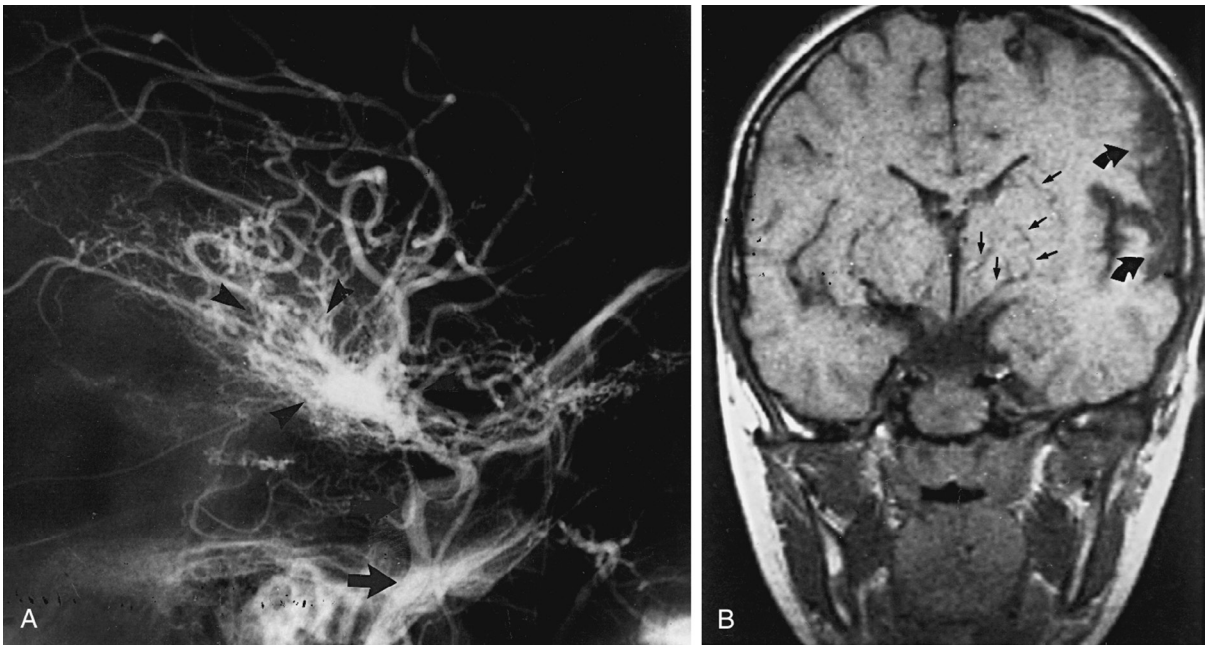

FIGURE 29.31 Sudden onset of right hemiparesis in a 6-year-old boy. *A,* Cerebral angiogram shows the left internal carotid artery *(arrow)* leading to a highly arborized, telangiectatic network of vessels *(arrowheads)* typical of moyamoya disease. The typical middle cerebral artery vascular tree is absent. *B,* Cranial coronal magnetic resonance imaging scan shows region of low signal in the middle cerebral artery territory and denotes infarction *(curved arrows).* Flow voids in the basal ganglia *(straight arrows)* are radiographic manifestations of the basilar collateral circulation typical of this vascular anomaly.

(See *Nelson Textbook of Pediatrics*, p. 1065.)

Intracranial Hemorrhage

Coagulopathies

The hemophilias (A and B) are X-linked disorders that may result in intracranial bleeding. Bleeding may occur in either intraparenchymal or subarachnoid locations. Hemophilia A arises from factor VIII deficiency. Patients with this disorder may experience intracranial bleeding in association with head trauma. Unfortunately, spontaneous intracranial bleeding not associated with head trauma also occurs. The risk of spontaneous bleeding rises with the severity of factor VIII deficiency.

Hemophilia B derives from a deficiency of factor IX. Intracranial bleeding is seen less frequently among these patients than among patients with hemophilia A. Hemophilia B is encountered much less frequently than hemophilia A, and this difference may account for the less frequent observation of intracranial bleeding. Clinical symptoms depend on the intracranial location of the hemorrhage. If the bleeding occurs in the subarachnoid space, symptoms of severe headache, nuchal rigidity, and meningismus are found. Mental status is frequently altered. If bleeding occurs within brain parenchyma, focal features, including hemiparesis, may be found.

Thrombocytopenia

Severe thrombocytopenia rarely leads to cerebral hemorrhage, especially if the cause is idiopathic (immune) thrombocytopenic purpura. Thrombocytopenia caused by bone marrow failure (drug-induced suppression, aplastic anemia, malignancy) may pose a greater risk. Significant risk of intracranial hemorrhage is thought not to occur until the platelet count is less than 20,000/mm^3. Small petechial hemorrhages into white matter are thought to be more common than are large parenchymal hemorrhages.

Causes of thrombocytopenia include idiopathic immune thrombocytopenic purpura, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, infection, and malignancy (replacement of bone marrow or drug-induced suppression). The features of these underlying causes dominate the clinical picture (see Chapter 38).

Vascular Malformations

AVM of the brain is the most common cause of intracranial hemorrhage in preadolescent children. The malformation represents a developmental anomaly that manifests with hemorrhage much more frequently in children than in adults. The AVM consists of dilated vascular channels, some of which reveal the highly muscularized walls of arterioles. Gliotic neural tissue resides in and among the vascular branches of the malformation. It is more common in boys. The most frequent presenting events associated with AVM in children are seizures and hemorrhage. Most AVMs reside in the cerebral hemispheres; 10% arise in the posterior fossa.

The clinical features of AVM hemorrhage consist of those found in IPH. Focal features depend on the area of brain in which the bleeding has occurred. A higher mortality rate has been observed in children than in adults harboring hemorrhagic AVMs. The risk of hemorrhage from an unruptured AVM is approximately 3% per year. The introduction of MRI has led to better localization of the malformation (Fig. 29.32).

Intracranial aneurysms constitute the most common cause of intracranial bleeding in all patients younger than 20 years and are more frequent in boys. The most common site of aneurysmal bleeding in children is along the intracranial portion of the internal carotid artery. The vertebral and basilar arteries are other common sites of intracranial aneurysm in children. In addition, intracranial aneurysms discovered in children tend to be larger than those found in adults. Although most aneurysms constitute vascular developmental anomalies, other causes exist, including mycotic aneurysms associated with bacterial endocarditis (Fig. 29.33). Acquired cerebral artery aneurysms have been reported in children infected with the human immunodeficiency virus. Intracranial aneurysms are found with increased frequency among patients suffering from polycystic renal disease, those with aortic coarctation, and those with Ehlers–Danlos syndrome in comparison with the general pediatric population. Intracranial aneurysms have been noted to exist in close association with AVMs in some pediatric cases.

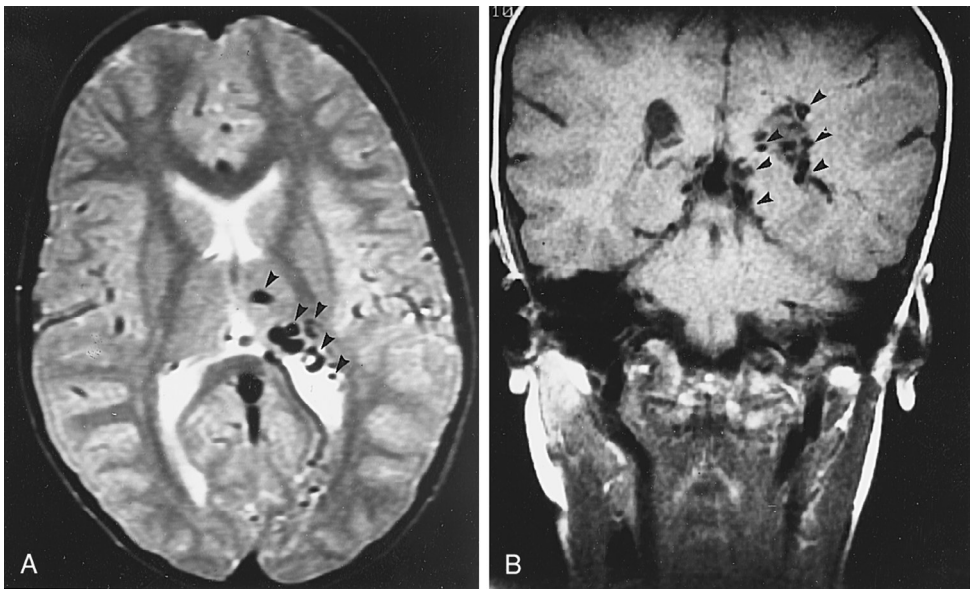

FIGURE 29.32 Cranial magnetic resonance imaging scan of a 6-year-old girl with recurrent headache. *A,* Axial view demonstrates flow voids deep in the left hemisphere near the lateral ventricle *(arrowheads),* consistent with arteriovenous malformation. *B,* Coronal view through parietal lobes also demonstrates numerous flow voids *(arrowheads)* indicative of arteriovenous malformation.

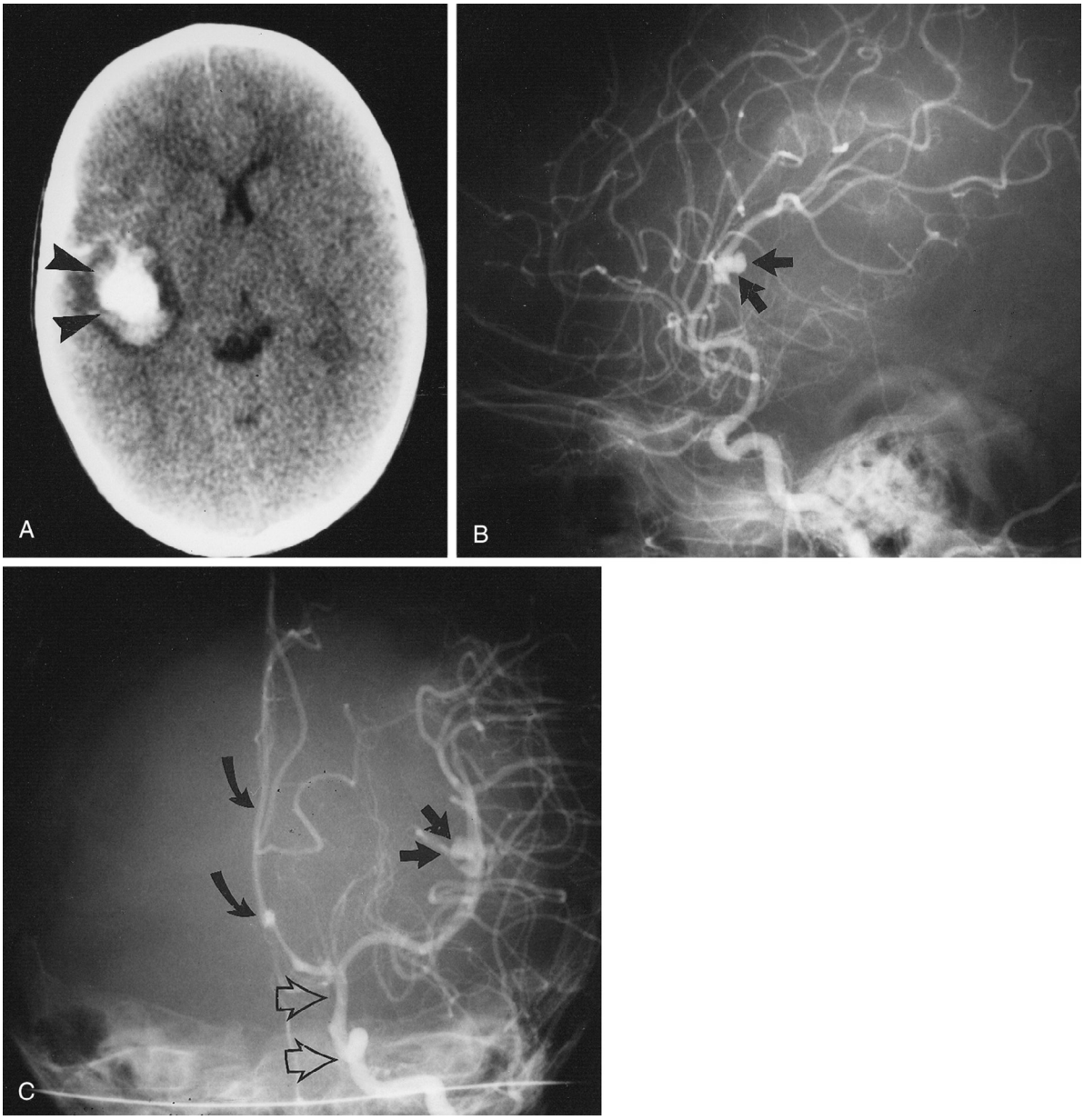

FIGURE 29.33 Mycotic Cerebral Aneurysm Hemorrhage. *A,* A cranial computed tomographic scan reveals a hyperdense area in the left temporal lobe *(arrowheads)* representing intraparenchymal hemorrhage. *B,* Cerebral angiography in a lateral view shows a lobulated structural abnormality representing the mycotic aneurysm, most probably residing in the middle cerebral artery tree *(arrows). C,* An anteroposterior angiographic view confirms the location of the aneurysm in the middle cerebral artery *(straight arrows)* located laterally rather than in the more medial anterior cerebral artery *(curved arrows).* The internal carotid artery *(open arrows)* gives rise to both the anterior and the middle cerebral arteries.

All affected patients should be studied with angiography after aneurysmal bleeding. Patients should be closely observed for development of hydrocephalus and increased intracranial pressure. Aneurysmal bleeding resulting in significant SAH can precipitate cerebral vasospasm. Vasospasm, in turn, can cause a secondary cerebral infarction. Vasospasm occurs most commonly 7-10 days after the aneurysmal bleeding. Prophylaxis is the most effective treatment for vasospasm. Maintenance of blood pressure through intravascular volume expansion has been shown to reduce the incidence of posthemorrhagic vasospasm.

The syndrome of posterior fossa brain malformations, facial hemangiomas, arterial anomalies, coarctation of the aorta, and cardiac and eye defects (**PHACE**) is a constellation of disorders. CNS malformations affect the posterior fossa and include Dandy–Walker malformation, arachnoid cysts, cerebellar hypoplasia, and enlarged cisterna magna. Vascular anomalies include brachiocephalic artery and aortic arch anomalies (coarctation of aorta), cerebrovascular arterial hypoplasia, aneurysms, stenosis and aberrancies, and progressive occlusive arterial disease leading to stroke.

Evaluation of Stroke in Children

Neuroimaging provides the foundation of evaluation. Intracranial blood is rapidly seen with CT. The early stages of ischemic stroke, however, are detected with difficulty. MRI provides evidence of

ischemia in the early stages of stroke. Magnetic resonance angiography (MRA) has provided reliable information about the blood flow in and the structure of large intracranial vessels. Small intracranial vessels are poorly seen on MRA, however, and invasive contrast angiography remains the radiologic procedure of choice for full elucidation of the cerebral vasculature (see Fig. 29.19). Laboratory studies helpful in the evaluation of the child who has suffered stroke are determined by the patient's clinical features (Table 29.33).

ADOLESCENTS

The causes of adolescent stroke include those discussed for preadolescent children. Determination of stroke mechanism—embolic, thrombotic, or hemorrhagic—remains important. Nonetheless, stroke among adolescents may also be caused by other entities not commonly found in neonates or preadolescent children.

Fibromuscular Dysplasia

Fibromuscular dysplasia involves arteries throughout the body. First described in renal arteries, the pathologic features of fibromuscular dysplasia have been found in carotid, vertebral, and intracranial arteries. Fibromuscular dysplasia involves irregularly spaced focal zones of fibrous and muscular hyperplasia of the media, disruption of the elastic lamina, and eventration of the media. The constricted regions of vascular fibrosis alternate with regions of luminal dilation to create the characteristic beaded appearance on angiography. Fibromuscular dysplasia is more common in young girls and has been found in adolescents; with carotid involvement, a bruit may be auscultated in the neck. If renal arteries are affected, hypertension may be present. Neurologic symptoms signifying cerebrovascular involvement most commonly consist of TIAs and mild strokes. A thrombotic mechanism is presumed but has never been proven.

Sexual Activity, Oral Contraception, and the Puerperium

Sexual intercourse generates marked increases in systemic blood pressure. Sustained hypertension elevates the risk of hypertensive intracranial hemorrhage. The risk for such a hemorrhage is heightened by the existence of an intracranial aneurysm or arteriovenous hemorrhage.

Oral contraceptives have been associated with stroke in young women. In some series, the combination of migraine headache and concurrent oral contraceptive use has been cited as a risk factor for stroke.

Pregnancy and the postpartum state have been considered periods of hypercoagulability. In addition, venous stasis increases. These 2 factors are believed to promote the occurrence of cerebral venous thrombosis and resultant cerebral venous infarction in pregnant patients and in patients immediately after parturition. Frequently, the initial manifestation is headache. Seizures, either focal or generalized, are common. Acute hemiparesis is the most common focal feature on neurologic examination. Papilledema can appear as intracranial pressure rises caused by resultant venous outflow obstruction in the head. The appearance of these signs or symptoms in a gravid or postpartum adolescent should raise suspicion about the existence of underlying cerebral venous thrombosis. Diagnosis is made with cranial neuroimaging; MRI provides the best noninvasive assessment.

Cocaine Use

SAH can result from cocaine use. The probability of this occurrence is higher in cocaine users with occult intracranial aneurysms or AVMs. Irrespective of the method of cocaine administration, SAH may occur. Cocaine produces tachycardia, hypertension, and vasoconstriction.

TABLE 29.33 Radiologic, Laboratory, and Cardiovascular Assessment of Stroke in Children

Radiologic Assessment
Rapid Detection of Intracranial Blood
Cranial CT
Cranial MRI (also detects extravascular blood but is not as rapidly obtained as cranial CT images)
Detection of Brain Parenchymal Changes Related to Stroke
Cranial MRI, including diffusion-weighted imaging
Cranial CT (reveals changes later in course than MRI)
Detection of Abnormal Vascular Structure
Percutaneous cerebral angiogram (provides the most complete and accurate demonstration of extracranial and intracranial vasculature)
Cranial MRA
Laboratory Assessment
Disturbance of RBC, WBC, or Platelet Number
Hematocrit
Platelet count
WBC count with differential
Disturbance of Coagulation
PT, PTT
Antithrombin III level
Protein C level, protein S level; resistance to protein C assay
Lupus anticoagulant detection, anticardiolipin antibody, antiphospholipid antibody
MTHFR gene mutation, prothrombin 20210A gene mutation analysis
Metabolic Disturbances
Serum electrolytes, glucose
Serum amino acids
Urine organic acids
Serum/CSF lactate and pyruvate
Urine toxicology screen
Disturbance of Hemoglobin
Hemoglobin concentration
Hemoglobin electrophoresis
Inflammatory Disturbances
ESR
ANA, RF
CSF studies: glucose, protein, cell counts, special stains, cultures
Lipid and lipoprotein disturbances
Serum triglycerides
Serum cholesterol; if high, obtain fasting HDL
Cardiovascular Assessment
ECG
Standard and transesophageal echocardiogram

ANA, antinuclear antibodies; CSF, cerebrospinal fluid; CT, computed tomography; ECG, electrocardiography; ESR, erythrocyte sedimentation rate; HDL, high-density lipoproteins; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; MTHFR, methyltetrahydrofolate reductase; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell; RF, rheumatoid factor; WBC, white blood cell.

The resultant sudden rise in systemic blood pressure is thought to precipitate SAH. Ischemic lesions have also been found. Nonetheless, intracranial hemorrhage appears to occur more commonly than ischemic infarction.

Causes of Stroke Unrelated to Age

Pharyngeal Infection

Pharyngeal infections have been associated with stroke caused by thrombotic occlusion of the carotid arteries in their cervical course. In childhood, stroke resulting from carotid occlusion more commonly occurs in the intracranial segment of the carotid artery. Infections of the cervical region such as tonsillitis, pharyngitis, cervical lymphadenitis, and necrotizing fasciitis have been found in children experiencing acute hemiplegia. In these instances, angiography has shown occlusion of the internal carotid artery located in its cervical segment. Neuroimaging has demonstrated ischemic infarction of the cortical region served by the middle cerebral artery, which arises from the carotid circulation. It is speculated that the soft tissue infection leads to an inflammatory arteritis. Vessel wall inflammation and direct pressure on the artery then lead to intravascular thrombosis and occlusion. Neurologic symptoms are noted in a patient with evidence of infection: fever, lethargy, sore throat or neck, difficulty swallowing, or cervical lymphadenopathy.

Head and Neck Trauma

Head and neck trauma is an important cause of stroke in children. Neurologic symptoms may be delayed more than 24 hours in their appearance in relation to the time of the inciting trauma. Stroke caused by carotid artery injury has been well documented. Most often, these cerebrovascular events occur after head and neck trauma sustained in motor vehicle accidents, bicycle accidents, fights, or falls. Hemiparesis is a common symptom at presentation if the cause resides in the carotid artery. Carotid angiography reveals internal carotid artery occlusion. The site of occlusion most often exists at the level of the carotid bifurcation. Pathologically, an intimal tear is found with attendant thrombus blocking the arterial lumen. In some cases, arterial dissection is found.

Vertebral artery injury from trauma may cause stroke in children. Traction injuries of the neck appear to cause vertebral artery injury. The vertebral artery is most vulnerable to traumatic injury at its atlantoaxial portion. The resultant strokes occur in the vertebrobasilar portion of the cerebral circulation. Symptoms are referable to the structures receiving blood from this system: brainstem, cerebellum, occipital lobes, and temporal lobes. Clinical symptoms of vertebrobasilar stroke include difficulty swallowing, ataxia, facial weakness, tinnitus, vertigo, anisocoria, extraocular movement palsies, dysmetria, cortical blindness, and mental status changes. Because both the long sensory and the motor tracts course through the brainstem, symptoms of general sensorimotor impairment may be found. Vertebral artery injury in children has been reported in the setting of athletic endeavor or automobile accidents. The resultant vertebrobasilar strokes are caused by thrombosis or vertebral artery dissection.

Migraine Headache

Stroke may occur in the setting of migraine headache. The occurrence of focal motor deficits during a migraine headache denotes **complicated migraine** (see Chapter 28). Acute hemiparesis has been well documented during these episodes and is believed to reflect the involvement of the cerebral circulation derived from the carotid artery. Symptoms such as ataxia, cortical blindness, and cranial nerve dysfunction are correlated with vertebrobasilar circulation involvement. Focal symptoms may be fixed or may occur as TIAs.

Initially, an association between migrainous stroke and discharged emboli from mitral valve prolapse was hypothesized, but studies have not supported the association. Although oral contraceptives confer hypercoagulability thought to predispose to stroke, the postulated additive risk for stroke with migraine headaches and oral contraceptives has been challenged. Angiographic studies on patients with focal deficits consistent with stroke in the setting of migraine headache reveal vasoconstriction of vessels in either the vertebrobasilar or the carotid circulations. The anatomic position of the constricted vessels correlated with the location of the observed deficits. Ischemia provoked by vasoconstriction during prolonged migraine has been hypothesized as the mechanism of stroke in these patients.

SUMMARY AND RED FLAGS

In the neonate and older infant, hypotonia is more commonly associated with systemic diseases that indirectly affect the central nervous system. However, various disorders are related to the nervous system and necessitate immediate attention. Meningomyelocele is usually discovered by prenatal fetal ultrasonography or at birth. Like an encephalopathic infant, any child with an acute neurologic process needs a thorough investigation. Hypotonia and weakness can arise from dysfunction at many potential sites of the nervous system. An accurate diagnosis requires careful anatomic localization.

Ascending motor weakness with absence of deep tendon reflexes that develops over a few days suggests GBS and is a medical emergency. In addition, spine pain, a motor-sensory level, bowel and bladder dysfunction, and upper motor neuron signs strongly suggest a lesion in the spinal cord and constitute a medical and possibly a surgical emergency.

Acute hemiplegia most frequently represents stroke. Because stroke occurs most often in children as a consequence of an underlying process, the clinician should evaluate the patient carefully to determine whether such a predisposing condition exists.

Red flags in children with stroke include manifestations of underlying primary processes (e.g., trauma, medications, inborn errors of metabolism, malignancy, coagulopathy), depressed level of consciousness, a positive family history of early-onset stroke (younger than 30 years), signs of increased intracranial pressure (see Chapter 31), a carotid bruit, hypertension, and the presence of prior TIAs.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Hypotonic Infant

Birdi K, Prasad AN, Prasad C, et al. The floppy infant: retrospective analysis of clinical experience (1990-2000) in a tertiary care facility. *J Child Neurol*. 2005;20:803-808.

Bodensteiner JB. The evaluation of the hypotonic infant. *Semin Pediatr Neurol*. 2008;15:10-20.

David WS, Jones HR Jr. Electromyography and biopsy correlation with suggested protocol for evaluation of the floppy infant. *Muscle Nerve*. 1994;17:424-430.

Harris SR. Congenital hypotonia: clinical and developmental assessment. *Dev Med Child Neurol*. 2008;50:889-892.

Johnston H. The floppy weak infant revisited. *Brain Dev*. 2003;25:155-158.

Laugel V, Cossee M, Matis J, et al. Diagnostic approach to neonatal hypotonia: retrospective study on 144 neonates. *Eur J Pediatr*. 2008;167:517-523.

Miller VS, Delgado M, Iannaccone ST. Neonatal hypotonia. *Semin Neurol*. 1993;13:73-83.

Paro-Panjan D, Neubauer D. Congenital hypotonia: is there an algorithm? *J Child Neurol*. 2004;19:439-442.

Prasad AN, Prasad C. The floppy infant: contribution of genetic and metabolic disorders. *Brain Dev*. 2003;25:457-476.

Richer LP, Shevell MI, Miller SP. Diagnostic profile of neonatal hypotonia: an 11-year study. *Pediatr Neurol*. 2001;25:32-37.

Sparks SE. Neonatal hypotonia. *Clin Perinatol*. 2015;42:363-371.

Arthrogryposis

Bamshad M, Van Heest AE, Pleasure D. Arthrogryposis: a review and update. *J Bone Joint Surg Am*. 2009;91(suppl 4):40-46.

Haliloglu G, Topaloglu H. Arthrogryposis and fetal hypomobility syndrome. *Handb Clin Neurol*. 2013;113:1311-1319.

Hall JG, Aldinger KA, Tanaka KI. Amyoplasia revisited. *Am J Med Genet A*. 2014;164A:700-730.

Hypoxic-Ischemic Encephalopathy

Chau V, Poskitt KJ, Dunham CR, et al. Magnetic resonance imaging in the encephalopathic term newborn. *Curr Pediatr Rev*. 2014;10:28-36.

Huppi PS, Inder TE. Magnetic resonance techniques in the evaluation of the perinatal brain: recent advances and future directions. *Semin Neonatol*. 2001;6:195.

Rafay MF, Cortez MA, de Veber GA, et al. Predictive value of clinical and EEG features in the diagnosis of stroke and hypoxic ischemic encephalopathy in neonates with seizures. *Stroke*. 2009;40:2402-2407.

Rivkin M. Hypoxic ischemic brain injury in the term newborn: neuropathology, clinical aspects, and neuroimaging. *Clin Perinatol*. 1997;24:607.

Robertson R, Ben-Sira L, Robson CD, et al. Magnetic resonance line scan diffusion imaging of term neonates with hypoxic-ischemic brain injury. *AJNR Am J Neuroradiol*. 1999;20:1658.

Central Nervous System

Cardoso C, Leventer RJ, Ward HL, et al. Refinement of a 400-kb critical region allows genotypic differentiation between isolated lissencephaly, Miller-Dieker syndrome, and other phenotypes secondary to deletions of 17p13.3. *Am J Med Genet*. 2003;72:918-930.

Knebusch M. Acute transverse myelitis in childhood: nine cases and review of the literature. *Dev Med Child Neurol*. 1998;40:631-639.

Systemic Disorders

Area-Gomez E, Schon EA. Mitochondrial genetics and disease. *J Child Neurol*. 2014;29:1208-1215.

Bosch AM, Abeling NG, Ijlst L, et al. Brown-Vialetto-Van Laere and Fazio Londe syndrome is associated with a riboflavin transporter defect mimicking mild MADD: a new inborn error of metabolism with potential treatment. *J Inherit Metab Dis*. 2011;34:159-164.

Bosch AM, Stroek K, Abeling NG, et al. The Brown-Vialetto-Van Laere and Fazio Londe syndrome revisited: natural history, genetics, treatment and future perspectives. *Orphanet J Rare Dis*. 2012;7:83.

Cassidy SB, Dykens E, Williams CA. Prader-Willi and Angelman syndromes: sister imprinted disorders. *Am J Med Genet*. 2000;97:136-146.

Conte MI, Pescatore A, Paciolla M, et al. Insight into IKBKG/NEMO locus: report of new mutations and complex genomic rearrangements leading to incontinentia pigmenti disease. *Hum Mutat*. 2014;35:165-177.

DiMauro S, Hirano M. *MELAS*. Seattle (WA): University of Washington: GeneReviews (Internet); 2001 Feb 27.

DiMauro S, Hirano M. *MERRF*. Seattle (WA): University of Washington: GeneReviews (Internet); 2003 Jun 3.

Driscoll DJ, Miller JL, Schwartz S, Cassidy SB. *Prader-Willi Syndrome*. Seattle (WA): University of Washington: GeneReviews (Internet); 1998 Oct 6.

Knoll JH, Wagstaff J, Lalande M. Cytogenetics and molecular studies in the Prader-Willi and Angelman syndromes: an overview. *Am J Med Genet*. 1993;46:2-6.

Liang C, Ahmad K, Sue CM. The broadening spectrum of mitochondrial disease: shifts in the diagnostic paradigm. *Biochim Biophys Acta*. 2014;1840:1360-1367.

Spinal Muscular Atrophy

d'Ydewalle C, Sumner CJ. Spinal muscular atrophy therapeutics: where do we stand? *Neurotherapeutics*. 2015;12:303-316.

Lunn MR, Wang CH. Spinal muscular atrophy. *Lancet*. 2008;371:2120-2133.

Zanetta C, Nizzardo M, Simone C, et al. Molecular therapeutic strategies for spinal muscular atrophies: current and future clinical trials. *Clin Ther*. 2014;36:128-140.

Peripheral Neuropathy

Abd-Allah SA, Jansen PW, Ashwal S. Intravenous immunoglobulin as therapy for pediatric Guillain-Barré syndrome. *J Child Neurol*. 1997;12:376.

Baets J, Deconinck T, De Vriendt E, et al. Genetic spectrum of hereditary neuropathies with onset in the first year of life. *Brain*. 2011;134:2664-2676.

Centers for Disease Control and Prevention (CDC). Acute flaccid paralysis syndrome associated with West Nile virus infection—Mississippi and Louisiana, July-August 2002. *MMWR Morb Mortal Wkly Rep*. 2002;51:825-828.

De Jonghe B, Sharshar T, Lefaucheur JP, et al. Paresis acquired in the intensive care unit. *JAMA*. 2002;288:2859-2867.

Dematteis M, Pepin JL, Jeanmart M, et al. Charcot-Marie-Tooth disease and sleep apnoea syndrome: a family study. *Lancet*. 2001;357:267-272.

Dyck PJ, Dyck PJB. Atypical varieties of chronic inflammatory demyelinating neuropathies. *Lancet*. 2000;355:1293-1294.

Hughes RAC. Sensory form of Guillain-Barré syndrome. *Lancet*. 2001;357:1465-1466.

Hughes RAC. Peripheral neuropathy. *BMJ*. 2002;324:466-469.

Hund EF, Borel CO, Cornblath DR, et al. Intensive management and treatment of severe Guillain-Barré syndrome. *Crit Care Med*. 1993;21:433-446.

Jansen PW, Perkin RM, Ashwal S. Guillain-Barré syndrome in childhood: natural course and efficacy of plasmapheresis. *Pediatr Neurol*. 1992;9:16-20.

Johnson-Kerner BL, Roth L, Greene JP, et al. Giant axonal neuropathy: an updated perspective on its pathology and pathogenesis. *Muscle Nerve*. 2014;50:467-476.

Ryan MM. Pediatric Guillain-Barre syndrome. *Curr Opin Pediatr*. 2013;25:689-693.

Tabarki B, Coffinieres A, Van den Bergh P. Critical illness neuromuscular disease: clinical, electrophysiological, and prognostic aspects. *Arch Dis Child*. 2002;86:103-107.

Vedanarayanan VV, Evans OB, Subramony SH. Tick paralysis in children: electrophysiology and possibility of misdiagnosis. *Neurology*. 2002;59:1088-1090.

Yiu EM, Ryan MM. Genetic axonal neuropathies and neurnopathies of pre-natal and infantile onset. *J Peripher Nerv Syst*. 2012;17:285-300.

Neuromuscular Junction

Amato A, Russell J. *Neuromuscular Disorders*. New York: McGraw-Hill; 2008.

Darras BT, Jones HR. Diagnosis of pediatric neuromuscular disorders in the era of DNA analysis. *Pediatr Neurol*. 2000;23:289-300.

Horslen SP, Clayton PT, Harding BN, et al. Olivopontocerebellar atrophy of neonatal onset and disialotransferrin developmental deficiency syndrome. *Arch Dis Child*. 1991;66:1027-1032.
Ionita CM, Acsadi G. Management of juvenile myasthenia gravis. *Pediatr Neurol*. 2013;48:95-104.
Rosow LK, Strober JB. Infant botulism: review and clinical update. *Pediatr Neurol*. 2015;52:487-492.
Vasta I, Kinali M, Messina S, et al. Can clinical signs identify newborns with neuromuscular disorders? *J Pediatr*. 2005;146:73-79.
Vincent A, Palace J, Hilton-Jones D. Myasthenia gravis. *Lancet*. 2001;357:2122-2128.

Myopathies

Bönnemann CG, Wang CH, Quijano-Roy S, et al. Diagnostic approach to the congenital muscular dystrophies. *Neuromuscul Disord*. 2014;24:289-311.
Conte MI, Pescatore A, Paciolla M, et al. Insight into IKBKG/NEMO locus: report of new mutations and complex genomic rearrangements leading to incontinentia pigmenti disease. *Hum Mutat*. 2014;35:165-177.
Dagli AI, Weinstein DA. *Glycogen Storage Disease Type VI*. Seattle (WA): University of Washington: GeneReviews (Internet); 2009 Apr 23.
Dagli A, Sentner CP, Weinstein DA. *Glycogen Storage Disease Type III*. Seattle (WA): University of Washington: GeneReviews (Internet); 2010 Mar 9.
Darras BT, Friedman NR. Metabolic myopathies: a clinical approach; part I. *Pediatr Neurol*. 2000;22:87-97.
Darras BT, Friedman NR. Metabolic myopathies: a clinical approach; part II. *Pediatr Neurol*. 2000;22:171-181.
Dasouki M, Jawdat O, Almadhoun O, et al. Pompe disease: literature review and case series. *Neurol Clin*. 2014;32:751-776, ix.
Echenne B, Bassez G. Congenital and infantile myotonic dystrophy. *Handb Clin Neurol*. 2013;113:1387-1393.
Emery AEH. The muscular dystrophies. *Lancet*. 2002;359:687-695.
Findlay AR, Goyal NA, Mozaffar T. An overview of polymyositis and dermatomyositis. *Muscle Nerve*. 2015;51:638-656.
Ghosh PS, Sorenson EJ. Diagnostic yield of electromyography in children with myopathic disorders. *Pediatr Neurol*. 2014;51:215-219.
Goldstein J, Austin S, Kishnani P, Bali D. *Phosphorylase Kinase Deficiency*. Seattle (WA): University of Washington: GeneReviews (Internet); 2011 May 31.
Leslie N, Tinkle TB. *Glycogen Storage Disease Type II (Pompe Disease)*. Seattle (WA): University of Washington: GeneReviews (Internet); 2007 Aug 31.
Magoulas PL, El-Hattab AW. *Glycogen Storage Disease Type IV*. Seattle (WA): University of Washington: GeneReviews (Internet); 2013 Jan 3.
Manole A, Fratta P, Houlden H. Recent advances in bulbar syndromes: Genetic causes and disease mechanisms. *Curr Opin Neurol*. 2014;27:506-514.
Martín MA, Lucia A, Arenas J, et al. *Glycogen Storage Disease Type V*. Seattle (WA): University of Washington: GeneReviews (Internet); 2006 Apr 19.
Mendell JR. Congenital muscular dystrophy: searching for definition after 98 years. *Neurology*. 2001;56:993-994.
North KN, Wang CH, Clarke N, et al. Approach to the diagnosis of congenital myopathies. *Neuromuscul Disord*. 2014;24:97-116.
Pizzuti A, Fu YH. An unstable triplet repeat in a gene related to myotonic muscular dystrophy. *Science*. 1992;255:1256.
Ptacek LJ, Johnson KJ, Griggs RC. Genetics and physiology of the myotonic muscle disorders. *N Engl J Med*. 1993;328:482-488.
Sharp LJ, Haller RG. Metabolic and mitochondrial myopathies. *Neurol Clin*. 2014;32:777-799, ix.
Wein N, Alfano L, Flanigan KM. Genetics and emerging treatments for Duchenne and Becker muscular dystrophy. *Pediatr Clin North Am*. 2015;62:723-742.

Stroke: General

Bernard TJ, Rivkin MJ, Scholz K, et al. Emergence of the primary pediatric stroke center: impact of the thrombolysis in pediatric stroke trial. *Stroke*. 2014;45:2018-2023.
Bodey C, Goddard T, Patankar T, et al. Experience of mechanical thrombectomy for paediatric arterial ischaemic stroke. *Eur J Paediatr Neurol*. 2014;18:730-735.
Boelman C, Shroff M, Yau I, et al. Antithrombotic therapy for secondary stroke prevention in bacterial meningitis in children. *J Pediatr*. 2014;165:799-806.
Fullerton HJ, Wu YW, Zhao S, et al. Risk of stroke in children: ethnic and gender disparities. *Neurology*. 2003;61:189.
Ganesan V, Chong WK, Cox TC, et al. Posterior circulation stroke in childhood. *Neurology*. 2002;59:1552.
Goeggel Simonetti B, Cavelti A, Arnold M, et al. Long-term outcome after ischemic stroke in children and young adults. *Neurology*. 2015;84:1941-1947.
Gumer LB, Del Vecchio M, Aronoff S. Strokes in children: a systematic review. *Pediatr Emerg Care*. 2014;30:660-664.
Gunny RS, Lin D. Imaging of perinatal stroke. *Magn Reson Imaging Clin N Am*. 2012;20:1-33.
Hand PJ, Kwan J, Lindley RI, et al. Distinguishing between stroke and mimic at the bedside: the brain attack study. *Stroke*. 2006;37:769-775.
Kirton A, deVeber G. Paediatric stroke: pressing issues and promising directions. *Lancet Neurol*. 2015;14:92-102.
Kirton A, Shroff M, Pontigon AM, et al. Risk factors and presentations of periventricular venous infarction vs arterial presumed perinatal ischemic stroke. *Arch Neurol*. 2010;67:842-848.
Lanni G, Catalucci A, Conti L, et al. Pediatric stroke: clinical findings and radiological approach. *Stroke Res Treat*. 2011;2011:172168.
Lo W, Gordon A, Hajek C, et al. Social competence following neonatal and childhood stroke. *Int J Stroke*. 2014;9:1037-1044.
Lynch J, Hirtz DG, DeVeber G, et al. Report of the National Institute of Neurological Disorders and Stroke workshop on perinatal and childhood stroke. *Pediatrics*. 2002;109:116-123.
Mackay MT, Chua ZK, Lee M, et al. Stroke and non-stroke brain attacks in children. *Neurology*. 2014;82:1434-1440.
Mallick AA, Ganesan V, Kirkham FJ, et al. Childhood arterial ischaemic stroke incidence, presenting features, and risk factors: a prospective population-based study. *Lancet Neurol*. 2014;13:35-43.
Mittal SO, ThatiGanganna S, Kuhns B, et al. Acute ischemic stroke in pediatric patients. *Stroke*. 2015;46:e32-e34.
Moharir M, Deveber G. Pediatric arterial ischemic stroke. *Continuum (Minneap Minn)* 2014;20:370-386.
Monagle P, Chan AK, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e737S-e801S.
Moraitis E, Ganesan V. Childhood infections and trauma as risk factors for stroke. *Curr Cardiol Rep*. 2014;16:527.
Rivkin MJ, deVeber G, Ichord RN, et al. Thrombolysis in pediatric stroke study. *Stroke*. 2015;46:880-885.
Shellhaas RA, Smith SE, O'Tool E, et al. Mimics of childhood stroke: characteristics of a prospective cohort. *Pediatrics*. 2006;118:704-709.
Tibussek D, Sinclair A, Yau I, et al. Late-onset group B streptococcal meningitis has cerebrovascular complications. *J Pediatr*. 2015;166:1187.e1-1192.e1.
Tournier-Lasserve E. New players in the genetics of stroke. *N Engl J Med*. 2002;347:1711.
Wintermark M, Hills NK, deVeber GA, et al. Arteriopathy diagnosis in childhood arterial ischemic stroke: results of the vascular effects of infection in pediatric stroke study. *Stroke*. 2014;45:3597-3605.
Wraige E, Pohl KR, Ganesan V. A proposed classification for subtypes of arterial ischemic stroke in children. *Dev Med Child Neurol*. 2005;47:252-256.
Yock-Corrales A, Mackay MT, Mosley I, et al. Acute childhood arterial ischemic and hemorrhagic stroke in the emergency department. *Ann Emerg Med*. 2011;58:156-163.
Zanaty M, Chalouhi N, Starke RM, et al. Endovascular stroke intervention in the very young. *Clin Neurol Neurosurg*. 2014;127:15-18.

Stroke: Neonate

Coker S, Beltran R, Myers T, et al. Neonatal stroke: description of patients and investigation into pathogenesis. *Pediatr Neurol*. 1988;4:219.

Grunt S, Mazenauer L, Buerki SE, et al. Incidence and outcomes of symptomatic neonatal arterial ischemic stroke. *Pediatrics*. 2015;135:e1220-e1228.
Lanska M, Lanska D, Horwitz S, et al. Presentation, clinical course and outcome of childhood stroke. *Pediatr Neurol*. 1991;7:333.
Lehman LL, Rivkin MJ. Perinatal arterial ischemic stroke: presentation, risk factors, evaluation, and outcome. *Pediatr Neurol*. 2014;51:760-768.
McKinstry RC, Miller JH, Snyder AZ, et al. A prospective, longitudinal diffusion tensor imaging study of brain injury in newborns. *Neurology*. 2002;59:824-833.

Polycythemia

Black V, Lubchenco L, Koops B, et al. Neonatal hyperviscosity: Randomized study of effect of partial plasma exchange transfusion on long-term outcome. *Pediatrics*. 1985;75:1048.
Cario H, McMullin MF, Pahl HL. Clinical and hematological presentation of children and adolescents with polycythemia vera. *Ann Hematol*. 2009;88:713-719.

Neonatal Cerebral Venous Thrombosis

Ichord RN, Benedict SL, Chan AK, et al. Paediatric cerebral sinovenous thrombosis: findings of the International Paediatric Stroke Study. *Arch Dis Child*. 2015;100:174-179.
Rivkin M, Anderson M, Kaye E. Neonatal idiopathic cerebral venous thrombosis: an unrecognized cause of transient seizures or lethargy. *Ann Neurol*. 1992;32:51.
Wu YW, Miller SP, Chin K, et al. Multiple risk factors in neonatal sinovenous thrombosis. *Neurology*. 2002;59:438.

Intracranial Hemorrhage in the Neonate

Bruno CJ, Beslow LA, Witmer CM, et al. Haemorrhagic stroke in term and late preterm neonates. *Arch Dis Child Fetal Neonatal Ed*. 2014;99:F48-F53.

Children Aged 1-13 Years: Congenital Heart Disease

Fox CK, Sidney S, Fullerton HJ. Community-based case-control study of childhood stroke risk associated with congenital heart disease. *Stroke*. 2015;46:336-340.
Lechat P, Mas J, Lascault G, et al. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med*. 1988;318:1148.
Sinclair AJ, Fox CK, Ichord RN, et al. Stroke in children with cardiac disease: report from the International Pediatric Stroke Study Group Symposium. *Pediatr Neurol*. 2015;52:5-15.

Children Aged 1-13 Years: Procoagulopathies

Golomb MR, MacGregor DL, Domi T, et al. Presumed pre- or perinatal arterial ischemic stroke: risk factors and outcomes. *Ann Neurol*. 2001;50:163.
Levine S, Deegan M, Futrell N, et al. Cerebrovascular and neurologic disease associated with antiphospholipid antibodies: 48 cases. *Neurology*. 1990;40:1181.
Nestoridi E, Buonanno FS, Jones RM, et al. Arterial ischemic stroke in childhood: the role of plasma-phase risk factors. *Curr Opin Neurol*. 2002;15:139.
Strater R, Becker S, von Eckardstein A, et al. Prospective assessment of risk factors for recurrent stroke during childhood—a 5-year follow-up study. *Lancet*. 2002;360:1540.
Torres VM, Saddi VA. Systematic review: hereditary thrombophilia associated to pediatric strokes and cerebral palsy. *J Pediatr (Rio J)*. 2015;91:22-29.

Children Aged 1-13 Years: Autoimmune Disorders

Graf W, Milstein J, Sherry D. Stroke and mixed connective tissue disease. *J Child Neurol*. 1993;8:256.
Kohrman M, Huttenlocher P. Takayasu arteritis: a treatable cause of stroke in infancy. *Pediatr Neurol*. 1986;2:154.
Lanthier S, Lortie A, Michaud J, et al. Isolated angiitis of the CNS in children. *Neurology*. 2001;56:837.
Rodrigues M, Amaral D, Barreira JL, et al. Childhood polyarteritis nodosa presenting as stroke and arterial hypertension. *BMJ Case Rep*. 2014; Oct 29. pii: bcr2014207866. doi:10.1136/bcr-2014-207866.
Sigal L. The neurologic presentation of vasculitic and rheumatologic syndromes. *Medicine (Baltimore)*. 1987;66:157.

Children Aged 1-13 Years: Metabolic Disorders Causing Stroke

Koga Y, Povalko N, Nishioka J, et al. MELAS and L-arginine therapy: pathophysiology of stroke-like episodes. *Ann N Y Acad Sci*. 2010;1201:104-110.

Moyamoya Disease

Karasawa J, Touho H, Ohnishi H, et al. Long-term follow-up after extracranial-intracranial bypass surgery for anterior circulation ischemia in childhood moyamoya disease. *J Neurosurg*. 1992;77:84.
McLean M, Gebarski S, Van der Spek A, et al. Response of moyamoya disease to verapamil. *Lancet*. 1985;1:163.
Rooney C, Kaye E, Scott R, et al. Modified encephaloduroarteriosynangiosis as surgical treatment of childhood moyamoya disease: report of 5 cases. *J Child Neurol*. 1991;6:24.

Sickle Cell Disease

DeBaun MR, Gordon M, McKinstry RC, et al. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. *N Engl J Med*. 2014;371:699-710.
Fasano RM, Meier ER, Hulbert ML. Cerebral vasculopathy in children with sickle cell anemia. *Blood Cells Mol Dis*. 2015;54:17-25.
Meier ER, Wright EC, Miller JL. Reticulocytosis and anemia are associated with an increased risk of death and stroke in the newborn cohort of the Cooperative Study of Sickle Cell Disease. *Am J Hematol*. 2014;89:904-906.
Scahtz J, Brown RT, Pascual JM, et al. Poor school and cognitive functioning with silent cerebral infarcts and sickle cell disease. *Neurology*. 2001;56:1109.
Steen RG, Xiong X, Langston JW, et al. Brain injury in children with sickle cell disease: prevalence and etiology. *Ann Neurol*. 2003;54:564.
Wang W, Kovnar E, Tonkin I, et al. High risk of recurrent stroke after discontinuance of five to twelve years of transfusion therapy in patients with sickle cell disease. *J Pediatr*. 1991;118:377.

Children Aged 1-13 Years: Thrombocytopenia

Woerner S, Abildgaard C, French M. Intracranial hemorrhage in children with idiopathic thrombocytopenic purpura. *Pediatrics*. 1981;67:453.

Children Aged 1-13 Years: Vascular Malformations

Broechler J, Thron A. Intracranial arterial aneurysms in children. *Neurosurg Rev*. 1990;13:309.
Brown Y, Wiebers K, Forbes G. Unruptured intracranial aneurysms and arteriovenous malformations: frequency of intracranial haemorrhage and relationship of lesions. *J Neurosurg*. 1990;73:859.
Ito M, Yishuhara M, Wachi A, et al. Cerebral aneurysms in children. *Brain Dev*. 1992;14:263.
Konsiolka D, Humphreys R, Hoffman H, et al. Arteriovenous malformations of the brain in children: a forty year experience. *Can J Neurol Sci*. 1992;19:40.

Adolescents

Akshintala S, Avery RA, Murnick J, et al. Isolated midbrain ischemic infarct in association with hyperbetalipoproteinemia (a): a report of 2 adolescent patients. *J Pediatr Hematol Oncol*. 2015;37:315-318.
Cregler L, Mark H. Medical complications of cocaine abuse. *N Engl J Med*. 1986;315:1495.
Klonoff D, Andrews B, Obana W. Stroke associated with cocaine use. *Arch Neurol*. 1989;46:989.
Smith D, Smith L, Hasso A. Fibromuscular dysplasia of the internal carotid artery treated by operative transluminal balloon angioplasty. *Radiology*. 1985;155:645.
Toffol G, Biller J, Adams H. Nontraumatic intracerebral hemorrhage in young adults. *Arch Neurol*. 1987;44:479.

Causes of Stroke Unrelated to Age: Pharyngeal Infection

Bush J, Givner L, Whitaker S, et al. Necrotizing fasciitis of the parapharyngeal space with carotid artery occlusion and acute hemiplegia. *Pediatrics*. 1984;73:343.

Shillito J. Carotid arteritis: a cause of hemiplegia in childhood. *J Neurosurg*. 1964;21:540.

Causes of Stroke Unrelated to Age: Head and Neck Trauma

Garg B, Ottinger C, Smith R, et al. Strokes in children due to vertebral artery trauma. *Neurology*. 1993;43:2555.

Hope E, Bodensteiner J, Barnes P. Cerebral infarction related to neck position in an adolescent. *Pediatrics*. 1983;72:335.

Lewis D, Berman P. Vertebral artery dissections and alternating hemiparesis in an adolescent. *Pediatrics*. 1986;78:610.

Causes of Stroke Unrelated to Age: Migraine Headache

Bogousslavsky J, Regli F, Van Melle G, et al. Migraine stroke. *Neurology*. 1988;38:223.

Caplan L. Migraine and vertebrobasilar ischemia. *Neurology*. 1991;41:55.

Causes of Stroke Unrelated to Age: Conditions Resembling Stroke

Bourgeois M, Aicardi J, Goutieres F. Alternating hemiplegia of childhood. *J Pediatr*. 1993;122:673.

Casaer P. Flunarizine in alternating hemiplegia in childhood. An international study in 12 children. *Neuropediatrics*. 1987;18:191.

Hanson P, Chodos R. Hemiparetic seizures. *Neurology*. 1978;28:920.

Yarnell P. Todd's paralysis: a cerebrovascular phenomenon. *Stroke*. 1975;6:301.

30

Paroxysmal Disorders

Priya Monrad

INTRODUCTION

Paroxysmal neurologic symptoms are often referred to by the generic term "spells"; these paroxysmal events can be neurologic, cardiovascular, or gastrointestinal in origin. Most paroxysmal neurologic symptoms can be properly evaluated, diagnosed, and managed by following a systematic approach. A detailed history will often be sufficient to make the diagnosis or to significantly narrow down the diagnostic differential. A few well-selected tests will then allow the physician to correctly diagnose and treat the child. The physician should aim first to assess for signs of serious or emergent neurologic disease, and second to form a differential diagnosis to guide further investigations and treatment (Fig. 30.1).

◆ History

A careful description of the event or events from beginning to end, including re-enactments by the parents of any unclear physical symptoms, is critical.

Pertinent questions include:

- Was this the first such event, or have there been multiple events?
- Is there a single type of event, or multiple events?
- What was the child doing at the time of each spell—were they awake, asleep, playing, or sitting quietly?
- If they were asleep, how long had they been asleep, or what time of day or night did the spell occur?
- If abnormal tone or movements were involved, was the child rigid or limp, and which limbs were involved? Were the movements rhythmic and synchronous, or were they alternating, migratory, or stop-start?
- If the child was unresponsive or had alteration of awareness, what did the parents do to ascertain their level of responsiveness? Did the parents try touching them to regain their attention, or merely call their name?
- How long did the event last, and how did the child behave afterward?
- Did the child describe any symptoms prior to the onset of the actual event, or was there any abnormal behavior that the parents witnessed prior to the event?
- Were there any signs or symptoms of illness associated with the spell? Were any fevers documented?
- Has there been any behavioral, developmental, or academic regression since the start of the events?
- Is the child developmentally normal? If not, has the child's development always been abnormal, or was there a regression at some point?
- Were there any problems during pregnancy or the delivery?
- Has the child ever had a significant head injury or central nervous system (CNS) infection?
- Is there any family history of similar events, or any other neurologic disorders?

Parents frequently record videos of these spells on their mobile devices, which are ideal for the physician to review.

◆ Physical Examination

The physician should compare vital signs, including blood pressure and head circumference, to previous measurements if possible. Elevated blood pressure can be indicative of pain, anxiety, increased intracranial pressure, or hypertensive encephalopathy. Hypotension may suggest syncopal events or sepsis. Dramatic increases in head circumference in infants may indicate intracranial pathology.

A general physical examination, including the cardiopulmonary and abdominal examinations, should be performed; abnormalities may indicate a nonneurologic cause for spells. **Dysmorphic** features or **cutaneous** findings can provide clues toward an underlying syndrome.

An **ophthalmologic** examination can be as simple as obtaining a red reflex and observation of eye movements in young children. Eye movements may be observed by having the patient track a moving object or toy; abnormalities such as deviation, nystagmus, or new-onset limitations in range of motion may indicate a structural cause for the spells such as hydrocephalus or a mass lesion. In cooperative older children, the physician should attempt a funduscopic examination. **Papilledema** is a clue to increased intracranial pressure but unfortunately is only readily appreciable after 2-3 weeks of increased intracranial pressure; it will not be present with acute disturbances leading to increased intracranial pressure.

The child will provide important information about their **mental status** and **developmental status** through simple conversation. Conversations about toys, school, or family members in the room can provide information about orientation, aphasia, dysarthria, and fund of knowledge for age. If there are any questions about whether any facial asymmetry is new-onset, parents may be able to provide old photographs; most people have some degree of facial asymmetry at baseline that may only be noticed after a frightening event causes the parents to observe the child more closely.

Muscle strength can be ascertained by manual testing in a cooperative older child, or observing natural play or strength of resistance to examination in a younger child. If a child can easily perform age-appropriate actions such as crawling, walking, running, climbing, or grabbing for objects, and strongly resists examination, they are fairly likely to have grossly normal strength in their major muscle groups. **Tone** can be checked by passively moving the patient's limbs, or suspending an infant in your hands to check if they start to slide through your grip. Low tone (hypotonia) can also be detected by observing gait or observing how the child sits; "W"-sitting (sitting with knees together and heels outside of their hips) may be another clue. Low strength

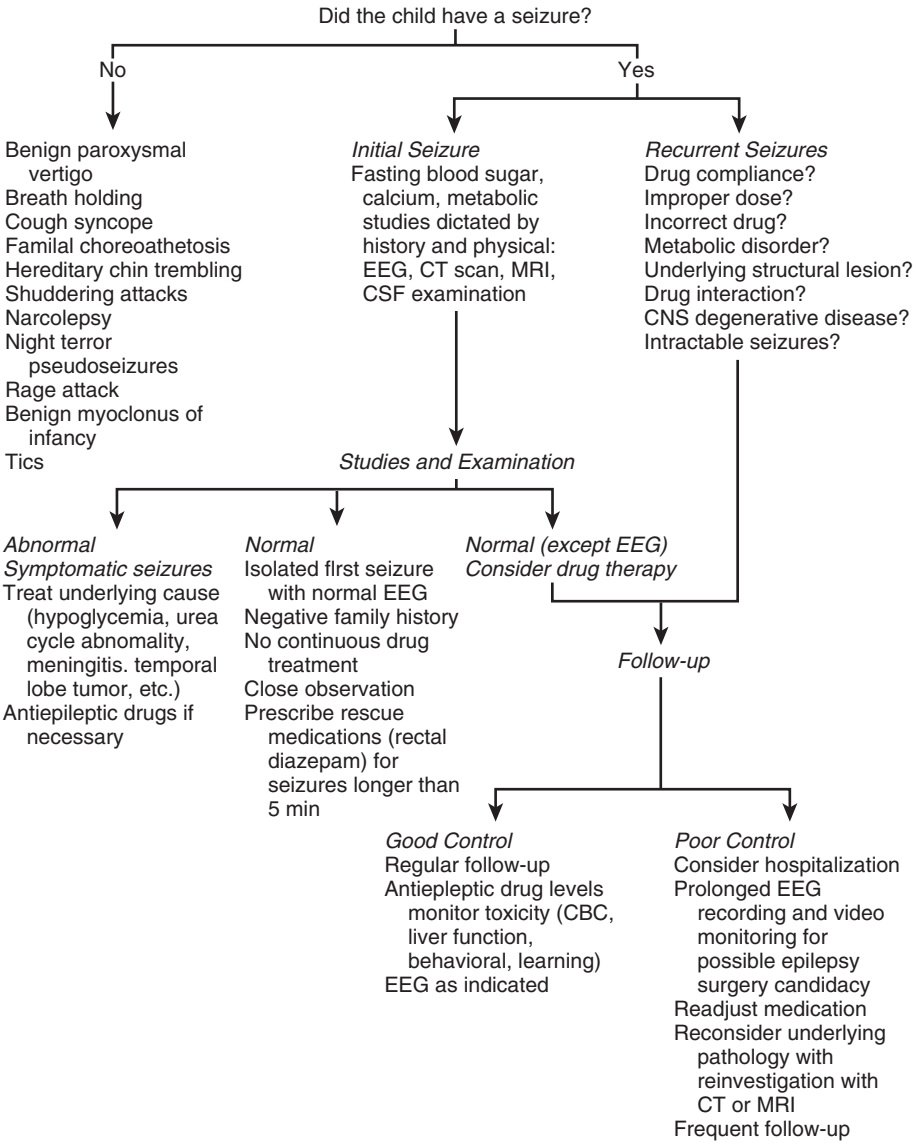

FIGURE 30.1 Approach to the child with a suspected convulsive disorder. CBC, complete blood count; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalography; MRI, magnetic resonance imaging.

(weakness) should be distinguished from hypotonia or ataxia; an example of normal strength but low tone might be an infant with motor delays and head lag who vigorously opposes examination; a child with normal strength but ataxia might vigorously oppose examination but cannot accurately reach to push away the examiner.

A normal physical examination does not rule out the presence of a neurologic disorder, but generally indicates a disorder that does not require immediate intervention and that more time can be spent carefully evaluating all diagnostic possibilities. In children with baseline neurologic abnormalities, such as children with cerebral palsy, knowledge of their base line physical examination, abilities, and behavior is critical in deciding how urgently they need to be evaluated further. Parents can be very helpful in determining a child's baseline behavior in this case.

RED FLAGS

After obtaining a history of the events, the presence of "red flags" in the history or examination should strongly prompt referral to the emergency room:

Increased Intracranial Pressure or Large Intracranial Mass

- Hypertension and bradycardia
- 3rd or 6th nerve palsy; anisocoria, ptosis, diplopia
- Forced-seeming and persistent downward deviation of both eyes (tonic downward gaze deviation)
- Papilledema
- Severe vomiting that is exquisitely positional (i.e., strongly provoked by the transition from lying to sitting)
- Engorged scalp veins
- Bulging fontanel or split cranial sutures in an infant
- Presence of a ventriculoperitoneal shunt (VP shunt) with any of the above symptoms should prompt concern about shunt malfunction

Ongoing Status Epilepticus

- Waxing and waning responsiveness after a convulsive seizure has ended, particularly with periods of complete unresponsiveness
- Persistent eye deviation after a convulsive seizure has ended

- Persistent tachycardia after a convulsive seizure has ended
- Persistent confusion or delirium, even if the child is able to speak and walk

Stroke or Complicated Migraine

- Focal weakness or numbness, particularly if accompanied by slurred speech or confusion (if the spell is remote and the patient has returned to a normal baseline, suggest expedited referral to a neurologist)

Meningitis

- Fever
- Nuchal rigidity
- Positive Kernig or Brudzinski signs
- Bulging fontanel

The following red flags should prompt an urgent or even emergent referral to a pediatric neurologist, including direct communication with a neurologist for proper triaging:

- Infantile spasms
- Clusters of abdominal "crunches" or "startles," particularly when the child is falling asleep or waking up from sleep
- Developmental plateau or regression
- Loss of visual attentiveness

Any developmental regression in infants or toddlers that has been present for more than 1 month (or sooner, for dramatic or progressive regressions) is concerning; change in handedness after 4-5 years of age is also a red flag.

PAROXYSMAL SPELLS OF ALTERED BEHAVIOR OR MOVEMENT

Paroxysmal neurologic symptoms can have neurologic, psychiatric, pulmonary, cardiovascular, or gastrointestinal causes. For this reason, during the investigation of a paroxysmal event, generic terms such as "spells," "convulsions," or "altered mental status" are more appropriate to use rather than "seizures," which implies a very specific etiology and may falsely eliminate diagnostic possibilities. Witnesses may use terms such as "grand mal," "petit mal," or even "generalized tonic-clonic" (GTC) to describe events; these descriptors should not be taken at face value or thought to only describe epileptic seizures.

EPILEPTIC SEIZURES

An epileptic seizure is a paroxysmal alteration in behavior, motor function, and/or autonomic function occurring in association with excessive synchronous neuronal activity in the CNS. Seizures may be considered "provoked" or "unprovoked," referring to whether they were precipitated by an acute cause such as illness, concussion, metabolic derangement, or toxic ingestion. The term "symptomatic" refers to whether the seizures represent a symptom of a known chronic disorder, such as a structural, genetic, or metabolic abnormality. *Epilepsy* is a disorder in which there are *recurrent* unprovoked epileptic seizures (Table 30.1).

Epileptic seizures must be clearly distinguished from nonneurologic paroxysmal disorders caused by psychiatric, cardiovascular, pulmonary, or gastrointestinal causes. There are also paroxysmal disorders that are neurologic but nonepileptic in nature, such as tics, dystonias, stereotypies, or other movement disorders. The correct diagnosis is critical to avoid unnecessary testing, interventions, and medication trials. However, multiple types of events, both epileptic and nonepileptic, may occur in the same patient, necessitating that each spell be properly characterized.

EPIDEMIOLOGY AND CAUSES OF SEIZURES AND EPILEPSY

If febrile seizures are included, approximately 3.5% of children experience some kind of seizure by the age of 15 years; most seizures occur before the age of 3 years. The majority of children who present with a seizure do not have or will not develop epilepsy. Many children presenting with a seizure have febrile convulsions, which are a provoked, age-dependent paroxysmal neurologic condition; 13% of children with seizures have acute symptomatic seizures other than febrile convulsions; and 8% have single, unprovoked seizures of unknown cause. The incidence of acute symptomatic seizures is highest in the 1st year of life; the most common causes of these predominantly neonatal seizures are infection and metabolic disorders. After age 4 years, head injury is the most common cause of acute symptomatic seizures, and infection is the next most common.

The incidence of epilepsy among children younger than 15 years is 45-85/100,000 in developed countries. It is highest in younger children; in those younger than 1 year, it is ~100/100,000. The prevalence of active epilepsy in patients taking antiepileptic drugs (AEDs) is between 4.3 and 9.3/1000, or about 0.5-1% of the population. Traditionally, between 60% and 80% of children with epilepsy have no identifiable etiologic factors for the disease; however next-generation gene sequencing technology has moved the estimated underlying genetic etiology to approximately 40%. Of those children in whom a cause is identified, population-based studies report the following presumed causes: infection in 5%; head trauma in 3%; and miscellaneous causes (tumors, malformations of cortical development, vascular malformations, and cerebral infarction) in 2%. Epilepsy is found in association with other long-standing neurodevelopmental abnormalities in 13% of children.

GENETICS

It is estimated that a genetic etiology underlies epilepsy in approximately 40% of individuals. In some circumstances, unique clinical phenotypes can be a guide to the underlying etiology. Apnea or **systemic shock** requiring intubation and ventilation is seen in severe metabolic epileptic encephalopathic syndromes such as nonketotic hyperglycinemia, pyridoxine-5'-phosphate oxidase deficiency, molybdenum cofactor deficiency, pyridoxine-dependent epilepsy, Leigh syndrome, congenital neuronal ceroid lipofuscinosis, and atypical *MECP2*. The characteristic syndactyly of the 2nd and 3rd toes is seen in steroid metabolism disorders, Smith–Lemli–Opitz syndrome in particular, which additionally has associated genitourinary tract abnormalities. Skin **exanthems** are highly suggestive of biotinidase deficiency. Atypical coarse or thin hair and wormian bones are seen in copper disorders such as Menkes syndrome. **Cardiomyopathy** is characteristic of mitochondrial disorders including Barth syndrome and fatty acid oxidation disorders and is also seen in RASopathies and cobalamin C deficiency. **Atypical fat distribution** and a prominent suprapubic fat pad are seen in congenital disorders of glycosylation. The value of genetic testing and the circumstances in which genetic testing should be offered varies widely between centers. Gene panels are available that provide sequencing information from 20 genes to greater than 400 genes dependent on the commercial testing facility being utilized. Heterogeneity is mostly responsible for this variability in clinical testing; 1 gene can cause various types of seizure disorders (clinical heterogeneity), or a specific

TABLE 30.1 Types of Epileptic Seizures

Self-Limited Seizure Types

Focal Seizures

Focal sensory seizures
- With elementary sensory symptoms (e.g., occipital and parietal lobe seizures)
- With experiential sensory symptoms (e.g., temporoparietooccipital junction seizures)

Focal motor seizures
- With elementary clonic motor signs
- With asymmetric tonic motor seizures (e.g., supplementary motor seizures)
- With typical (temporal lobe) automatisms (e.g., mesial temporal lobe seizures)
- With hyperkinetic automatisms
- With focal negative myoclonus
- With inhibitory motor seizures

Gelastic seizures
Hemiclonic seizures
Secondarily generalized seizures
Reflex seizures in focal epilepsy syndromes

Generalized Seizures

Tonic-clonic seizures (includes variations beginning with a clonic or myoclonic phase)
Clonic seizures
- Without tonic features
- With tonic features

Typical absence seizures
Atypical absence seizures
Absence with special features:
- Eyelid myoclonia
- Myoclonic absence

Tonic seizures
Myoclonic seizures
Myoclonic atonic seizures
Negative myoclonus
Atonic seizures
Reflex seizures in generalized epilepsy syndromes

Unknown

Epileptic Spasms

Continuous Seizure Types

Generalized status epilepticus
Generalized tonic-clonic status epilepticus
Clonic status epilepticus
Absence status epilepticus
Tonic status epilepticus
Myoclonic status epilepticus

Focal Status Epilepticus

Epilepsia partialis continua of Kojevnikov
Aura continua
Limbic status epilepticus (psychomotor status)
Hemiconvulsive status with hemiparesis

Precipitating Stimuli for Reflex Seizures

Visual stimuli
- Flickering light—color to be specified when possible
- Patterns
- Other visual stimuli

Thinking
Music
Eating
Praxis
Somatosensory
Proprioceptive
Reading
Hot water
Startle

Modified from Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE commission on classification and terminology, 2005–2009. *Epilepsia.* 2010;51:676-685.

subtype of seizure may have several genes with causal associations (genetic heterogeneity). Gene panels are designed to group disorders with common ages of onset and phenotypic characterizations together, thereby offering broad coverage in a cost-effective manner. There are circumstances in which targeted sequencing is still warranted (Tables 30.2 and 30.3).

Whole-exome sequencing should not be considered "end of the line" or "last resort," as the window of opportunity for targeted intervention may pass while more conventional options are investigated in the interim. This is particularly relevant in new-onset intractable or refractory seizures. There are several cases reported with digenic seizure disorders or rare metabolic disorders that will not be easily detected through more routine metabolite analysis, but benefit from early targeted intervention to reduce morbidity and improve overall quality of life. The general consensus for evaluating patients with suspected congenital disorders of glycosylation, mitochondrial disorders, or otherwise complex atypical disorders is to utilize exome sequencing as a first-line diagnostic test, with yields of up to 30% in these circumstances.

SEIZURE CLASSIFICATION AND TERMINOLOGY

Seizures are characterized according to their clinical semiology and presumptive etiology (see Table 30.1). Seizures can be difficult to classify and identify without a careful description of their onset, unfolding, and aftermath. Multiple seizure types may have the same brief general description, such as "twitching" or "staring." Without further details as to duration, additional symptoms, and postictal behavior, they may be incorrectly classified as to type, even if they are accurately determined to be seizures. This is clinically relevant because improper classification can lead to inappropriate treatment; for example, some antiepileptic medications for focal seizures will exacerbate generalized seizures.

Clonic movements are rhythmic, nonsuppressible, position-independent jerking movements (low frequency, high amplitude) caused by involvement of the motor cortex. They can be unilateral or bilateral, and can start with 1 body part and spread. If bilateral, they are synchronous, and do not alternate from 1 side to the other in a bicycling fashion. This should be distinguished from **clonus**, which is rhythmic twitching of a limb, generally the foot, caused by

TABLE 30.2 Clinical Conditions for Targeted Gene Sequencing

Targeted Gene Sequencing	Clinical Condition	Advantage of Testing
SCN1A	Dravet syndrome. Consider testing for recurrent episodes of febrile status epilepticus, intractable tonic–clonic seizures during the 1st year of life, epileptic encephalopathy attributed to vaccination, and adults with a history consistent with Dravet syndrome	Avoidance of sodium channel blockers, aggressive seizure management, justification of stiripentol, bromides, etc.
PCDH19	Females presenting with multiple clusters of brief febrile seizures and developmental delay or regression, particularly if there is a family history consistent with paternal transmission	Prognosis and potential forthcoming treatment options
SLC2A1	Onset of absence seizures <4 yr old, particularly if there is a family history of paroxysmal exercise-induced dyskinesia	Initiation of a ketogenic diet
POLG	Prior to starting valproic acid in patients with drug-resistant seizures and developmental delay or regression	Avoidance of potentially fatal liver failure starting as early as 2 mo after initiation of valproic acid therapy
HLA-B*1502	Prior to starting carbamazepine, oxcarbazepine, phenytoin, and lamotrigine in patients of Asian descent	Avoidance of a potentially fatal reaction (Stevens-Johnson syndrome/ toxic epidermal necrolysis)

Modified from Ream MA, Patel AD. Obtaining genetic testing in pediatric epilepsy. *Epilepsia* 2015:56:1505-1514.

hyperreflexia and lack of descending cortical inhibition due to CNS injury such as is seen in cerebral palsy or stroke. This is generally provoked by movement, excitement, and positioning, and can be suppressed or halted by gently repositioning the affected limb. There is no alteration of alertness with clonus. In newborns, **jitteriness** (high frequency, low amplitude) may also be mistaken for clonic seizure activity; this tends to be stimulus-provoked and suppressible.

The term **tonic** refers to a change in tone as a manifestation of seizure activity, which clinically presents as stiffening or arching. This can occur as the only manifestation of a seizure (tonic seizure), or may be followed by clonic jerking, which is the so-called tonic-clonic seizure (GTC or grand mal). **Atonic** seizures refer to seizures where a sudden, brief loss of tone in the neck or entire body causes a head nod or fall to the ground. This type of seizure must be distinguished from falls due to complete loss of consciousness or those due to tonic stiffening of the entire body. With atonic seizures, the loss of tone is sudden but brief, and the patient is quickly responsive afterward.

Automatisms are semipurposeful movements that usually occur with impairment of consciousness either during or after a seizure, and can be very useful for identifying a spell as a seizure. They may be a perseveration of an activity in progress at ictal onset, such as turning pages of a book, or novel semipurposeful movements arising during the seizure. These novel movements are most often a mixture of masticatory, oral, and lingual movements (lip smacking or grimacing) and simple fragmentary limb movements, such as fidgeting with a held object or pulling at clothing. In infants, orofacial automatisms are more likely than complex gestures and must be distinguished from the normal behavior of infants. Automatisms can both be seen in focal seizures, specifically those of temporal lobe onset, as well as in some generalized seizures, specifically absence epilepsy, so they are not specific to a broad category of seizure.

Impairment of consciousness, defined as an alteration in awareness of external stimuli, may be combined with a complete loss or impairment of responsiveness to external stimuli. Assessment of consciousness during seizures is often difficult, particularly in young children. It is possible to be unresponsive because of an inability to speak or articulate clearly (aphasia, apraxia, or paralysis). It is also possible to be responsive to external stimuli, but to have altered awareness, often demonstrated by complete amnesia for events immediately before, during, or after the seizure, which implies that memory was not acquired during the seizure because of ongoing neuronal dysfunction. It is possible to have complex motor behaviors without loss of complete awareness or amnesia; frontal lobe seizures commonly have this presentation, and must be carefully distinguished from nonepileptic events. Both focal and generalized seizures can be associated with impairment of consciousness; the term **dyscognitive** is used to describe this symptom.

Seizure etiology was previously divided into *idiopathic, cryptogenic,* and *symptomatic*. There were also separate categories for infantile spasms and neonatal seizures. The terms *genetic, structural, metabolic,* and *unknown* are currently used to characterize presumptive etiologies (Table 30.4).

FOCAL SEIZURES

Localization-Related Seizures, Partial Seizures

Focal seizures are seizures in which the first clinical and electroencephalogram (EEG) changes indicate initial activation of a system of neurons limited to part of 1 cerebral hemisphere. The clinical symptoms and signs of focal seizures reflect the functional anatomy of the region of the brain undergoing the abnormal neuronal discharge.

When consciousness is impaired, this was historically known as a **complex** partial seizure; if there is no apparent loss of consciousness, this was known as a **simple** partial seizure. These terms have been replaced by the more descriptive terms **focal seizure with impairment of consciousness** or **focal dyscognitive seizure** in the case of complex partial seizures, and **focal seizure without impairment of consciousness** for simple partial seizures.

An **aura** is the portion of a seizure that is experienced before any loss of consciousness. Some auras can be difficult for a patient to describe; asking them if they know a seizure will happen before it happens, even if they cannot articulate precisely what they are experiencing, is one way to approach the topic. Examples of auras include an epigastric rising sensation; nausea; visual, auditory, or olfactory hallucinations; or limbic symptoms such as fear or a sensation of déjà vu. An aura may be suspected in very young children if there is a change in behavior before seizures, such as interrupting an activity to seek out parents, or complaining of abdominal pain. The presence of

TABLE 30.3 Identified Genes for Epilepsy Syndromes*†

Epilepsy Type	Gene	Protein
Infantile Onset		
Benign familial neonatal seizures	*KCNQ2* *KCNQ3*	Potassium voltage-gated channel Potassium voltage-gated channel
Benign familial neonatal infantile seizures	*SCN2A*	Sodium channel protein type 2α
Early familial neonatal infantile seizures	*SCN2A*	Sodium channel protein type 2α
Early infantile epileptic encephalopathy (EIEE)	*CDKL5 (EIEE2)* *ARX (EIEE1)* *TSC1* *TSC2* *SCN1A (EIEE6)* *PCDH19 (EIEE9)* *KCNQ2 (EIEE7)* *STXBP1 (EIEE4)* *SLC2A1* *ALDH7A1* *POLG* *SCN2A (EIEE11)* *PLCβ1 (EIEE12)* *ATP6AP2* *SPTAN1 (EIEE5)* *SLC25A22 (EIEE3)* *PNPO*	Cyclin-dependent kinase-like 5 Aristaless-related homeobox Hamartin Tuberin Sodium channel protein type 1α Protocadherin-19 Potassium voltage-gated channel Syntaxin binding protein 1 Solute carrier family 2, facilitated glucose transporter member 1 α-Aminoadipic semialdehyde dehydrogenase (antiquitin) DNA polymerase subunit γ1 Sodium channel protein type 2α Phospholipase C β1 Renin receptor α_2-Spectrin Mitochondrial glutamate carrier 1 Pyridoxine-5′-phosphate oxidase
Generalized epilepsy with febrile seizures plus (early onset)	*SCN1A* *SCN1B* *GABRG2* *SCN2A*	Sodium channel protein type 1α Sodium channel protein type 1β γ-Aminobutyric acid receptor subunit γ2 Sodium channel protein type 2α
Childhood Onset		
Childhood-onset epileptic encephalopathies	*SCN1A* *PCDH19* *SLC2A1* *POLG* *SCN2A*	Sodium channel protein type 1α Protocadherin-19 Solute carrier family 2, facilitated GTM1 DNA polymerase subunit γ1 Sodium channel protein type 2α
Early-onset absence seizures, refractory epilepsy of multiple types, at times with movement disorder	*GLUT-1* deficiency syndrome, *SLC2A1* gene	Solute carrier family 2, facilitated GTM1
Generalized epilepsy with febrile seizure plus	*SCN1A* *SCN1B* *GABRG2* *SCN2A*	Sodium channel protein type 1α Sodium channel protein type 1β γ-Aminobutyric acid receptor subunit γ2 Sodium channel protein type 1α
Juvenile myoclonic epilepsy (more commonly presents in adolescence)	*EFHC1* *CACNB4* *GABRA1*	EF-hand domain-containing protein 1 Voltage-dependent L-type calcium channel γ-Aminobutyric acid receptor subunit α1
Progressive myoclonic epilepsy (different forms present from infancy through adulthood)	*EPM2A* *NHLRC1* *CSTB* *PRICKLE1* *PPT1, TPP1, CLN3, CLN5, CLN6, CLN8, CTSD, DNAJC5, MFSD8*	Laforin NHL repeat-containing protein 1 (malin) Cystatin-B Prickle-like protein 1 Multiple proteins causing neuronal ceroid lipofuscinosis
Autosomal dominant nocturnal frontal lobe epilepsies (presents in childhood through adulthood)	*CHRNA4* *CHRNB2* *CHRNA2*	Neuronal acetylcholine receptor α4 Neuronal acetylcholine receptor β2 Neuronal acetylcholine receptor α2

Continued

TABLE 30.3 Identified Genes for Epilepsy Syndromes—cont'd

Epilepsy Type	Gene	Protein
Adolescent Onset		
Juvenile myoclonic epilepsy (JME)	See Childhood-Onset JME	
Progressive myoclonic epilepsy (PME)	See Childhood-Onset PME	
Autosomal dominant nocturnal frontal lobe epilepsies (AD-NFLE)	See Childhood-Onset AD-NFLE	
Autosomal dominant lateral temporal lobe epilepsy (usually presents in adulthood)	*LGI1*	Leucine-rich glioma-inactivated protein 1

*Note that the same gene (different mutations) often appears as causing different epilepsy syndromes.
†Most of these genes can be tested for through commercially available targeted single-gene sequencing or through commercially available gene panels or though exome sequencing (http://www.ncbi.nlm.nih.gov/sites/GeneTests/review?db=genetests).

TABLE 30.4 Suggested Scheme for an Etiologic Classification of Epilepsy

Main Category	Subcategory	Examples*
Idiopathic epilepsy	Pure epilepsies due to single-gene disorders	Benign familial neonatal convulsions; autosomal dominant nocturnal frontal lobe epilepsy; generalized epilepsy with febrile seizures plus; severe myoclonic epilepsy of childhood; benign adult familial myoclonic epilepsy
	Pure epilepsies with complex inheritance	Idiopathic generalized epilepsy (and its subtypes); benign partial epilepsies of childhood
Symptomatic epilepsy	Childhood epilepsy syndromes	West syndrome; Lennox-Gastaut syndrome
Predominantly genetic or developmental causation	Progressive myoclonic epilepsies	Unverricht-Lundborg disease; dentato-rubro-pallido-luysian atrophy; Lafora body disease; mitochondrial cytopathy; sialidosis; neuronal ceroid lipofuscinosis; myoclonus renal failure syndrome
	Neurocutaneous syndromes	Tuberous sclerosis; neurofibromatosis; Sturge-Weber syndrome
	Other neurologic single-gene disorders	Angelman syndrome; lysosomal disorders; neuroacanthocytosis; organic acidurias and peroxisomal disorders; porphyria; pyridoxine-dependent epilepsy; Rett syndrome; urea cycle disorders; Wilson disease; disorders of cobalamin and folate metabolism
	Disorders of chromosome function	Down syndrome; fragile X syndrome; 4p– syndrome; isodicentric chromosome 15; ring chromosome 20
	Developmental anomalies of the cerebral structure	Hemimegalencephaly; focal cortical dysplasia; agyria-pachygyria-band spectrum; agenesis of the corpus callosum; polymicrogyria; schizencephaly; periventricular nodular heterotopia; microcephaly; arachnoid cyst
Predominantly acquired causation	Hippocampal sclerosis	Hippocampal sclerosis
	Perinatal and infantile causes	Neonatal seizures; postneonatal seizures; cerebral palsy
	Cerebral trauma	Open head injury; closed head injury; neurosurgery; epilepsy after epilepsy surgery; nonaccidental head injury in infants
	Cerebral tumor	Glioma; ganglioglioma and hamartoma; DNET; hypothalamic hamartoma; meningioma; secondary tumors
	Cerebral infection	Viral meningitis and encephalitis; bacterial meningitis and abscess; malaria; neurocysticercosis; tuberculosis; HIV
	Cerebrovascular disorders	Cerebral hemorrhage; cerebral infarction; degenerative vascular disease; arteriovenous malformation; cavernous hemangioma
	Cerebral immunologic disorders	Rasmussen encephalitis; SLE and collagen vascular disorders; inflammatory and immunologic disorders
	Degenerative and other neurologic conditions	Alzheimer disease and other dementing disorders; multiple sclerosis and demyelinating disorders; hydrocephalus and porencephaly
Provoked epilepsy	Provoking factors	Fever; menstrual cycle and catamenial epilepsy; sleep-wake cycle; metabolic and endocrine-induced seizures; drug-induced seizures; alcohol- and toxin-induced seizures
	Reflex epilepsies	Photosensitive epilepsies; startle-induced epilepsies; reading epilepsy; auditory-induced epilepsy; eating epilepsy; hot water epilepsy
Cryptogenic epilepsies†		

*These examples are not comprehensive, and in every category there are other causes.
†By definition, the causes of the cryptogenic epilepsies are "unknown." However, these are an important category, accounting for at least 40% of epilepsies encountered in adult practice and a lesser proportion in pediatric practice.
DNET, dysembryoplastic neuroepithelial tumor; HIV, human immunodeficiency virus; SLE, systemic lupus erythematosus.
From Shorvon SD. The etiologic classification of epilepsy. Epilepsia. 2011;52:1052-1057.

an aura is traditionally thought to be indicative of a focal seizure without impairment of consciousness, as it implies focal cortical dysfunction, but some studies have reported that up to 64% of patients with documented idiopathic generalized epilepsy experience some form of aura, possibly due to asymmetric propagation of the discharges through the thalamocortical networks.

Nonepileptic events such as **migraines** or **syncope** may also have a prodrome, further highlighting the value of a comprehensive history in distinguishing types of events.

The progressive symptoms of some seizures after the initial aura reflect the spread of the abnormal electrical discharge beyond the region of onset, which is why a detailed history is critical for evaluating paroxysmal spells and determining the likelihood that they represent seizure activity.

Focal seizures can have motor and/or sensory components, depending on which areas of what is termed *eloquent cortex* become involved in the seizure. However, the seizure may originate in a portion of the cortex that does not produce obvious physical symptoms (termed the *silent* or *noneloquent cortex*), and physical signs of the seizure only develop if the seizure discharge spreads to involve eloquent cortex. Seizures with clear electrical abnormalities but minimal or absent physical symptoms are commonly referred to as *electrographic seizures* or *subclinical seizures*. Subclinical electrographic seizures, particularly during sleep, can be associated with deterioration in development, behavior, attention, and learning.

Focal motor seizures produce rhythmic jerking (clonic) movements of the limb or limbs *contralateral* to the primary motor cortex involved. Other focal motor seizures include involuntary turning of the head and eyes in 1 direction (version), vocalization, and speech arrest. There may be tonic stiffening and extension of the arm ipsilateral to the seizure onset.

Involvement of the sensory cortex produces simple *somatosensory* experiences such as paresthesia or numbness, often with a dysesthetic quality, and visual, auditory, olfactory, or gustatory phenomena. Some of these sensory phenomena can be quite complex, including structured visual hallucinations, sensations of depersonalization, and affective symptoms such as anxiety or fear. Epileptic phenomena are a rare cause for such phenomena, and a broad differential diagnosis should be considered for paroxysmal spells where the primary symptoms are sensory or affective.

As the seizure continues to spread, both cerebral hemispheres may become engaged, and there is generalized clonic jerking of the body that closely resembles a GTC seizure. These secondarily generalized seizures may be mistaken for a generalized seizure if the onset is not witnessed. Occasionally after a seizure, there is persistent focal weakness or hemiparesis known as **Todd palsy**, which is strongly suggestive of a contralateral focal onset to the seizure.

Generalized Seizures

Generalized seizures are defined as seizures in which the first clinical changes indicate initial involvement of both hemispheres. Motor involvement, if present, is bilateral, as are the initial EEG changes. Consciousness is impaired in most generalized seizures, but not in all; for instance, brief myoclonic seizures and some atonic seizures may not be associated with any impairment of consciousness.

Absence (petit mal) seizures begin with sudden interruption of activity and staring; they are usually brief and end abruptly without postictal confusion. Simple absence seizures consist of only motionlessness and a blank stare lasting for several seconds, with immediate postictal reanimation. Lip-smacking, fumbling, or searching hand movements, or convulsive swallowing can appear during longer seizures, or preictal activities may be continued in a slow, automatic manner. Paroxysmal alterations in autonomic function may also accompany absence seizures, including pupillary dilation, pallor, flushing, sweating, salivation, piloerection, or a combination of these. Absence seizures that are more typically accompanied by eyelid fluttering, facial twitching, or myoclonic jerks of the trunk or extremities are referred to as *complicated* absence seizures. Atypical absence seizures are described as absence seizures with a less abrupt beginning and end, with more pronounced changes in muscle tone, and of longer duration. Distinctions should be made between the clinical features of absence seizures, focal dyscognitive seizures, and episodic daydreaming (Table 30.5). Staring spells that are prolonged beyond 15-20 seconds are less likely to represent absence seizures due to incorrect duration. Staring spells in infants and toddlers are also unlikely to represent absence seizures due to incorrect age of onset. Early-onset generalized epilepsy is associated with rare genetic syndromes. Children with prolonged staring spells, particularly starting at a young age, are at higher risk of partial-onset seizures or behavioral spells.

Tonic-clonic seizures are perhaps the most dramatic of the epileptic seizures. The **tonic phase** begins with sudden sustained contraction of facial, axial, and limb muscle groups, and there may be an initial involuntary stridorous cry or a moan secondary to contraction of the diaphragm and chest muscles against a partially closed glottis (the *ictal cry*). The tonic contraction is maintained for seconds to 10s of seconds, during which time the child falls if standing, is apneic and may become cyanotic, may bite the sides of their tongue, and may pass urine. The **clonic phase** of the seizure begins when the tonic contraction is repeatedly interrupted by momentary relaxation of the muscular contraction. This gives the appearance of generalized jerking as the contraction resumes after each relaxation. At the end of the clonic phase, the body relaxes and the patient is unconscious with deep respiration. If roused, the patient is confused, may complain of muscle soreness, and usually wishes to sleep.

Myoclonic seizures are sudden, brief, shocklike contractions of muscles. They may involve the whole body or a portion of the axial musculature such as the face and trunk, or they may be limited to the limbs. They can be isolated or repetitive, irregular or rhythmic. Myoclonic seizures arise from the cortex and are associated with a distinct EEG pattern. Some forms of myoclonus are of brainstem or spinal origin; those occurring without other seizure types are not regarded as epileptic myoclonus but thought of as *movement disorders*.

Generalized tonic seizures begin in the same way as tonic-clonic seizures; a massive generalized contraction produces any combination of facial grimacing, neck and trunk flexion or extension, abduction or elevation of the arms, and flexion of the hips. Subtle tonic seizures may produce only facial grimacing and slight neck and trunk flexion. Tonic seizures may be accompanied by pronounced autonomic activity with diaphoresis, flushing, pallor, and tachycardia, even when the muscular contraction is slight.

Atonic seizures are characterized by a sudden decrease or loss of postural muscle tone. The extent of muscle involvement may vary; an atonic seizure may be limited to a sudden head drop with slack jaw or may result in a fall because of loss of axial and limb muscle tone. The falls are referred to as *drop attacks*, and because they are unexpected and sudden in onset, they often result in injury.

DIAGNOSTIC EVALUATION OF A SEIZURE DISORDER

Electroencephalographic Studies

The incidence of EEG epileptiform activity in normal children without a history of seizures is very low (<2%); such findings are associated

TABLE 30.5 Differential Diagnosis of Episodic Unresponsiveness Without Convulsions

Clinical	Absence Seizures	Focal Dyscognitive Seizures	Staring, Inattention
Frequency	Multiple daily	Rarely more than 1-2/day	Daily, situation dependent: e.g., may occur only at school
Duration	Often <10 sec, rarely >30 sec	Average duration >60 sec, rarely <10 sec	Seconds to minutes
Aura	Not present	May be present	Not present
Abrupt interruption of child's activity	Yes: e.g., speech arrest midsentence; pause while eating, playing, or fighting	Yes	Activities such as play or eating are not abruptly interrupted, no sudden onset
Eyelid flutter	Common, often with upward eye movement	Uncommon, but may be present	No
Myoclonic jerks	Common	Uncommon	Not present
Automatisms	Occur in longer absences, usually mild	Frequent and often prominent	No
Responsiveness	Unresponsive	Unresponsive	Responds to touch
Postictal impairment	None	Postictal confusion and malaise is typical; drowsiness may also occur	No
EEG	Generalized 3-Hz spike-and-wave complexes	Regional epileptic discharges (most often frontal or temporal)	Normal
MRI	Normal	Focal structural lesions not uncommon (e.g., tumor)	Normal
First-line medication	Valproate, ethosuximide	Carbamazepine, phenytoin, valproate	None

EEG, electroencephalogram; MRI, magnetic resonance imaging.

with a strong family history of genetic epilepsy. The incidence of recurrent epileptic seizures in patients with focal EEG spikes is 83%. In a child with suspected seizures, the finding of focal or generalized epileptiform activity on the EEG supports a diagnosis of epilepsy, whereas multiple negative EEG studies capturing both wakefulness *and* sleep argue against such a diagnosis, and should prompt the physician to consider alternative diagnoses and to attempt to record the episodes.

There are 2 basic types of EEGs: *conventional* and *amplitude-integrated*. A conventional EEG utilizes 19 or more electrodes distributed symmetrically over both hemispheres and along the midline. A routine outpatient EEG is run for at least 20 minutes, and more often 40-60 minutes. A prolonged EEG, or long-term monitoring, is run for over 24 hours, and can even be performed for over a week at a time. This type of prolonged study can be performed on an ambulatory basis at home, or as an inpatient in an epilepsy monitoring unit. Amplitude-integrated EEG, by contrast, utilizes only 2 or 4 EEG electrodes, and is primarily used in neonatal intensive care units.

An EEG should always attempt to capture sleep, and most will include hyperventilation and photic stimulation, all of which potentially activate epileptiform discharges, increasing the diagnostic yield. Hyperventilation produces absence seizures in about 80% of children with childhood absence epilepsy. Intermittent photic stimulation produces generalized epileptic discharges in several of the generalized epileptic syndromes, but photosensitivity is overall rare in epilepsy. Recording during wakefulness and sleep performed after sleep deprivation may have the highest yield. Overnight recording in the hospital provides for prolonged sampling of the interictal EEG in wakefulness and spontaneous sleep. For any patient with refractory seizures or an uncertain diagnosis, the use of video and EEG monitoring is usually helpful in clarifying the diagnosis. Defining the exact seizure type may lead to modification of drug treatment or consideration of epilepsy surgery, or a nonepileptic paroxysmal disorder may be discovered.

A single normal EEG does not definitively exclude a seizure disorder, particularly in people with infrequent seizures or seizures in specific contexts, such as illness or sleep.

Neuroimaging Studies

Magnetic resonance imaging (MRI) is superior to computed tomography for the evaluation of epilepsy. Any patient with a history or examination suspicious for focal-onset epilepsy should have MRI of the brain, unless the syndrome is clearly that of benign focal epilepsy of childhood with centrotemporal spikes. MRI may also reveal an abnormality in patients with symptomatic generalized epilepsy. Functional neuroimaging is important in the assessment of candidates for surgical resection in patients with intractable seizures. When available, a 3.0 Tesla MRI of the brain with specific protocols dedicated to epilepsy evaluation (e.g., proper alignment of the imaging axis with the hippocampi) is preferred.

Evaluation of the First Seizure

There is no clinical sign or diagnostic investigation that determines with certainty whether a child presenting with a first seizure has epilepsy or has had an isolated seizure. The assessment of patients with a first seizure must include a search for etiologic agents and features that may indicate the risk of recurrence. Factors to be considered include the circumstances of the seizure, the health of the child in the time before the seizure, the recent sleep patterns, the possibility of abuse or trauma, and the chance of ingestion of prescription or street drugs or syndromes such as the neurocutaneous disorders (Table 30.6).

The recurrence risk after a first unprovoked seizure, usually defined as a seizure or flurry of seizures within 24 hours in patients older than 1 month, is ~40-50%.

The most important predictor of recurrence appears to be the existence of an underlying neurologic disorder. The existence of intellectual disabilty or cerebral palsy is a common antecedent to epilepsy,

TABLE 30.6 Neurocutaneous Syndromes

Clinical Syndromes and Findings	Investigations
Sturge-Weber Syndrome	
Facial hemangioma, "port-wine stain" upper face, division of cranial nerve V; bilateral in 30%, absent in 5%, associated truncal and limb hemangiomas in 45%	CT scan: calcification, MRI scan with gadolinium
Intracranial leptomeningeal angiomatosis	EEG: attenuation of background rhythms, epileptiform discharges
Epilepsy in 70-90%, usually before 2 yr and before hemiparesis, intractable in 35%	
Intellectual disability in 50-60%	
Hemiparesis in 30%, often with hemisensory deficit and hemianopia	
Tuberous Sclerosis	
Diagnostic criteria*	
Any 1 of the following:	
Facial angiofibroma (adenoma sebaceum, nasolabial folds, and nose becomes more prominent with age) or periungual fibromas	Physical examination
Cortical tubers, subependymal nodule, giant cell astrocytoma	MRI examination: T1 and T2 sequences with gadolinium
Multiple retinal hamartomas (usually asymptomatic) or multiple renal angiomyolipomas (usually asymptomatic, may manifest as hematuria, hypertension, or renal failure)	Funduscopic examination and renal ultrasonography, abdominal CT scan
Or any 2 of the following:	
Infantile spasms (seizures in 90%, most commonly generalized; infantile spasms and myoclonus)	History and physical, EEG; focal or generalized abnormalities
Hypomelanotic papules (ash leaf spots; in 80-90%, 1-2 cm oval or leaf-shaped)	Wood lamp examination in darkened room
Single retinal hamartoma	Funduscopic examination
Subependymal or cortical calcification on CT scan	CT scan of the brain
Single renal angiomyolipomas or cysts	Renal ultrasonography or abdominal CT scan
Cardiac rhabdomyomas (single or multiple; may obstruct outflow, cause arrhythmias, or cause conduction defects)	Echocardiography, ECG
First-degree relative with tuberous sclerosis (autosomal dominant disorder, 80% of cases represent new mutations)	Examination of parents; echocardiography, MRI scans
Also associated:	
Mental retardation in 50-66%	
Shagreen patches; hamartomatous skin lesion in lumbosacral region in 50%	
Pulmonary involvement, fibrosis	Chest radiograph
Skeletal abnormalities	Hand, feet (cystic), long bone (sclerotic) radiographic changes
Epidermal Nevus Syndrome	
Hamartomatous lesions; subclassified according to most predominant histologic and clinical features (e.g., linear nevus sebaceus, see below)	Careful examination of the scalp, skin folds, and conjunctiva; funduscopic examination
Sporadic, affects both sexes equally; CNS abnormalities are common with epidermal nevus syndrome, including seizures (25% of patients), intellectual disability, and neoplasia; also, skeletal abnormalities, including kyphoscoliosis and hemiatrophy	Spine and limb radiographs, as appropriate
Linear nevus sebaceus; hairless verrucous yellow-orange or hyperpigmented plaques on the face and scalp	
Epilepsy in 76%	
Intellectual disabiity in 60%	
Associated neuronal migration disorders	MRI scan of the brain
Malignant transformation of a skin lesion	
Other Neurocutaneous Syndromes Associated with Seizures	
Neurofibromatosis; cutaneous lesions include café-au-lait spots, axillary freckling, neural tumors; seizure types include generalized tonic-clonic, partial complex, and partial simple-motor	MRI scan of the brain
Incontinentia pigmenti; involvement includes linear papular-vesicular cutaneous lesions at birth, later pigmentation, ocular and dental anomalies; female-to-male ratio > 20:1 (boys may die in utero); seizure types include neonatal onset and later generalized tonic-clonic	Skin biopsy; ophthalmology examination
Hypomelanosis of Ito (incontinentia pigmenti achromians)	

*See http://www.tsalliance.org/healthcare-professionals/diagnosis/.
CNS, central nervous system; CT, computed tomography; ECG, electrocardiogram; EEG, electroencephalogram; MRI, magnetic resonance imaging.

as is a history of significant head injury. An EEG with generalized or focal epileptiform discharges or with focal or generalized slowing is also predictive of recurrence. Focal seizures are more likely to be associated with recurrence, although patients with such seizures are also more likely to have an existing neurologic deficit or an abnormal EEG. The duration of the first seizure or a presentation in status epilepticus is not associated with a higher incidence of recurrence. A family history of epilepsy is not a predictor of recurrence. Earlier age at onset, particularly before the age of 12 months, has been associated with a higher risk of recurrent seizures.

Most authorities believe that the majority of patients with a first seizure should not be treated unless the risk of recurrence is judged to be significantly higher than average. An abnormal neurologic examination, an abnormal MRI of the brain, and abnormal EEG all increase the risk of recurrence; the greater the number of risk factors, the more likely an AED may be initiated after a first known seizure, although some neurologists will still elect to wait for a second confirmed seizure. In adults or adolescents, the issues of driving and employment may influence the decision to treat a first seizure, but in otherwise healthy and developmentally normal children, there is almost no indication for chronic AED treatment in response to a single seizure. *Activities such as bathing, driving, and swimming must be carefully supervised.*

The decision to begin AED therapy is usually made after a patient has had 2 or more seizures in a short interval of time (6-12 months). Treatment with AEDs lowers the recurrence rate by about 50%.

STATUS EPILEPTICUS

Status epilepticus *is a medical emergency* where epileptic seizures are prolonged or occur in rapid succession without recovery between the seizures. There are 2 general categories of status epilepticus: convulsive and nonconvulsive ("subclinical") status epilepticus. **Convulsive status epilepticus** may involve repetitive or prolonged GTC, myoclonic, or tonic seizures. **Nonconvulsive status epilepticus** may involve repeated or continuous absence seizures or focal dyscognitive seizures with an altered state of consciousness lasting hours or even days.

The most common duration of a seizure defined as status epilepticus is 30 minutes or longer, but seizures continuing for more than 5-10 minutes warrant immediate attention, as they are statistically likely to progress to status epilepticus. One third of children presenting with status epilepticus have no history of epilepsy, another third have a history of chronic epilepsy, and an acute illness or injury has caused status epilepticus in another third. One of the most common precipitants of status epilepticus in people with a known history of epilepsy is abrupt *discontinuation* of a daily AED.

Status epilepticus has a significant acute mortality rate, partly because of the underlying cause of the seizures; intracranial infections (meningitis, encephalitis), poisoning, acute metabolic disorders, and head injuries are some of the most common causes.

The goals of the emergency management of status epilepticus are as follows:

1. Maintain normal cardiorespiratory function and cerebral oxygenation.
2. Stop clinical and electrical seizure activity, and prevent its recurrence.
3. Identify precipitating factors.
4. Correct any metabolic disturbances (hypoglycemia, hyponatremia) and prevent systemic complications such as cardiovascular collapse, cardiac arrhythmia, pneumonia, and renal failure.

Table 30.7 sets out a plan of initial assessment and management of convulsive status epilepticus. Lorazepam and diazepam are rapidly acting anticonvulsants when given intravenously, but must be combined with a primary AED, as their duration of action is short. Side effects include sedation, depressed respiration, decreased ability to protect the airway, and hypotension.

Phenytoin, fosphenytoin, phenobarbital, or valproic acid could be used in conjunction with the benzodiazepines in providing longer-lasting anticonvulsive action.

Phenytoin is less commonly used. It has a rare but serious complication called *purple glove syndrome,* which occurs in 1.7-5.9% of intravenous administrations; within 2 hours of administration, there is pain, bluish discoloration, and swelling of the affected limb. Treatment involves discontinuation of the phenytoin, elevation, and icing of the affected limb; compartment syndrome is a potential complication.

Fosphenytoin, a prodrug of phenytoin, can be administered either intravascularly or intramuscularly. Fosphenytoin has a maximum infusion rate of 150 mg PE/min; when it is infused faster, hypotension and arrhythmias may occur.

Valproate can be given intravenously and may be the appropriate therapy for patients with known idiopathic and symptomatic generalized epilepsies. It is also generally appropriate for children with a known static cerebral injury presenting with status epilepticus as their first seizure, such as a child with a history of neonatal hypoxic-ischemic encephalopathy who presents at age 4 in status epilepticus. It is contraindicated in children with known or suspected mitochondrial disease, multisystemic disease of unknown etiology, known hepatic disease, or in children under the age of 2 years.

Nonconvulsive status epilepticus may arise when frequent focal dyscognitive seizures or absence seizures occur. In both of these settings, discrete seizures may not be identifiable; instead, the child may present with confusion, clouded consciousness, and partial responsiveness or a stuporous state, all of which can last hours or even days. It should be treated urgently as soon as it is identified, especially if focal dyscognitive status is suspected, in which case treatment should follow that outlined for convulsive status epilepticus. In absence status epilepticus, intravenous benzodiazepines are usually effective but should be used in conjunction with intravenous valproate or oral ethosuximide.

CLASSIFICATION OF EPILEPSIES AND EPILEPTIC SYNDROMES

The clinician should attempt to determine whether the seizure disorder is focal or generalized, and then whether there is evidence of underlying brain dysfunction. Both the focal and generalized epilepsies in otherwise developmentally normal children respond favorably to treatment, and there is a good chance of long-term remission. Structural epilepsies may benefit from surgical intervention. Genetic and metabolic epilepsies respond less predictably to treatment, and the chance of remission is less certain.

Identification of 1 of the epileptic encephalopathies of infancy and childhood has grave prognostic significance (Table 30.8). These epilepsies vary in the seizure types and EEG features, but have certain features in common: specific age at onset and expression, intractable seizures, cognitive dysfunction, arrest in development, conspicuous interictal epileptic discharges on the EEG, and a poor response to treatment.

Neonatal Period

The paroxysmal disorders seen in the neonatal period (birth to 8 weeks) are presented in Table 30.9.

Paroxysmal Nonepileptic Disorders

Jitteriness. Jitteriness or tremulousness is a common movement disorder of neonates. It can be confused with seizures, especially if superimposed on normal tonic postural reflexes. Jitteriness,

TABLE 30.7 Management of Convulsive Status Epilepticus

Priority	Examination and Laboratory Investigations	Management
On arrival	Airway patency and respiratory rate, inspect pharynx, chest auscultation, BP, pulse, temperature; level of consciousness; response to command, pain; serum Na, K, glucose, creatinine, Ca, Mg; CBC, liver function studies, AED levels; serum and urine toxins screen; arterial blood gases, chest radiograph	Airway protection; suction pharynx and give supplemental oxygen Rectal antipyretic to lower temperature if elevated, IV access and administer: 25% glucose IV, 2-4 mL/kg, and lorazepam* IV, 0.1 mg/kg (to a maximum of 8 mg) as a bolus and fosphenytoin IV, 20 mg/kg at 150 mg/min with ECG monitoring and collection of serum level after loading dose *If immediate IV access is not possible, give diazepam 0.3-0.5 mg/kg rectally and fosphenytoin IM and arrange for central line or intraosseous access
After initial treatment	Neck stiffness, funduscopy, signs of trauma, rashes, symmetry of motor function and reflexes	If patient is febrile: appropriate cultures, other studies depending on age and other symptoms If any suspicion of head injury: obtain urgent CT scan
If seizures continue	Patient's level of consciousness becomes depressed with lorazepam and PB, and an EEG is necessary to assess adequacy of therapy	Arrange ICU bed and consider intubation; give further bolus of lorazepam 0.05-0.1 mg/kg, and push PHT serum level above 30 mg/L with further loading dose (~10 mg/kg) In an ICU setting, if seizures continue with PHT levels of 30-40 mg/L, then add PB 20 mg/kg IV loading over 15-30 min Continued clinical or electrical seizures may necessitate induction of pentobarbital therapy: loading dose of 5-15 mg/kg, followed by IV infusion of 1-3 mg/kg/hr titrated by EEG monitoring to achieve burst suppression pattern; maintain for 24-48 hr and review Elective intubation and ventilation, arterial line, BP monitoring
After stabilization or in tandem with escalating therapy	LP; if acute febrile illness with papilledema or focal neurologic signs, then CT/MRI first	If LP is delayed and intracranial infection is suspected, then cover with antibiotic and antiviral therapy

*Give lorazepam if actively convulsing; this may not be required in patients with serial seizures who can be quickly loaded with fosphenytoin.
AED, antiepileptic drug; BP, blood pressure; Ca, calcium; CBC, complete blood count; CT, computed tomography; ECG, electrocardiogram; ICU, intensive care unit; IM, intramuscularly; IV, intravenously; K, potassium; LP, lumbar puncture; MRI, magnetic resonance imaging; Na, sodium; Mg, magnesium; PB, phenobarbital; PHT, phenytoin.

TABLE 30.8 Cryptogenic and Symptomatic Epileptic Encephalopathies

Neonates and Infants
Early epileptic encephalopathy
Early infantile myoclonic epilepsy
Migratory partial seizures of infancy
West syndrome (infantile spasms)
Severe myoclonic epilepsy of infants
Epilepsy in association with inherited disorders of metabolism (see Table 30.10)
- Lysosomal storage disorders
- Urea cycle disorders
- Aminoacidurias

Children and Adolescents
Lennox-Gastaut syndrome
Myoclonic-astatic epilepsy
Atypical benign partial epilepsy
Acquired epileptic aphasia (Landau-Kleffner syndrome)
Continuous spike-and-wave patterns in slow-wave sleep
Epilepsy in association with inherited disorders of metabolism
Mitochondrial encephalomyopathies
Progressive myoclonus epilepsies
Epilepsy in association with systemic disorders involving the central nervous system
Systemic lupus erythematosus, other vasculitides

TABLE 30.9 Paroxysmal Disorders of the Neonatal Period

Paroxysmal Nonepileptiform Disorders
Jitteriness
Benign neonatal sleep myoclonus

Acute Symptomatic Seizures and Occasional Seizures
Hypoxic-ischemic encephalopathy
Intraventricular hemorrhage
Acute metabolic disorders*
Sepsis-meningitis

Epileptic Syndromes
Benign idiopathic neonatal convulsions
Familial
Nonfamilial
Ohtahara
Symptomatic focal epilepsy
Brain tumor
Malformations of cortical development
Inherited metabolic disease; mitochondrial disorders
Early-onset generalized epileptic syndromes with encephalopathy
Early myoclonic encephalopathy
Early infantile encephalopathic epilepsy

*Hypoglycemia, hypocalcemia, hypomagnesemia, hyponatremia, hypernatremia, hyperammonemia.

characterized by rhythmic alternating movements of all extremities with equal velocity in flexion and extension, only occasionally has a true synchronized clonic appearance. Jitteriness is not accompanied by eye deviation or staring, is stimulus sensitive, and can usually be stopped by gentle passive flexion of the moving limb.

Jitteriness in the newborn can be associated with hypoxic-ischemic encephalopathy, hypoglycemia, hypocalcemia, and drug withdrawal; if any of these causative factors are identified, there may also be a higher risk of epileptic seizures. In otherwise healthy infants, jitteriness seems to be a benign movement disorder, resolving by 10-14 months of age.

Benign neonatal sleep myoclonus. Myoclonic jerks may appear during sleep in some healthy neonates. It has been reported within hours of birth and may disappear over the next few months or persist into childhood. The jerks can be bilateral and synchronous or asymmetric; they may migrate between muscle groups during an episode. They are repetitive but do not disturb sleep. These jerks have been described in all stages of sleep but are most prominent in quiet sleep; they are not confined to sleep onset. Features distinguishing this phenomenon from epilepsy are its presence exclusively during sleep with disappearance on awakening, normal EEGs, and normal psychomotor development.

Acute Symptomatic Seizures and Occasional Seizures

Most neonatal seizures are acute symptomatic seizures, and the number of children who continue to have seizures after the neonatal period is relatively small. Neonatal seizures have been classified according to the clinical features as subtle, tonic, clonic, and myoclonic. However, not all of these clinical seizure types have consistent ictal EEG patterns. The classification of neonatal seizures reflects the variable, poorly organized, and often subtle clinical expression of epileptic seizures at this age. Typical GTC or absence seizures are not seen at this age, perhaps because of the limited capacity of the neonatal brain for interhemispheric synchrony. Patterns include the following:

- Clinical seizures *consistently* associated with an EEG seizure pattern:
  - *Clonic seizures* with focal or multifocal jerking of the face or extremities fit this category, as do focal tonic seizures with focal tonic posturing of a limb or asymmetric posturing of the axial musculature. Clinical seizures with consistent focal jerking or posturing of 1 limb are most consistently correctly identified at the bedside, and are most commonly associated with a focal structural defect, such as a focal perinatal stroke.
- Clinical seizures *sometimes* associated with an EEG seizure pattern:
  - *Myoclonic seizures* consist of single or multiple flexor jerks of the upper or lower limbs. An ictal EEG pattern is not always seen in this group. Fragmentary (multifocal) myoclonus is not always associated with an ictal EEG.
- Clinical seizures *not consistently* associated with an EEG seizure pattern:
  - These include *motor automatisms* characterized by a diversity of signs, including any of the following: wide-eyed staring, rapid blinking, eyelid fluttering, drooling, sucking, repetitive limb movements such as rowing or swimming with the arms or pedaling with the legs, apnea, hyperpnea, tonic eye deviation, and vasomotor skin color changes. This group of **subtle seizures** is generally associated with EEG background abnormalities such as suppression; the seizure itself may not have a consistent EEG correlate. This is reflective of diffuse cerebral dysfunction, such as seen in hypoxic-ischemic encephalopathy or metabolic disorders.
  - Generalized tonic seizures and focal and multifocal myoclonus are also often not associated with neonatal ictal EEG patterns, and when seen in stuporous or comatose children, the jerks may not be epileptic. However, if the EEG is completely normal, it is unlikely that the behaviors of concern represent subtle seizures.

Some simple clinical observations should guide the assessment of neonates with episodic abnormal behaviors. Epileptic behaviors are typically repetitive and stereotyped, but are not provoked by stimulation of the child or increased with increasing intensity of a stimulus. Nonepileptic movements may disappear with repositioning of a limb or the child. Gentle restraint of a limb should be able to suppress or abort nonepileptic motor activity, whereas epileptic movements are still palpable. The association of abnormal eye movements with unusual behavior or limb movements suggests a seizure rather than nonepileptic behavior.

Diagnostic investigations. EEG monitoring is useful in the evaluation of suspicious fluctuations in vital signs in neonates who are paralyzed and intubated or comatose, or in neonates with subtle but repetitive episodes of unusual behavior.

Many neonatal intensive care units have the capability to perform amplitude-integrated EEG (aEEG), which is a reduced electrode monitoring method that uses time-compressed baseline trends of 2 or 4 channels of EEG to allow the bedside practitioner to look for changes suspicious for seizure. However, both the sensitivity and specificity of aEEG are lower than that of full-montage conventional EEG; less than 50% if only a single channel of aEEG is available, but up to 76% and 78%, respectively, when 2 channels of raw EEG are available for comparison and direct review by expert aEEG interpreters. Conventional EEG is recommended over aEEG when both are available; however, the use of aEEG is associated with lower total seizure duration in neonates compared to no monitoring.

Proper treatment must include a thorough search for the cause of the seizures, because many conditions necessitate specific treatment. The possible etiologic factors are numerous and diverse (Tables 30.10 and 30.11). The most common cause is hypoxic-ischemic encephalopathy (60-65%); it is important to make a positive diagnosis of this historically and to exclude conditions such as local anesthetic toxicity, pyridoxine-dependent seizures, prenatal injury, and metabolic encephalopathies that may masquerade as perinatal asphyxia.

Prognosis. The prognosis for normal development after neonatal seizures depends on the cause of the seizures. Approximately 50% of neonates with seizures develop normally, 30% have neurologic sequelae, and 15-20% die. Neonates with seizures caused by CNS infection, hypoglycemia, structural brain malformations, intraventricular hemorrhage, and hypoxic-ischemic encephalopathy have a higher risk of poor outcome due to the prevalence of global brain injury in these conditions. Fifty percent of neonates with hypoxic-ischemic encephalopathy–related seizures develop normally, but fewer than 10% of neonates with seizures and intraventricular hemorrhage develop normally. In contrast, those infants with seizures caused by hypocalcemia (in the absence of asphyxia), drug withdrawal (from maternal drug use), and focal arterial ischemic stroke usually do well, as these are either caused by reversible, transient, or focal etiologies. The likelihood of recurrent seizures is 15-30% overall.

The EEG may add prognostic information; neonates with a normal background pattern are unlikely to have any neurologic deficits and are less likely to have seizures as a cause for their paroxysmal events, but persistent severe abnormalities of the background rhythms, such as burst-suppression patterns, suppression of background rhythms, and electrocerebral silence, have over 90% chance of a poor outcome, including death. Moderate abnormalities of the EEG in the form of amplitude asymmetries and patterns immature for the patient's conceptional age are associated with intermediate outcomes and are of less

TABLE 30.10 Causes of Neonatal Seizures

Ages 1-4 Days
- Hypoxic-ischemic encephalopathy
- Drug withdrawal, maternal drug use of narcotics or barbiturates
- Drug toxicity: lidocaine, penicillin
- Intraventricular hemorrhage
- Acute metabolic disorders
  - Hypocalcemia
    - Perinatal asphyxia, small for gestational age
    - Sepsis
    - Maternal diabetes, hyperthyroidism, or hypoparathyroidism
  - Hypoglycemia
    - Perinatal insults, prematurity, small for gestational age
    - Maternal diabetes
    - Hyperinsulinemic hypoglycemia
    - Sepsis
  - Hypomagnesemia
  - Hyponatremia or hypernatremia
    - Iatrogenic or inappropriate antidiuretic hormone secretion
- Inborn errors of metabolism
  - Galactosemia
  - Hyperglycinemia
  - Urea cycle disorders
  - Pyridoxine deficiency (must be considered at any age)

Ages 4-14 Days
- Infection
  - Meningitis (bacterial), encephalitis (enteroviral, herpes simplex)
- Metabolic disorders
  - Hypocalcemia
    - Diet, milk formula
  - Hypoglycemia, persistent
    - Inherited disorders of metabolism: galactosemia, fructosemia, leucine sensitivity
    - Hyperinsulinemic hypoglycemia
    - Anterior pituitary hypoplasia, pancreatic islet cell tumor
    - Beckwith syndrome
- Drug withdrawal, maternal drug use of narcotics or barbiturates
- Benign neonatal convulsions, familial and nonfamilial
- Kernicterus, hyperbilirubinemia

Ages 2-8 Weeks
- Infection
  - Herpes simplex or enteroviral encephalitis, bacterial meningitis
- Head injury
  - Subdural hematoma, child abuse
- Inherited disorders of metabolism
  - Aminoacidurias, urea cycle defects, organic acidurias
  - Neonatal adrenoleukodystrophy
- Malformations of cortical development
  - Lissencephaly
  - Focal cortical dysplasia
- Tuberous sclerosis
- Sturge-Weber syndrome

value in isolation from other clinical data; these will require long-term neurologic follow-up.

Treatment. The primary treatment for neonatal seizures is the treatment of the underlying cause. All neonates with seizures should have a trial of pyridoxine and folinic acid treatment if the cause is not identified and seizures persist. Some neonates also require treatment with an AED, traditionally phenobarbital, but levetiracetam and fosphenytoin are also used. Protein binding is lower in neonates than in older children, and the speed of hepatic metabolism changes significantly in the first few days of life, so frequent serum levels of protein-bound, hepatically metabolized AEDs such as phenobarbital or fosphenytoin are necessary for the first several days of treatment, or when making major adjustments.

At an intravenous loading dose of 18-20 mg/kg, phenobarbital should produce a serum level of approximately 18-20 mg/L (Table 30.12). A daily maintenance dose of 3-5 mg/kg, either administered once daily or in 2 divided doses daily, keeps serum levels in this range. The serum level can be increased to 40-60 mg/L with further loading doses before consideration of a second drug for persistent seizures.

If a self-limited or correctable short-term insult is the cause, the clinician may administer a loading dose with phenobarbital and give no maintenance therapy, simply observing for recurrent seizures. Alternative management would be to administer a loading dose of phenobarbital and give maintenance doses throughout an illness or to treat for a maximum of 3-6 months if the time during which the child is at risk for seizures is uncertain.

Epileptic Syndromes

Benign idiopathic neonatal convulsions, familial and nonfamilial. Some neonatal seizures occur in otherwise healthy neonates without perinatal risk factors or identifiable causes that remit spontaneously and are not followed by developmental delay; these include benign idiopathic neonatal convulsions and benign familial neonatal convulsions. These are diagnoses of exclusion and a complete work-up for other causes of neonatal seizures must be performed before deciding upon these etiologies.

Benign idiopathic neonatal convulsions are common and may account for 2-7% of neonatal seizures. The disorder is sometimes referred to as **5th-day fits**, although the seizures may begin between 1 and 7 days of age. The seizures are typically focal and multifocal clonic seizures that may, in rare cases, develop into status epilepticus. The seizures remit within hours or days. Although normal at the onset of seizures, affected neonates may become drowsy and hypotonic during the seizures and for a few days after the seizures remit. Long-term follow-up data are not yet complete, but the majority of affected children appear to have normal psychomotor development and no increased risk for the development of epilepsy.

Benign familial neonatal convulsions are less common. There is a distinctive family history of transient neonatal seizures that shows autosomal dominant inheritance. The onset of seizures is usually between 2 and 4 days after birth, but in some cases, onset may occur at 1-3 months of age. The neonates are otherwise healthy without risk factors for seizures. The seizures are usually brief clonic seizures, but some neonates have tonic seizures. This group differs from the nonfamilial cases in that the seizures may persist longer, the interictal EEG is generally nonspecific, and later seizures occur more frequently in approximately 10-15% of children. Abnormalities in 2 potassium channel genes, *KCNQ2* on chromosome 20 and *KCNQ3* on chromosome 8, have been found in some kindreds (see Table 30.3).

Vitamin-dependent seizures. There are rare metabolic disorders that present in the first few days of life with encephalopathy and refractory seizures; a smaller percentage of these disorders can be treated with early diagnosis and administration of the correct vitamin. Pyridoxine-dependent and folinic acid-dependent seizures are 2 such disorders; pyridoxine is essential for amino acid metabolism, and folinic acid is necessary for DNA synthesis and repair. Multidisciplinary care with a geneticist and a neurologist is ideal for children with these rare disorders.

TABLE 30.11 Inherited Disorders of Metabolism and Neurodegenerative Diseases Associated with Seizures in Infants

Disorder	Clinical Features and Laboratory Findings	Investigations
Neonates		
These disorders are rare. The clinical features are nonspecific and usually do not distinguish between the inherited disorders of metabolism; however, they may suggest that a search for these conditions is warranted: Metabolic or degenerative disorder in another sibling Normal immediately after birth with symptoms and signs developing in the first days to weeks of life Food intolerance; vomiting, diarrhea, not settling after feedings Lethargy, may become stuporous after feeding Hypotonia Seizures; tonic, clonic, subtle neonatal seizures; myoclonus in some disorders Late signs: weight loss, failure to thrive, psychomotor retardation		Initial investigations in neonatal seizures: Glucose, urinalysis, ketones Serum glucose, Na^+, K^+, Ca^{2+}, Mg^{2+}, blood urea nitrogen, creatinine Serum ammonia, lactate, and pyruvate Liver function tests, complete blood cell count, arterial blood gas measurements Lumbar puncture and CSF analysis EEG CT or MRI scan may be indicated
Aminoacidurias		
Maple syrup urine disease	An unusual maple syrup odor of the urine may be detected; severe metabolic acidosis and increased anion gap; urine positive for ketones; boiled urine reacts with 2,4-DNPH to give yellow precipitate	Serum amino acid analysis; elevated serum leucine, isoleucine, and valine
Organic acidurias		
Propionic acid Methylmalonic acid Isovaleric acid Glutaric acid	Hyperammonemia, metabolic acidosis and increased anion gap, ketosis, low blood urea nitrogen; secondary elevation of lactate and hypoglycemia may be present and secondary carnitine deficiency may occur; glycine level may be elevated in these disorders Thrombocytopenia, neutropenia, and anemia Characteristic body odor in some of these disorders	Urine organic acid analysis Serum carnitine measurement Serum acylcarnitine profile
Urea cycle disorders	Hyperammonemia without hypoglycemia, ketoacidosis or hematologic abnormalities	Serum ammonia. Plasma amino acids and urine orotic acid can help define the specific urea cycle defect
Nonketotic hyperglycinemia D-glyceric acidemia	Intractable seizures and severe encephalopathy, often with coma, within the first weeks of life; may have the clinical syndrome of early myoclonic encephalopathy; myoclonic seizures, burst suppression on EEG, severe psychomotor retardation	Elevated urine and plasma glycine levels, normal organic acid pattern and ammonia level. Ratio of CSF : serum glycine necessary to make the diagnosis
Pyridoxine dependency	No specific clinical features; must be suspected in all neonatal seizures without alternative cause and especially in those not responding to simple measures	Therapeutic trial of pyridoxine; high dosage must be given for a period of weeks
Peroxisomal diseases Zellweger syndrome Adrenoleukodystrophy Refsum disease	Characteristic facies Neonatal form Infantile form	Screen with serum very-long-chain fatty acid analysis, specific measurement of phytanic acid, prystanic acid, pipecolic acid, red cell plasmalogens, and bile acids for biochemical diagnosis. Molecular diagnostics using comprehensive gene panels
Infants		
Pyruvate dehydrogenase deficiency Pyruvate carboxylase deficiency	Metabolic acidosis and increased anion gap, lactic acidosis, with normal lactate-to-pyruvate ratio (10 : 20); hyperammonemia may be seen; normoglycemic; serum and CSF alanine levels may be elevated Lactate-to-pyruvate ratio is normal or elevated The clinical features are nonspecific: encephalopathy, hypotonia, and seizures; intermittent hyperventilation may be present. Both these disorders can manifest later in childhood with developmental delay and episodic symptoms such as ataxia and vomiting	Serum lactate and pyruvate measurement Serum and CSF amino acids measurement
Biotinidase deficiency	Refractory seizures, rash, alopecia; lactic and organic acidosis	
Aminoacidurias		
Phenylketonuria	Onset in infancy with developmental delay and seizures; seizures occur in about 25%, and the infant may have severe epilepsy with West syndrome; deficiency of phenylalanine hydroxylase causes the accumulation of phenylalanine and phenylacetic acid	Nearly 100% identified through New Born Screening. Plasma amino acids will identify elevated phenylalanine in affected individuals

TABLE 30.11 Inherited Disorders of Metabolism and Neurodegenerative Diseases Associated with Seizures in Infants—cont'd

Disorder	Clinical Features and Laboratory Findings	Investigations
Phenylketonuria variant with biopterin deficiency	Hypotonia and seizures develop at or after 6 mo of age; generalized motor seizures, erratic myoclonus, and oculogyric seizures	Nearly 100% identified through New Born Screening. Plasma amino acids will identify elevated phenylalanine in affected individuals
Tay-Sachs disease GM_2 gangliosidosis	Abnormalities appear in the first weeks to months of life with irritability and acoustic startle or myoclonus, not seizures, in the first months; developmental delay and cherry-red macular spots are present; seizures develop in the second year of life; erratic myoclonus, focal seizures, and slowing of background rhythms on EEG	Blood sample and skin biopsy; hexosaminidase A deficiency detectable in blood lymphocytes and cultured fibroblasts
Sandhoff disease GM_2 gangliosidosis type II	Similar in phenotype to Tay-Sachs disease	Hexosaminidase B deficiency detectable in blood lymphocytes and cultured fibroblasts
GM_1 gangliosidosis	Dysmorphic features; three clinical subtypes, *infantile* with rapid progression in first 6 mo of life, seizures are frequent without specific characteristics; cherry-red spots on the maculae; juvenile or late onset form (6 mo to 3 yr), chronic form (4 to 30 yr). Dysmorphic features and skeletal changes similar to Morquio mucopolysaccharide storage disorder	Skin biopsy, blood β-galactosidase deficiency found in blood lymphocytes and cultured fibroblasts
Leigh disease (subacute necrotizing encephalopathy)	A clinical syndrome resulting from various abnormalities of mitochondrial oxidative phosphorylation Usually manifesting in infancy with regression of motor skills, hypotonia, lethargy, respiratory disorders (typically hyperventilation and apnea), and seizures; other features are nuclear and supranuclear oculomotor paralysis, brainstem dysfunction, choreoathetosis, cerebellar ataxia, and pyramidal signs	CSF lactate measurement; MRI of the brain (may show midbrain periaqueductal signal abnormalities) Muscle biopsy for oxidative metabolism analysis and DNA studies
Menkes disease	Sex-linked inheritance on long arm of X chromosome; hypotonia, failure to thrive, abnormal temperature regulation, hypothermia or hyperthermia, fragile wiry hair, poor pigmentation, generalized seizures, often infantile spasms	Deficiency of serum copper and ceruloplasmin
Krabbe disease	Appears before 3-6 mo of age; rigidity develops in an irritable, crying infant; opisthotonic posturing of the neck and trunk; generalized motor seizures may occur, but must be distinguished from tonic spasms; affected children become blind with optic atrophy	Skin biopsy and blood galactocerebrosidase deficiency
Angelman syndrome	Developmental delay from birth, characteristic facies, ataxia with jerky limb movements, inappropriate laughter ("happy puppet"), seizures in 86% of patients	Abnormal methylation of maternally inherited imprinted region of chromosome 15q11.2. Four known genetic mechanisms can cause Angelman syndrome; approximately 70% of cases result from de novo maternal deletions involving chromosome 15q11.2-q13; approximately 2% result from paternal uniparental disomy of 15q11.2-q13; a subset of the remainder result from other imprinting defects and pathogenic variants in the gene encoding the ubiquitin-protein ligase E3A gene *(UBE3A)*
Early infantile type of ceroid-lipofuscinosis Batten disease	Severe myoclonus at 3-18 mo; hypotonia, ataxia, impaired vision, dementia; diffuse cerebellar and cerebral atrophy EEG; no enzymatic defect identified; diagnosis must be based on clinical features and skin biopsy showing ceroid	Skin biopsy, inclusion bodies on electron microscopy of peripheral lymphocytes (buffy coat EM), rectal biopsy; genetic testing available
Other Rare Metabolic Disorders with Encephalopathy Seizures in Infancy Glutaric aciduria type II, multiple acyl-CoA dehydrogenase deficiency Medium-chain acyl–CoA dehydrogenase deficiency Canavan–van Bogaert disease Molybdenum cofactor deficiency		Specific testing based on suspected diagnosis

CoA, coenzyme A; CSF, cerebrospinal fluid; CT, computed tomography; DNPH, dinitrophenylhydrazine; EEG, electroencephalogram; MRI, magnetic resonance imaging.

TABLE 30.12 Neonatal Antiepileptic Medication: Pharmacokinetic Parameters

	Routes of Administration	% Protein Bound	Half-Life Loading Dose	Maintenance (hr)	Therapeutic Antiepileptic Dosage (mg/kg/day)	Range (mg/L)
Phenobarbital	IV, PR, PO	24	20 mg/kg	40-200	3-5	10-30
PHT	IV, PO	85-90	15-20 mg/kg	6.9-140*	IV: 8-10; PO: 18-20	5-20
Fosphenytoin	IV, IM	70, displaces PHT	15-20 mg/kg†	Fosphenytoin > PHT, 8-15 min	18-20	5-20
Diazepam	IV, PR	84	0.1-0.3 mg/kg/dose‡	31-75	3	0.3-0.7
Lorazepam	IV	85	0.05 mg/kg/dose§	18-73	NA	NA

*Great variation, shorter if exposed to enzyme-inducing drugs (e.g., phenobarbital) and within 1st 2-3 wk of life.
†Dosage is in PHT equivalents per kg.
‡Can be given every 15 min to a maximum of 2 mg.
§Up to 2 doses only.
IM, intramuscularly; IV, intravenously; NA, not applicable; PHT, phenytoin; PO, per os (orally); PR, per rectum.

Pyridoxine-dependent seizure is a rare autosomal recessive disorder in which seizures usually appear within the first 3 months of life, often within hours of birth, but in rare cases, as late as 2-5 years of age. The EEG may show focal, multifocal, and generalized epileptiform activity, and the child is encephalopathic. The seizures (myoclonic, GTC, and partial), and EEG discharges disappear over hours in response to 100 mg of intravenous pyridoxine (vitamin B_6), which can be repeated 3-5 times as necessary. The children require long-term pyridoxine, 50-100 mg/day.

Folinic acid-responsive seizures present very similarly to pyridoxine-dependent seizures, with medically intractable, relentless seizures of multiple types, often within the first days of life. The seizures respond to 2.5-5 mg of folinic acid twice daily.

These are rare disorders, but as they are neurologically devastating or fatal if untreated, it is reasonable to administer a trial dose of pyridoxine and/or folinic acid to seizing, encephalopathic infants where no other cause has been found for their seizures and encephalopathy. If there is a clinical, and ideally electrographic, response to the vitamin trial, then it is also reasonable to continue the supplement. Nonetheless, even with early diagnosis and treatment, these children may have developmental delays.

Structural focal epilepsy. **Malformations of cortical development**. Disorders of cell migration within the CNS may result in profound anatomic abnormalities and dysfunction or a spectrum of lesser abnormalities, ranging from focal areas of cortical dysgenesis and clinical deficits to subcortical collections of neurons (heterotopia) seen only under the microscope. Migrational abnormalities are rare but are commonly associated with seizures. Although these abnormalities are present from birth, seizures may develop at any age.

Lissencephaly, or agyria, is a profound abnormality characterized by a smooth brain without development of the normal gyral pattern and sulci; there are often large heterotopia in the white matter, and neuroimaging studies may reveal the appearance of a double cortex.

Hemimegalencephaly is characterized by gross enlargement of 1 hemisphere with no normal cortical development within that hemisphere. More restricted abnormalities may occur in the form of a limited area of gyral enlargement and distortion called pachygyria.

Schizencephaly refers to unilateral or bilateral clefts in the cerebral hemispheres, usually with abnormal arrangement (polymicrogyria) of the cortical gray matter lining the clefts.

Porencephaly refers to fluid-filled cavities within the brain. Porencephalic cysts communicate with both the subarachnoid space and the ventricular system and are lined not by cortical gray matter but rather by white matter because they result from loss of tissue as a consequence of insults, typically infarction or hemorrhage, during development.

Early-onset generalized epileptic syndromes with encephalopathy. **Early myoclonic encephalopathy** appears in neonates before 2-3 months of age, usually within the first 2 weeks of life. Myoclonus appears at the onset but may be fragmentary. Partial motor seizures, massive myoclonus, or infantile spasms may also occur. The EEG shows a suppression-burst pattern that may later evolve into a hypsarrhythmic pattern. There is a failure or arrest of psychomotor development and a high rate of mortality before 12 months of age. A number of patients have an inborn error of metabolism, including nonketotic hyperglycinemia, D-glyceric acidemia, propionic acidemia, and methylmalonic acidemia.

Early epileptic encephalopathy with suppression-burst EEG pattern (Ohtahara syndrome) has an onset during the same period. The affected child experiences intractable tonic seizures or epileptic spasms, and the EEG shows a suppression-burst pattern. Affected children have a severe encephalopathy, and the prognosis for remission from seizures or for normal development is very poor. Many of these patients have malformations of cortical development.

There appear to be neonates in whom the EEG features and clinical course of these 2 syndromes overlap; these syndromes may evolve into West syndrome and Lennox-Gastaut syndrome.

Infancy

The paroxysmal disorders of infancy (8 weeks to 2 years) are shown in Tables 30.3 and 30.13.

Paroxysmal Nonepileptic Disorders

Infantile syncope

Cyanotic infant syncope (breath-holding spells). Cyanotic infant syncope consists of episodes of loss of consciousness followed by tonic stiffening in crying infants. The peak incidence is between 6 and 18 months of age, but it may occur in neonates or in children as old as 6 years of age. The typical clinical picture is an infant who is frightened, frustrated, or surprised; begins to cry vigorously; and then becomes apneic and cyanotic before becoming unconscious, stiff, or limp. In rare cases, typical infant syncope may evolve into a brief GTC seizure. The child regains consciousness rapidly after being positioned horizontally or stimulated without a prolonged postictal state, although there may be a tendency to sleep.

TABLE 30.13 Paroxysmal Disorders in Infants

Nonepileptiform Disorders
Infantile syncope*
Cyanotic breath-holding spells
Pallid syncope
Shivering attacks
Paroxysmal torticollis
Extrapyramidal drug reactions, dystonia
Gastroesophageal reflux with dystonia†
Rumination†
Stereotypical; movements, autism, Rett syndrome, coexisting deafness and blindness†
Withholding, constipation†
Masturbation
Spasmus nutans
Opsoclonus
Benign paroxysmal vertigo
Myoclonus
Nonepileptic; anxiety, excitement, acute metabolic encephalopathy
Benign myoclonus of early infancy
Hyperexplexia†
Alternating hemiplegia of childhood
Sleep disorders*
Jactatio capitis, head banging

Acute Symptomatic Seizures, Occasional Seizures
Febrile convulsions*
Meningitis, encephalitis*
Head injury, child abuse
Poisoning
Intercurrent medical illness, renal, and liver disease, cardiac left-to-right shunt, and embolism
Metabolic disease, rickets

Epileptic Syndromes
Symptomatic focal epilepsy†
West syndrome
Early myoclonic encephalopathy‡
Early infantile encephalopathic epilepsy‡
Malformations of cortical development‡
Neurocutaneous disorders (see Table 30.6)
- Tuberous sclerosis
- Sturge-Weber syndrome
- Incontinentia pigmenti
- Epidermal nevus syndrome

Severe myoclonic epilepsy in infancy (Dravet syndrome)

*Common.
†See childhood section for discussion.
‡See neonatal section for discussion.

These episodes have also been called breath-holding spells, anoxic seizures, and convulsive syncope, but *cyanotic infant syncope* may be a better term because the loss of consciousness appears to be the result of transient impairment of cerebral perfusion. The subsequent tonic posturing in the typical attack is not epileptic, but is thought to have the same brainstem origin as decerebrate or decorticate posturing.

Cyanotic infant syncope is common and is seen in 4.6% of a large cohort of children monitored from birth. A thorough history is usually sufficient for diagnosing this condition. The crucial diagnostic point is the history of an external event precipitating the episode. The differential diagnosis is noted in Table 30.14.

Although the spells appear to be unpleasant for the child and can be frightening to the parents, they do not result in neurologic sequelae and do not necessitate intensive investigation. The child should be evaluated for anemia; treatment of iron deficiency anemia reduces the frequency of syncopal events. Treatment with carbamazepine, phenytoin, or valproate may decrease the frequency or severity of postsyncopal convulsions in the rare child with epileptic seizures triggered by the anoxic event. Children with known brainstem or posterior fossa malformations may also be at higher risk of prolonged syncope and clinically significant anoxia due to their abnormal respiratory drive, and these children may benefit from treatment.

Pallid infant syncope. Pallid infant syncope occurs in response to transient cardiac asystole in children with a hypersensitive cardioinhibitory reflex. This form is less common but more alarming. There is minimal crying, perhaps only a gasp, and no obvious apnea before the loss of consciousness. Again, there is a precipitating event; the child appears to lose consciousness after minimal injury or fright, collapses limply, and then may have posturing and clonic movements before regaining consciousness (see Table 30.14).

Pallid infant syncope, if frequent and troublesome or if followed by prolonged GTC convulsions, can be treated with atropine, which blocks the vagus nerve–mediated asystole. Most affected children require no medical treatment.

Hyperekplexia. A startle response is normally seen in children and adults in response to sudden, unexpected stimuli. There are 2 phases to a startle response: the initial startle followed by an orienting response to locate the stimulus. Hyperekplexia is characterized by an excessive startle response interfering with daily living, usually causing patients to fall stiffly with preserved consciousness. This disorder may present as early as infancy with hypertonia and dramatic startle responses that do not habituate or extinguish with repeated stimuli (meaning they continue to startle, no matter how many times a stimulus is given in a short period of time). The excessive startle and hypertonia can lead to genuinely life-threatening apneas and breath-holding spells when startled or upset. Generalized seizures have been reported in some cases; intellectual disability and delayed motor development appear to be common. The background EEG is usually normal. There may be some improvement with benzodiazepines or valproic acid.

Mutations in the *GLRA1* gene, encoding the α-1 subunit of the glycine receptor, have been found in families with an autosomal dominant or recessive inheritance pattern. Glycine is a co-agonist for the *N*-methyl-D-aspartate (NMDA) receptor, which is an excitatory receptor critical for learning and neuronal plasticity.

Sleep disorders. Also referred to as head banging or rocking, jactatio capitis nocturna consists of rhythmic to-and-fro movements of the head or rocking of the body. It occurs typically at the transition from wakefulness to sleep, early in the evening, or after arousal during the night. This behavior is quite common, occurring in up to 15% of children; it begins in infancy or early childhood, but may persist up to 10 years of age. The child is not awake during the episode and does not remember the events, which usually last less than 15 minutes. In most cases, it is sufficient to ensure that the bed area is padded to prevent injury.

Shivering attacks. Shivering or shuddering attacks are brief episodes characterized by sudden flexion of the head and trunk associated with a rapid tremulous contraction of the musculature. The appearance is exactly that of a sudden brief shudder experienced normally when exposed to cold. In this condition, the shuddering occurs repeatedly. Some infants experience more than 100 brief shudders per day. There may be clustering, with intervals of several weeks free of the

TABLE 30.14 Differential Diagnosis of Infantile Syncope

Clinical	Infantile Syncope	Pallid Syncope	Tonic-Clonic Seizures	Infantile Spasms
Age range	1-6 yr; peak, 6-18 mo	1-6 yr	All ages	4-12 mo
Precipitating factors	Present (e.g., minor trauma, frustration, fright)	Present (e.g., minor trauma, frustration, fright)	Usually none	None
Occurrence in sleep	Never	Never	Common	At transition from awake to sleep and sleep to awake
Sequence of events	Crying → exhale; apnea → cyanosis, loss of consciousness; opisthotonos → relaxation, resumption of breathing	Upset, usually not crying → sudden pallor → limp fall with fainting → tonic posture, or clonic jerks may occur	Sudden loss of consciousness → increased tone, followed by synchronous jerking of body and limbs → unconsciousness; duration, 1-2 min	Sudden sustained flexion or extension of proximal limbs and trunk; duration, 2-20 sec; seizures usually occur multiple times daily
Postictal symptoms	Usually minimal; infant may be lethargic and irritable	Usually minimal; quick return to normal	Usually marked; unconsciousness initially, then confusion and lethargy	Rapid return to preictal state
Interictal EEG	Normal	Normal	Frequently abnormal with epileptiform discharges	Abnormal background and epileptiform discharges
Ictal EEG	Reflects global cerebral hypoxia, diffuse rhythmic slowing → suppression → slowing with return of consciousness	Reflects global cerebral hypoxia; diffuse, rhythmic slowing → suppression → slowing with return of consciousness	EEG seizure patterns; postictal diffuse suppression, then slowing	High-amplitude slow transient waves → diffuse suppression
Pathophysiology	Respiratory arrest without asystole	Vagal bradycardia or temporary asystole	Primary CNS event	Primary CNS event, age-related epileptic seizure

CNS, central nervous system; EEG, electroencephalogram.

episodes. The child may assume a characteristic posture with flexion of head, trunk, and elbows and adduction of elbows and knees.

The attacks have been described in children between the ages of 4 months and 10 years, although most often the onset seems to occur in infancy and early childhood. The phenomenon is nonepileptic and benign, eventually disappearing. Some children and their relatives have been reported to have an essential tremor. The shuddering is faster and of lower amplitude than myoclonus and is paroxysmal, not sustained, as occurs with a tremor. An important epileptic disorder that must be ruled out is infantile spasms.

Paroxysmal torticollis. Torticollis is an abnormal posturing of the head and neck, with the head flexed toward the shoulder and the neck rotated with the chin turned toward the opposite shoulder. The posturing is paroxysmal, although variable in duration, lasting minutes or days, and there is no loss of consciousness. Some children have associated pallor, agitation, and vomiting, and the disorder has been suspected to result from labyrinthine dysfunction, like benign paroxysmal vertigo of childhood. The disorder is self-limited and remits in early childhood. There is an association with migraine in patients later in life and among their relatives.

In older children, torticollis may occur as a **focal dystonia** persisting to adulthood. Familial cases have been described, and in some, the torticollis may be the earliest manifestation of a more generalized dystonia.

Sustained abnormal posturing should prompt appropriate radiologic investigations to exclude inflammatory or neoplastic disorders of the upper cervical spinal cord, posterior fossa, cervical spine, or soft tissues of the neck (particularly a retropharyngeal abscess). In very rare cases, gastroesophageal reflux manifests with dystonic posturing of the neck and upper trunk. Adverse extrapyramidal reactions to phenothiazines and related drugs may produce dystonic posturing of the neck and trunk.

The pharmacologic treatments for torticollis cover a number of different medication classes, including anticholinergics (trihexyphenidyl), dopamine agonists (pramipexole), nonsteroidal antiinflammatory drugs (NSAIDs), baclofen, benzodiazepines (clonazepam), and β blockers (propranolol). Botox injections may be used for more refractory cases. Physical therapy can also be very helpful. The most severe cases can be evaluated for surgical intervention, such as selective denervation or sternocleidomastoid release.

Infantile masturbation. Episodes of genital self-stimulation may occur in young children. Toddlers may assume stereotyped posturing with tightening of the thighs or applied pressure to the suprapubic or pubic area not associated with manual stimulation of the vulva or rhythmic movements. The episodes vary in duration from minutes to hours and are often accompanied by irregular breathing, facial flushing, and diaphoresis, and the child may be irritated and cry if interrupted. A thorough history or a video of the episodes may be sufficient to make this diagnosis.

Spasmus nutans. Spasmus nutans is a rare disorder of unknown origin characterized by nystagmoid eye movements, head nodding, and torticollis. Head nodding may develop before the nystagmus and can be horizontal, vertical, or mixed. Both the head movements and the nystagmus may be paroxysmal, allowing confusion with seizures. There is no loss of consciousness during an episode. Small-amplitude rapid eye movements are typical; they tend to be asymmetric between the eyes and may even be monocular. The eye movements vary in prominence with different directions of gaze.

This is usually a self-limited disorder with onset between 4 and 18 months of age and not persisting after age 3 years, although nystagmus alone may persist in some children. Investigations should include imaging of the brain with special focus on the optic nerves, optic chiasma, and brainstem, because some cases have been associated with CNS tumors.

Benign paroxysmal vertigo. Benign paroxysmal vertigo may be confused with seizures because attacks develop suddenly, are accompanied by ataxia, and may cause the infant or young child to fall. There is pallor, distress, and assumption of a motionless, often supine, position, but no loss of consciousness; older children can recall the event. There may be vomiting with associated nystagmus. Attacks last seconds to minutes and vary in frequency, sometimes occurring daily. Older children can identify symptoms of nausea and vertigo and are less likely to be thought to be experiencing seizures. The children are normal between attacks. The condition is closely related to **migraine**, with many shared symptoms and the later development of more typical migrainous headache.

Benign myoclonus of early infancy. This uncommon syndrome may resemble the cryptogenic form of infantile spasms at onset, with bilateral myoclonic jerks developing in a previously normal infant. However, this is a benign, probably nonepileptic condition occurring in infants 3-8 months of age and disappearing after a period of weeks or months. The pattern of myoclonus may differentiate it from infantile spasms, including predominant involvement of the head, neck, and upper limbs with adversive head movements or tremors without involving the lower limbs. The EEG is normal. Myoclonic movements are not accompanied by an EEG seizure pattern. These abnormal movements may necessitate monitoring to establish a nonepileptic diagnosis. There is no arrest of normal development or regression as is seen in West syndrome. Most important, the myoclonus remits, not persisting after 2 years of age, and there is increased risk for other seizure patterns after its cessation.

Alternating hemiplegia of childhood. Alternating hemiplegia of childhood is a rare syndrome of episodic hemiplegia that usually manifests in infancy with the following diagnostic criteria:

1. Onset before age 18 months, often before age 6 months
2. Recurrent episodes of fluctuating hemiparesis or hemiplegia affecting both sides of the body and disappearing during sleep
3. Other paroxysmal phenomena: tonic seizures, dystonic posturing, choreoathetosis, nystagmus, and other paroxysmal oculomotor disturbances; and autonomic dysfunction, occurring during or between hemiplegic episodes
4. Progressive cognitive and neurologic deficits

The pathophysiologic mechanism remains unknown, although there are reports of mitochondrial dysfunction in some cases and an autosomal dominant pattern of inheritance in others. The differential diagnosis includes paroxysmal choreoathetosis and dystonia syndromes, familial hemiplegic migraine, transient ischemic attacks associated with cerebral vascular abnormalities such as moyamoya disease or cardiac emboli, mitochondrial disorders, hyperviscosity, sickle cell anemia crises, inherited disorders of metabolism (pyruvate dehydrogenase deficiency and Leigh disease), and epileptic seizures with postictal paralysis. Symptomatic treatment is available with calcium channel blockers; flunarizine is the one most commonly cited in the literature, but is not available in the United States or Japan. An alternative calcium channel blocker would be nimodipine.

There have been case reports of a similar-appearing disorder with nocturnal paroxysmal events of flaccid hemiplegia lasting up to several hours at a time. The key differentiating factors are that these children are essentially normal prior to diagnosis, the events occur during sleep, and the children appear to outgrow these spells by mid-childhood without significant long-term neurologic sequelae. This is known as **benign nocturnal alternating hemiplegia of childhood.** No consistent genetic mutations have been associated with this disorder, and there is no consistent response to antiepileptics or calcium channel blockers.

Acute Symptomatic Seizures and Occasional Seizures

Febrile convulsions. Febrile convulsions are common and are defined as seizures occurring between the ages of 6 months and 5 years in association with a fever in the absence of intracranial infection. Patients with a history of previous afebrile seizures are not included in the affected population. The temperature elevation is variable. The highest incidence of febrile convulsions occurs between 1 and 2 years of age, and 85% of febrile convulsions occur before the age of 4 years. The incidence is between 2% and 5%; it is slightly more common in boys.

The seizures are usually brief with generalized clonic or tonic-clonic motor involvement without any postictal paralysis or a prolonged postictal state of confusion or drowsiness. The seizures generally occur well within the first 24 hours of a febrile illness, not necessarily when the fever is highest; they may be the first indication of illness. **Complicated febrile convulsions** are defined as those lasting longer than 15 minutes, recurring during a single febrile illness, having unilateral or focal features, or followed by postictal paralysis. Seizures occurring late in a febrile illness should raise suspicions of encephalitis, brain abscess, or meningitis. Febrile delirium and even rigors may be mistaken for seizure activity.

The initial investigation must include a search for the cause of the febrile illness. For this diagnosis, it is essential that primary CNS infection be ruled out as the cause of both the fever and the seizures. A lumbar puncture is recommended in children younger than 12 months of age if there is any suspicion of intracranial infection, and when features of the seizure or postictal state suggest a focal or lateralized seizure. Herpes simplex encephalitis in particular should be considered in children presenting with evidence of encephalitis and focal seizures. Computed tomography, MRI, and EEG may be part of the work-up if an underlying CNS infection is suspected or a neurologic deficit has been revealed by the history or examination.

However, if the history is consistent with a febrile seizure, the child is in the appropriate age range and is developmentally normal, a fever has been documented, and an obvious source of infection has been found, extensive investigations are unnecessary. Many clinicians would not perform a lumbar puncture or obtain an EEG in an otherwise healthy child with an uncomplicated febrile seizure over the age of 2 years who has an obvious source of infection such as otitis media or a urinary tract infection.

Treatment of a child still in convulsion on arrival at the hospital should include prompt attention to protection of the airway and circulation. Giving acetaminophen rectally should lower the fever. Nasal or rectal diazepam or intravenous lorazepam should be administered if the child has been seizing for more than 10 minutes. Some children may require hospital admission. The family should be advised that future fevers with temperatures above 38°C (100.4°F) may be treated with regular acetaminophen or ibuprofen to make the child more comfortable; however, this does not guarantee that future febrile convulsions will be prevented, even if the parents respond to the first elevated temperature.

There is no increased rate of mortality from true febrile convulsions, and the mental and neurologic development can be expected to be normal after a simple febrile convulsion. However, approximately 30% of febrile convulsions recur in future febrile illness, and the parents should be warned of this. Recurrence is most likely in the first 6-12 months after the initial febrile convulsion. Other factors that increase the chance of recurrence are onset at a young age, preexisting neurologic abnormalities, and family history of epilepsy or febrile convulsions.

Most authorities would advise no treatment for almost all children with febrile convulsions. Rare exceptions include children presenting

with prolonged (>15 minutes) seizures and children younger than 12 months old with multiple recurrences. For children with recurrent prolonged febrile seizures, rectal diazepam could be considered as an abortive therapy. Children with recurrent episodes of **febrile status epilepticus**, particularly starting under 1 year of age, with focal features, or associated with any insidious neurologic or cognitive decline, should be referred to a neurologist for further evaluation, particularly for sodium channelopathies such as **Dravet syndrome** or **generalized epilepsy with febrile seizures plus (GEFS+)**, as detailed in Tables 30.3 and 30.15. Informing and reassuring parents of the benign nature and usual course of febrile convulsions are very important and may be of greater value than any medication.

There appears to be an increased risk of epilepsy among children with febrile convulsions. Overall, the risk is approximately 3%. Risk factors increasing the likelihood of future epilepsy include existence of a prior neurologic abnormality, prolonged convulsions (>30 minutes), focal or lateralized features of the seizure, and repeated convulsions within 24 hours. The incidence of epilepsy increases from 3% of those without risk factors to 49% of those with 3 risk factors. Risk factors for epilepsy with generalized seizures are more than 3 febrile seizures and epilepsy in a first-degree relative, which suggests that febrile convulsions in these individuals may be a manifestation of an increased predisposition to epilepsy. For epilepsy with focal seizures, the risk factors are prolonged convulsions, focal features of the seizure, and repeated seizures within 24 hours, which suggest either a causative role of febrile convulsions in partial epilepsy or a preexisting brain lesion. The number of recurrences of febrile seizures has not been shown to be a risk factor for later epilepsy. There is no evidence that AED treatment of febrile seizures affects the risk for later development of afebrile seizures.

Epileptic Syndromes

West syndrome

- Peak presentation: ages 4-8 months
- Red flags: daily clusters of brief hiccupping or startle-type seizures, particularly upon waking up or falling asleep. Developmental regression.
- Acuity: emergent to urgent; ideally obtain an EEG within a week and call a neurologist if this diagnosis is suspected. Must be managed by a neurologist due to atypical treatment needs (adrenocorticotropic hormone [ACTH]), which may require hospital admission.
- Prognosis: generally poor, particularly if the diagnosis is missed

West syndrome, or severe encephalopathic epilepsy in infants, is characterized by infantile spasms, the hypsarrhythmic EEG pattern, and developmental delay. It is a severe and devastating form of epilepsy, usually with evidence of diffuse cerebral dysfunction and a poor prognosis in most cases. The incidence is about 1/4000-6000 infants with onset between 3 and 12 months of age; peak onset is 4-8 months.

A spasm is a brief bilateral tonic contraction of muscles of the trunk, neck, and limbs, usually but not always symmetric. These seizures are commonly overlooked by both families and physicians for weeks to months; they can be confused for hiccupping, startling, the Moro reflex, or be subtle enough to be missed entirely. They classically occur in multiple daily clusters lasting 10-15 minutes, with each cluster containing anywhere from a few spasms to dozens. The clusters occur during the transitions between wakefulness and sleep, so are most common in the early morning and evening, or occasionally around naptimes.

The extent of muscle involvement varies from a powerful contraction that *jackknifes* the body to minimal contraction of truncal muscles that causes only stiffening. Spasms may involve truncal flexion, extension, or both; the child may fling out their arms or elevate them for

TABLE 30.15 Paroxysmal Disorders of Childhood

Nonepileptiform Disorders

- Breath-holding spells*†
- Syncope‡
- Migraine and migraine equivalents, recurrent abdominal pain, cyclic vomiting*
- Tic*
- Spasmodic torticollis†
- Drug reactions, dystonia
- Paroxysmal choreoathetosis
- Gastroesophageal reflux
- Benign paroxysmal vertigo†
- Myoclonus, nonepileptic; anxiety, excitement, acute metabolic encephalopathy†
- Hyperexplexia
- Masturbation†
- Withholding, constipation*
- Daydreaming, staring spells*
- Stereotypical movements, autism, coexistent deafness and blindness
- Factitious syndrome by proxy (Munchausen syndrome by proxy)
- Hyperventilation‡
- Psychogenic seizures‡
- Transient global amnesia‡
- Sleep*
- Head banging, jactatio capitis†
- Pavor nocturnus
- Somnambulism, somniloquy

Acute Symptomatic Seizures, Occasional Seizures

- Febrile convulsions*
- Brain tumor
- Meningitis, encephalitis
- Head injury, child abuse
- Poisoning
- Intercurrent medical illness; renal, liver disease; cardiac right-to-left shunt; and embolism
- Metabolic disease, rickets

Epileptic Syndromes

- Benign partial epilepsies*
- Symptomatic focal epilepsy*
- Epilepsia partialis continua
- Rasmussen encephalitis
- Autosomal dominant nocturnal frontal lobe epilepsy
- Epileptic encephalopathy with continuous spike-and-wave pattern during sleep
- Benign epilepsy with centrotemporal spikes (benign rolandic epilepsy)
- Hemiconvulsion hemiplegia syndrome
- Childhood absence epilepsy*
- Epilepsy with myoclonic absences
- Lennox-Gastaut syndrome
- Epilepsy with myoclonic atonia (previously astatic) seizures (Doose syndrome)
- Landau-Kleffner syndrome
- Febrile seizures plus
- Panayiotopoulos syndrome

*Common.
†See infant section for discussion.
‡See adolescent section for discussion.

several seconds. Eye movements are commonly associated with the spasm, either as deviation or as repetitive nystagmoid upward jerks. Apnea is common, but tachypnea is uncommon. Children may cry out or seem to giggle at the end of the spasm.

As the spasms continue, there may be insidious loss of developmental motor milestones such as sitting, rolling, babbling, or head control. Another commonly described regression is a decline in visual attentiveness, meaning that the child no longer easily regards faces, tracks moving objects, or reaches for toys. This is due to the progressive cortical dysfunction caused by the underlying hypsarrhythmic EEG pattern.

The differential diagnosis can include colic, exaggerated Moro reflexes, or normal myoclonic jerks on falling asleep or waking. Multiple myoclonic seizure syndromes, both benign and otherwise, occur in this age group and must be distinguished from infantile spasms by a neurologist.

Evaluation: EEG, MRI. The term **hypsarrhythmia** in an EEG report is specific for a diagnosis of infantile spasms. The hypsarrhythmic EEG pattern is a high-amplitude, chaotic slowing of generalized distribution without interhemispheric synchronization and with multifocal epileptiform discharges throughout. Hypsarrhythmia is more frequent in younger infants and early in the course of the disorder, and it is more common to find some modified variant of it. In a child with a strong clinical suspicion of infantile spasms, sleep must be captured in the EEG, as early in the course, the hypsarrhythmic pattern is only evident during sleep.

Investigation of patients with infantile spasms is directed at determining the cause and then determining whether there is an underlying genetic, structural, or metabolic etiology. Infantile spasms can be caused by a wide variety of neurologic insults; the most common etiologic factor is perinatal hypoxic-ischemic encephalopathy. Other important associations include intrauterine infection, prematurity, intracranial hemorrhage, malformations of cortical development, tuberous sclerosis, head injury, CNS infection, and inborn errors of metabolism. If infantile spasms are seen in conjunction with agenesis of the corpus callosum and retinal abnormalities on eye examination, this suggests a diagnosis of **Aicardi syndrome**.

Approximately 95% of children with an identified cause (structural, genetic, or metabolic) have a prognosis of moderate-to-severe neurologic injury, including refractory epilepsy, cognitive impairment, or permanent developmental sequelae.

Approximately 10-15% of patients have no identifiable underlying cause and a history of normal development before the onset of their illness; this subset is referred to as cryptogenic, or idiopathic, West syndrome. This subset of patients is likely to have a much better long-term outcome: 38% of these patients are normal or mildly impaired, in comparison with only 5% of symptomatic patients.

A unique subset of patients who may develop infantile spasms is children with **trisomy 21 (Down syndrome)**. The incidence of infantile spasms in this group is 1-5%. Though they have a genetic disorder and baseline neurologic abnormalities, these children have a particularly high response rate to treatment with ACTH with rapid resolution of the abnormal hypsarrhythmia on EEG.

About 50% of infants go on to have other seizure types when spasms cease. Persistence of the epilepsy in most of the patients is associated with loss of the spasms and development of other seizure types, such as tonic seizures, focal seizures, and tonic-clonic seizures. Approximately half of children with Lennox-Gastaut syndrome, a combination of cognitive disability, generalized seizures, and a distinctive abnormal EEG pattern, have a history of infantile spasms. Seizures very similar in appearance to infantile spasms (brief myoclonic or tonic seizures occurring in clusters) may recur later in childhood, and these are referred to as epileptic spasms.

Treatment with corticosteroids aborts the spasms in a significant number of infants. There are 2 approaches: intramuscular injections of synthetic ACTH gel or high-dose oral steroids. Both treatment regimens generally last 8-12 weeks, and both require frequent monitoring for side effects. The spasms should cease and the EEG patterns improve if the child has responded. The pediatrician may be called upon to monitor electrolytes, blood pressures, or signs of illness while the child is under treatment. Live vaccinations are generally held for 6-12 months after a course of immunomodulatory therapy.

Vigabatrin is another effective AED for infantile spasms, and it has been shown to be particularly effective in the treatment of infantile spasms with tuberous sclerosis or other focal cortical dysplasias. However, this medication is currently strictly regulated in its prescription, and patients on vigabatrin require examinations by an ophthalmologist every 3 months due to the small risk of permanent peripheral vision loss with prolonged use of the medication. Most patients with infantile spasms take vigabatrin for 6 months or fewer.

Many other antiepileptic medications, including topiramate, lamotrigine, valproic acid, and benzodiazepines, have had some efficacy in isolated cases, but this response is unpredictable. ACTH, corticosteroids, and vigabatrin are the most commonly used medications with the highest efficacy across multiple etiologies.

Severe myoclonic epilepsy in infancy (Dravet syndrome)

- Peak presentation: ages 9-18 months
- Red flags: normal development until the onset of multiple episodes of prolonged febrile status epilepticus, often with focal features; seizures provoked by warm ambient temperatures, hot baths, fever, or vaccinations
- Acuity: urgent due to the development of medically refractory epilepsy and potential for multiple episodes of status epilepticus
- Prognosis: poor; identified cause of some cases of so-called vaccine encephalopathy

Severe myoclonic epilepsy in infancy is a rare generalized epilepsy appearing in the first year of life. The syndrome differs from the myoclonic syndromes already described (early myoclonic encephalopathy and early infantile encephalopathic epilepsy) by its later onset and the EEG findings. A mutation of a voltage-gated sodium channel gene *(SCN1A, SCN9A)* is seen in up to 79% of cases (see Table 30.3).

The child may present with febrile or afebrile seizures, usually with normal psychomotor development preceding the onset of seizures, and often with a family history of epilepsy. The seizures are generalized or unilateral clonic seizures; myoclonic seizures appear later (and may not be a major feature of the disorder, despite the name), between 8 months and 4 years of age; and focal seizures and atypical absences may occur. The interictal EEG may be normal initially and only later show fast, generalized, spike-and-wave epileptiform discharges and focal abnormalities.

The seizures are usually refractory to many commonly used AEDs due to the fact that these AEDs act on sodium channels and this disorder is generally caused by sodium channel mutations. Antiepileptic medications that may worsen seizures or be ineffective in Dravet syndrome include phenytoin, lamotrigine, carbamazepine, oxcarbazepine, and vigabatrin.

Childhood

The paroxysmal disorders of childhood (2-12 years) are given in Table 30.15.

Paroxysmal Nonepileptic Disorders

Migraine and migraine equivalents. Migraine is a common disorder, and some episodes may be confused with seizures because of their

paroxysmal nature and association with neurologic deficits or altered consciousness (see Chapter 28). The presentation of migraines in children may also be markedly different than that in adolescents and adults; "migraine equivalents" are paroxysmal disorders that are strongly associated with the later development of migraines and may share similar underlying pathophysiologic mechanisms.

When evaluating paroxysmal events suspected to be migraines or migraine equivalents, the following **red flags** should prompt expedited neuroimaging, specialist evaluation, or emergency room evaluation, depending upon the severity of the symptom and how ill the child appears:

- Sudden severe head pain that awakens the child from sleep
- Positional symptoms, meaning that the child's headache or vomiting dramatically worsens or improves with simple positional changes from lying to sitting
- Abnormal eye movements, such as prominent nystagmus (jerky eye movements) or a forced downward gaze
- Focal neurologic symptoms including focal limb weakness or facial droop
- Altered mental status

In **cyclic vomiting**, recurrent attacks of nausea, vomiting, and abdominal pain occur on a daily or weekly basis without any evidence of intercurrent illness or objective evidence of gastrointestinal pathology. There is no confusion or disorientation associated with these spells. Typically, there are symptom-free intervals lasting weeks to months, and recurrence is unpredictable. There may be a strong family history of migraine, and there appears to be some overlap of the cyclic vomiting with migraine.

Tic disorders

- Peak presentation: age 5-7 years
- Classical features: no alteration of awareness, stereotyped behaviors, a sensation of "compulsion" to perform the behavior and "relief" once it is completed.
- Acuity: low
- Prognosis: excellent, although disabling tics and psychiatric comorbidities should be addressed, if present

Tics are common and are sudden, brief, purposeless involuntary movements or vocalizations that occur during wakefulness only; children may describe a sense of compulsion and can briefly suppress the behavior, but have a sense of relief when performing the suppressed action (Table 30.16). Children may have phonic tics (such as tongue clicking or throat clearing), motor tics (such as blinking, sniffing, or shrugging), or any combination of both. Tics are treated when they become disruptive, socially unacceptable, or physically uncomfortable, but otherwise they are considered benign and normally do not require pharmacologic treatment. Common comorbidities that should be screened for include anxiety, attention-deficit/hyperactivity disorder (ADHD), and obsessive-compulsive disorder.

TABLE 30.16 Abnormal Involuntary Movements

Movement	Characteristics	Associations
Tics	Brief involuntary movements (motor tics) or sounds (phonic or vocal tics) occurring against a background of normal motor activity Tics may be simple, sudden brief movements such as shrugging a shoulder, blinking, or grimacing; or complex, more coordinated movement that might appear purposeful, such as hitting or touching Snorting, sniffing, or throat clearing are examples of simple phonic tics and short utterances, echolalia, or coprolalia are complex phonic tics	Idiopathic tic disorders Tourette syndrome
Tremor	Movements caused by rhythmically alternating contractions of a muscle group and its antagonists The movements may involve proximal and axial muscles Classified as resting, postural, or action tremors according to the response to these maneuvers	Physiologic tremor, essential tremor
Chorea	Random brief limb movements of variable duration; these can be incorporated into voluntary movements by the patient	SLE Wilson disease Rheumatic fever Autoimmune encephalitis Postinfectious
Athetosis	Slow writhing movements of the extremities, often distal extremities The movements are random Often involuntary movements of this type have some features of chorea and are termed *choreoathetoid*	Kernicterus
Dystonia	Sustained muscle co-contraction of agonist and antagonist muscle groups, frequently causing twisting and repetitive movements or abnormal postures The velocity of the movements varies, usually being sustained at the height of the involuntary contraction for 1 sec or longer The duration also varies in different syndromes; in spasmodic torticollis, there may be rhythmic jerks or spasms into the abnormal posture Subclassified by extent (focal, segmental, multifocal, and generalized) and relationship to movement (action and rest)	Idiopathic (inherited) syndromes Postlesional syndromes
Myoclonus	Rapid brief muscle jerks with an irregular or occasionally rhythmic quality Can be epileptic or nonepileptic in origin	Encephalopathies Idiopathic and symptomatic epilepsies
Ballismus	Wild, large-amplitude, irregular limb movements	Postlesional
Asterixis	Repetitive movements caused by sudden, brief, irregular lapses in posture of an extremity	Metabolic encephalopathies
Dyskinesia	Sometimes used as a general term to describe abnormal involuntary movements	

SLE, systemic lupus erythematosus.

They often become noticeable in early grade school years, around the time that some children start stimulant medications for attention deficit disorder. This temporal association has led to the misconception that the stimulant medications have caused the tics.

α_2-Agonists such as clonidine are common first-line treatments for disruptive or disabling tics; more severe tics can be treated with atypical antipsychotics such as risperidone.

Tourette syndrome is diagnosed when a child has had multiple motor tics and at least 1 phonic tic present for longer than 1 year. Other tic disorders can be purely motor or purely phonic, and are classified according to their symptoms and duration (transient vs. chronic).

Table 30.16 outlines some of the clinical features of episodic abnormal movements that may appear in children.

Sleep disorders

- Peak presentation: age 2-7 years
- Classical features: occurring a few hours after falling asleep ("around midnight"), nonstereotyped behaviors, screaming, agitation, and inconsolability despite being apparently awake, no memory of frightening imagery
- Acuity: low
- Prognosis: excellent, although children with frequent episodes may need to be monitored by their parents to prevent injury during a panicked state

Night terrors and confusional arousals. Night terrors are a common phenomenon in children and are most frequent in boys aged 5-7 years. Up to 15% of children younger than 7 years have experienced some form of these episodes. The attacks are characterized by sudden arousal from sleep, often screaming in terror, and then crying with agitation and tachycardia. There may be vigorous and potentially injurious motor activity in older children, such as running or hitting the bed or wall. The striking feature of these episodes is that the child is inconsolable but seemingly awake. The episodes arise out of slow-wave non–rapid eye movement sleep, usually occurring 1-2 hours after bedtime, and are not responses to dream imagery (i.e., not nightmares). Episodes last several minutes. Prior sleep deprivation, febrile illness, emotional stress, and some medications (sedatives/hypnotics, neuroleptics, stimulants, antihistamines) may be precipitants. In contrast to the experience of nightmares, children are amnestic for the events and their distress in night terrors.

Confusional arousals are less dramatic attacks with similar origin from slow-wave sleep and are more typical in younger children. The affected child stirs and begins crying and whimpering inconsolably. These arousals may be prolonged in infants, lasting up to 30-40 minutes.

There is no specific treatment for these events; parents should be educated about the nature of these arousals and reassured that they are self-limited.

The most important mimic of parasomnias is nocturnal seizures. **Nocturnal frontal lobe seizures** occur during sleep and can have bizarre hypermotor behaviors such as rolling, turning, picking, yelling, and fumbling. In school-aged children, **benign rolandic epilepsy** manifests itself as seizures when coming out of sleep with gurgling, salivation, hemifacial and hemibody twitching, and often partially preserved consciousness of the event. Important distinguishing historical factors between seizures and parasomnias are the time of onset (seizures: shortly after falling asleep or early in the morning), duration (most seizures last 1-2 minutes, and parasomnias can have a significantly longer duration), and any associated tongue bite, urinary incontinence, or insidious behavioral or developmental regression.

Somnambulism. Somnambulism, or sleepwalking, is common in childhood. Approximately 15% of children have walked in their sleep, especially in the 2-3 years old age group, and 2.5% are habitual sleepwalkers, having episodes at least once a month. The age at onset peaks between 4 and 10 years. There is a family history of sleepwalking and other parasomnias in 60-80% of patients. These episodes of apparent unresponsiveness and "automatisms" could be mistaken for focal dyscognitive seizures or a postictal state.

Self-stimulatory behavior/stereotypies. Repetitive purposeless movements may be performed by children on the autism spectrum or with cognitive disabilities. Combined with unresponsiveness, these behaviors may be mistaken for automatisms in focal dyscognitive seizures. The important features that distinguish such behavior from epileptic activity are the setting in which it occurs, the variable content and duration of the "attacks," and the complete failure of the episodes to interrupt more stimulating activities. However, it may be very difficult to determine the nature of the episodes by interview; video and EEG monitoring may be required. These behaviors are not harmful and may provide soothing sensory input to the child performing them.

Acute Symptomatic Seizures and Occasional Seizures

Febrile convulsions remain one of the most common causes of occasional seizures in early childhood. Head injury is more common in childhood than in infancy, but the list of other potential causes of seizures, including brain tumor, intracranial infection, and poisoning, is very similar. In addition, some metabolic and neurodegenerative disorders manifest in childhood, not in infancy (Table 30.17).

Epileptic Syndromes

Benign partial epilepsies of childhood. Focal seizures and focal EEG discharges usually suggest the presence of a localized cerebral lesion. There is a group of idiopathic partial epilepsies beginning in children without abnormalities on neurologic examination or neuroimaging studies, and frequently, with a family history of epilepsy. The benign partial epilepsies of childhood (BPECs) are characterized by focal seizures and focal epileptiform discharges, both with age-dependent spontaneous recovery, in the absence of anatomic lesions.

Clinically, the seizures begin between 18 months and 12 years of age, most often at 8-10 years; there is no neurologic deficit or developmental delay. The seizures are brief and stereotyped in an individual, although they vary among patients. The seizures do not have a prolonged postictal deficit, are usually infrequent, and respond well to AED treatment. The focal epileptiform discharges occur with normal background rhythms. The sharp waves or spikes have a characteristic structure and are often very frequent, increasing during sleep. Rare generalized epileptiform discharges may occur, but if they are prominent, the diagnosis of BPEC should be questioned.

The most well-defined form of BPEC is **benign epilepsy with centrotemporal spikes and seizures (BECTS)**, often referred to as **benign Rolandic epilepsy**. Brief hemifacial motor seizures with anarthria and drooling are typical, frequently when coming out of sleep. Consciousness is typically preserved, although this may not be true with longer seizures. A somatosensory aura involving the tongue, cheek, or gums may precede the motor seizure. Many seizures occur at night as tonic-clonic seizures, presumably secondary generalized with unwitnessed partial onset. Onset is between 3 and 13 years, with a peak onset at 9-10 years; there is a male-to-female predominance of approximately 3:2.

Management depends on seizure frequency; if the typical EEG discharges have been found in a child without seizures or after a first seizure, there is usually no indication to treat with AEDs. If seizures are infrequent and nocturnal, the option of no treatment should be discussed. AED treatment should be considered for patients experiencing more frequent seizures, troublesome seizures during the day, or seizures associated with any morbidity such as postictal headaches or

TABLE 30.17 Inherited Disorders of Metabolism and Neurodegenerative Diseases Associated with Seizures in Childhood and Adolescence

Name	Clinical Features and Laboratory Findings	Investigations
Syndrome of Progressive Myoclonus Epilepsy		
Multiple specific disorders cause the clinical syndrome of PME Prominent myoclonus: irregular repetitive, spontaneous or with action, stimulus sensitive Associated seizure types: usually tonic-clonic, but also tonic, absence, and partial seizures Progressive neurologic deterioration, with prominent ataxia and other motor signs developing later Progressive dementia, varying in degree between the specific disorders		
Most Cases Are Caused by the Following 5 Disorders:		
Unverricht-Lundborg	Onset, ages 8-15 yr; myoclonus and GTC seizures, cerebellar ataxia, slowly progressive but mild cognitive decline; patients have long survival in comparison to other disorders in this group	Chromosome 21q22; cystatin B mutations Clinical diagnosis must exclude other causes of PME syndrome
Myoclonus epilepsy and ragged red fibers (MERRF)	Onset, ages 5-12 yr (range, 3-62 yr); myoclonus, GTC seizures, progressive ataxia, dementia Other features include deafness, optic atrophy, neuropathy, myopathy, pyramidal signs, dysarthria, and nystagmus There may be clinical overlap with other mitochondrial encephalomyopathies: mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes (MELAS) and Kearns-Sayre syndrome	Serum and CSF lactate and pyruvate measurements Muscle biopsy; light microscopy, electron microscopy (EM), biochemical analysis of oxidative metabolism, and DNA studies
Lafora body disease	Onset, ages 10-19 yr; generalized clonic, GTC, and partial seizures with visual auras; myoclonus develops later and becomes very disabling; severe dementia; death within 5 yr of disease onset Lafora bodies (intracellular amyloid inclusions) are found in skin, muscle, neurons, and hepatocytes	Biopsy of skin must include eccrine sweat glands (i.e., axilla) to exclude lafora bodies Chromosome 6q24; gene *EPM2A* produces laforin
Neuronal Ceroid Lipofuscinosis		
Late infantile form (Jansky-Bielschowsky)	Onset, ages 2-4 yr; severe epilepsy, myoclonic, GTC, atonic, atypical absence seizures (not tonic, vs Lennox-Gastaut syndrome), progressive severe dementia, ataxia, pyramidal and extrapyramidal signs, visual loss later, usually death in adolescence Ophthalmologic examination necessary; on EEG, marked photic sensitivity to 1-Hz stimulation, electroretinogram (ERG) and visual evoked potential (VEP) abnormalities	Skin, conjunctival, or rectal mucosal biopsy; skin biopsy is the most practical and least morbid. EM of circulating lymphocytes can be used for screening Lipopigment accumulation in lysosomes best seen in eccrine secretory cells; the inclusions have a characteristic structure on EM that differs between the different subtypes of neuronal ceroid lipofuscinosis EEG, ERG, and VEP testing
Juvenile form (Batten-Spielmeyer-Vogt)	Onset, ages 4-10 yr; usually manifests with decreased visual acuity secondary to retinal degeneration, psychomotor delay, cerebellar and extrapyramidal signs, later onset of seizures, and GTC and myoclonus Progressive severe dementia accompanies the other neurologic signs Death in early adulthood ERG and VEP abnormalities	Same as for the late infantile form
Adult onset (Kufs)	Onset, ages 11-50 yr; dementia, psychiatric symptoms, cerebellar signs, and extrapyramidal signs are most prominent; seizures often tonic; visual disturbances are less common; fundi are normal; on EEG, marked photic sensitivity to 1-Hz stimulation	
Sialidosis		
Type 1	Onset, ages 8-20 yr; decreased visual acuity and macular cherry-red spot; action- and stimulus-induced myoclonus; cerebellar ataxia; no dementia or decreased length of survival A peripheral neuropathy may be present	Urine specimen, blood sample for cultured leukocytes, and skin biopsy to obtain cultured fibroblasts for enzyme analysis
Type 2	Onset, ages 10-30 yr; described in Japanese patients Coarse facial features and PME syndrome Elevated excretion of urinary sialylated oligosaccharides, enzyme analysis shows deficiency of α-N-acetylneuraminidase (both type 1 and type 2)	Same as for type 1

TABLE 30.17 Inherited Disorders of Metabolism and Neurodegenerative Diseases Associated with Seizures in Childhood and Adolescence—cont'd

Name	Clinical Features and Laboratory Findings	Investigations
Less Common Causes of PME Syndrome in This Age Group:		
Juvenile neuronopathic Gaucher disease; PME, supranuclear palsy, and splenomegaly; no dementia; pancytopenia on CBC, leukocytes show low β-glucocerebrosidase activity		CBC, leukocytes for enzyme analysis
Dentatorubral-pallidoluysian atrophy, seen in Japanese patients; PME is 1 manifestation		Clinical diagnosis in life
Neuroaxonal dystrophy; may appear as PME; also, chorea, lower motor neuron signs; axon steroids in neurons, may be seen in autonomic nerve endings around eccrine secretory coils		Peripheral nerve biopsy, skin biopsy
Late-onset GM_2 gangliosidosis; sensitivity to acoustic stimulus; myoclonus, severe dementia, dystonia, pyramidal signs; cherry-red spot may be seen on the macula		Hexosaminidase A activity
Hallervorden-Spatz disease		Clinical diagnosis in life
Action myoclonus–renal failure syndrome, described in French-Canadians; tremor, PME, and, later, proteinuria and renal failure; no dementia		Clinical diagnosis, renal function
Other Rare Disorders with Seizures in Childhood and Adolescence		
Juvenile Huntington disease	Onset, age >3 yr; developmental delay; dystonia; parkinsonian features may be present	GTC, atypical absence, myoclonic seizures
Alpers syndrome	Progressive neurologic degeneration of childhood A clinical syndrome; suspected to be a mitochondrial encephalopathy Normal at birth, then failure to thrive with developmental delay, myoclonic jerks, seizures, episodes of status epilepticus, hypotonia, and visual loss followed by spastic quadriparesis Epilepsy partialis continua may be present The spectrum of clinical features includes deafness, ataxia, chorea, and liver disease	Muscle biopsy
Rett syndrome	Onset, ages 1-2 yr; in girls only; delay or regression in motor development, loss of language, ataxia, "hand-ringing" mannerism Seizures occur later; myoclonic, partial, and GTC Episodes of apnea, ataxic breathing, and hyperventilation; pyramidal signs	Muscle biopsy for mitochondrial enzyme analysis and histologic study, although cause is unknown, genetic testing
Maple syrup urine disease	Less severe forms may manifest late, even in adulthood, with episodic symptoms of encephalopathy and ataxia	Serum amino acids and possibly seizures
Porphyria	Onset, late adolescence, after puberty; 15% of affected patients have seizures during an acute attack of porphyria	Urinary and/or stool porphyrins

CBC, complete blood cell count; CSF, cerebrospinal fluid; EEG, electroencephalogram; GTC, generalized tonic-clonic; PME, progressive myoclonus epilepsy.

lethargy. The seizures are usually controlled easily with a variety of AEDs, including carbamazepine or levetiracetam.

The seizures of BPEC resolve spontaneously before 16 years of age, and the EEG may be helpful in deciding when to withdraw treatment. Patients older than 14 years who are seizure-free for 1-2 years with normal EEGs should withdraw from treatment; the clinician should strongly consider a trial of withdrawal in patients 10-14 years old who are seizure-free and have a normal EEG. Younger patients with active EEGs are likely to have recurrence of seizures with AED withdrawal; if seizures and/or abnormal EEGs persist well into the teenage years, syndromic diagnosis should be reconsidered. Subtle neuropsychologic deficits may be present in children with BECTS, suggesting that this disorder may not be entirely as "benign" as thought.

Benign childhood epilepsy with occipital paroxysms forms a subset of idiopathic partial epilepsies of childhood. There are 2 types of this subset: 1 with early onset (peak onset at 3-5 years), nocturnal seizures with tonic eye deviation, and vomiting; and another with later onset (peak onset at 7-9 years) characterized by seizures beginning with visual symptoms, which is consistent with an occipital origin. These are also referred to as **Panayiotopoulos syndrome** and the **benign occipital epilepsy of Gastaut**, respectively. Hemiclonic seizures or the automatisms of temporal lobe complex seizures often follow according to whether the seizure spreads to suprasylvian or infrasylvian regions. A severe headache may follow the visual auras and a diagnosis of childhood migraine is often considered. The EEG typically shows high-amplitude sharp waves or spike-and-wave complexes recurring at 0.5-1 Hz posteriorly, usually maximal in the occipital regions. The discharges are present when the eyes are closed and should disappear with eye opening. There is some controversy about the specificity of the electroclinical features and whether these cases are true variants of benign childhood epilepsy. The conditions are relatively uncommon, and the same EEG pattern may be seen with symptomatic occipital epilepsy.

Acquired epileptic aphasia and continuous spike-and-wave patterns in slow-wave sleep. These 2 conditions are age-related epileptic encephalopathies with disturbances in language and cognition occurring in association with persistent focal or bilaterally synchronous epileptiform activity and seizures without an underlying structural

lesion. In each, the epileptiform activity is thought to disturb synaptogenesis and connectivity in the maturing brain. Although they are rare, some authorities consider them part of the spectrum of benign childhood epilepsy.

Epileptic aphasia, *or* **Landau-Kleffner syndrome,** begins in a previously normal child (peak age at onset, 5-7 years) with the regression of language. There is severe auditory agnosia, speech may disappear, and the child often appears to be deaf due to impairment of cortical processing of sound and language. There is usually a marked deterioration in behavior as well, and social interactions become altered. Childhood psychosis and the autistic spectrum disorders are often considered in the differential diagnosis, although the age of behavioral regression is atypical for those disorders and should be a red flag when this clinical history presents. Seizures occur, but are not frequent and cannot explain the language deficits. The EEG in sleep shows almost continuous bilateral epileptiform discharges maximal over the temporal regions. The seizures are partial and easily controlled with medication, but the language regression and the EEG discharges do not remit with conventional AEDs. Treatment with corticosteroids does improve the condition in many children, but more than half have persistent language and learning deficits, despite the eventual disappearance of the EEG abnormalities.

In **continuous spike-and-wave patterns in slow-wave sleep** or **electrical status epilepticus of slow-wave sleep** (CSWS and ESES, respectively), there is a more diffuse cognitive dysfunction, and more than 85% of the sleep EEG record is occupied by epileptiform discharges. The disorder typically manifests at 5-7 years of age, and there is a broader spectrum of seizure types, including absences, atonic seizures, and focal dyscognitive seizures, which may be frequent in some patients. In Landau-Kleffner, the speech and auditory disturbances are the most striking feature, and in CSWS, executive and behavioral dysfunction predominate. Both are caused by heterozygous mutations in the ionotropic NMDA glutamate receptor subunit 2A gene *(GRIN2A)* and inherited as an autosomal dominant.

Symptomatic focal (localization-related) epilepsy. The most common seizure type in children with focal epilepsy with an identified cause is the **focal dyscognitive seizure**. Focal dyscognitive seizures may arise from temporal, frontal, parietal, or occipital lobes, but most often from the temporal lobe. The causes of focal epilepsy in childhood are diverse and include birth asphyxia, later anoxic episodes, head injury, neoplasms, infection, malformations of cortical development, the cerebral lesions of neurocutaneous syndromes, vascular malformations, and cerebral infarction. MRI is a crucial diagnostic procedure and can reveal a variety of structural abnormalities.

Focal epilepsy commonly evolves as a medically refractory disorder; in some patients, it can be amenable to surgical resection. The investigation of children for epilepsy surgery is a highly specialized process that follows documentation of medical intractability, which is defined as failure of at least 2 appropriately chosen and optimized antiepileptic medications. Concordant evidence of a single epileptogenic region within the brain must be found with ictal video and EEG monitoring, both structural neuroimaging (MRI) and functional neuroimaging (single-photon emission computed tomography and positron emission tomography), and neuropsychologic evaluation. If a focus can be demonstrated, it must be shown that resection of that area will not cause unacceptable loss of sensorimotor or cognitive function.

Childhood absence epilepsy. Childhood absence epilepsy is an idiopathic generalized epilepsy beginning in previously normal children between 4 and 12 years of age, with peak incidence at 6-7 years of age; girls are more frequently affected. It accounts for only about 8-10% of school-aged children with epilepsy. There is a family history of epilepsy in approximately 15-25% of patients. The absence seizures are simple, or more often, complicated with mild automatisms or other motor features. Absence seizures are very frequent, occurring daily, but they generally respond well to antiepileptic therapy. The EEG is normal apart from runs of 3-Hz spike-and-wave complexes; clinical seizures are associated with discharges lasting more than 2-3 seconds. The discharges and clinical seizures can be produced by hyperventilation. Prognosis is generally favorable, with remission in approximately 80% of cases by late adolescence. GTC seizures occur in 40-50% of patients with childhood absence epilepsy. They typically develop years after the onset of absences and may appear after remission from the absence seizures. Usually, the tonic-clonic seizures are infrequent and medically controllable.

Treatment with ethosuximide or valproate controls absence seizures in most patients. However, ethosuximide offers no protection against tonic-clonic seizures, whereas valproate is also effective against tonic-clonic seizures. Therefore, valproate is the drug of choice if both seizure types are present. If either ethosuximide or valproate proves ineffective after an adequate trial at maximum tolerated doses, a trial of the other should be commenced. Combination ethosuximide and valproate therapy has been effective in some patients with absence seizures not controlled by either drug alone. Clonazepam may also be effective, but it is associated with sedative and behavioral side effects. Alternatives may include lamotrigine, topiramate, or zonisamide; medications such as carbamazepine or phenytoin that are specific for focal-onset seizures will in fact exacerbate absence seizures.

Epilepsia partialis continua and Rasmussen encephalitis. Epilepsia partialis continua describes continuous focal motor seizures usually manifesting as repetitive clonic jerks of the face, upper limb, lower limb, or larger portion of one-half of the body that continue in this localized manner for hours to days or months. These seizures are caused by cortical processes that directly overlie the motor cortex that include vascular lesions, focal cortical dysplasia, neoplasms, and unidentified focal areas of atrophy. More generalized metabolic disorders such as mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes (MELAS) and an inherited disorder of metabolism (nonketotic hyperglycinemia) have also been reported to cause epilepsia partialis continua.

The focal seizures in this condition are generally impossible to control with AEDs, and surgical management with a limited cortical resection may be necessary. The risk of motor and sensory deficits limits possible resections, and careful mapping of the site of seizure onset and its relationship to functional cortex is required.

Rasmussen encephalitis is a clinically defined syndrome of predominantly hemispheric cerebral dysfunction, with onset of seizures between 2 and 10 years of age. A variety of seizure types can occur, including focal motor seizures and focal dyscognitive seizures with secondary generalization, myoclonus, and epilepsia partialis continua; they are refractory to management with AEDs. The disorder is characterized by a progressive hemiparesis, language disturbances if the dominant hemisphere is affected, and intellectual decline. Progressive hemispheric atrophy, maximal in the central, temporal, and frontal regions, can be documented with neuroimaging studies. Pathologic specimens show nonspecific changes suggestive of encephalitis, although no etiologic agent has been identified. Worsening of the neurologic deficits can be expected over time, although the seizures may lessen and even "burn out."

Functional hemispherectomy performed early in the course of the disease before complete hemiparesis should control seizures, arrest the motor deterioration, and in most cases, lead to stabilization or even improvement in language and intellectual function. However, significant morbidity and mortality rates are associated with the surgery, and

the child is left with a paretic upper limb, although he or she can walk unaided.

Lennox-Gastaut syndrome. Lennox-Gastaut syndrome is characterized by generalized seizures and epileptiform discharges with delayed mental development and behavioral problems beginning between the ages of 1 and 8 years. The patients have a mixed seizure disorder with multiple seizure types; the typical seizures are tonic seizures, atypical absences, and atonic seizures, although patients may also have tonic-clonic, myoclonic, and focal dyscognitive seizures. The seizures are not easily controlled and are usually frequent, often with several occurring per day. Episodes of status epilepticus are common, and nonconvulsive stupor with continuous spike-and-wave discharges or a stuporous state with repeated tonic seizures is typical. The waking EEG has abnormally slow background activity, and the EEG correlates of sleep may also be poorly organized. The epileptiform abnormalities consist of slow (<3 Hz) spike-and-wave discharges, multifocal spikes, or sharp waves and paroxysmal fast activity (>10 Hz) in sleep.

Treatment is always indicated, but AEDs are rarely able to control seizures completely. More often, some reduction in frequency and severity of seizures may be obtained. Patients commonly need combinations of AEDs to address their multiple seizure types. Valproate should be used as a first-line agent for patients with atonic, tonic, and myoclonic seizures and may be helpful with tonic-clonic seizures. Patients with refractory tonic-clonic seizures or focal seizures as well as generalized seizures may benefit from the addition of lamotrigine. Combinations of AEDs must be monitored carefully for drug toxicity and unwanted interactions. Carbamazepine has been reported to exacerbate atypical absence seizures in some patients. Phenytoin can be an effective drug in controlling GTC and tonic seizures. Barbiturates may be effective, although they are often poorly tolerated in children with abnormalities of tone, and drug-related drowsiness may exacerbate tonic seizures in some patients. Other alternatives include clonazepam, topiramate, and levetiracetam. Felbamate has been reported to improve control of the debilitating tonic or atonic "drop attacks" in patients with this syndrome.

A major source of morbidity and an important management issue are repeated falls associated with tonic and atonic seizures. Appropriate restriction in daily activities and the wearing of helmets with face protection are often required. Division of the anterior portion of the corpus callosum (anterior corpus callosotomy) has been successful in controlling the falls associated with tonic or atonic seizures, but it is considered a palliative and not a curative surgical procedure, and the goal is not complete seizure freedom.

Adolescence

The paroxysmal disorders of adolescence (12-18 years) are shown in Table 30.18.

Paroxysmal Nonepileptiform Disorders

Syncope. Loss of consciousness with falling is the salient feature of syncope (see Chapter 6 and Table 30.19). Children may be able to describe a distinct trigger, such as needles or the sight of blood, and often describe palpitations, tunnel vision, and nausea. There may be a family history in vasovagal syncope. Cardiac arrhythmias should be ruled out; autonomic testing may be beneficial in patients with very frequent syncope.

Paroxysmal psychiatric events. **Nonepileptic behavioral events** (psychogenic seizures) are events where the patient may have dramatic convulsions, stiffening, unresponsiveness, or dissociative symptoms including amnesia of the events. They are common, but are frequently misdiagnosed as epileptic seizures, leading to unnecessary interventions including intubation, hospitalization, invasive testing, or simply years of antiepileptic medications that do not help the patient (see Table 30.19). Most cases are best thought of as a manifestation of psychiatric illness, such as post-traumatic stress disorder, anxiety, or depression. Nonepileptic behavioral events should be treated compassionately by the physician as a sign of significant psychiatric distress, and not as malingering or a factitious disorder.

Among adults, 20% of patients referred with refractory seizures are found to have psychogenic nonepileptic behavioral events; in children, the number is smaller. *Both epileptic seizures and nonepileptic behavioral events can coexist in the same person*, likely due to the high incidence of anxiety and depression in people living with epilepsy, as well

TABLE 30.18 Paroxysmal Disorders of Adolescence

Nonepileptiform Disorders

More Common
Syncope
Migraine
Psychogenic nonepileptic behavioral events
Dissociative states, conversion disorders
Panic attacks, hyperventilation
Daydreaming
Sleep
Nocturnal myoclonus, hypnic jerks
Narcolepsy
Somnambulism
Somniloquy

Less Common
Episodic rage
Malingering
Paroxysmal choreoathetosis
Tremor
Tic
Drug reactions, dystonia
Transient global amnesia

Acute Symptomatic Seizures, Occasional Seizures

More Common
Drug abuse
Reflex seizures (see Table 30.1)
Head injury
Meningitis and encephalitis

Less Common
Brain tumor
Intercurrent medical illness, endocrine disorder, systemic neoplasia

Epileptic Syndromes

More Common
Reflex seizures (see Table 30.1)
Symptomatic localization-related epilepsy
Juvenile myoclonic epilepsy

Less Common
Juvenile absence epilepsy
Epilepsy with generalized tonic-clonic seizures on awakening
Epilepsia partialis continua (Kojewnikow syndrome)
Rasmussen encephalitis
Progressive myoclonic epilepsy
Autosomal dominant epilepsy with auditory features (ADEAF)

TABLE 30.19 Differential Diagnosis of Syncope

Clinical	Syncope	Tonic-Clonic Seizures
Precipitating factors	Almost always patient is standing; environment is warm; fright; pain	Usually none, although sleep deprivation or awakening may be contributory
Prodrome	Lightheaded, dizzy, queasy; vision dims; loss of color, "grey out"; sweating May be averted by head down or recumbency	Aura or sense of déjà vu or jamais vu may be present
Occurrence in sleep	Never	Common
Evolution	Limp faint → fall → motionless unconsciousness, often with pallor, clammy skin; there may be a tonic phase with generalized stiffening	Sudden loss of consciousness → increased tone and massive truncal flexion or extension, followed by synchronous jerking of body and limbs with rubor or cyanosis and sweating → unconsciousness
Skin	Pale and cool	Flushed, cyanosed, warm
Incontinence	Rare	Occasional
Self-injury	Rare	Common (biting tongue)
Degree of postictal confusion	Minimal	Marked
Family history	Often positive for syncope	May be positive for seizures
Interictal EEG	Usually normal	Frequently abnormal, epileptiform discharges

EEG, electroencephalogram.

as the stress associated with an unpredictable chronic illness. Typically, they are characterized by marked motor activity such as pelvic thrusting, arching of the back, thrashing of the limbs, and even self-injury. The episodes may have a gradual onset with buildup of motor activity, and they usually last longer than epileptic seizures (Table 30.20). Other forms that the psychogenic nonepileptic behavioral events may take include a gradual slump to a motionless supine position with unresponsiveness and eyes closed, often with some flickering of the eyelids.

Other types of paroxysmal psychiatric events include panic attacks *and* rage attacks. **Panic attacks** may begin without the patient being able to identify an external precipitant, and then the sense of dread or fear may be mistaken for a psychic aura. Many of the symptoms experienced, including palpitations, paresthesia, formication, lightheadedness, and carpopedal spasm, result from hyperventilation and tachycardia. There may be some apparent disturbance of consciousness. Historically, the sequence of events is important, especially the hyperventilation and associated symptoms. The patient may be asked to hyperventilate in the office to see whether symptoms are reproduced; hyperventilation must continue for 3-5 minutes with good effort for a negative result to be useful.

Rage attacks may also be confused with epileptic seizures. Often seen in intellectually impaired patients, they represent intense frustration in the presence of an inability to vent the frustration in other ways or to communicate it. Rage attacks may also occur in children with normal intelligence or in those taking anabolic steroids.

The interictal EEG is repeatedly normal in patients with psychogenic nonepileptic behavioral events, but may be abnormal in children with both epileptic and nonepileptic events. For definitive diagnosis, it may be necessary to record a clinical episode with continuous video and EEG monitoring.

Treatment of psychogenic nonepileptic behavioral events must include an identification of underlying psychosocial and psychiatric problems. Major mood disorders and severe environmental stress, especially sexual abuse, are common among children and adolescents with psychogenic seizures and should be considered in every case. This history, though uncomfortable for both parties to discuss, must be specifically asked about and may require multiple visits to develop the necessary rapport to receive a truthful answer.

Presentation of a nonepileptic diagnosis to the patient after monitoring of a typical spell must be positive ("These attacks are not epileptic and will not necessitate chronic medication or further neurologic investigation") and truthful ("We don't know exactly what is causing them, but emotional factors are clearly playing a major role"). This diagnosis can be received with disbelief or hostility by families for multiple reasons. First, the societal stigma against psychiatric illness may make it difficult for parents to accept that a child has a psychiatric disorder; a genuine neurologic disorder is almost preferable to some families and they may visit multiple medical centers searching for a positive organic diagnosis. Second, even if the family accepts the diagnosis, there may be the perception that these events are "all in the child's head" or "attention-seeking," leading to a nontherapeutic familial and medical response to the diagnosis. If the child has been having events for a prolonged period of time, there is immense social pressure to continue having events, as they may feel that their peers, family, and school would react negatively to the psychiatric diagnosis after having been supportive of the presumptive epileptic diagnosis.

Terminology and phrasing is critical when discussing this diagnosis with families. Referring to them as "psychiatric" or "hysteric" or "conversion disorders" may come across as dismissive, particularly given the stigma around mental illness. The terms "psychogenic seizures" or "pseudoseizures" frequently confuse sufferers and families, as they then believe they are similar to epileptic seizures in pathology.

The prognosis of nonepileptic behavioral events in the pediatric population is much better than in adults, with 80% of patients seizure-free at the 3-year follow-up. Involvement of psychiatry and counseling is critical; in particular, cognitive-behavioral therapy appears to be specifically helpful in allowing people to achieve some conscious control over the physical symptoms of their psychiatric illness and to modulate their stress responses. However, the practitioner should be familiar with the concept of nonepileptic behavioral events. The degree and duration of pretreatment disability (school withdrawal, etc.) is a prognostic marker of response to treatment.

Acute Symptomatic Seizures and Occasional Seizures

The causes of acute symptomatic seizures in adolescence include those described in the preceding neonatal and childhood sections, except for

TABLE 30.20 Differential Diagnosis of Psychogenic Seizures

Clinical Factors	Psychogenic Seizures	Epileptic Seizures
Age at onset	Usually older than 8-10 yr Predominates in girls; 15-30% of patients are boys	Either sex; no sex predominance
Duration of seizures	May be very prolonged	Usually seconds to minutes
Evolution	May have a very gradual onset and ending	Usually more abrupt onset
Quality of convulsive movements	Thrashing, asynchronous limb movements, often with partial responsiveness	Usually rhythmic and synchronous with loss of consciousness
Stereotypical attacks	Typically variable	Typically stereotyped
Examination during the seizure	May resist examination, combative	Usually unresponsive and amnestic for ictal events
Self-injury	Rare	Common in GTC seizures
Incontinence	Rare	Common in GTC seizures
During sleep	No; may occur nocturnally, but while the patient is awake	Common
Changes in seizure frequency with medication	Rare	Usual
Interictal EEG	Repeatedly normal	Often abnormal
Ictal EEG	No EEG seizure patterns; normal rhythms while patient is unresponsive	EEG seizure patterns
Pitfalls in diagnosis	1. Psychologic factors may not be immediately apparent 2. Misleading information may be given by parents (as in factitious [Munchausen] syndrome by proxy)	1. Asynchronous vigorous automatisms are found in frontal lobe seizures 2. Bilateral limb movements and posturing without loss of consciousness occurs in supplementary motor seizures 3. EEG seizure patterns may be absent during some seizures (e.g., auras, SMA)

EEG, electroencephalogram; GTC, generalized tonic-clonic; SMA, supplementary motor area.

febrile convulsions. Head injury may be more common among adolescents, because participation in contact sports and motor vehicle accidents occur in the middle-to-late teen years. Street drug abuse can be associated with seizures.

Epileptic Syndromes

Juvenile myoclonic epilepsy. Juvenile myoclonic epilepsy has an onset between 12 and 18 years of age. The hallmark of the disorder is early-morning myoclonus involving axial and upper limb muscles, usually with sparing of the facial muscles. Episodes typically occur on awakening. Tonic-clonic seizures occur in the majority of patients. A history of early-morning myoclonic jerks may not be volunteered, and should be asked of all patients presenting with GTC seizures. The patients may not have identified the myoclonus and instead describe nervousness, shakiness, or clumsiness for the first 1-2 hours of a morning, such as dropping their toothbrush or spilling their cereal. Fatigue, sleep deprivation, stress, and alcohol exacerbate the seizures; some patients have their first seizure shortly after starting college due to a combination of the above risk factors. The tonic-clonic seizures typically begin with a clustering of repeated myoclonic jerks. Absence seizures occur in 15-40% of patients. Neurologic examination findings, brain MRI, and cognition are normal. The interictal EEG shows spike-and-wave complexes at 3.5-6 Hz. Linkage analysis of patients and their family members has suggested that the disorder is linked to chromosome 21.

Valproate is the preferred AED, as it has efficacy on all seizure types in this disorder. Lamotrigine is another effective agent and is preferentially used in adolescent and adult women because of the potential side effect profile of valproate (weight gain, teratogenicity, and potential hormonal disturbances including polycystic ovarian syndrome). Alternatives may include topiramate, zonisamide, and benzodiazepines, although extensive data concerning their efficacy in this setting are not available.

The seizures are well controlled in 80-90% of patients, but lifelong treatment is required. It is estimated that more than 90% of patients suffer relapse within the first 6-12 months after cessation of AEDs, and relapse is still common, even with prolonged periods of seizure freedom. Although many benign childhood-onset epilepsies remit with adolescence, most adolescent-onset epilepsies do not remit.

Juvenile absence epilepsy. In comparison with *childhood* absence epilepsy, juvenile absence epilepsy has a later onset, at about the time of puberty, and the seizures are less frequent (less than daily). Neurologic examination findings and IQ are normal. The EEG shows generalized spike-and-wave discharges, usually at rates faster than 3 Hz. Tonic-clonic seizures may occur, usually on awakening, more frequently than in childhood absence epilepsy.

The treatment is the same as that for childhood absence epilepsy, but the prognosis for complete remission therapy is less favorable.

Epilepsy with generalized tonic-clonic seizures on awakening. This idiopathic generalized epilepsy involves GTC seizures occurring more than 90% of the time within 2 hours of awakening or in an early-evening period of relaxation. Sleep deprivation and disruption are often potent precipitants of seizures. The age at onset of the seizures is usually between 10 and 20 years; a family history of epilepsy occurs in approximately 10-13% of cases. Myoclonic and absence seizures may also be present, and the distinction between juvenile myoclonic epilepsy and juvenile absence epilepsy is not clear. The EEG may show generalized spike-and-wave complexes or polyspikes.

Treatment starts with valproate, although barbiturates may be very effective. Lamotrigine is also used because of concern about the side effects of valproate. Topiramate and zonisamide may also be helpful. The prognosis for complete control of seizures with therapy is very

good: 65-79% of patients have experienced remission with therapy. Avoidance of precipitating factors that disrupt sleep patterns is important. The relapse rate if AEDs are stopped is high (83%).

PRINCIPLES OF ANTIEPILEPTIC DRUG USE

The goal of AED therapy is to use a single agent in adequate dosages to completely control seizures. If seizures recur, the dosage of an AED should be gradually increased to achieve the maximum tolerated dose for the patient without causing symptoms of drug toxicity. Therapeutic ranges are derived from population studies in which the serum levels of patients with seizures controlled by an AED were compared with those of patients experiencing side effects. The therapeutic levels should be used as a guide, and may also be used to assess compliance.

Around 67% of all seizure patients achieve seizure freedom on their first antiepileptic medication; the response rate is strongly tied to underlying etiology. If 1 agent does not control the seizures, another AED should be substituted and tried as monotherapy with a period of overlap during the transition period from 1 antiepileptic to another. An adequate trial of therapy entails the maximum tolerated dose of an AED for a period of time in which several of the patient's seizures (or clusters of seizures) would usually occur or for at least 2 months, whichever is longer. This interval may be shortened in infants and children with very frequent seizures. Changes in AED dosages and regimens should be made gradually, and due regard must be given to time taken to reach steady-state serum concentrations on the new regimen (Tables 30.21, 30.22, 30.23, and 30.24). Drug changes can be made gradually on an outpatient basis, but the physician must warn the parents and child that AED toxicity or an increase in the seizure frequency may occur during the changeover period. More rapid medication changes, especially if barbiturates are to be stopped, often require that the patient be admitted to the hospital during the changeover period.

Only about an additional 10% of patients achieve better control with the addition of a second drug to the first; 20-30% of patients with epilepsy have medically refractory epilepsy. Failure to respond to 2 AEDs at maximum tolerated doses should prompt a referral for assessment in a specialty epilepsy program. In some patients, resistance to AEDs may be genetically determined by mutations affecting drug transport or in metabolizing proteins such as the multidrug resistance–associated family of drug transporters.

It is important to design dosage schedules that are realistic. Dosing more often than 3 times a day may result in a high incidence of poor compliance. Parents must be advised to be careful with other prescribed and over-the-counter medications. Many medications may interfere with AED metabolism. Table 30.22 outlines indications for monitoring AED serum levels.

Special considerations for women with epilepsy who take antiepileptic medications and are of childbearing age include the teratogenicity of several antiepileptic medications, including valproic acid. Additionally, valproic acid is known to increase the risk of polycystic ovarian syndrome, with its attendant hormonal and metabolic disturbances. Finally, several antiepileptic medications have significant interactions with hormonal contraception, and the provider should familiarize themselves with these interactions to avoid failure of either medication.

Choice of Antiepileptic Drugs

Focal Epilepsies

Focal seizures and secondary generalized tonic-clonic seizures. Among the traditional AEDs, phenytoin, carbamazepine, phenobarbital, and primidone are equally effective in controlling partial and secondary GTC seizures in adults. In the symptomatic focal epilepsies, only approximately 35-50% of patients become seizure-free with AED monotherapy; another 20-30% experience more than a 75% reduction in seizure frequency. First-line treatment in this group of seizures is usually with carbamazepine, oxcarbazepine, or levetiracetam (see Table 30.23). Although the barbiturates and the benzodiazepines have been shown to be effective, the sedative and cognitive side effects prevent them from being drugs of first choice; they are generally reserved for patients in whom first-line drugs are not effective or tolerated. Valproate is also effective against focal seizures in children, although large comparative studies are not available.

Other drugs, including lamotrigine, vigabatrin, gabapentin, topiramate, and zonisamide, can be efficacious in treating refractory focal seizures.

Idiopathic Generalized Epilepsy

Primary generalized tonic-clonic seizures. It is widely thought that valproate should be the first-choice drug for primary GTC seizures, especially if they occur in association with absence seizures or myoclonic seizures. However, its side effect profile (teratogenicity, increased risk of polycystic ovarian syndrome) makes this medication less appropriate for use in adolescent women, but may be used in prepubescent girls. However, if valproate is the most efficacious antiepileptic medication for an adolescent woman after alternatives have been tried, it is reasonable to continue it after a risk-benefit discussion with the family.

Lamotrigine, topiramate, and zonisamide have also been shown to be effective for this seizure type (see Table 30.23). Phenytoin, carbamazepine, and valproate are equally effective in controlling primary GTC seizures in adults, and between 60% and 70% of patients can become seizure-free. Phenytoin does not control any associated absence seizures, and carbamazepine may exacerbate absence seizures. Phenobarbital and primidone are not the drugs of first choice because of potential adverse sedative and cognitive effects.

Absence seizures. Ethosuximide and valproate are the 2 drugs of first choice for absence seizures (see Table 30.23). Monotherapy with valproate controls absence seizures in more than 90% of children with childhood absence epilepsy. Ethosuximide and valproate have been successfully combined in patients with refractory absence seizures. Clonazepam is also effective but has the disadvantages of sedation and development of tolerance with chronic treatment. Lamotrigine, topiramate, and zonisamide have been effective for absence seizures, but experience is limited.

Myoclonic seizures. Specific myoclonic syndromes associated with absence seizures and tonic-clonic seizures, such as juvenile myoclonic epilepsy, are usually treated with valproate (see Table 30.23). Approximately 80% of patients with this epilepsy can become seizure-free, although lifelong treatment is required with juvenile myoclonic epilepsy. Clonazepam is also useful in myoclonic syndromes, although sedation occurs, and it does not tend to be useful in the long term because of tolerance; there are even some reports of exacerbation of seizures with long-term high-dose clonazepam. Exacerbation of seizures is particularly frequent with this drug when abrupt withdrawal is attempted. Clonazepam must be withdrawn very gradually, and the daily dose is reduced by only 0.25 mg every 3 weeks. Lamotrigine, topiramate, and zonisamide have a role in the treatment of myoclonus. Lamotrigine is an effective agent for juvenile myoclonic epilepsy and may become an alternative monotherapy option for this syndrome in young women. Valproate is associated with the development of ovarian cysts and teratogenicity.

TABLE 30.21 Dosages of Selected Antiepileptic Drugs

Medication	FDA Approval (Age Approved)	Maintenance Oral Dosage (mg/kg/day) Unless Otherwise Specified	Usual Dosing	Therapeutic Levels	Preparations
Acetazolamide	Absence seizures (adults)	1-12 mo: 10; <1 yr: 20-30	bid or tid	10-15 mg/L	125, 250, 500 mg tabs
Bromide		50-100	bid or qd	10-15 mEq/L	Supplied as triple bromide soln (240 mg/mL of bromide salt)
Carbamazepine*	Partial and GTC (all ages)	10-20	tid or qid SR usually bid	3-12 mg/L	150, 300 mg ER caps 100, 200, 400 mg ER tabs 100 mg chewable tabs 200 mg tabs 100 mg/5 mL susp
Clobazam†	LGS (all ages above 2 yr)	Up to 1	bid or tid	60-200 μg/L	5 mg, 10 mg, 20 mg tabs 2.5 mg/mL soln
Clonazepam†	Absence sz, LGS, myoclonic sz (all ages)	0.05-0.2	bid or tid	25-85 μg/L	0.5, 1, 2 mg tabs 0.125, 0.25, 0.5 mg orally disintegrating tabs
Diazepam	Partial sz (all ages >6 mo)	0.25-1.5 0.01-0.25 IV 0.2-0.5 mg/kg rectal (according to age)	bid or tid	100-700 μg/L	2, 5, 10 mg tabs 5 mg/mL, 5 mg/5 mL soln Rectal gel that can be dialed to dispense 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20 mg
Ethosuximide	Absence sz (>3 yr)	20-30	bid or tid	40-100 mg/L	250 mg caps 250 mg/5 mL syrup, soln
Ezogabine	Partial sz (adults)	No pediatric dose approved	tid	—	50, 200, 300, 400 mg tabs
Felbamate	LGS (>2 yr), p sz (>14 yr)	15-45	bid or tid	50-110 mg/L	400, 600 mg tabs 600 mg/5 mL susp
Gabapentin‡	Partial sz (>3 yr)	30-60	tid	2-20 mg/L	100, 300, 400 mg caps 600, 800 mg tabs
Lacosamide	Partial sz (>17 yr)	No FDA-approved dose 4-12	bid	≤15 μg/L	50, 100, 150, 200 mg tabs 10 mg/mL oral soln
Lamotrigine	LGS, partial and tonic-clonic sz (age >2 yr)	5-15§ 1-5¶	tid bid	1-15 mg/L	25, 100, 150, 200 mg tabs 5, 25 mg chewable dispersible tabs 25, 50, 100, 200 mg ODTs 25, 50, 100, 200, 250, 300 mg ER tabs
Levetiracetam†	Myoclonic, partial, and tonic-clonic sz (age >4-6 yr)	20-40	bid or tid	6-20 mg/L	250, 500, 750 mg tabs 100 mg/mL soln 500, 750 mg SR (ER) tabs
Lorazepam	Status epilepticus (all ages)	0.05-0.1	bid or tid	20-30 μg/L	0.5, 1, 2 mg tabs 2 mg/mL soln
Methsuximide (or methsuximide)	Absence sz (children and older)	10-30	bid or tid	10-50 mg/L	150, 300 mg caps
Nitrazepam	—	0.25-1	bid or tid	<200 μg/L	5 mg tabs
Oxcarbazepine*	Partial sz (>2 yr)	20-40	bid	13-28 mg/L	150, 300, 600 mg tabs 300 mg/5 mL susp
Perampanel	Partial sz (>12 yr)	2-12 mg/day (older than 12 yr)	qhs	—	2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg tabs
Phenobarbital	Myoclonic, partial, and tonic-clonic sz and status epilepticus (all ages)	<5 yr, 3-5 >5 yr, 2-3	bid or qd	10-40 mg/L	15, 30, 60, 90, 100 mg tabs 4 mg/mL soln
Phenytoin	Partial, tonic–clonic sz and status epilepticus (all ages)	<3 yr, 8-10 >3 yr, 4-7	tabs, susp: tid caps: qd	5-20 mg/L	50 mg tabs 30, 100 mg caps 125 mg/5 mL susp

Continued

TABLE 30.21 Dosages of Selected Antiepileptic Drugs—cont'd

Medication	FDA Approval (Age Approved)	Maintenance Oral Dosage (mg/kg/day) Unless Otherwise Specified	Usual Dosing	Therapeutic Levels	Preparations
Pregabalin	Partial sz (adults)	2-14	bid	Up to 10 μg/mL	25, 50, 75, 100, 150, 200, 225, 300 mg caps 20 mg/mL soln
Primidone	Partial and tonic-clonic sz (all ages)	10-20	bid or tid	4-13 mg/L	50, 250 mg tabs, susp
Rufinamide†	LGS (age >4 yr)	30-45	bid	<60 μg/mL	200, 400 mg tabs
Sulthiame‖		5-15	bid or tid	1.5-20 μg/mL	50, 200 mg caps Not available in all countries
Tiagabine	Partial sz (age >2 yr)	0.5-2	bid, tid, qid	80-450 μg/L	2, 4, 12, 16 mg tabs
Topiramate†	LGS, partial and tonic-clonic sz (all ages)	3-9, slow titration	bid or tid	2-25 mg/L	25, 100, 200 mg tabs 15, 25 mg sprinkle caps
Valproate	Absence, myoclonic, partial and tonic-clonic sz (age >2 yr)	15-40. Higher doses are used if the patient is on enzyme inducers (up to 60 kg/day)	Sprinkle caps: bid Soln: tid	50-100 mg/L	250 mg caps 125 mg sprinkle caps 125, 250, 500 mg tabs 250 mg/5 mL soln
Vigabatrin	Infantile spasms and partial sz (age >1 mo)	50-150	bid	20-160 μg/mL	500 mg tabs 500 mg powder for soln
Zonisamide	Partial sz (age >16 yr)	4-8	bid or qd	10-40 mg/L	100 mg caps

Unless specified otherwise, as above, one would usually target the lower range of the therapeutic dose, then adjust as needed depending on response and/or levels. Dosing schedule (e.g., bid or tid) can depend on if a sustained-release preparation is available and if the patient is on enzyme inducers (e.g., carbamazepine) or inhibitors (e.g., valproic acid) that could affect that drug (as indicated in the dosing in the table and in the text).

*Usually start by one-fourth maintenance dose and increase by one-fourth every 2-3 days to full dose.

†Usually start with one-fourth maintenance dose and increase by one-fourth every 7 days to full dose.

‡Usually start with one-fourth maintenance dose and increase by one-fourth every day to full dose.

§Child on enzyme inducers.

‖Available in some European countries.

¶Child on valproate.

bid, twice daily; cap, capsule; ER, extended release; FDA, US Food and Drug Administration; GTC, generalized tonic–clonic; IV, intravenously; LGS, Lennox-Gastaut syndrome; ODT, orally disintegrating tablet; qd, once daily; qid, 4 times a day; qhs, at bedtime; soln, solution; SR, sustained release; susp, suspension; sz, seizure(s); tab, tablet; tid, 3 times a day.

TABLE 30.22 Indications for Anticonvulsant Serum Level Monitoring

Introduction and stabilization of a patient on phenytoin
Alteration in seizure pattern or frequency
A change in the dosage of an anticonvulsant
Commencement or withdrawal of other medications that interfere with anticonvulsants
Symptoms of toxicity
To check patient compliance

Symptomatic Generalized Epilepsies

Tonic, atonic, and atypical absence seizures. These seizures are most commonly seen in children with complex, medically refractory epilepsy syndromes such as Lennox-Gastaut syndrome. They require specialist care due to the high incidence of polypharmacy and complex antiepileptic monitoring needs.

Drugs useful in the treatment of these seizures include valproate and benzodiazepines such as clonazepam and clobazam. Valproate monotherapy should be introduced first, although complete control of seizures is likely to occur in only 10-30% of patients (see Table 30.23). Carbamazepine and phenytoin are often not effective, and carbamazepine may exacerbate absence seizures in Lennox-Gastaut syndrome. Primidone and phenobarbital often have unacceptable side effects of drowsiness or worsening intellectual handicap at the dosages needed to control seizures; sedation may increase the frequency of tonic seizures. Benzodiazepines such as clonazepam, or in particular, clobazam in combination with valproate, are often used. Felbamate has been shown to be a useful drug as an adjunctive treatment for tonic and atonic seizures in Lennox-Gastaut syndrome. Lamotrigine, topiramate, and zonisamide have efficacy against the spectrum of seizures in the symptomatic generalized epilepsies, and their use is being explored. The combination of valproate and lamotrigine has been shown to be very effective in the control of intractable generalized seizure disorders.

The **ketogenic diet** is a high-fat, low-carbohydrate, low-protein diet designed to promote the use of fatty acids rather than carbohydrates for adenosine triphosphate (ATP) production in the brain. It is an effective treatment option in some children with intractable generalized seizures. The diet is most often used as second-line treatment for intractable structural, genetic, or metabolic generalized epilepsies,

TABLE 30.23 Comparison of Recommendations for the Treatment of Pediatric Epilepsy

Seizure Type or Epilepsy Syndrome	FDA Approved	Sign (2005)	NICE (2012)	AAN (2004)	ILAE (2013)*	Pediatric Expert Consensus Survey (North America–2005)	Pediatric Expert Consensus Survey (Europe–2007)
Partial-onset	CBZ, ezogabine, lacosamide, LEV, LTG, OXC, PB, perampanel, PHT, TPM, VGB	CBZ, CLB, LTG, OXC, PHT, TPM, VGB, VPA	CBZ, LEV, LTG, OXC, VPA	CBZ, GBP, LTG, OXC, PB, PHT, TPM	A: OXC B: None C: CBZ, PB, PHT, TPM, VGB, VPA D: CLB, CZP, LTG, ZNS	CBZ, OXC	CBZ, OXC
BCECT	None	Not specifically mentioned	CBZ, LEV, LTG, OXC, VPA	Not surveyed	A, B: None C: CBZ, VPA D: GBP, LEV, OXC, STM	CBZ, OXC	VPA
Childhood absence epilepsy	ESM, VPA	ESM, LTG, VPA	ESM, LTG, VPA	LTG	A: ESM, VPA B: None C: LTG D: None	ESM	VPA
Juvenile myoclonic epilepsy	LEV, LTG, TPM	VPA	LEV, LTG, TPM, VPA	Not surveyed	A, B, C: None D: TPM, VPA	LTG, VPA	VPA
Lennox-Gastaut syndrome	CLB, FLB, LTG, rufinamide (atonic), TPM	CLB, LTG, VPA	VPA	Not surveyed	Not reviewed	LTG, VPA	VPA
Infantile spasms	VGB	Nitrazepam, TPM, VGB, VPA	Corticosteroids, VGB	ACTH, VGB (updated IS guidelines 2012)	Not reviewed	ACTH, VGB	VGB
Primary generalized tonic-clonic seizures	LEV, LTG, TPM	TPM, VPA	LTG, TPM, VPA	No evidence given	A: None B: None C: CBZ, PB, PHT, TPM, VPA D: OXC		

*ILAE recommendations are listed according to levels of evidence supporting the efficacy of the options. Level A: ≥1 class I randomized controlled trial (RCT) or ≥2 class II RCTs; Level B: 1 class II RCT or ≥2 class III RCTs; Level C: ≥2 class III RCTs; Level D: 1 class III double-blinded or open-label study *or* 1 class IV clinical study *or* data from expert committee reports, opinions from experienced clinicians.
AAN, American Academy of Neurology; ACTH, adrenocorticotropic hormone; BCECT, benign childhood epilepsy with centrotemporal spikes; CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; ESM, ethosuximide; FDA, Food and Drug Administration; FLB, felbamate; GBP, gabapentin; ILAE, International League Against Epilepsy; IS, infantile spasms; LEV, levetiracetam; LTG, lamotrigine; NICE, National Institute for Clinical Excellence; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; SIGN, Scottish Intercollegiate Guidelines Network; STM, sulthiame; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; ZNS, zonisamide.
Modified and updated from Wheless JW, Clarke DF, Arzimanoglou A, et al. Treatment of pediatric epilepsy: European expert opinion. *Epileptic Disord.* 2007;9:353-412; Perucca E, Tomson T. ILAE Subcommission on AED Guidelines. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia.* 2013;54:551-563.

especially those with myoclonus. One specific indication for implementing the diet is in the context of *GLUT1* gene mutations in which the glucose transporter is defective and, in the presence of low cerebrospinal fluid (CSF) glucose, an alternative energy source for neural tissue optimizes chances for seizure control. Efficacy varies among studies, but approximately 50% of children achieve a clinically significant reduction in seizures. The diet requires a tremendous effort on the part of the parents and is successful only with proper education and close support by experienced ketogenic dietitians and physicians. Children are at risk for osteopenia, hypoglycemia, growth retardation, metabolic acidosis, and renal calculi with use of the diet; aspiration of the ketogenic diet formula by a hypotonic child can cause a life-threatening pneumonia due to the high lipid content. For these reasons, this diet must only be undertaken under close medical supervision; the ketogenic diet plans intended for weight loss would be completely inappropriate for a child with refractory epilepsy who needs to maintain sufficient caloric intake for normal growth. Some adolescents and adults opt for a **modified Atkins diet** instead, again under close supervision of a ketogenic dietitian.

Palliative epilepsy surgery is available for patients with intractable tonic or atonic seizures causing "drop attacks" and falls. Surgical division of the corpus callosum can modify the intensity of these seizures

TABLE 30.24 Management of Seizures Refractory to Medical Therapy

Incorrect Diagnosis

Review seizure type
Focal dyscognitive seizures may be mistaken for absence seizures
Reflex epilepsy with uncontrolled precipitating factors, photosensitivity, reading epilepsy
Repeat EEG with hyperventilation, photic stimulation, and sleep recording. If results are negative, consider nonepileptic paroxysmal disorders
Psychogenic nonepileptic behavioral events (see Table 30.20)
Migraine
Porphyria, hypoglycemia, hypocalcemia
Continuing seizures: admit for video/EEG monitoring to record the event

Inappropriate Medication

Review anticonvulsant levels
A second AED may have caused a drop in the serum level of a first-line drug
Review seizure type
Phenobarbital and carbamazepine may exacerbate atypical absence seizures
Drowsiness caused by phenobarbital and benzodiazepines may exacerbate tonic seizures
Phenytoin often worsens the function of patients with progressive myoclonus epilepsy syndromes

Noncompliance with Medication or Medical Advice

Check AED levels; ask patient to record medication doses taken
Check sleep habits, drug use; arrange review by social worker, psychiatrist
Inability to cope with epilepsy and avoidance of precipitating factors (adolescence, low intelligence, dysfunctional home situation)
Review all patient's prescribed and over-the-counter medication; urine drug screen for drug abuse
Exacerbation by other medication or toxins

Intercurrent Illness or Metabolic Complication from Another Medication

Serum Na^+, K^+, glucose, Ca^{2+}, Mg^{2+}, creatinine, liver function studies, complete blood cell count, pregnancy test

Intractable Epilepsies

Up to one-third of cases of symptomatic focal epilepsy are refractory to current medical therapy
After an adequate attempt with 2 first-line medications and available new AEDs, refer for epilepsy surgery assessment
Symptomatic generalized epilepsies such as West syndrome and Lennox-Gastaut syndrome are often refractory
Need to reassess goals of therapy
Refer for surgical assessment if there are recurrent falls caused by tonic or atonic seizures in an older child
Epilepsy with progressive neurologic deterioration: e.g., brain tumor, inherited disorders of metabolism, degenerative neurologic disease, progressive myoclonus epilepsy, phakomatosis, systemic or cerebral vasculitis
Review history, family history, and physical examination; repeat neuroimaging; repeat EEG studies

AED, antiepileptic drug; EEG, electroencephalogram.

so that the patient does not fall. Hemispherectomy may be indicated in Rasmussen syndrome. Local resection of areas of mesial temporal sclerosis in patients with refractory temporal lobe seizures is a highly successful therapy. **Vagal nerve stimulation**, through surgical placement of a stimulating electrode on the left vagus nerve in the neck, is a technique developed to treat intractable focal seizures resistant to medication. It has also been used effectively in the symptomatic generalized epilepsies.

Stopping Antiepileptic Drugs

Most children (60-75% of patients) remain seizure-free when AEDs are withdrawn after a seizure-free interval on medication for more than 2 years. If relapse occurs, it is generally in the first few months after cessation of medication, and 60-80% of the relapses occur before 12 months after cessation. Patients with underlying neurologic disorders and deficits and those with multiple seizure types are more likely to suffer relapse. A long duration of epilepsy before remission carries a slightly higher risk of relapse. The EEG is a strong predictor in idiopathic epilepsy; among patients with frequent epileptic discharges that are recorded in generalized epilepsy, the rate of relapse is higher. For most children with epilepsy, it is recommended that children who have been seizure-free for 2 years undergo a trial of AED withdrawal.

LIFESTYLE

Parents should be encouraged to let their children lead a normal lifestyle, although some activities are inherently more dangerous for people with epilepsy. In general, climbing to significant heights, bathing, and swimming alone are not safe for children with active epilepsy. However, the clinician must stress the importance of avoiding overprotection of the child. Participation in sports and other school activities should be encouraged within the limits of avoiding dangerous activities such as rock climbing and scuba diving, in which even a brief loss of awareness could result in serious injury or death. If seizures are well controlled, minimal restrictions apply. In children with active seizures characterized by loss of consciousness, the physician has to make judgments on the basis of an individual assessment considering the nature of the seizures, their frequency, and the degree of supervision during the activity in question. Driving restrictions vary from state to state; it is advisable that an adolescent be seizure-free for at least 2 years before applying for a driver's permit. In general, heavy-impact contact sports such as football are best avoided by children with active epilepsy, but are not contraindicated for children in remission. In adolescents, some advice regarding birth control may be necessary because many adolescents are unaware of the interaction of AEDs and oral contraceptives.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

General

Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE commission on classification and terminology, 2005-2009. *Epilepsia*. 2010;51(4):676-685.

Berg AT, Shinnar S, Levy SR, et al. How well can epilepsy syndromes be identified at diagnosis? a reassessment 2 years after initial diagnosis. *Epilepsia*. 2000;41:1269-1275.

Brown TR, Holmes GL. Epilepsy. *N Engl J Med*. 2001;344:1145-1151.

Bye AM, Kok DJ, Ferenschild FT, et al. Paroxysmal non-epileptic events in children: a retrospective study over a period of 10 years. *J Paediatr Child Health*. 2000;36:244-248.

Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia*. 1989;30:389-399.

Dreifuss FE, Nordli DR. Classification of epilepsies in childhood. In: Pellock J, Dodson WE, Bourgeois BFD, eds. *Pediatric Epilepsy: Diagnosis and Therapy*. 2nd ed. New York: Demos; 2001:69-80.

Kotagal P, Lüders HO, eds. *The Epilepsies: Etiologies and Prevention*. San Diego, CA, Academic Press; 1999.

Kramer U, Nevo Y, Neufeld MY, et al. Epidemiology of epilepsy in childhood: a cohort of 440 consecutive patients. *Pediatr Neurol*. 1998;18:46-50.

Lerche H, Jurkat-Rott K, Lehmann-Horn F. Ion channels and epilepsy. *Am J Med Genet*. 2001;106:146-159.

Shorvon SD. The etiologic classification of epilepsy. *Epilepsia*. 2011;52(6):1052-1057.

Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus - Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia*. 2015;56(10):1515-1523.

Wyllie E, ed. *The Treatment of Epilepsy: Principles and Practice*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001.

Neonatal Period

Daoust-Roy J, Seshia SS. Benign neonatal sleep myoclonus: a differential diagnosis of neonatal seizures. *Am J Dis Child*. 1992;146:681.

Parker S, Zuckerman B, Bauchner H, et al. Jitteriness in full-term neonates: prevalence and correlates. *Pediatrics*. 1990;85:17-23.

Shuper A, Zalzberg J, Weitz R, et al. Jitteriness beyond the neonatal period: a benign pattern of movement in infancy. *J Child Neurol*. 1991;6:243-245.

Acute Symptomatic Seizures and Occasional Seizures

Mizrahi EM. Neonatal seizures and neonatal epileptic syndromes. *Neurol Clin*. 2001;19:427-463.

Painter MJ, Scher MS, Stein AD, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. *N Engl J Med*. 1999;341:485-489.

Epileptic Syndromes

Mizrahi EM, Clancy RR. Neonatal seizures: early-onset seizure syndromes and their consequences for development. *Ment Retard Dev Disabil Res Rev*. 2000;6:229-241.

Plouin P. Benign familial neonatal convulsions and benign idiopathic neonatal convulsions. In: Engel JP, Pedley TA, eds. *Epilepsy: A Comprehensive Textbook*. Philadelphia: Lippincott-Raven; 1997:2247-2255.

Watanabe K, Miura K, Natsume J, et al. Epilepsies of neonatal onset: seizure type and evolution. *Dev Med Child Neurol*. 1999;41:318-322.

Early-Onset Generalized Epileptic Syndromes With Encephalopathy

Dulac O. Epileptic encephalopathy. *Epilepsia*. 2001;42(suppl 3):23-26.

Lombroso C. Early myoclonic encephalopathy, early infantile epileptic encephalopathy, and benign and severe infantile myoclonic epilepsies: a critical review and personal contributions. *J Clin Neurophysiol*. 1990;7:380-408.

Wang PJ, Lee WT, Hwu WL, et al. The controversy regarding diagnostic criteria for early myoclonic encephalopathy. *Brain Dev*. 1998;20:530-535.

Cyanotic and Pallid Infant Syncope

DiMario FJ. Prospective study of children with cyanotic and pallid breath-holding spells. *Pediatrics*. 2001;107:265-269.

Kelly AM, Porter CJ, McGoon MD, et al. Breath-holding spells associated with significant bradycardia: successful treatment with permanent pacemaker implantation. *Pediatrics*. 2001;108:698-702.

Mocan H, Yildiran A, Orhan F, et al. Breath holding spells in 91 children and response to treatment with iron. *Arch Dis Child*. 1999;81:261-262.

Sleep Disorders

Dyken ME, Lin-Dyken DC, Yamada T. Diagnosing rhythmic movement disorder with video-polysomnography. *Pediatr Neurol*. 1997;16:37-41.

Shivering Attacks

Kanazawa O. Shuddering attacks—report of four children. *Pediatr Neurol*. 2000;23:421-424.

Paroxysmal Torticollis

Chaves-Carballo E. Paroxysmal torticollis. *Semin Pediatr Neurol*. 1996;3:255-256.

Drigo P, Carli G, Laverda AM. Benign paroxysmal torticollis of infancy. *Brain Dev*. 2000;22:169-172.

Masturbation

Finklestein E, Amichai B, Jaworowski S, et al. Masturbation in prepubescent children: a case report and review of the literature. *Child Care Health Dev*. 1996;22:323-326.

Spasmus Nutans

Shaw FS, Kriss A, Russel-Eggitt I, et al. Diagnosing children presenting with asymmetric pendular nystagmus. *Dev Med Child Neurol*. 2001;43:622-627.

Benign Paroxysmal Vertigo

Herraiz C, Calvin FJ, Tapia MC, et al. The migraine: benign paroxysmal vertigo of childhood complex. *Int Tinnitus J*. 1999;5:50-52.

Russell G, Abu-Arafeh I. Paroxysmal vertigo in children—an epidemiological study. *Int J Pediatr Otorhinolaryngol*. 1999;49(suppl 1):S105-S107.

Benign Myoclonus of Early Infancy

Maydell BV, Berenson F, Rothner AD, et al. Benign myoclonus of early infancy: an imitator of West's syndrome. *J Child Neurol*. 2001;16:109-112.

Pachatz C, Fusco L, Vigevano F. Benign myoclonus of early infancy. *Epileptic Disord*. 1999;1:57-61.

Alternating Hemiplegia of Childhood

Chaves-Vischer V, Picard F, Andermann E, et al. Benign nocturnal alternating hemiplegia of childhood: six patients and long-term follow-up. *Neurology*. 2001;57:1491-1493.

Ducros A, Denier C, Joutel A, et al. The clinical spectrum of familial hemiplegic migraine associated with mutations in a neuronal calcium channel. *N Engl J Med*. 2001;345:17-24.

Mikati MA, Kramer U, Zupanc ML, et al. Alternating hemiplegia of childhood: clinical manifestations and long-term outcome. *Pediatr Neurol*. 2000;23:134-141.

Acute Symptomatic Seizures and Occasional Seizures

Baumann RJ, Duffner PK. Treatment of children with simple febrile seizures: The AAP practice parameter. American Academy of Pediatrics. *Pediatr Neurol*. 2000;23:11-17.

Knudsen FU. Febrile seizures: treatment and prognosis. *Epilepsia*. 2000;41:2-9.

Shinnar S, Pellock JM, Berg AT, et al. Short-term outcomes of children with febrile status epilepticus. *Epilepsia*. 2001;42:47-53.

Epileptic Syndromes

Dulac O, Plouin P, Schlumberger E. Infantile spasms. In: Wyllie E, ed. *The Treatment of Epilepsy: Principles and Practice*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001:415-452.

Wong M, Trevathan E. Infantile spasms. *Pediatr Neurol*. 2001;24:89-98.

Severe Myoclonic Epilepsy in Infancy

Scheffer IE, Wallace R, Mulley JC, et al. Clinical and molecular genetics of myoclonic-astatic epilepsy and severe myoclonic epilepsy in infancy (Dravet syndrome). *Brain Dev*. 2001;23:732-735.

Paroxysmal Nonepileptic Disorders

Rand DC, Feldman MD. Misdiagnosis of Munchausen syndrome by proxy: a literature review and four new cases. *Harv Rev Psychiatry*. 1999;7: 94-101.

Rosenow F, Wyllie E, Kotagal P, et al. Staring spells in children: descriptive features distinguishing epileptic and nonepileptic events. *J Pediatr*. 1998;133:660-663.

Wyllie E, Glazer J, Benbadis S, et al. Psychiatric features of children and adolescents with pseudoseizures. *Arch Pediatr Adolesc Med*. 1999;153:244-248.

Tic Disorders

Jankovic J. Tourette's syndrome. *N Engl J Med*. 2001;345:1184-1192.

Marcus D, Kurlan R. Tics and its disorders. *Neurol Clin*. 2001;19:735-758.

Sleep Disorders

Guilleminault C, Pelayo R. Narcolepsy in children: a practical guide to its diagnosis, treatment and follow-up. *Paediatr Drugs*. 2000;2:1-9.

Laberge L, Tremblay RE, Vitaro F, et al. Development of parasomnias from childhood to early adolescence. *Pediatrics*. 2000;106:67-74.

Ohayon MM, Guilleminault C, Priest RG. Night terrors, sleepwalking, and confusional arousals in the general population: their frequency and relationship to other sleep and mental disorders. *J Clin Psychiatry*. 1999;60:268-276.

Stores G. Children's sleep disorders: modern approaches, developmental effects, and children at special risk. *Dev Med Child Neurol*. 1999;41:568-573.

Hyperekplexia

Vergouwe MN, Tijssen MA, Peters AC, et al. Hyperekplexia phenotype due to compound heterozygosity for GLRA1 gene mutations. *Ann Neurol*. 1999;46:634-638.

Self-Stimulatory Behavior

Tan A, Salgado M, Fahn S. The characterization and outcome of stereotypic movements in non-autistic children. *Mov Disord*. 1997;12:47-52.

Epileptic Syndromes

Andermann F, Zifkin B. The benign occipital epilepsies of childhood: an overview of the idiopathic syndromes and of the relationship to migraine. *Epilepsia*. 1998;39(suppl 4):S9-S23.

Baglietto MG, Battaglia FM, Nobili L, et al. Neuropsychological disorders related to interictal epileptic discharges during sleep in benign epilepsy of childhood with centrotemporal or rolandic spikes. *Dev Med Child Neurol*. 2001;43:407-412.

Holmes GL. Clinical spectrum of benign focal epilepsies of childhood. *Epilepsia*. 2000;41:1051-1052.

Koutroumanidis M. Panayiotopoulos syndrome. *BMJ*. 2002;324:1228-1229.

Robinson R, Gardiner M. Genetics of childhood epilepsy. *Arch Dis Child*. 2000;82:121-125.

Symptomatic Focal (Localization-Related) Epilepsy

Berg AT, Shinnar S, Levy SR, et al. Early development of intractable epilepsy in children: a prospective study. *Neurology*. 2001;56:1445-1452.

Canafoglia L, Franceschetti S, Antozzi C, et al. Epileptic phenotypes associated with mitochondrial disorders. *Neurology*. 2001;56:1340-1346.

Shields WD. Catastrophic epilepsy in childhood. *Epilepsia*. 2000;41(suppl 2):S2-S6.

Childhood Absence Epilepsy

Panayiotopoulos CP. Absence epilepsies. In: Engel JP, Pedley TA, eds. *Epilepsy: A Comprehensive Textbook*. Philadelphia: Lippincott-Raven; 1997:2327-2346.

Wirrell E, Camfield C, Camfield P, et al. Prognostic significance of failure of the initial antiepileptic drug in children with absence epilepsy. *Epilepsia*. 2001;42:760-763.

Epilepsia Partialis Continua and Rasmussen Encephalitis

Hart Y, Andermann F. Rasmussen's syndrome. In: Lüders HO, Comair YG, eds. *Epilepsy Surgery*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2001:145-156.

Lennox-Gastaut Syndrome

Farrell K. Symptomatic generalized epilepsy and the Lennox-Gastaut syndrome. In: Wyllie E, ed. *The Treatment of Epilepsy: Principles and Practice*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001:525-536.

Myoclonic Astatic Epilepsy

Oguni H, Fukuyama Y, Tanaka T, et al. Myoclonic-astatic epilepsy of early childhood—clinical and EEG analysis of myoclonic-astatic seizures, and discussions on the nosology of the syndrome. *Brain Dev*. 2001;23:757-764.

Singh R, Andermann E, Whitehouse WP, et al. Severe myoclonic epilepsy of infancy: extended spectrum of GEFS. *Epilepsia*. 2001;42:837-844.

Adolescence

Andriola MR, Ettinger AB. Pseudoseizures and other nonepileptic paroxysmal disorders in children and adolescents. *Neurology*. 1999;53(5 suppl 2):S89-S95.

Epileptic Syndromes

Dugan P, et al. Auras in generalized epilepsy. *Neurology*. 2014;83(16):1444-1449.

Genton P, Gelisse P. Juvenile myoclonic epilepsy. *Arch Neurol*. 2001;58:1487-1490.

Janz D. The idiopathic generalized epilepsies of adolescence with childhood and juvenile age of onset. *Epilepsia*. 1997;38:4-11.

Scheffer IE. Autosomal dominant nocturnal frontal lobe epilepsy. *Epilepsia*. 2000;41:1059-1060.

Diagnostic Evaluation of a Seizure Disorder

Duchowny M. Recent advances in candidate selection for pediatric epilepsy surgery. *Semin Pediatr Neurol*. 2000;7:178-186.

Kuzniecky RI, Barkovich AJ. Malformations of cortical development and epilepsy. *Brain Dev*. 2001;23:2-11.

Liamsuwan S, Grattan-Smith P, Fagan E, et al. The value of partial sleep deprivation as a routine measure in pediatric electroencephalography. *J Child Neurol*. 2000;15:26-29.

Raybaud C, Guye M, Mancini J, et al. Neuroimaging of epilepsy in children. *Magn Reson Imaging Clin N Am*. 2001;9:121-147.

Strain JD, Kushner DC, Babcock DS, et al. Imaging of the pediatric patient with seizures. American College of Radiology. ACR Appropriateness Criteria. *Radiology*. 2000;215(suppl):787-800.

Antiepileptic Drugs

Bourgeois BFD. New antiepileptic drugs in children: which ones for which seizures. *Clin Neuropharmacol*. 2000;23:119-132.

Diaz-Arrastia R, Agostini MA, Van Ness PC. Evolving treatment strategies for epilepsy. *JAMA*. 2002;287:2917-2920.

Gericke CA, Picard F, de Saint-Martin A, et al. Efficacy of lamotrigine in idiopathic generalized epilepsy syndromes: a video–EEG-controlled, open study. *Epileptic Disord*. 1999;1:159-165.

O'Brien TJ, Cascino GD, So EL, et al. Incidence and clinical consequence of the purple glove syndrome in patients receiving intravenous phenytoin. *Neurology*. 1998;51:1034-1039.

Panayiotopoulos CP. Treatment of typical absence seizures and related epileptic syndromes. *Paediatr Drugs*. 2001;3:379-403.

Pedley TA, Hirano M. Is refractory epilepsy due to genetically determined resistance to antiepileptic drugs? *N Engl J Med*. 2003;15:1480-1482.

Wallace SJ. Myoclonus and epilepsy in childhood: a review of treatment with valproate, ethosuximide, lamotrigine and zonisamide. *Epilepsy Res*. 1998;29:147-154.

Wallace SJ. Newer antiepileptic drugs: advantages and disadvantages. *Brain Dev*. 2001;23:277-283.

Genetics

Poduri A, Sheidley BR, Shostak S, et al. Genetic testing in the epilepsies—developments and dilemmas. *Nat Rev Neurol*. 2014;10:293-299.

Pong AW, Pal DK, Chung WK. Developments in molecular genetic diagnostics: an update for the pediatric epilepsy specialist. *Pediatr Neurol*. 2011;44:317-327.

Ream MA, Patel AD. Obtaining genetic testing in pediatric epilepsy. *Epilepsia*. 2015;56(10):1505-1514.

31

Altered Mental Status

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Coma is the lack of any awareness of self and environment despite painful or other external stimulation (Table 31.1). **Delirium** is an alternation in consciousness that falls along the spectrum from normal awareness to coma and is characterized by irritability, agitation, lack of contact with the environment, and confusion. Periods of lucidity may alternate with the delirious state, and patients may proceed rapidly from delirium to lethargy or coma. Any alteration in the level of consciousness whether delirium, lethargy, obtundation, stupor, or coma must be managed as a life-threatening emergency until proven otherwise.

BACKGROUND

Arousal and awareness form the foundation for normal cognitive function. **Arousal** is determined in the brainstem's ascending reticular activating system, and **awareness** is generated in the cortex. The cortex is the central processing center that interprets neuronal input and generates awareness. Injury to these areas creates an alteration in consciousness. *Standardized language is necessary to properly diagnose and treat alterations in consciousness since terms, such as lethargy, obtundation, stupor, and coma, are qualitative descriptions.* Rating scales allow different observers to follow the progression of the patient's mental status over time and facilitate effective communication of clinical information. The most widely used grading system is the **Glasgow Coma Scale (GCS)** (Table 31.2), which has been modified for children less than 5 years of age based on their age-appropriate developmental abilities (Table 31.3). The GCS was initially intended for use in traumatic injury but has been successfully applied in patients with nontraumatic altered mental status. This 15-point scale evaluates 3 areas of central nervous system (CNS) function: eye opening, verbal response, and motor response. A score of 15 indicates full function, whereas a score of 3 indicates no function. The 1st area of assessment is eye opening, in which the arousability and alertness of the patient are evaluated. Spontaneous eye opening indicates intact arousal mechanisms but does not imply awareness. The 2nd area, verbal response, requires a high degree of integration within the CNS. Oriented responses indicate awareness of person, place, and time. The 3rd area, motor functioning, reflects mentation as well as the integrity of the major CNS pathways. For purposes of gauging global brain function, the best motor response from any limb is taken as the score. Variation in response from one side of the body to the other is indicative of an asymmetric brain lesion. Spinal cord lesions resulting in paralysis or significant orthopedic injuries to the extremities prevent evaluation of the motor portion of the GCS.

The GCS can provide a general assessment of consciousness but is not intended to take the place of a complete neurologic evaluation (Table 31.4). The scale is an objective measure of the improvement or worsening of the patient's level of consciousness over time, and interventions are often based on the score. Most patients with traumatic brain injury should undergo endotracheal intubation if their score is 8 or less. Deterioration of a patient's score by 2 or more points indicates a need for quick re-evaluation of the patient and the possible need for interventions such as endotracheal intubation and diagnostic studies such as a brain computed tomography (CT) scan. The score has been used to assign a prognosis to patients with brain injury, particularly with traumatic brain injury. It may take days to weeks for patients with initial scores of 3-5 to become conscious as opposed to a few days in patients with scores of 6 or higher.

The GCS score has also been used as a prognostic indicator in nontraumatic coma. Children presenting after near-drowning with an initial score of 6 or higher have a good outcome. Patients presenting with a score of 5 or less have a high probability of mortality or profound neurologic sequelae, although a patient with a score of 4 or 5 may survive with minimal impairment. A score of 3 on transfer to an intensive care unit after near-drowning has been associated with a nearly 100% rate of poor outcome.

Although the GCS is a widely applied tool for assessment, it does not assess *brainstem function* and fails to discriminate between low scores and intubated patients. The **Full Outline of Unresponsiveness (FOUR)** scale is another tool to assess consciousness that has been validated in several different settings with high inter-rater consistency. The FOUR score evaluates eye response, motor response, brainstem reflexes, and respiratory effort on a 4-point scale. The FOUR score eye and motor responses are defined very similar to the GCS (see Table 31.2). The assessment of brainstem response focuses on the pupillary and corneal reflexes. The respiratory assessment includes the intubated patient along with respiratory effort. Because the FOUR score includes brainstem responses and not only recognizes but differentiates intubated patients, this scale is better able to discriminate an unresponsive patient with a GCS of 3. In children with nontraumatic impairment of consciousness, using endpoints of mortality and functional outcome, both scales have similar predictive value. Regardless of the scoring system used, reporting the score for each element can increase the precise description of alteration in consciousness in order to make management decisions.

Other scales have been developed to measure the level of consciousness in specific disease states, such as poisonings, and hepatic failure. The **Reed classification** of coma has been used in the setting of poisoning or intoxication (Table 31.5) and is used to evaluate increasing depths of coma encountered with CNS-depressant drugs. The cardiovascular system is included in this classification because toxic ingestions may depress myocardial contractility or cause vasodilation. Neurologic function in a patient with **hepatic encephalopathy** is graded according to the scoring system in Table 31.6.

TABLE 31.1 States of Altered Consciousness or Unresponsiveness

Coma: A state of unarousable unresponsiveness; even strong exteroceptive stimuli fail to elicit recognizable psychologic responses; unresponsive to pain

Stupor: Spontaneous unarousability interruptible only by vigorous, direct external stimulation; responsive only to pain

Hypersomnia, pathologic drowsiness, obtundation: Terms applied to an increase above the patient's normal sleep/wake ratio, often accompanied during wakefulness by reduced attention and interest in the environment; responsive to pain and other stimuli

Delirium: An acute or subacute reduction in awareness, attention, orientation, and perception ("clouding of consciousness"), usually fluctuating and accompanied by abnormal sleep/wake patterns and often psychomotor disturbances

Syncope: Brief loss of consciousness caused by global failure of cerebrovascular perfusion

Dementia: A sustained or permanent multidimensional or global decline in cognitive functions

Vegetative state: A sustained, complete loss of cognition, with sleep/wake cycles and other autonomic functions remaining relatively intact; can either follow acute, severe bilateral cerebral damage or develop gradually as the end stage of a progressive dementia

Locked-in state: Preservation of intellectual activity accompanied by severe or total incapacity to express voluntary responses as a result of damage to or dysfunction of descending motor pathways in the brain or peripheral motor nerves; most, but not all, such patients can use vertical eye movements to signal by code

Modified from Plum F. Neurology/disturbances of consciousness and arousal. In: Wyngaarden JB, Smith LH, Bennett JC, eds. *Cecil Textbook of Medicine.* 19th ed. Philadelphia: WB Saunders; 1992:2049.

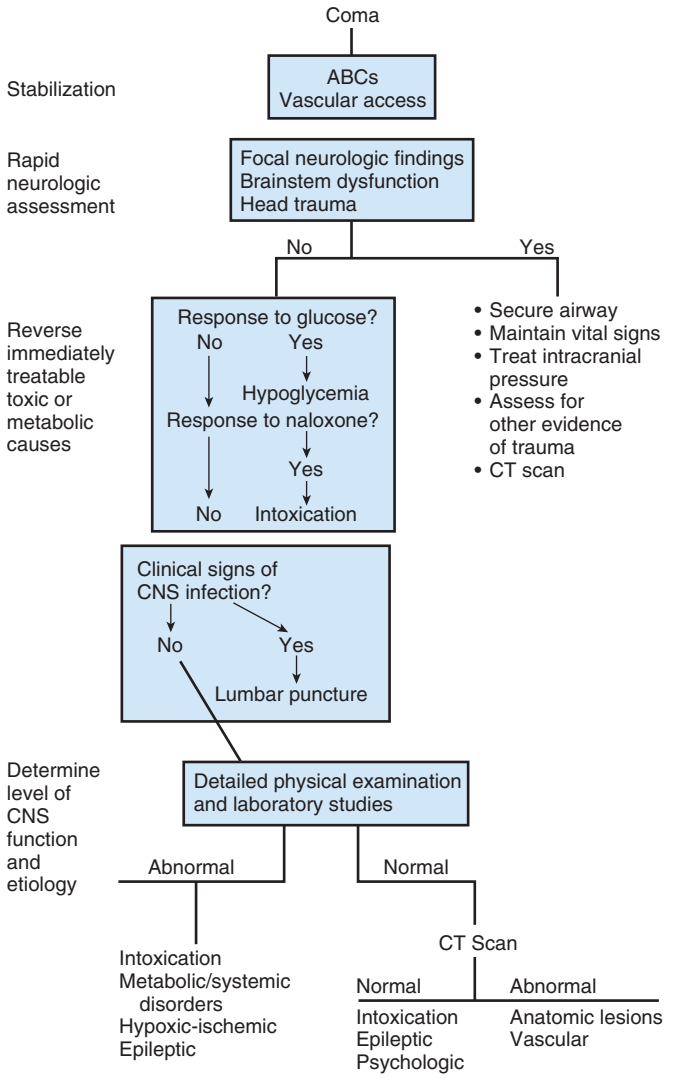

FIGURE 31.1 Management approach to coma. ABCs, airway, breathing, and circulation; CNS, central nervous system; CT, computed tomography.

◆ Differential Diagnosis

Coma is caused by 1 of 3 etiologies: structural brain disease, diffuse neuronal injury, or to a lesser degree, psychogenic causes. Within these 3 categories, the differential diagnosis of coma in the child is extensive. Excluding traumatic head injuries, broad category causes of altered mental status in children include intracranial infections, hypoxic-ischemic, epilepsy, metabolic encephalopathies, abusive head trauma, toxic ingestion, anatomic abnormalities, and cerebral vascular abnormalities such as emboli or vasculitis (Table 31.7). Some diagnoses (subdural hematoma, hydrocephalus, cerebral edema) may apply to more than 1 category. The age of the patient can help the clinician differentiate the likely causes of coma, although there is considerable overlap (Table 31.8). Patients with delirium must be differentiated from an acute psychotic event (Table 31.9). In addition, in patients who are awake but presenting with an altered mental status, performing an appropriate mental status exam may help evaluate the degree of impairment and potential etiology (Table 31.10). The mental status exam is most abnormal with organic (encephalopathy, encephalitis) causes of altered behavior and mental status.

◆ Management Approach

The approach to the child with an alteration of consciousness can be divided into 4 parts: (1) stabilization, (2) rapid clinical assessment, (3) reversal of immediately treatable toxic or metabolic causes, and (4) determination of level of CNS function and of the cause of the coma (Fig. 31.1).

Stabilization

Initial stabilization includes assessment of the patient's airway, breathing, and circulation (ABCs), as well as securing a patent airway, establishing access, and ensuring adequate circulatory volume. Evaluating a patient's airway and responding appropriately to ensure patency is the 1st step in management. This may involve positioning, suctioning, or intubating. This is closely tied to the assessment of respiratory drive via auscultation and observation. Obtunded, stuporous, or comatose patients usually require intubation unless their mental status is improving or can be readily reversed to secure an airway, treat hypoventilation, protect the airway if a gag reflex is not present, and to facilitate hyperventilation therapy in a child with suspected intracranial hypertension. Manipulation of the neck, particularly extension, should be avoided when an airway is being stabilized or secured, unless the cervical spine has been cleared via history or imaging.

Attention is next directed toward an assessment of the circulation; this mandates evaluation of vital signs, presence and volume of peripheral pulses, and adequacy of end-organ perfusion. Blood pressure must

TABLE 31.2 Glasgow Coma Scale Versus Full Outline of Unresponsiveness Score

Glasgow Coma Scale (GCS)		Full Outline of Unresponsiveness (FOUR)	
Eye Opening:		**Eye Response:**	
1	Does not open eyes	4	Eyelids open and comply with verbal stimuli
2	Opens eyes in response to noxious stimuli	3	Eyelids open but not tracking
3	Opens eyes in response to voice	2	Eyelids closed but open to loud noise
4	Opens eyes spontaneously	1	Eyelids closed but open to noxious stimuli
		0	Eyelids remain closed
Verbal Response:		**Motor Response:**	
1	No verbal response	4	Thumbs up, fist or peace sign
2	Incomprehensible sounds	3	Localize to pain
3	Inappropriate words	2	Flexion to pain
4	Confused and disoriented fluid speech	1	Extension to pain
5	Oriented with normal speech	0	No response to pain or myoclonus
Motor Response:		**Brainstem Reflexes:**	
1	No movements	4	Pupil and corneal reflexes present
2	Extension to noxious stimuli	3	One pupil wide and fixed
3	Flexion to noxious stimuli	2	Pupil or corneal reflex absent
4	Withdrawal to pain	1	Pupil and corneal reflexes absent
5	Localizes to pain	0	Absent pupil, corneal, and cough reflex
6	Obeys commands		
		Respirations:	
		4	Regular breathing pattern
		3	Cheyne–Stokes respirations
		2	Irregular breathing
		1	Intubated but breathing above the vent
		0	Breathing at vent rate or apnea
TOTAL SCORE 3-15		TOTAL SCORE 0-16	

TABLE 31.3 Pediatric Glasgow Coma Scale

Activity	Best Response	Score
Eye opening	Spontaneously	4
	To speech	3
	To pain	2
	None	1
Verbal	Oriented	5
	Words	4
	Vocal sounds	3
	Cries	2
	None	1
Motor	Obeys commands	5
	Localizes pain	4
	Flexion to pain	3
	Extension to pain	2
	None	1
Normal Total Score Based on Age		
Birth–6 mo		9
7-12 mo		11
1-2 yr		12
2-5 yr		13
>5 yr		14

Modified from Simpson D, Reilly P. Pediatric coma scale. *Lancet.* 1982;2:450.

(See *Nelson Textbook of Pediatrics*, Table 67-3.)

TABLE 31.4 The Neurologic Examination in Coma

1. Guarantee vital functions.
2. Feel the scalp for hematomas (overlying fracture lines); be sure the neck is not fractured; test gently for stiff neck.
3. Test language. Test arousability by words, loud sounds, noxious stimuli. If vocalizations occur, check quickly for appropriate phrases, actual words, and presence or absence of aphasia.
4. Perform a neuro-ophthalmologic examination.
   Funduscopy (if difficult, can be deferred until patient is stabilized).
   Papilledema (increased intracranial or venous sinus pressure)
   Hemorrhages (subarachnoid hemorrhage; hypertensive encephalopathy; hypoxic-hypercarbic encephalopathy)

   Pupils
   Light reaction: Use bright flashlight and, if necessary, a magnifying glass to be certain of findings. Absence means potentially fatally deep sedative poisoning or acute or chronic structural brainstem damage.
   Equality: 15% of normal patients have mild anisocoria, but new or >2-mm dilation means parasympathetic (3rd nerve) palsy.
   Extraocular movements: Absence acutely means deep drug poisoning, severe brainstem damage, polyneuropathy, or botulism.
   Dysconjugate deviation: At rest, this means an acute 3rd, 4th, or 6th nerve palsy or internuclear ophthalmoplegia. Tonic conjugate deviation toward a paralytic arm and leg means forebrain seizures or a contralateral pontine destructive lesion; such deviation away from the paralytic arm and leg means forebrain gaze paralysis.
   Spontaneous eye movements: In comatose patients, nystagmus, bobbing, and independently moving eyes all mean brainstem damage.
   Oculocephalic (away from direction of head turning) or oculovestibular (toward cold caloric irrigation) responses: Absence of responses means drug overdose or severe brainstem disease; dysconjugate responses with equal pupils mean internuclear ophthalmoplegia; responses with unequal pupils mean 3rd nerve disease.
5. Examine the motor systems.

   Strength
   Unilateral weakness or motionlessness of arm and leg means contralateral supraspinal upper motor neuron lesion, most often cerebral; if of arm, leg, and face, contralateral cerebral lesion. Occasionally, arm and leg weakness reflects contralateral brainstem lesion.
   Weakness or motionlessness of all 4 extremities implies metabolic disease; less likely is brainstem disease (tone and reflexes increased) or peripheral disease (tone and reflexes decreased).

   Attempt to Elicit Reflex Posturing
   Arm flexed, leg extended: contralateral deep cerebral-thalamic lesion
   Arm and leg extended: thalamic or mesencephalic lesion
   Arms extended and legs flexed or flaccid: pontine lesion
   Legs flexed, arms flaccid: pontomedullary or spinal lesion
   Compare side-to-side reflexes and examine plantar responses.
6. Seek seizure activity or abnormal movements: (1) generalized, (2) focal, (3) multifocal, and (4) myoclonic.
   Control (1) immediately, (2) and (3) deliberately; if (4) is present, treat underlying disease.
   Acute tremor, asterixis, multifocal myoclonus: seek metabolic cause.
7. Inspect breathing.
   Regular hyperpnea: metabolic acidosis; pulmonary infarction; congestive failure or alveolar infiltration; sepsis; salicylism; hepatic coma
   Cyclically irregular (Cheyne–Stokes): low cardiac output plus bilateral cerebral or upper brainstem dysfunction
   Irregularly irregular gasping, slow or weak: lower, brainstem dysfunction (including hypoglycemia, drug effects); less often, peripheral ventilatory paralysis
8. Proceed with laboratory tests and emergency management as described in text.

Modified from Plum F. Neurology/sustained impairments of consciousness. In: Wyngaarden JB, Smith LH, Bennett JC, eds. *Cecil Textbook of Medicine*. 19th ed. Philadelphia: WB Saunders; 1992:2057.

be high enough to support perfusion of vital organs. Patients may be in shock with a normal blood pressure and may manifest tachycardia and often, tachypnea. In early shock, except for septic shock, peripheral pulses are diminished in comparison with central pulses. As shock progresses and stroke volume decreases, the pulse pressure narrows, and the peripheral pulses become weak or "thready" and finally nonpalpable. Early septic shock or "warm" shock is often characterized by a widened pulse pressure and bounding pulses.

End-organ perfusion is best evaluated in the skin, kidneys, and brain. The skin should be checked for temperature, color, and capillary refill. Cool extremities, pallor, mottling, peripheral cyanosis, and capillary refill of more than 2 seconds indicate poor perfusion. As perfusion worsens, the coolness of the extremities extends proximally. Urine output may not be helpful in the initial evaluation of a patient, but it becomes an important marker to monitor during therapy. As renal perfusion improves, urine flow rate increases. The patient's alteration in consciousness may be a consequence of shock. In early stages of shock, the patient is typically lethargic or confused, and lethargy alternating with combativeness is often seen.

Rapid Clinical Assessment

After initial stabilization, attention should turn to rapid clinical assessment including focused history from available friends, family, witnesses, 1st responders and the medical record as applicable, and a physical exam with a targeted neurologic examination. Using this data, the etiology of coma (structural, diffuse neuronal dysfunction, and

TABLE 31.5 Reed Classification of Coma

Grade 0*	Asleep Can be aroused Will answer questions
Grade 1*	Comatose Withdraws from painful stimuli Intact reflexes
Grade 2*	Comatose Does not withdraw from painful stimuli No respiratory, circulatory depression Intact reflexes
Grade 3†	Comatose Reflexes absent No respiratory, circulatory depression
Grade 4†	Comatose Reflexes absent Respiratory or circulatory problems

*Good prognosis.
†Very serious, may need measures to enhance elimination.
Modified from Ellenhorn MJ, Barceloux DE. *Medical Toxicology: Diagnosis and Treatment of Human Poisoning*. New York: Elsevier Science; 1988:17.

TABLE 31.6 Classification of Hepatic Encephalopathy

Grade 0	Normal
Grade I	Altered spatial orientation, sleep patterns, and affect
Grade II	Drowsy but arousable, slurred speech, confusion, and asterixis
Grade III	Stuporous but responsive to painful stimuli
Grade IV	Unresponsive, with decorticate or decerebrate posturing possible

From Rogers EL, Perman JA. Gastrointestinal and hepatic failure. In: Rogers MC, ed. *Textbook of Pediatric Intensive Care*. 2nd ed. Baltimore: Williams & Wilkins; 1992:1151.

psychiatric) may be clarified for initial treatment decisions. Pertinent questions include recent history preceding the change in mental status, the patient's medical history, and family history, particularly of seizures or encephalopathy. Specific questions should be targeted at identifying any traumatic injuries in the previous few days, and any recent fevers or other signs or symptoms of infection or systemic disease. A dietary history in infants presenting with a depressed level of consciousness is paramount and may raise suspicion of hypoglycemia (fasting or emesis) or hyponatremia (ingestion of free water). Exposure to drugs or toxins should be suspected in any patient with a sudden onset of unexplained symptoms (coma, seizures) or a gradual onset of symptoms preceded by a period of confusion or delirium. The caregivers should be asked directly about possible access to medications, illicit drugs, and environmental toxins.

After collecting the available historical information, the next phase in management is completing a physical exam including a rapid neurologic assessment (see Table 31.4), which should take no more than a few minutes. The general physical exam should include assessment of vital signs with emphasis on the cardiovascular, respiratory, and head and neck exams as well as a general assessment. Special attention should be paid to identify any physical exam findings that may suggest a specific toxidrome. The absence of a history of trauma or physical findings suggestive of a rapidly progressive intracranial process does not preclude a traumatic or an anatomic cause of coma. Traumatic injuries can result in life-threatening illnesses at any age, including newborns. The head and neck should be carefully inspected and the skull palpated for evidence of trauma (Table 31.11). In infants, a bulging fontanel represents raised intracranial pressure, which may have various causes. In the absence of a febrile illness, trauma, including that caused by abusive head trauma, should be suspected in any infant with a bulging fontanel. Retinal hemorrhages are often present on funduscopic examination in children with abusive head trauma. In addition to abusive head trauma, a child may have a subarachnoid hemorrhage (ruptured aneurysm, arteriovenous malformation) or hydrocephalus without any of the aforementioned signs or symptoms of raised intracranial pressure.

After completing a brief general physical exam and noting impaired consciousness, a rapid neurologic assessment is required. The neurologic assessment should focus on identifying lateralizing or focal findings, recognizing brainstem dysfunction, and defining severity of illness. Intrinsic to this assessment is differentiating 1 hemisphere with mass effect versus both hemispheres involvement versus suspected brainstem dysfunction (Table 31.12). The presence of focal findings can be determined by examination of a child's pupils for asymmetry in size or reactivity and examination of the motor system for asymmetric movement of the extremities or face. The motor response is part of the GCS and FOUR scores as referenced previously. Motor response should be tested by 1st observing spontaneously purposeful movement, then movement in response to command and finally, movement in response to noxious stimuli. Because localization to pain relies on the contralateral arm to cross the midline to address pain, both sides should be tested.

Brainstem function is evaluated by observing the child's respiratory pattern, assessing corneal reflexes, and testing oculocephalic (doll's eye) or oculovestibular (cold caloric) reflexes. The oculocephalic reflex should not be checked unless a cervical spine injury has been ruled out. Significant brainstem dysfunction is rarely associated with a normal breathing pattern (Fig. 31.2). Cheyne–Stokes respiration is a pattern of breathing in which periods of hyperpnea alternate with shorter apneic phases, observed in the presence of bilateral hemispheric or diencephalic dysfunction. It may also precede transtentorial herniation. The hyperpneic periods have a characteristic smooth, crescendo-decrescendo pattern.

Central neurogenic hyperventilation is encountered with midbrain dysfunction; patients with this problem are tachypneic and hyperpneic. Apneustic breathing is associated with damage in the middle to lower pontine region. This pattern is characterized by a prolonged pause at full inspiration. Clusters of breaths separated by periods of apnea may be observed in patients with low pontine to upper medullary lesions, whereas medullary lesions result in ataxic or irregular breathing, slow regular breathing, or agonal respiration. Absent or asymmetric corneal reflexes or abnormal oculocephalic or oculovestibular reflexes suggest serious brainstem involvement. Normal brainstem response combined with withdrawal to pain suggests a supratentorial abnormality. Roving eye movements suggest an intact brainstem, whereas vertical malalignment suggests the brainstem is affected.

Increasing intracranial pressure is a worrisome sign. Indications of clinically significant intracranial hypertension are usually apparent during an assessment of pupillary responses, vital signs, and motor responses (Tables 31.13 and 31.14). A unilaterally fixed and dilated pupil in a patient who is not awake represents uncal herniation precipitated by an increase in intracranial pressure in the supratentorial space. Anisocoria or ptosis may be a sign of increased intracranial pressure.

TABLE 31.7 Etiologic Classification of Altered Mental Status in Children

Infectious	Metabolic/ Systemic	Toxic*	Traumatic*	Anatomic	Hypoxic-Ischemic	Epileptic	Vascular	Psychologic
Viral	Hypoglycemia*	Sympathomimetics	Concussion*	Tumor	Cardiac arrest	Postictal state*	Embolism	Conversion disorders*
Aseptic meningitis*	Inborn errors of metabolism*	Anticholinergics	Cerebral contusion	Hydrocephalus	Cardiac arrhythmia	Status epilepticus*	Spontaneous intraparenchymal hemorrhage	Catatonic schizophrenia
Encephalitis*	Hyperammonemia	Phenothiazines	Epidural hematoma	Hydrocephalus with shunt malfunction	Severe shock	Absence status	Subarachnoid hemorrhage	
? Reye syndrome	Hepatic failure	PCP	Subdural hematoma	Subdural hematoma	Near-drowning	Complex partial seizure	Venous sinus thrombosis	
? Hemorrhagic shock and encephalopathy syndrome	Renal diseases	LSD		Epidural hematoma	Neonatal asphyxia*		Vasculitis	
Postinfectious encephalomyelitis	Uremic encephalopathy	Marijuana	Brainstem	Brain abscess	Hypoxemic respiratory failure		Lupus erythematosus	
	Hypertensive encephalopathy	Cocaine	Epidural contusion	Subdural empyema	Carbon monoxide poisoning		Hypertensive encephalopathy	
Systemic infection with shock	Dialysis encephalopathy (dysequilibrium syndrome)	Heavy metals (lead)	Diffuse axonal shear injury	Epidural empyema	Cyanide toxicity		Acute confusional migraine*	
Bacterial	Hyperosmolar states	Salicylates		Cerebral edema	Anaphylaxis			
Meningitis*	Hypernatremia	Organophosphates and carbamates	Cerebral edema*	Intracranial hemorrhage	Asthma			
Brain abscess	Hyperglycemia–diabetes mellitus*	Antihistamines	Intraparenchymal hemorrhage	Cerebrovascular accident				
Epidural empyema	Hypo-osmolar states	Industrial solvents (inhaled)	Intraventricular hemorrhage (neonate)*					
Subdural empyema	Hyponatremia*	Alcohols	Obstructive hydrocephalus					
Systemic infection with shock	Rapid decrease in osmolality in hyperosmolar states	Narcotics	Posttraumatic seizure					

Toxic shock syndrome	Endocrine disorders	Sedative-hypnotics	Fat embolism
Rickettsial infection	Adrenal insufficiency	Barbiturates	
Fungal	Hyperthyroidism and hypothyroidism	Carbon monoxide	
Fungal meningitis	Hypoparathyroidism	Tricyclic antidepressants	
Fungal brain abscess	Mineral abnormalities	Carbamazepine	
Protozoan	Hypercalcemia	Cyanide	
Meningitis	Hypocalcemia	Methaqualone	
Abscess	Hypermagnesemia	Burn encephalopathy	
Postimmunization encephalopathy	Hypomagnesemia		
	Hypophosphatemia		
	Hypercapnia		
	Hypoxia*		
	Shock*		
	Vitamin deficiency and dependency states		
	Nicotinic acid		
	Pantothenic acid		
	Pyridoxine		
	Thiamine		
	Vitamin B_{12}		
	Intussusception encephalopathy		
	Methemoglobinemia		
	Acidosis		
	Alkalosis		
	Porphyria		
	Reye syndrome		
	? Hemorrhagic shock and encephalopathy syndrome		
	Mitochondrial encephalopathies		

*Common.
LSD, lysergic acid diethylamide; PCP, phenylcyclohexyl piperidine (phencyclidine HCl); ?, unknown etiology.

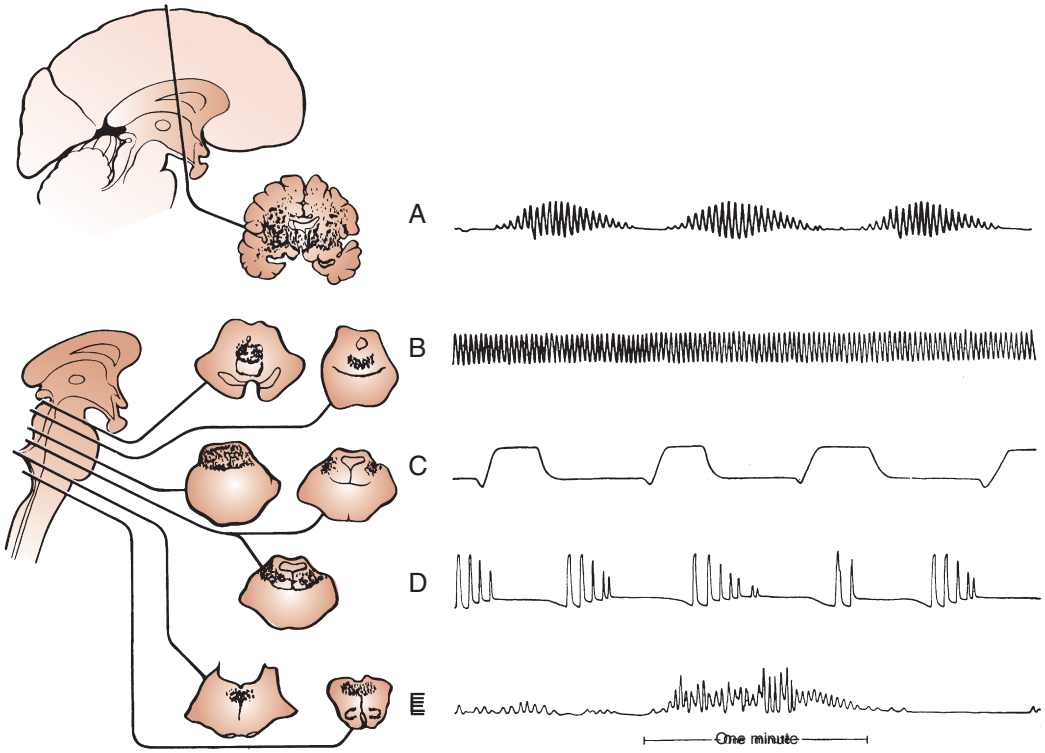

FIGURE 31.2 Abnormal respiratory patterns. *A,* Cheyne-Stokes respiration. *B,* Central neurogenic hyperventilation. *C,* Apneusis. *D,* Cluster breathing. *E,* Ataxic breathing. *Shaded areas* show location of brain pathology associated with abnormal respiratory pattern.

TABLE 31.8 Common Causes of Altered Mental Status by Age

Neonate	Infant	Child	Adolescent
Hypoglycemia	Meningitis	Meningitis	Meningitis
Birth asphyxia	Bacterial	Bacterial	Bacterial
Congenital anomalies of the central nervous system	Viral	Viral	Viral
Systemic infection with shock	Trauma	Encephalitis	Encephalitis
Cardiogenic shock	Abuse/shaken baby syndrome	Trauma	Intentional ingestion
Congenital infection	Asphyxia	Ingestion	Recreational drug/alcohol use
Bacterial meningitis	Apparent life-threatening event	Reye syndrome	Suicide gesture or attempt
Inborn errors of metabolism	Intentional suffocation	Systemic infection with shock	Often involves multiple agents
Hypocalcemia	Systemic infection with shock	Seizure	Trauma
Intraventricular hemorrhage	Ingestion	Near-drowning	Seizures
Seizures	Inborn errors of metabolism	Hypoglycemia	Diabetic ketoacidosis
Birth trauma	Hypoglycemia	Intussusception encephalopathy	Systemic infection with shock
	Hyponatremia	Diabetic ketoacidosis	Toxic shock syndrome
	Hypocalcemia		Reye syndrome
	Encephalitis		Spontaneous intracranial hemorrhage
	Postimmunization encephalopathy		Psychologic
	Hemorrhagic shock and encephalopathy syndrome		Lupus
	Intussusception encephalopathy		
	Seizures		

TABLE 31.9 Special Problems in the Differential Diagnosis of Delirium*

Clinical Feature	Delirium	Dementias	Schizophrenia	Depression
Course	Acute onset; hours, days, or more	Insidious onset†; months or years; progressive	Insidious onset, 6 mo or more; acute psychotic phases	Insidious onset, at least 2 wk, often months
Attention	Markedly impaired attention and arousal	Normal early; impairment later	Normal to mild impairment	Mild impairment
Fluctuation	Prominent in attention arousal; disturbed day/night cycle	Prominent fluctuations absent; lesser disturbances in day/night cycle	Absent	Absent
Perception	Misperceptions; hallucinations, usually visual, fleeting; paramnesia	Perceptual abnormalities much less prominent‡; paramnesia	Hallucinations, auditory with personal reference	May have mood-congruent hallucinations
Speech and language	Abnormal clarity, speed, and coherence; disjointed and dysarthric; misnaming; characteristic dysgraphia	Early anomia; empty speech; abnormal comprehension	Disorganized, with a bizarre theme	Decreased amount of speech
Other cognition	Disorientation to time, place; recent memory and visuospatial abnormalities	Disorientation to time, place; multiple other higher cognitive deficits	Disorientation to person; concrete interpretations	Mental slowing; indecisiveness; memory retrieval difficulty
Behavior	Lethargy or delirium; nonsystematized delusions; emotional lability	Disinterested; disengaged; disinhibited; delusions and other psychiatric symptoms	Systematized delusions; paranoia; bizarre behavior	Depressed mood; anhedonia; lack of energy; sleep and appetite disturbances
Electroencephalogram	Diffuse slowing; low-voltage fast activity; specific patterns	Normal early; mild slowing later	Normal	Normal

*The characteristics listed are the usual ones and not exclusive.
†Patients with vascular dementia may have an abrupt decline in cognition.
‡Patients with dementia with diffuse cortical Lewy bodies often have a fluctuating mental status and hallucinations.
From Mendez MF, Padilla CR. Delirium. In: Daroff RB, Jankovic J, Mazziotta JC, et al., eds. *Bradley's Neurology in Clinical Practice*. 7th ed. Philadelphia: Elsevier; 2016:32; Table 4.2.

Impending central herniation from increased pressure on the caudal brainstem may be preceded by the **Cushing triad** of hypertension, bradycardia, and irregularities of respiration. Decerebrate or opisthotonic posturing should also be considered a sign of raised intracranial pressure in an unresponsive patient. A lateral rectus palsy (cranial nerve VI) may also be an early sign of intracranial hypertension.

Reversal of Immediately Treatable Toxic or Metabolic Causes

If the etiology for altered consciousness is not yet known, emphasis should shift to a systemic review of the reversible causes. Hypoglycemia and narcotic intoxication are 2 rapidly reversible causes of coma. Hypoglycemia is a medical emergency that must be reversed because sustained hypoglycemia may result in permanent neurologic damage. A blood glucose level should be obtained as soon as possible in an altered child. Once an intravenous catheter has been placed, all unresponsive children should receive dextrose unless a diagnosis other than hypoglycemia is apparent. In the absence of a central line, the percent dextrose solution used may vary; however, the absolute dose of glucose remains the same. If the child's mental status improves or if there is laboratory confirmation of hypoglycemia, the dextrose bolus should be followed by a continuous infusion of glucose and electrolytes to prevent rebound hypoglycemia.

Naloxone is also administered to children who have marked depression of consciousness without an obvious cause, particularly if hypoventilation is observed and opioid ingestion is suspected. Miosis is not a necessary finding because ingestion of multiple agents, including narcotics, may not result in small, constricted pupils. Large ingestions of narcotics may necessitate larger single doses of naloxone because of the competitive nature of its antagonistic effect, or they may necessitate multiple doses because its half-life is shorter than that of the narcotic ingested.

Another reversible cause of coma is a benzodiazepine ingestion. Flumazenil, a specific competitive antagonist of benzodiazepines, should only be given if benzodiazepine ingestion is suspected as administration of flumazenil to a patient who has ingested multiple agents may precipitate seizures.

When there are clinical signs or symptoms of meningitis or encephalitis, the child should be assessed for the presence of a bulging fontanel, nuchal rigidity, and Kernig or Brudzinski signs. Prior administration of antibiotics does not affect meningeal irritation. Most (85%) children with meningitis have an alteration in mental status (53% lethargic, 22% stuporous, 10% comatose). If meningitis is suspected, a lumbar puncture, including measurement of the opening pressure, should be performed unless the procedure is contraindicated (Table 31.15). If a contraindication exists, the child should be stabilized, receive empirical antimicrobial therapy, and undergo head CT imaging. The patient should undergo lumbar puncture as soon as it is no longer contraindicated. If a patient presents with sudden nuchal rigidity not preceded by a prodromal illness, a subarachnoid hemorrhage should be suspected and a CT scan performed before the lumbar puncture.

Level of Central Nervous System Function and Cause

The coma can be initially considered stable if (1) focal neurologic findings are not present, (2) there is no evidence of significant brainstem dysfunction, (3) intracranial pressure is not raised, (4) there is no evidence of head trauma or CNS infection, and (5) the child does not have a rapidly reversible toxic or metabolic cause. At this point a

TABLE 31.10 Mini-Mental Status Examination

Test	Maximum Score
Orientation	
1. What is the year? Season? Date? Day? Month?*	5
2. Where are we? State? County? City? Hospital? Floor?*	5
Registration	
3. Name 3 objects. Ask the patient to name the items.* Repeat the answers until the patient learns all 3.	3
Attention and Calculation	
4. Serial sevens (ask the patient to begin with 100 and count backwards by sevens, stopping after 5 subtractions: 93, 86, 79, 72, 65).* or Spell "word" backwards.*	5
Recall	
5. Ask the patient to name the 3 objects learned under "registration," above.*	3
Language	
6. Point to a pencil and watch, asking the patient to name both items.*	2
7. Have the patient repeat "No ifs, ands, or buts."	1
8. Have the patient follow a 3-stage command. For example, say "Take a paper in your right hand. Fold the paper in half. Put the paper on the floor."*	3
9. Have the patient read and obey the following sentence, written in large letters: "Close your eyes."	1
10. Have the patient write a sentence.†	1
11. Have the patient copy a picture of 2 intersecting pentagons.	1
Total	30

*Give 1 point for each correct answer.
†The sentence should make sense and contain a subject and object to earn the 1 point: spelling errors are ignored.
Modified from Anthony JC, LeResche L, Niaz U, et al. Limits of the "mini-mental state" as a screening test for dementia and delirium among hospital patients. *Psychol Med*. 1982;12:397-408; Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.

TABLE 31.11 Signs of Head Trauma Possibly Associated with Intracranial Disease

General	Signs of Basilar Skull Fracture
Lacerations	Hemotympanum
Hematomas	CSF rhinorrhea
Ecchymosis	CSF otorrhea
Swelling	"Raccoon eyes"
Palpable crepitations	Battle sign
Step-off of skull	

CSF, cerebrospinal fluid.

detailed physical examination and expanded laboratory evaluation can be undertaken to determine the level of CNS function and the cause of the coma.

Coma can be thought of as resulting from hemispheric or brainstem (including reticular activating formation) dysfunction. Dysfunction in either location may be produced by anatomic or nonstructural causes and a detailed physical examination may provide further clues to the cause of the coma (Table 31.16). The origin of coma (hemispheric vs brainstem) and its cause (metabolic vs structural) can be elucidated by evaluation of pupillary size and reactivity, eye movements, motor responses, and respiratory pattern.

Pupillary light reflexes are generally preserved in metabolic encephalopathy, whereas their absence strongly suggests a structural lesion. The only exception to the latter is drug effect, particularly with potent anticholinergic compounds, such as glutethimide, atropine, or scopolamine, which produce fixed and dilated pupils. The balance between sympathetic and parasympathetic stimulation, which result in pupillary dilation and constriction, normally determines pupillary size and reactivity. A **unilaterally dilated and fixed pupil** is a sign of uncal herniation with entrapment of the oculomotor nerve. Parasympathetic fibers innervating the eye accompany the oculomotor nerve. Sympathetic fibers originate from at least 4 hypothalamic nuclei so that diencephalic dysfunction results in small, reactive pupils. Hypothalamic damage often results in ipsilateral miosis associated with **Horner syndrome** (miosis, ptosis, and anhidrosis).

Injury to nuclei located in the midbrain disrupts both sympathetic and parasympathetic pathways, resulting in midsized, fixed pupils. Damage to the midbrain tectal regions also produces mid-position or slightly large, fixed pupils. In contrast to nuclear damage, however, accommodation may be intact, so that pupillary size fluctuates spontaneously. Pontine lesions, principally hemorrhage, interfere with descending sympathetic fibers, causing symmetrically small pupils for which a magnifying glass may be needed to detect a light reflex. Lateral medullary lesions may also produce Horner syndrome, whereas central herniation results in fixed, dilated pupils. Fig. 31.3 summarizes pupillary findings in comatose patients.

Evaluation of eye movements is helpful in differentiating hemispheric from brainstem causes of coma. Frontal regions of the cerebral hemispheres are responsible for voluntary eye movements, the quick phase of nystagmus, and control over brainstem reflexes that determine eye movements. Bilateral hemispheric depression may result in

TABLE 31.12 Neurologic Findings That Help to Localize Site of Structural Brain Disease by Location of Lesion

Neurologic Findings	
Bilateral hemispheric	Spontaneous eye movements (roving, dipping,* ping-pong, nystagmoid jerks) Upward or downward eye deviation Intact oculovestibular reflexes Intact pupillary and corneal reflexes Variable motor responses Adventitious limb movements (subtle manifestations of seizures, myoclonus, asterixis)
Brainstem displacement from a hemispheric mass	Anisocoria or unilateral fixed and dilated pupil (predominant lateral displacement) Midposition fixed pupils (predominant downward displacement) Extensor or flexor posturing Central hyperventilation (diencephalic)
Brainstem displacement from a cerebellar mass	Direction-changing or vertical nystagmus from the cerebellar lesion Ocular bobbing† Absent corneal reflexes with intact pupillary reflexes Extensor or flexor posturing Facial or abducens nerve palsy Skew deviation (vertical misalignment of eyes) Internuclear ophthalmoplegia
Intrinsic brainstem lesion	Vertical nystagmus or bobbing Miosis (with pontine lesions) Internuclear ophthalmoplegia Variable pupillary and corneal reflexes (can both be absent) Absent oculocephalic and oculovestibular responses Extensor or flexor posturing Ataxic breathing (pontomedullary damage)

*Slow eye movement down followed by rapid return up to the mid plane.
†Rapid eye movement up followed by slow return down to the mid plane.
From Edlow JA, Rabinstein A, Traub SJ, et al. Diagnosis of reversible causes of coma. *Lancet*. 2014;382:2064-2076.

roving eye movements if brainstem function is intact. Because stimulation of a frontal gaze center causes conjugate deviation of the eyes to the opposite side, tonic lateral deviation of the eyes implies a seizure emanating from the contralateral hemisphere. Eye deviation may also result from an ipsilateral hemispheric injury with unopposed stimulation from the undamaged hemisphere or from a contralateral pontine lesion. The degree of eye deviation is usually more dramatic with hemispheric damage than with brainstem damage.

If the patient's eyes are not moving, then reflex eye movements are tested by the oculocephalic and oculovestibular responses (Fig. 31.4). These maneuvers involve the same major neuronal pathways. Afferent fibers from the labyrinth, cerebellum, and cervical muscles reach the vestibular nuclei (cranial nerve VIII) in the medulla. Fibers from the vestibular nuclei then course to the ipsilateral abducens nuclei (cranial nerve VI). Fibers from the abducens nuclei then decussate in the midpons and ascend in the medial longitudinal fasciculus to reach the contralateral oculomotor nuclei (cranial nerve III). Positive reflexes indicate the absence of cortical input on an intact brainstem.

The oculocephalic reflex is elicited by rotating the child's head from side to side and observing the eye movements. If brainstem function is intact, the eyes deviate in a direction opposite to the head movement. Both left and right lateral rotation should be tested. This reflex should then be tested in a vertical plane by rapidly flexing and extending the neck. A positive response is upward gaze when the neck is flexed and downward deviation when the head is extended. Such maneuvers are contraindicated if cervical spine injury is suspected.

The oculovestibular reflex is tested by instilling ice water into the ear canal. The ear canal must be visualized to ensure that there is no obstruction and that the tympanic membrane is intact. The head is then placed at a 30-degree angle from the horizontal so that the semicircular canal is vertical, and up to 120 mL of ice water is then injected slowly into the external ear canal over a few minutes through an angiocatheter. After a minimum of 5 minutes, the other ear may be tested; this interval allows time for the oculovestibular system to re-equilibrate. A positive response in an awake patient is nystagmus with the slow component toward the irrigated ear and the fast component away from the stimulus. With bilateral hemispheric depression, the fast phase of nystagmus dissipates, and the eyes are tonically deviated toward the irrigated ear.

Both the oculocephalic and oculovestibular reflexes are absent in patients with low brainstem lesions because neurotransmission between the vestibular and abducens nuclei is interrupted. In patients with damage to the medial longitudinal fasciculus, the ipsilateral eye fails to adduct on irrigation of the contralateral ear canal. However, the

TABLE 31.13 Signs of Incipient Downward Herniation

	Central	Uncal
Arousal	Impaired early, before other signs	Impaired late, usually with other signs
Breathing	Sighs, yawns, sometimes Cheyne–Stokes respiration	No early change
Pupils	First, small reactive (hypothalamus); then 1 or both approach mid-position	Ipsilateral pupil dilates, followed by somatic 3rd nerve paralysis
Oculocephalic responses	Initially sluggish, later tonic conjugate	Unilateral 3rd nerve paralysis
Motor signs	Early hemiparesis opposite to hemispheric lesion followed late by ipsilateral motor paresis and extensor plantar response	Motor signs late, sometimes ipsilateral to lesion

From Plum F. Neurology/sustained impairments of consciousness. In: Wyngaarden JB, Smith LH, Bennett JC, eds. *Cecil Textbook of Medicine*. 19th ed. Philadelphia: WB Saunders; 1992:2050.

TABLE 31.14 Characteristics of Supratentorial Lesions Leading to Coma

Initiating symptoms usually cerebral-focal: aphasia; focal seizures; contralateral hemiparesis, sensory change, or neglect; frontal lobe behavioral changes; headache
Dysfunction moves rostral to caudal: e.g., focal motor → bilateral motor → altered level of arousal
Abnormal signs usually confined to a single or adjacent anatomic level (not diffuse)
Brainstem functions spared unless herniation develops

From Plum F. Neurology/sustained impairments of consciousness. In: Wyngaarden JB, Smith LH, Bennett JC, eds. *Cecil Textbook of Medicine*. 19th ed. Philadelphia: WB Saunders; 1992:2050.

TABLE 31.15 Contraindications to Lumbar Puncture

Clinically important cardiorespiratory compromise in a neonate or young infant
Signs of raised intracranial pressure (pupillary changes, ptosis, hypertension, bradycardia, posturing, cranial nerve VI palsy, retinal changes)
Skin or soft tissue infection overlying area where lumbar puncture is to be performed
Focal neurologic findings
Suspected brain abscess (illness duration longer than expected for meningitis; focality)

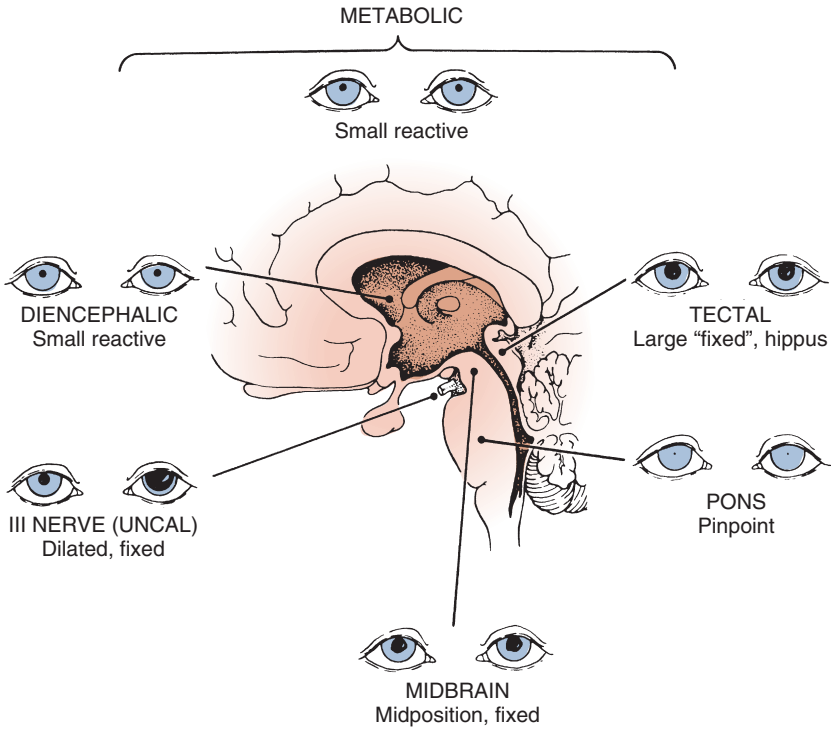

FIGURE 31.3 Pupils in comatose patients.

opposite eye abducts normally. For example, with a lesion in the left medial longitudinal fasciculus, the right eye abducts, but the left eye does not, in response to irrigating the right ear canal. This reaction is caused by disruption of fibers between the abducens and the contralateral oculomotor nuclei (see Fig. 31.4).

In addition to assessing ocular motility, the examiner should test the corneal reflex and determine the presence or absence of a blink. The absence of a blink in response to a loud noise or bright light implies dysfunction of the pontine reticular formation secondary to either metabolic or structural causes. Unilateral absence of a blink implies a facial nerve lesion. The afferent limb of the corneal reflex is carried by the trigeminal nerve (cranial nerve V). The normal effector response involves both upward deviation of the eye (oculomotor nerve) and closure of the eyelid (facial nerve). A normal reflex suggests that the integrity of pathways between the midbrain and the pons has not been violated.

Examination of the motor system includes observation of body position, spontaneous movements, and response to noxious stimuli (Fig. 31.5). A normal body position usually denotes an intact brainstem, as do spontaneous, nonposturing movements. Hemiparesis or hemiplegia implies a structural lesion in the contralateral hemisphere or subcortical region or an ipsilateral spinal cord injury. The presence of hypertonia or hyperreflexia suggests previous corticospinal tract disease or an acute brainstem injury at the midbrain-pontine level. It can also be observed in patients with severe metabolic derangements, such as hepatic coma, hypoglycemia, anoxia, and uremia. Hypotonia implies bilateral hemispheric dysfunction or a medullary or spinal cord lesion. In patients with severe depression of brain function, motor function can be assessed only after the application of a noxious stimulus, such as a sternal rub or increasing subungual pressure to the fingernails or toenails. Ascending sensory pathways to the cerebral hemispheres are intact, and descending motor pathways are

TABLE 31.16 Physical Examination and Diagnosis of Coma

System	Sign	Disorder
Skin	Dry	Dehydration, myxedema, adrenal insufficiency, anticholinergic poisoning
	Moist	Syncope
	Pigment	Addison disease, porphyria
	Nevi	Tuberous sclerosis with seizures
	Petechiae	Bacteremia, subacute bacterial endocarditis, idiopathic thrombocytopenic purpura
	Cyanosis	Hypoxia, congenital heart disease with cerebral embolism, methemoglobinemia
	Erythema	Carbon monoxide, atropine, or mercury intoxication
	Butterfly rash	Lupus erythematosus, tuberous sclerosis
	Desquamation	Vitamin A intoxication, scarlatina
	Jaundice	Hepatic disease, hemolytic anemia
	Nail changes	Splinter hemorrhage–endocarditis
		Mycotic infection and hypoparathyroidism
		Periungual fibroma (tuberous sclerosis)
Breath odor	Fruity	Diabetic ketoacidosis; amyl nitrate, alcohol, isopropyl alcohol poisoning
	Feculent	Hepatic encephalopathy
	Garlic	Selenium toxicity, arsenic poisoning, organophosphate poisoning
	Almonds	Cyanide poisoning
	Wintergreen	Methyl salicylate poisoning
	Ammoniacal	Uremia
	Acrid (pearl-like)	Paraldehyde, chloral hydrate poisoning
Scalp	Contusions	Trauma
	Vasodilation	Sagittal sinus thrombosis
Eyes	Chemosis	Cavernous sinus thrombosis
	Periorbital ecchymosis	Blow-out orbital fracture
	Subhyaloid hemorrhage	Subarachnoid hemorrhage
	Vasospasm (retina)	Hypertensive encephalopathy
Ears	Hemorrhage	Basilar skull fracture
	Otitis media	Brain abscess, lateral sinus thrombosis
Nose	Cerebrospinal fluid rhinorrhea	Basilar skull fracture
Mouth	Scarred tongue	Seizure disorder
	Pigmentation	Addison disease
	Lead lines	Plumbism (lead intoxication)
Neck	Rigid	Meningitis, pneumonia, subarachnoid hemorrhage, encephalitis
Thyroid	Enlarged	Myxedema, thyrotoxicosis
Heart	Murmur	Subacute endocarditis, brain abscess
Abdomen	Hepatomegaly	Leukemia, hepatic failure, heart failure
Extremities	Fracture	Trauma, fat embolism
	Ecchymosis	Trauma, hemorrhagic diathesis
	Osler nodes	Endocarditis

Modified from Tait VF, Dean JM, Hanley DF. Evaluation of the comatose child. In: Rogers MC, ed. *Textbook of Pediatric Intensive Care*. 2nd ed. Baltimore: Williams & Wilkins; 1992:741.

functioning to some degree if the response to a noxious stimulus includes verbalization or eye opening or a normal motor response, such as localization of the stimulus, withdrawal of the limb, or movement away from the stimulus.

Decorticate posturing implies hemispheric dysfunction with an intact brainstem; decerebrate posturing is more ominous (see Fig. 31.5). Opisthotonos with clenched teeth is a severe form of decerebration. This response usually suggests brainstem compression or a severe structural injury to the midbrain-pontine region. It can also occur in association with severe metabolic diseases, such as hepatic coma, anoxia, and hypoglycemia. Less commonly, decerebrate posture may represent delayed cortical demyelination after a hypoxic-ischemic injury. Pontomedullary or spinal cord damage is associated with a flaccid response to noxious stimulation.

A patient's breathing pattern is also helpful in localizing the area of CNS dysfunction. **Hyperventilation** can be observed not only in midbrain structural lesions but also in toxic-metabolic encephalopathies as a primary response to stimulation of the respiratory center (salicylate, theophylline, hepatic coma) or as a compensatory response to a metabolic acidosis. This pattern is also seen with raised intracranial hypertension, as may occur in a child with meningitis. **Hypoventilation** with a normal rhythm, particularly if associated with a symmetrically depressed motor examination, usually implies global CNS depression secondary to drug ingestion.

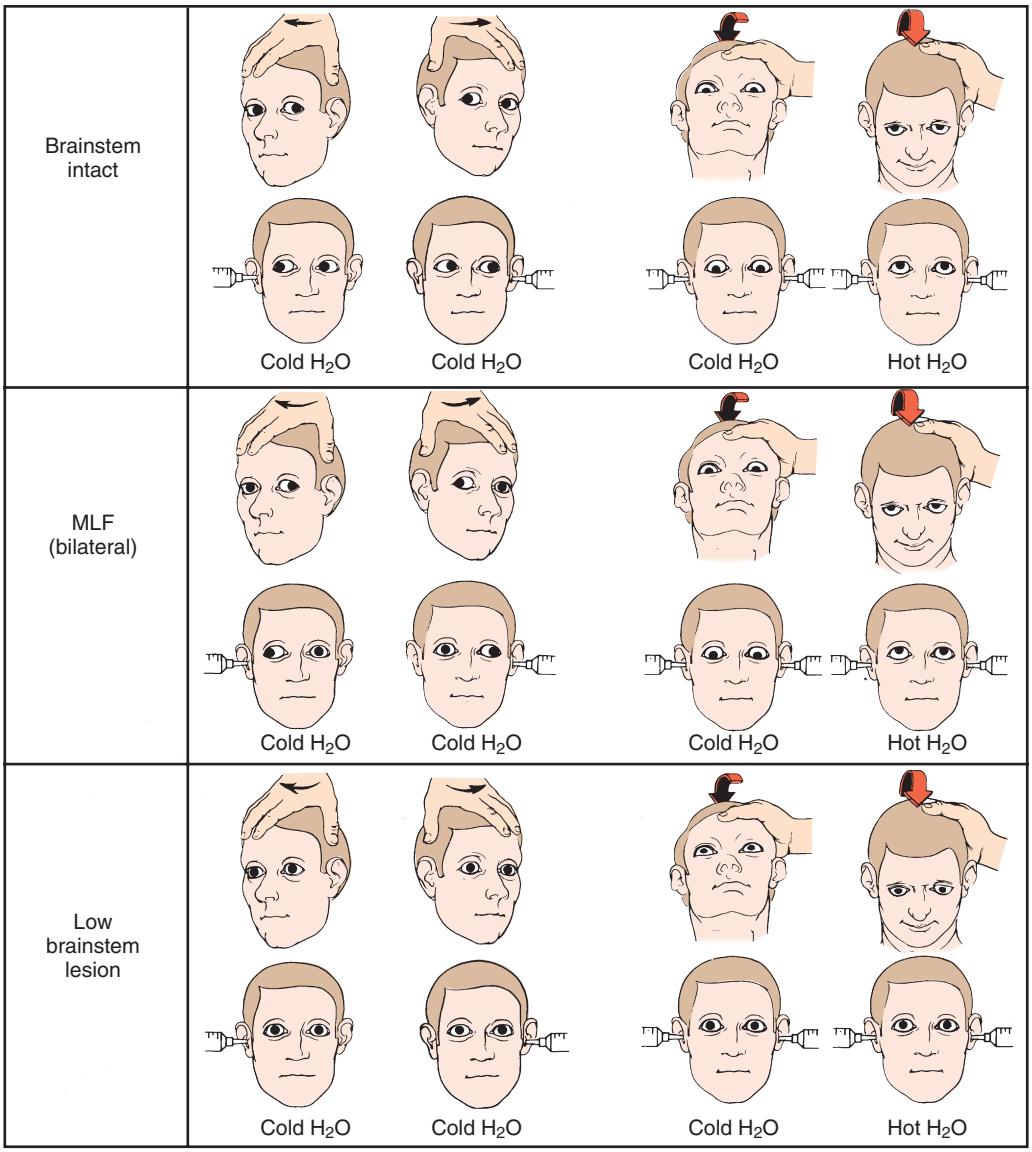

FIGURE 31.4 Ocular reflexes. MLF, medial longitudinal fasciculus.

Further laboratory assessment depends on clinical suspicions formulated from the detailed neurologic exam described earlier (Table 31.17). Patients with suspected anatomic causes of coma should undergo emergency head CT imaging, whereas those with a suspected CNS infection should undergo lumbar puncture. Other studies to consider are electrocardiography to rule out conduction abnormalities, seen with many drugs; liver function studies including coagulation factors; blood ammonia determination; measurement of calcium, magnesium, and phosphorus; and serum osmolality measurement. An osmolal gap, as well as an anion gap should be calculated. The osmolal gap is the difference between the measured and calculated serum osmolality (normal is <5-10 mOsm/kg H_2O). Table 31.18 summarizes the differential diagnoses of an elevated anion or osmolal gap. Toxicology screens may be of value with suspected ingestions; however, the results must be interpreted cautiously. Because toxicology screens are not standardized, a "negative" result does not rule out an undetermined ingestion. Screening for certain agents, such as methanol and ethylene glycol, needs to be requested specifically, whereas tests for other compounds may yield false-negative results. Patients with a history of constitutional symptoms such as headache, emesis, or upper respiratory illness that proceed to have psychiatric symptoms, language disintegration, and catatonia should be evaluated for anti-NMDA (*N*-methyl D-aspartate) receptor encephalitis with a lumbar puncture, brain imaging and antibody testing.

If physical examination and laboratory studies do not yield a diagnosis, a head CT scan should be obtained to rule out anatomic or vascular causes. Further diagnostic evaluation with magnetic resonance imaging (MRI) may be necessary to evaluate parenchymal abnormalities. Imaging may reveal subtle signs of edema, ischemia, or demyelination before these signs are visible on CT scan. Large tumefactive T2 lesions of similar age with variable enhancement in either the brain or spine, with MRI scanning, are consistent with acute disseminated encephalomyelitis (ADEM), an inflammatory demyelinating condition that can present with fever, headache, vomiting, meningeal signs, and seizures resulting in encephalopathy. Neuromyelitis optica (NMO) can occasionally present with encephalopathy similar to that

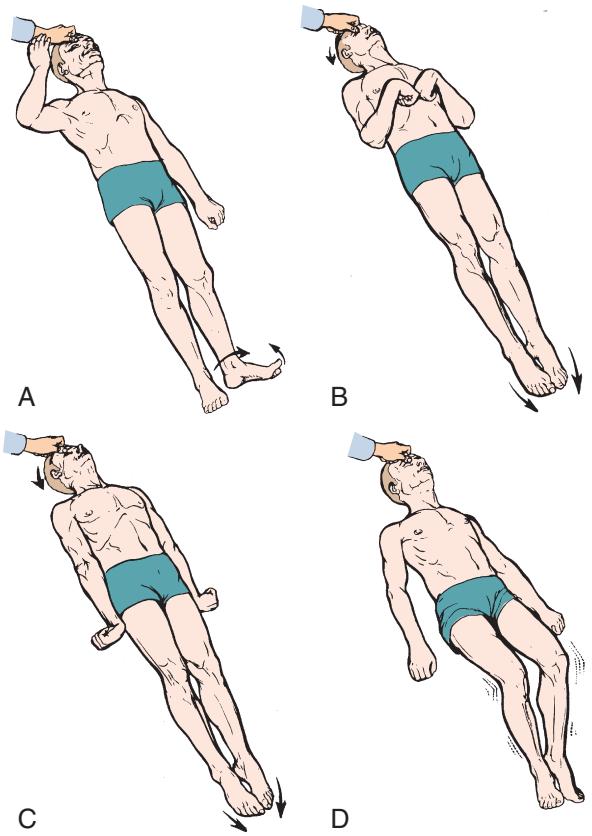

FIGURE 31.5 Motor response to noxious stimuli.

TABLE 31.17 Laboratory Evaluation of Metabolic Brain Disease

Test	Reason for Test
Immediate	
Glucose	Hypoglycemia, hyperosmolar coma
Na^+	Osmolar abnormalities
Ca^{2+}	Hypercalcemia or hypocalcemia
BUN	Uremia
Arterial blood pH, P_{CO_2}, P_{O_2}, oxygen saturation	Acidosis, alkalosis, hypoxia, CO, or methemoglobin
Lumbar puncture	Infection, hemorrhage, meningeal carcinomatosis
Later	
Liver function tests, ammonia level	Hepatic coma, Reye syndrome, urea cycle defect
Drug levels	Overdose
Blood and CSF culture	Sepsis, encephalitis, meningitis
Full electrolytes	Electrolyte imbalance including Mg^{2+}
Coagulation profile	Intravascular coagulation
EEG	Seizure disorder

BUN, blood urea nitrogen; CO, carbon monoxide; CSF, cerebrospinal fluid; EEG, electroencephalography; P_{CO_2}, partial pressure of carbon dioxide; P_{O_2}, partial pressure of oxygen.
Modified from Plum F. Neurology/sustained impairments of consciousness. In: Wyngaarden JB, Smith LH, Bennett JC, eds. *Cecil Textbook of Medicine*. 19th ed. Philadelphia: WB Saunders; 1992:2053.

TABLE 31.18 Toxins and Disease States Causing Elevated Anion and/or Osmolal Gaps

Anion Gap	Osmolal Gap
Ethanol	Ethanol
Ethylene glycol	Ethylene glycol
Methanol	Methanol
Toluene	Acetone
Iron	Propylene glycol
Isoniazid	Ethyl ether
Salicylates	Isopropyl alcohol
Paraldehyde	Mannitol
Strychnine	Trichloromethane
Renal failure	Renal failure
Diabetic ketoacidosis	Diabetic ketoacidosis
Lactic acidosis	

seen in ADEM, although it more commonly presents with optic neuritis, transverse myelitis, or focal brainstem findings. Brain imaging in a patient with NMO will typically have less defined hemispheric lesions.

If MRI results are normal, the most likely causes of coma are intoxication, psychologic factors, or related to seizure. An electroencephalogram is indicated if encephalitis, encephalopathy, or seizure disorder is suspected.

TOXIC ENCEPHALOPATHY

Toxic compounds are common causes of altered consciousness in children. More than 90% of poisonings in young children are accidental and involve a single substance. Many are prescription medications. Children in certain age groups are statistically at greater risk of being poisoned; 44% and 59% of all cases of poisonings reported to Poison Control Centers occur in children younger than 3 and 6 years of age, respectively. Of these ingestions, opioids, sedative-hypnotic, and cardiovascular medication ingestions are the most common. Intentional ingestions are far more common in adolescents. The clinician's index of suspicion should be dependent not only on the age of the patient but also on the history of the present illness; a poisoning should be suspected in a previously healthy child who presents with a sudden onset of unexplained symptoms (seizures, mental status changes, vomiting, hematemesis) or a gradual onset of symptoms preceded by a period of confusion or delirium. A correct diagnosis is usually established by integrating information from the history, physical examination, and ancillary tests and then identifying a toxidrome, a symptom complex associated with a given class of ingested drug. The most important aspects of the physical examination to identify a toxidrome are the level of consciousness, the pupillary examination, and the vital signs.

Level of Consciousness

Table 31.19 lists common agents responsible for different changes in mental status. Toxic exposures may also occur via routes other than the oral route; organophosphates may be absorbed through the skin, whereas other compounds, such as carbon monoxide, are inhaled.

Pupillary Examination

When the pupils are evaluated for size and reactivity, the presence of nystagmus should also be noted (Table 31.20). Most drugs cause

TABLE 31.19 Changes in Level of Consciousness Observed with Specific Drug Intoxications

Coma	Agitation	Confusions and/or Hallucinations	Seizures
Anticholinergics	Sympathomimetics	Anticholinergics	Cocaine
Antihistamines	Methylxanthines	Psychotropics	Amphetamines
Cholinergic agents	Phencyclidine	Lysergic acid diethylamide	Methylxanthines
Sedative-hypnotics	Salicylates	Mescaline	Tricyclic antidepressants
Alcohols	Alcohol	Marijuana	Cholinergic agents
Narcotics		Antihistamines	Neuroleptics
Neuroleptics			Salicylates
Tricyclic antidepressants			Camphor
Phencyclidine			Isoniazid
Salicylates			Phenytoin
Heavy metals			Antihistamines
Hypoxia			
Carbon monoxide			
Cyanide			

TABLE 31.20 Effect of Drugs on Pupillary Findings

Dilated	Constricted	Nystagmus
Sympathomimetics	Narcotics	Barbiturates
Anticholinergics	Phenothiazines	Alcohol
Cocaine	Cholinergic agents	Phenytoin
Tricyclic antidepressants	Benzodiazepines	Carbamazepine
Glutethimide	PCP	PCP
LSD	Clonidine	Glutehimide

LSD, lysergic acid diethylamide; PCP, phenylcyclohexyl piperidine (phencyclidine HCl).

TABLE 31.21 Compounds and Conditions Inducing Hyperthermia

Muscular Hyperactivity or Rigidity
- Amoxapine
- Amphetamines
- Cocaine
- Ethanol or sedative-hypnotic withdrawal
- Lithium
- LSD
- MAO inhibitors
- Phencyclidine
- Tricyclic antidepressants

Increased Metabolic Rate
- Dinitrophenol
- Pentachlorophenol
- Salicylates
- Thyroid hormone

Impaired Heat Dissipation or Thermoregulation
- Anticholinergic agents
- Antihistamines
- Antipsychotic agents
- Tricyclic antidepressants

Other/Unknown Mechanisms
- Metal fume fever

LSD, lysergic acid diethylamide; MAO, monoamine oxidase.
Modified from Olson KR, Pentel PR, Kelley MT. Physical assessment and differential diagnosis of the poisoned patient. *Med Toxicol.* 1987;2:40. Permission granted by AIDS International, Inc.

horizontal nystagmus; however, phenytoin may produce upbeat nystagmus, whereas phencyclidine may cause rotary nystagmus.

Vital Signs

Although fever is typically indicative of infection or a metabolic disturbance, such as the hemorrhagic shock and encephalopathy syndrome, many toxic compounds may induce **hyperthermia** (Table 31.21). The most common causes of fever in intoxicated children include anticholinergic compounds, antihistamines, salicylates, and sympathomimetic agents. **Hypothermia** may also be a sign of drug exposure (Table 31.22). Sedative-hypnotic agents, including ethanol, are common causes of hypothermia.

Bradycardia or **tachycardia** may result directly from the autonomic effect of a drug or may be a reflex response to a change in blood pressure. Intoxication with a β blocker, calcium channel blocker, α_2-adrenergic agonist (clonidine), or cholinergic agonist (organophosphate) characteristically manifests with bradycardia with or without hypertension. In mild clonidine ingestions or in the early stage of clonidine intoxication, the patient may be hypertensive as a result of the partial α_1-agonist effect of the drug. Bradycardia may be a reflex response to the precipitation of hypertension by a vasoconstrictor agent, such as an ergotamine or an α-adrenergic agonist, such as phenylpropanolamine. On the other hand, a β-adrenergic agonist or anticholinergic agent intoxication usually manifests with tachycardia as part of the symptom complex. Intoxication with drugs that possess both α- and β-adrenergic agonist properties may manifest with both tachycardia and hypertension, whereas several classes of compounds may cause hypotension with a reflex tachycardia. Examples of the latter include direct vasodilators or α-adrenergic blockers (hydralazine, phenothiazines, tricyclic antidepressants) and compounds that cause 3rd-space fluid losses (acute iron intoxication). The anticholinergic properties of the phenothiazines and tricyclic antidepressants contribute to the tachycardia seen with these agents. Cholinergic compounds, such as organophosphates and carbamates, may cause tachycardia

TABLE 31.22 Compounds and Conditions Inducing Hypothermia

Ethanol
Sedative-hypnotic agents (e.g., barbiturates, benzodiazepines)
Hypoglycemia
Isopropyl alcohol
Narcotics
Phenothiazines
Tricyclic antidepressants

Adapted from Olson KR, Pentel PR, Kelley MT. Physical assessment and differential diagnosis of the poisoned patient. *Med Toxicol.* 1987;2:41. Permission granted by AIDS International, Inc.

TABLE 31.23 Skin Manifestations of Intoxication

Manifestation	Toxin/Condition
Bullous lesions	Barbiturates, carbon monoxide, sedative-hypnotics, opioids
Diaphoresis	Cholinergic agents (organophosphates), sympathomimetics, mercury, arsenic, salicylates
Dry skin (and mucous membranes)	Anticholinergics, antihistamines, narcotics
Diffuse erythema	Anticholinergics, carbon monoxide, cyanide, boric acid, mercury
Cyanosis	Hypoxia, methemoglobinemia, ergotamines
Needle tracks	Opiates, phencyclidine, amphetamine
Jaundice	Acetaminophen

instead of bradycardia because acetylcholine is the neurotransmitter found at nicotinic receptors in the sympathetic chain ganglion.

Tachypnea or hyperpnea may result from a central effect of a drug (salicylates, methylxanthines) or from a metabolic acidosis (salicylates, alcohols) in addition to structural CNS lesions or cardiopulmonary compromise. Slow or shallow breathing should always raise the suspicion of drug ingestion, particularly with CNS depressants, such as narcotics and sedative-hypnotics. Hypoventilation may also be a presenting symptom of a clonidine overdose as a result of its opiate-like effects. In addition, organophosphate or carbamate intoxications may manifest with hypoventilation as a primary symptom as a result of weakness of respiratory muscles.

Odors emanating from the breath or clothing may offer invaluable clues as to the diagnosis. Not only do certain metabolic diseases, such as diabetic ketoacidosis and hepatic failure, produce characteristic breath odors but so also do a number of chemical compounds, including cyanide (bitter almonds); isopropyl alcohol, methanol, salicylate (acetone); methyl salicylate (wintergreen); arsenic, thallium, organophosphates (garlic); and turpentine (violets). Inspection of the skin and mucous membranes may also be helpful (Table 31.23).

Although a single sign or symptom may be attributable to many classes of drugs, combinations of symptoms (toxidrome) enable the clinician to narrow down the number of possible agents. Sympathomimetic agents, anticholinergics, and tricyclic antidepressants all cause mydriasis and tachycardia. If these symptoms occur in a patient with a prolonged QRS interval on an electrocardiogram, the most likely cause is a tricyclic compound, whereas if the former symptoms occur in a diaphoretic, tremulous patient, a sympathomimetic agent would be suspected. Table 31.24 outlines toxidromes of common classes of compounds ingested by children.

Management of most ingestions includes prevention of further absorption and supportive therapy. Activated charcoal is the preferred method for decreasing absorption of stomach contents. Gastric decontamination should be withheld if a nontoxic substance is ingested, if a nontoxic quantity of a toxic compound is ingested, if absorption is complete, or if a caustic agent is ingested. Under these circumstances, gastric decontamination carries risks but no benefits. Induction of emesis is contraindicated in patients with a depressed mental status or who are at risk for a sudden deterioration of their mental status.

Very few specific antidotes exist for substances that are ingested. If an antidote exists, its use depends on the patient's prognosis if it were not administered. For example, not all children require treatment with *N*-acetylcysteine after acetaminophen poisoning. If the patient is asymptomatic and has a serum acetaminophen concentration in a nontoxic range when plotted on the Rumack-Matthew nomogram, *N*-acetylcysteine therapy is not indicated. Table 31.25 is a partial list of available antidotes. Although not a true antidote, sodium bicarbonate is included as an antidote for salicylate and tricyclic antidepressant ingestions because its use can reduce symptoms by reducing tissue distribution of these compounds.

Some drugs lend themselves to procedures aimed at enhancing drug elimination from the body. These procedures include changing urinary pH (alkalinization to enhance salicylate excretion), using multiple doses of charcoal (theophylline, phenobarbital, carbamazepine), and performing extracorporeal drug removal (peritoneal or hemodialysis, charcoal hemoperfusion, exchange transfusion). Either patient-related or drug-related criteria should be met before the institution of extracorporeal drug removal (Table 31.26). When the management approach is not known, a resource such as a poison control center or a clinical pharmacologist should be consulted.

TRAUMA

Infants with head trauma may have evidence of intracranial hypertension: bulging fontanel, decerebrate posturing, and tachypnea. The clinical picture in a young infant may be confused with meningitis. In the absence of a febrile illness, trauma should be suspected, and the patient should be treated as if there is a rapidly progressive intracranial process.

Abusive head trauma, formerly referred to as shaken baby syndrome or nonaccidental trauma, describes a collection of abusive mechanisms that can result in pediatric neurotrauma. The 1st 2 years of life present a high risk period with an estimated incidence of 16-33 cases/100,000 children affected. Injury occurs by many different mechanisms including blunt force, acceleration/deceleration, penetrating trauma, or asphyxiation. Presenting symptoms can include lethargy (77%), respiratory depression or seizure (43-50%), developmental delay (12%), or nonspecific findings such as irritability, decreased oral intake, and vomiting (15%). The key to diagnosis is to maintain a high index of suspicion. In suspected cases of abusive trauma, utilizing a multidisciplinary care team including the primary physician, a child advocacy specialist, appropriate surgical providers (e.g., ophthalmology, neurosurgery, or orthopedic surgery) and social work can assist in making the correct diagnosis and treatment.

METABOLIC DISORDERS

Inborn errors of metabolism are complex and encompass many conditions. Table 31.27 is a partial list of inborn errors of metabolism that

(See *Nelson Textbook of Pediatrics,* p. 634.)

TABLE 31.24 Toxidromes of Common Classes of Drug

Drug Class	Level of Consciousness	Pupils	Vital Signs	Other
Sympathomimetics (amphetamines, cocaine, ephedrine, methylphenidate [Ritalin])	Agitation; psychosis	Dilated	↑ HR; ↑ BP; ↑ T	Tremors, sweating, arrhythmias; seizures
Anticholinergics (antihistamines, scopolamine, atropine, jimson weed, nightshade, phenothiazines, tricyclics)	Confusion; hallucinations	Dilated	↑ HR; ↑ T; ±↑ BP	Flushed; dry skin and mucous membranes; urinary retention; decreased bowel sounds
Opiates	Euphoria; coma	Pinpoint	↓ RR; ±↓ HR; ±↓ BP	Shallow respirations; dry mucous membranes
Cholinergic syndrome (organophosphates; carbamates, bethanechol, *Amanita* mushrooms)	Coma	Miosis	↓ or ↑ HR; ↓ or ↑ BP	Salivation, lacrimation, urination, defecation, bronchorrhea; muscle twitching before flaccidity; seizures
Sedative-hypnotics (alcohol, barbiturates, benzodiazepines)	Coma	± Miosis	↓ RR (shallow); hypothermia; ↓ BP	Ataxia; nystagmus; slurred speech
Neuroleptics (phenothiazines, butyrophenones)	Coma	Miosis (except thioridazine [Mellaril])	↑ HR; ↓ BP; ↓ or ↑ T	Dystonic reactions; ataxia; neuroleptic malignant syndrome; prolonged Q-T interval
Tricyclic antidepressants	Confusion; agitation; coma	Dilated	↑ HR; ↓ or ↓ BP; ↑ T; ↓ RR	Quinidine-like effect: prolonged QRS or Q-T interval and ventricular arrhythmias; seizures; anticholinergic effects (see above)
Salicylates	Disorientation; hyperexcitability; coma (severe)	—	↑ T; ↓ or ↑ RR + depth	Vomiting; tinnitus; metabolic acidosis; hypokalemia
Carbon monoxide	Lethargy; coma	—	—	Headache, nausea, flulike syndrome, dizziness, blurred vision
Theophylline	Agitation	—	↑ HR; ↓ BP; ±↑ RR; ± ↑ T	Protracted vomiting; tremors, seizures, arrhythmias
Phencyclidine	Delirium; combativeness; catatonia; coma	Miosis	—	Rotary nystagmus; seizures
SSRIs	Drowsiness; agitation; delirium; coma	Dilated or unreactive	↑ HR, ↑ T, ↓ BP	Nausea, vomiting, tremor, rigidity, myoclonus, hyperreflexia, diaphoresis

BP, blood pressure; HR, heart rate; RR, respiratory rate; SSRI, selective serotonin reuptake inhibitor; T, temperature.

TABLE 31.25 Specific Toxins and Their Antidotes

Toxin	Antidote
Acetaminophen	N-Acetylcysteine
Anticholinergics	Physostigmine
Arsenic	Dimercaprol
Benzodiazepines	Flumazenil
β-Blockers	Glucagon*
Calcium channel blockers†	Calcium
Carbamate insecticides	Atropine
Carbon monoxide	Oxygen
Cyanide	Amyl nitrite or sodium nitrate plus sodium thiosulfate
Digitalis	Digoxin-specific antibody fragments
Ethylene glycol	Ethanol or fomepizole
Heparin	Protamine
Iron	Deferoxamine
Lead	EDTA; dimercaprol; dimercaptosuccinic acid; penicillamine
Mercury	Dimercaprol
Methanol	Ethanol or fomepizole
Narcotics	Naloxone
Nitrites	Methylene blue
Organophosphates	Atropine; pralidoxime
Phenothiazines‡	Diphenhydramine or benztropine
Salicylates	Sodium bicarbonate
Tricyclic antidepressants	Sodium bicarbonate
Warfarin	Vitamin K

*May reverse cardiac toxicity.
†Usually requires saline infusion as well for bradyarrhythmias or conduction abnormalities.
‡Dystonic reactions only.
EDTA, ethylenediaminetetraacetic acid.

TABLE 31.26 Indications for Extracorporeal Drug Removal*

Patient Related

Severe intoxication refractory to medical management (e.g., refractory seizures)

Impairment of normal excretion routes that may lead to prolonged intoxication

Drug Related

Ingestion and probable absorption of a potentially lethal dose determined after gut decontamination

Documentation of a potentially lethal drug level

Presence of a significant quantity of a compound that is metabolized to a toxic metabolite (e.g., methanol)

*Patient- and drug-related criteria for extracorporeal drug removal. Only 1 criterion needs to be met.

TABLE 31.27 Inborn Errors of Metabolism Manifesting with Seizures, Lethargy, and Coma in the Neonatal Period

Disorders of Carbohydrate Metabolism	Disorders of Amino Acid Metabolism	Organic Acidemias	Urea Cycle Defects	Lysosomal Storage Disorders	Other
Fructose-1,6-biphosphatase deficiency	Maple syrup urine disease	Methylmalonic acidemia	Carbamyl phosphate synthetase deficiency	Farber disease	Congenital adrenal hyperplasia
Galactosemia	Hypervalinemia	Propionic acidemia (ketotic hyperglycinemia)	Ornithine transcarbamylase deficiency	Fucosidosis	Hypophosphatasia
Hereditary fructose intolerance	Periodic hyperlysinemia	Isovaleric acidemia	Citrullinemia		Menkes kinky hair syndrome
Glycogen storage disease, types I and II	Hyper-β-alaninemia	3-Methylcrotonyl CoA carboxylase deficiency	Argininosuccinic aciduria		Hereditary orotic aciduria
Pyruvate carboxylase deficiency	Nonketotic hyperglycinemia	Multiple carboxylase deficiency			Fatty acyl-CoA dehydrogenase deficiencies
Phosphoenolpyruvate carboxykinase deficiency	Pyroglutamic aciduria	Multiple acyl-CoA dehydrogenase deficiencies			Primary systemic carnitine deficiency
	Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH)	Hydroxymethylglutaryl (HMG)–CoA lyase deficiency			Zellweger syndrome
		2-Methyl-3-hydroxybutyric acidemia			Neonatal adrenoleukodystrophy
		D-Glyceric acidemia			

CoA, coenzyme A.

Modified from Burton BK. Inborn errors of metabolism: the clinical diagnosis in early infancy. *Pediatrics*.1987;79:359.

TABLE 31.28 Clinical Manifestations of Inborn Errors of Metabolism in the Neonatal Period

Lethargy

Coma

Seizures

Increased or decreased muscle tone

Poor suck and feeding

Vomiting

Diarrhea

Tachypnea and/or hyperpnea

Respiratory failure

Jaundice

Unusual odors

Cardiomegaly

Hepatomegaly

may manifest in the neonate with lethargy, seizures, and coma. Many of these conditions relate to defective enzymes that lead to accumulation of a toxic product. Newborn screening has increased the number of infants diagnosed and effectively treated during the asymptomatic phase of a disease. The clinical manifestations of metabolic disease in the neonate can be nonspecific (Table 31.28). The infants are often thought to have sepsis and are evaluated and treated for presumptive infection. The presence of a documented infection does not preclude metabolic disease because some of these infants are prone to infection (e.g., galactosemia and *Escherichia coli* sepsis). A family history of a previous infant dying from an unexplained illness or other children in the family with neurologic disorders may provide clues to a metabolic cause. Laboratory abnormalities that may be seen in metabolic disease are listed in Table 31.29.

Infants with urea cycle defects often manifest altered mental status, coma (recurrent), and emesis. They cannot metabolize waste nitrogen to urea; this leads to accumulation of ammonia in the blood. These disorders are inherited as autosomal recessive traits, except for ornithine transcarbamylase deficiency, which is X-linked. The keys to the diagnosis of inborn errors of metabolism in the neonate are a high

TABLE 31.29 Laboratory Evidence of Metabolic Disease

Acidosis,* alkalosis
Hypoglycemia
Hyperammonemia
Elevated liver enzyme levels
Direct hyperbilirubinemia
Urine-reducing substance
Urine ketones

*High anion gap if increased organic acids (ketoacids, lactic acid) are produced. Normal anion gap if associated renal tubular acidosis (type I glycogen storage disease, galactosemia) is present.

TABLE 31.30 Laboratory Evaluation of Suspected Metabolic Disease

Plasma ammonia
Arterial blood gas
Plasma amino acids
Plasma carnitine
Plasma pyruvate and lactate
Urinary amino acids
Urinary organic acids and arylcarnitine profile

TABLE 31.31 Characteristics of Metabolic Encephalopathy

Confusion, lethargy, delirium often precede or replace coma
Motor signs, if present, usually symmetric
Bilateral asterixis, myoclonus appear
Pupillary reactions usually preserved; tonic calorics often present
Sensory abnormalities usually absent
Hypothermia common
Abnormal signs reflect incomplete brain dysfunction at multiple anatomic levels

From Plum F. Neurology/sustained impairments of consciousness. In: Wyngaarden JB, Smith LH, Bennet JC, eds. *Cecil Textbook of Medicine*. 19th ed. Philadelphia: WB Saunders; 1992:2052.

degree of suspicion, the appropriate screening studies (see Table 31.29), and if the results are positive, a more detailed laboratory evaluation under the guidance of a specialist in metabolic diseases (Table 31.30).

Metabolic encephalopathy resulting from inborn errors of metabolism (partial, incomplete, stress, or fasting exacerbated) or from renal, hepatic, or toxic causes may also manifest in older children or adolescents. There may or may not be a family history or personal history of recurrent lethargy, emesis, repeated hospitalizations, or personality changes. Encephalopathy in older patients that results from endogenous substances (ammonia, organic acids, hypoglycemia, urea) or exogenous substances (opiates, barbiturates) may manifest within a wide range of symptoms (Table 31.31) and an electroencephalograph may be of added value.

SUMMARY AND RED FLAGS

Delirium and coma are common and potentially serious manifestations of a diverse group of life-threatening but potentially reversible disorders. Common causes vary by age, but toxic ingestion, trauma, seizures (postictal), infections, and metabolic disturbances, including inborn errors of metabolism, must be considered. Red flags include family or personal histories compatible with these disorders, signs of increased intracranial pressure, and rapidly progressive rostral-caudal deterioration.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Coma Scales

Akavipat P. Endorsement of the FOUR score for consciousness assessment in neurosurgical patients. *Neurol Med Chir (Tokyo)*. 2009;49:565-571.

Durham SR, Clancy RR, Leuthardt E, et al. CHOP infant coma scale ("infant face scale"): a novel coma scale for children less than two years of age. *J Neurotrauma*. 2000;17:729-737.

Fenichel GM. Altered states of consciousness. In: Fenichel GM, ed. *Clinical Pediatric Neurology: A Signs and Symptoms Approach*. 4th ed. Philadelphia: WB Saunders; 2001:47.

Kevric J, Jelinek GA, Knott J, et al. Validation of the full outline of unresponsiveness (FOUR) scale for conscious state in the emergency department: comparison against the Glasgow coma scale. *Emerg Med J*. 2011;28:486-490.

Kochar GS, Gulat S, Lodha R, et al. Full outline of unresponsiveness score versus Glasgow coma scale in children with nontraumatic impairment of consciousness. *J Child Neurol*. 2014;29:1299-1304.

Lieh-Lai MW, Theodorou AA, Sarnaik AP, et al. Limitations of the Glasgow coma scale in predicting outcome in children with traumatic brain injury. *J Pediatr*. 1992;120:195.

Simpson D, Reilly P. Pediatric coma scale. *Lancet*. 1982;2:450.

Stead LG, Wijdicks EF, Bhagra A, et al. Validation of a new coma scale, the FOUR score, in the emergency department. *Neurocrit Care*. 2009;10:50-54.

Tatman A, Warren A, Williams A, et al. Development of a modified paediatric coma scale in intensive care clinical practice. *Arch Dis Child*. 1997;77:519-521.

Wang MY, Griffith P, Sterling J, et al. A prospective population-based study of pediatric trauma patients with mild alterations in consciousness (Glasgow coma scale score of 13-14). *Neurosurgery*. 2000;46:1093-1099.

Wijdicks E, Bamlet WR, Maramattom BV, et al. Validation of a new coma scale: the FOUR Score. *Ann Neurol*. 2005;58:585-593.

Diagnosis and Management of Coma

Dalmau J, Lancaster E, Martinez-Hernandez E, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol*. 2011;10:63-74.

Edlow JA, Rabinstein A, Traub SJ, et al. Diagnosis of reversible causes of coma. *Lancet*. 2014;384:2064-2076.

Graham CA. Management of unexplained coma in children. *Eur J Emerg Med*. 2000;7:241-244.

Kirkham FJ. Non-traumatic coma in children. *Arch Dis Child*. 2001;85:303-312.

Liao YJ, So YT. An approach to critically ill patients in coma. *West J Med*. 2002;176:184-187.

Ness JN. Neuromyelitis optica and acute disseminated encephalomyelitis. In: Kliegman R, Stanton B, St. Geme J, Schor NF, et al., eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:2922-2925.

Wong CP, Forsyth RJ, Kelly TP, et al. Incidence, etiology, and outcome of non-traumatic coma: a population based study. *Arch Dis Child*. 2001;84:193-199.

Prognosis

Cheliout-Heraut F, Rubinsztajn R, Ioos C, et al. Prognostic value of evoked potentials and sleep recordings in the prolonged comatose state of children. Preliminary data. *Neurophysiol Clin*. 2001;31:283-292.

Christophe C, Fonteyne C, Ziereisen F, et al. Value of MR imaging of the brain in children with hypoxic coma. *AJNR Am J Neuroradiol*. 2002;23:716-723.

Forsyth RJ, Wong CP, Kelly TP, et al. Cognitive and adaptive outcomes and age at insult effects after non-traumatic coma. *Arch Dis Child*. 2001;84:200-204.

Mandel R, Martinot A, Delepoulle F, et al. Prediction of outcome after hypoxic-ischemic encephalopathy: a prospective clinical and electrophysiologic study. *J Pediatr*. 2002;141:45-50.

Robinson LR, Micklesen PJ, Tirschwell DL, et al. Predictive value of somatosensory evoked potentials for awakening from coma. *Crit Care Med*. 2003;31:960-967.

Wohlrab G, Boltshauser E, Schmitt B. Neurological outcome in comatose children with bilateral loss of cortical somatosensory evoked potentials. *Neuropediatrics*. 2001;32:271-274.

Toxicology

Abbruzzi G, Stork CM. Pediatric toxicologic concerns. *Emerg Med Clin North Am*. 2002;20:223-247.

Bryant S, Singer J. Management of toxic exposure in children. *Emerg Med Clin North Am*. 2003;21:101-119.

Hoffman RJ, Nelson L. Rational use of toxicology testing in children. *Curr Opin Pediatr*. 2001;13:183-188.

Jones A. Recent advances in the management of poisoning. *Ther Drug Monit*. 2002;24:150-155.

Liebelt EL, DeAngelis CD. Evolving trends and treatment advances in pediatric poisoning. *JAMA*. 1999;282:1113-1115.

McGuigan ME. Poisoning potpourri. *Pediatr Rev*. 2001;22:295-302.

Mokhlesi B, Leiken JB, Murray P, et al. Adult toxicology in critical care: part I: general approach to the intoxicated patient. *Chest*. 2003;123:577-592.

Powers KS. Diagnosis and management of common toxic ingestions and inhalations. *Pediatr Ann*. 2000;29:330-342.

Trauma

American Academy of Pediatrics. Committee on Child Abuse and Neglect: Shaken baby syndrome: Rotational cranial injuries—technical report. *Pediatrics*. 2001;108:206-210.

Duhaime AC, Christian CW, Rorke LB, et al. Nonaccidental head injury in infants—the "shaken-baby syndrome. *N Engl J Med*. 1998;338:1822-1829.

Gedeit R. Head injury. *Pediatr Rev*. 2001;22:118-124.

Hackbarth RM, Rzeszutko KM, Sturm G, et al. Survival and functional outcome in pediatric traumatic brain injury: a retrospective review and analysis of predictive factors. *Crit Care Med*. 2002;30:1630-1635.

Narang S, Clarke J. Abusive head trauma: past, present and future. *J Child Neurol*. 2014;29:1747-1756.

Ng SM, Toh EM, Sherrington CA. Clinical predictors of abnormal computed tomography scans in paediatric head injury. *J Paediatr Child Health*. 2002;38:388-392.

Prasad MR, Ewing-Cobbs L, Swank PR, et al. Predictors of outcome following traumatic brain injury in young children. *Pediatr Neurosurg*. 2002;36:64-74.

White JR, Farukhi Z, Bull C, et al. Predictors of outcome in severely head-injured children. *Crit Care Med*. 2001;29:534-540.

Inborn Errors of Metabolism

Bond GR, Woodward RW, Ho M. The growing impact of pediatric pharmaceutical poisoning. *J Pediatr*. 2012;160:265-270.

Burton BK. Inborn errors of metabolism in infancy: a guide to diagnosis. *Pediatrics*. 1998;102:E69.

Ellaway CJ, Wilcken B, Christodoulou J. Clinical approach to inborn errors of metabolism presenting in the newborn period. *J Paediatr Child Health*. 2002;38:511-517.

Vernon HJ. Inborn errors of metabolism advances in diagnosis and therapy. *JAMA Pediatr*. 2015;169:778-782.

32

Eye Disorders

Deborah M. Costakos

EYE AND VISUAL SYSTEM ANATOMY

The anatomies of the eye and visual system are shown in Figs. 32.1 and 32.2. The optic nerves, made up of the converging nerve fiber layer of the retina, have intraocular, intraorbital, intracanalicular, and intracranial portions. Partial decussation of the optic nerve fibers occurs in the chiasm, which gives binocular visual input to each side of the brain. The visual cortex is where the conscious process of seeing occurs.

DEVELOPMENT OF THE EYE AND VISUAL SYSTEM

The eyes and vision of a newborn are immature and require several years to reach adult proportions and functional status. By the 9th month of gestation, the retinal vessels have reached the periphery of the retina (an important factor in the pathogenesis of retinopathy of prematurity [ROP]), the optic nerve has completed myelination, and the pupillary membrane has disappeared. Postnatal reorganization of neuron-to-neuron connections in the visual cortex improve the poor visual acuity and other visual processes, which are not fully developed at birth. The visual acuity of the newborn has been estimated to be 20/400-20/600 and may reach the normal 20/20 level as early as 6-12 months of age as tested with visual evoked cortical responses. Acuity of 20/20 is not reached with other types of testing such as preferential looking with Teller acuity cards until ages 3-5 years. Visual acuity measured with conventional letter or symbol recognition methods does not reach 20/20 until 6 years of age because of cognitive factors. Binocular vision, including establishment of normal ocular alignment and depth perception, and improved facility of accommodation, the ability to focus on images at different distances, develop rapidly in the 1st year of life. The rapid maturation of visual function in the 1st year of life accounts for the critical period of visual development and the extreme sensitivity of the visual system to abnormal visual input from strabismus or cataracts. Children deprived of vision in this critical period will have limited visual potential and may develop nystagmus (abnormal eye movements).

The majority of newborns are moderately hyperopic. Heredity contributes to the refractive status of the eyes and the environment and visual experience also plays a role.

AMBLYOPIA AND VISION SCREENING

Amblyopia is defined as a unilateral or, less commonly, bilateral reduction in visual acuity that cannot be immediately corrected with glasses or surgery. In children in whom visual acuity can be accurately measured, a practical definition of amblyopia is a 2-line or greater difference between the best-corrected visual acuity of the eyes. For preverbal children, differences between the eyes in fixation and following behavior or fixation preference are used to diagnose amblyopia. Automated photoscreeners can aid in the diagnosis of risk factors for amblyopia and strabismus, particularly in preverbal children who perform poorly on subjective testing. Amblyopia results from abnormal visual experience early in life during the critical period for visual development. The sensitive period for amblyopia starts in early infancy and continues to at least the age of 6 years and often beyond the age of 8 years. There is a suggestion of cortical plasticity in adults that may allow for some vision improvement into adulthood. The prevalence of amblyopia in the North American population is 2-4%.

Unilateral amblyopia results from 3 types of abnormal visual experience: strabismus, anisometropia (unequal refractive errors), and monocular visual deprivation (e.g., cataract, corneal opacity, hemangioma (severe ptosis). **Bilateral amblyopia** results from bilateral media opacities or significant bilateral refractive errors (ametropia). Nearly all amblyopia is reversible if discovered at an early age and treated appropriately. Treatment effectiveness, however, declines after the age of 5 years.

Detection strategies for amblyopia can involve early recognition of factors that give rise to amblyopia or actual measurement of reduced visual acuity that may be caused by amblyopia. Most amblyopia risk factors can be detected through routine pediatric screening such as ocular history, red reflex evaluation, ocular motility, and vision assessment. Recommended screening and referral guidelines are shown in Table 32.1. Whenever possible, a line of symbols or isolated symbols with surrounding crowding bars is recommended for screening (Fig. 32.3). Isolated symbols can lead to overestimates of the visual acuity of an eye with amblyopia due to a crowding phenomenon or contour interaction in which symbols of a given size are more difficult to recognize if they are surrounded by similar symbols. Hence, visual acuity obtained with single optotypes without crowding bars can result in failure to detect amblyopia.

The treatment of amblyopia involves eliminating amblyopia risk factors, providing a focused retinal image with appropriate optical correction, and forcing use of the amblyopic eye through occlusion of the sound eye or blurring the image it receives. For patients with visual deprivation amblyopia, the depriving factor must be addressed medically or surgically. Optical correction including a bifocal is required for patients who have had cataract surgery. Intraocular implants are not generally placed in children under 1 year of age due to the high postoperative complication rates. For patients with anisometropic amblyopia, optical correction usually involves spectacles or, less commonly, contact lenses.

An adhesive patch worn over the sound eye most commonly achieves enforced use of the amblyopic eye. Occlusive devices can be

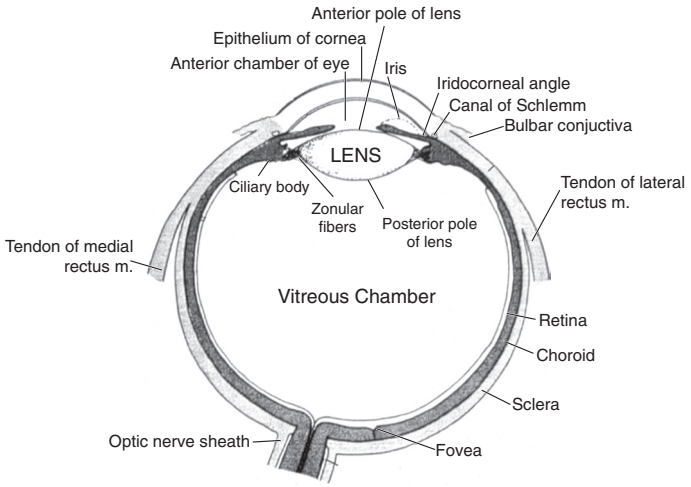

FIGURE 32.1 Anatomy of the eye as seen in cross section. (Modified from Reilly BM. *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991:36.)

attached to glasses but may be less reliable since the child can peek over the glasses or around the occlusive device. The use of the potent cycloplegic agent atropine sulfate may also be used to encourage use of the amblyopic eye. A drop of atropine is applied to the sound eye each day; this temporarily impairs its accommodative ability and, in the presence of sufficient hyperopia, prevents that eye from obtaining a clear retinal image. Atropine "penalization" for amblyopia works best in hyperopic patients with mild to moderate amblyopia (visual acuity of 20/100 or better). Close follow-up of patients being treated for amblyopia is important for monitoring compliance with treatment and for preventing the development of iatrogenic reverse amblyopia in the sound eye from excessive occlusion or penalization.

VISUAL FIELDS

Quantitative testing of the visual field of most children is difficult before the age of 10 years (see Fig. 32.2). Confrontation field tests can be performed to detect gross abnormalities of the visual field (hemianopsias) but even these are not reliable and need to be confirmed at an older age. Visual field defects in children are uncommon despite parental concerns about a child who seems to bump into objects frequently. Unilateral retinal or optic nerve disease can produce unilateral visual field defects, but these are almost always associated with reduced visual acuity in the involved eye. Bilateral visual field defects, particularly if symmetric (homonymous), indicate disease of the optic radiations or visual cortex. Visual acuity may be entirely normal. Causes of bilateral visual field defects in children include cerebrovascular accidents, pituitary or hypothalamic tumors, or congenital central nervous system (CNS) abnormalities.

STRABISMUS

Strabismus is derived from the Greek word *strabismos*, "to squint to look obliquely or askance." It implies misalignment of the eyes in such a way that they are not simultaneously viewing the same object. Terms to describe eye alignment and movement are noted in Table 32.2. Strabismus can be constant or intermittent and can be the same in all directions of gaze (comitant) or greater in 1 direction of gaze than in others (incomitant). Furthermore, it can be categorized as congenital or acquired, monocular or alternating. The direction of misalignment

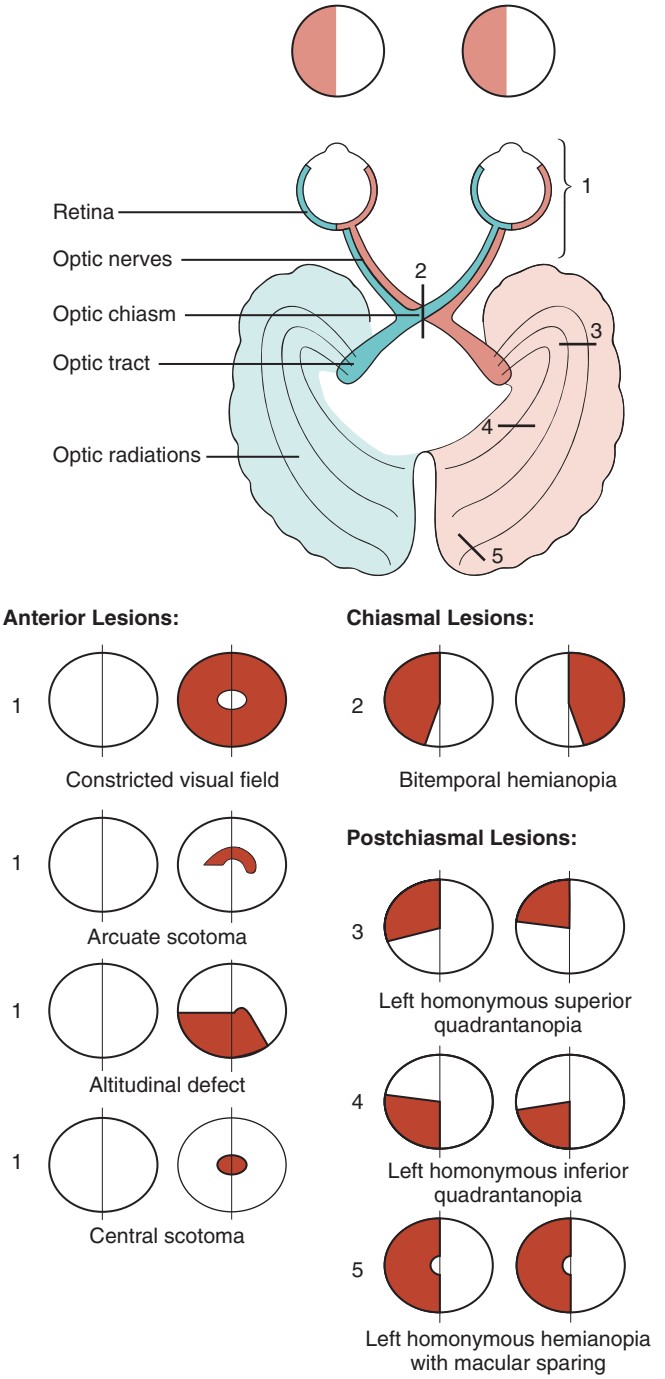

FIGURE 32.2 Anatomy of the visual pathways. The anatomy of the visual pathways appears at the top of the figure, the *pink shading* indicating how visual information from the left visual space eventually courses to the right brain. Visual field defects are at the bottom of the figure. Anterior defects (labeled *1* from disease of the optic nerve or retina) characteristically affect 1 eye and cause defects *(red shading)* that may cross the vertical meridian (i.e., the vertical meridian is the vertical line bisecting each visual field). Chiasmal defects (labeled *2*) and postchiasmal defects (labeled *3* for a lesion in the anterior temporal lobe, *4* for the parietal lobe, and *5* for the occipital cortex) characteristically affect both eyes and respect the vertical meridian. (Modified from McGee S. *Evidence-Based Physical Diagnosis*. 3rd ed. Philadelphia: Elsevier; 2012:514.)

TABLE 32.1 Vision Screening Recommendations

Age	Tests	Referral Criteria Comments
Newborn to 12 mo	• Ocular history • Vision assessment • External inspection of the eyes and lids • Ocular motility assessment • Pupil examination • Red reflex examination	• Refer infants who do not track well after 3 mo of age. • Refer infants with an abnormal red reflex or history of retinoblastoma in a parent or sibling.
12-36 mo	• Ocular history • Vision assessment • External inspection of the eyes and lids • Ocular motility assessment • Pupil examination • Red reflex examination • Visual acuity testing • Objective screening device "photoscreening" • Ophthalmoscopy	• Refer infants with strabismus. • Refer infants with chronic tearing or discharge. • Refer children who fail photoscreening.
36 mo to 5 yr	• Ocular History • Vision assessment • External inspection of the eyes and lids • Ocular motility assessment • Pupil examination • Red reflex examination • Visual acuity testing (preferred) or photoscreening • Ophthalmoscopy	• Visual acuity thresholds • Ages 36-47 mo: Must correctly identify the majority of the optotypes on the 20/50 line to pass. • Ages 48-59 mo: Must correctly identify the majority of the optotypes on the 20/40 line to pass. • Refer children who fail photoscreening.
5 yr and older* *Repeat screening every 1-2 yr after the age of 5 yr	• Ocular history • Vision assessment • External inspection of the eyes and lids • Ocular motility assessment • Pupil examination • Red reflex examination • Visual acuity testing • Ophthalmoscopy	• Refer children who cannot read at least 20/30 with either eye. Must be able to identify the majority of the optotypes on the 20/30 line. • Refer children not reading at grade level.

From American Academy of Pediatric Ophthalmology and Strabismus techniques for Pediatric Vision Screening. May, 2014.

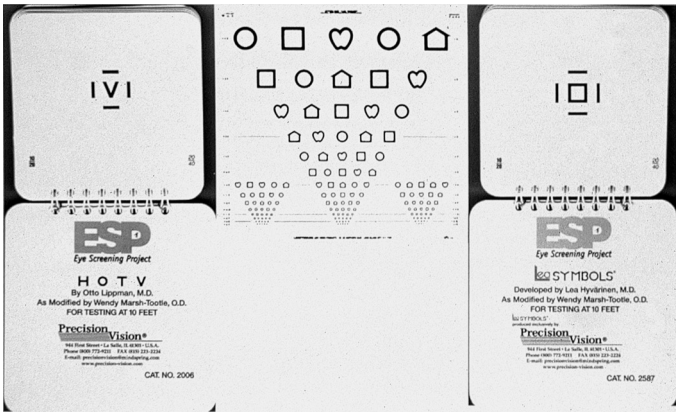

FIGURE 32.3 The Lea symbols in chart format *(middle)* and the Lea symbols and HOTV tests with crowding bars *(right and left)*. All tests should be administered at a distance of 10 feet.

can be vertical or horizontal. Vertical strabismus is referred to as a hypertropia of the higher eye. Horizontal strabismus can be convergent (esotropia) or divergent (exotropia). The importance of strabismus detection derives primarily from the fact that it is the leading cause of amblyopia. Other reasons for detecting strabismus are the possibility of being able to restore normal binocular use of the eyes, improving depth perception, and minimizing the social and economic drawbacks to strabismus in society.

Strabismus detection can be simple, as in patients with a large angle of deviation (Fig. 32.4), or difficult, as in patients with more subtle deviations or no deviation at all (pseudostrabismus) (Fig. 32.5). Evaluation of the symmetry of the corneal light reflexes from a penlight directed at the eyes can reliably detect many cases (see Fig. 32.4). With smaller angles of strabismus or when the results of the corneal light reflex are in doubt, the cover test should be performed (Fig. 32.6). It is important to provide attractive fixation targets for the child to view during the test.

Infantile esotropia is defined as convergent strabismus with onset within the 1st 6 months of life (see Fig. 32.4). Transient crossing or divergence of the eyes is common in newborns and is probably not significant unless it persists beyond 3 months of age. In the classic form of infantile esotropia, there is a large-angle, constant deviation. The child may alternate fixation (cross fixate) in which case the visual acuity is usually good in both eyes. Cross fixation may mimic bilateral 6th nerve palsy. If the crossing is present in only 1 eye, amblyopia occurs. The cause of infantile esotropia is not known, but hereditary factors play a definite role. The incidence of infantile esotropia is less than 1% among neurologically normal infants.

Early correction of infantile esotropia may result in full or nearly full restoration of normal binocular function, a result not believed to be obtainable with correction of misalignment at older ages. The ideal

TABLE 32.2 Description of Alignment and Movement

Normal Ocular Alignment: Orthophoria

Latency

-phoria: development of abnormality only during certain conditions (fatigue, illness, cover test)

-tropia: abnormality present during normal conditions; deviation may be constant or intermittent

Direction of Deviation

Eso-: inward, horizontal deviation ("crossing")

Exo-: outward, horizontal deviation ("wall eye")

Hyper-: upward, vertical deviation

Hypo-: downward, vertical deviation

Incyclo-: nasal torsional deviation of the superior pole of the cornea

Excyclo-: temporal torsional deviation of the superior pole of the cornea

Equality of Deviation

Concomitant: misalignment is equal in all positions of gaze

Noncomitant: misalignment varies significantly in different positions of gaze

Neuromuscular Dysfunction

Paralytic: misalignment secondary to a cranial nerve palsy, muscle weakness, or mechanical restriction (usually noncomitant)

Non-paralytic: no underlying neuromuscular dysfunction; usually concomitant but can be noncomitant

Tandem Movements of Both Eyes

-version: both eyes move in same direction (conjugate); direction of movement: leve- (left); dextro- (right); supra- (up); infra- (down)

-vergence: eyes move in opposite directions (disconjugate); convergence (inward movement), divergence (outward movement)

FIGURE 32.4 Corneal light reflex test reveals an asymmetrically placed reflex that is laterally displaced in the right eye. This indicates an inward deviation of the eye (esotropia). (From Lavrich JB, Nelson LB. Diagnosis and treatment of strabismus disorders. *Pediatr Clin North Am.* 1993;40:739.)

timing of surgery for infantile esotropia is not known, although usually done between 6 and 24 months to optimize binocularity. However when early surgery is done, there is a higher chance of needing further surgery. Early detection and prompt referral of infants with suspected esotropia are indicated.

A second category of esotropia occurs in children whose eyes are initially straight but start to cross, usually intermittently at first, at 1-3

FIGURE 32.5 A child with pseudoesotropia. Note that the wide nasal bridge and prominent epicanthal folds create the illusion of an esotropia. The corneal light reflexes are centered in each eye; therefore, the eyes are straight. (From Lavrich JB, Nelson LB. Diagnosis and treatment of strabismus disorders. *Pediatr Clin North Am.* 1993;40:741.)

years of age. These children have excessive hyperopia and an abnormal relationship between accommodation and convergence. This type of esotropia is called **accommodative esotropia**. Amblyopia frequently develops. Treatment consists of correcting amblyopia and providing spectacles to correct hyperopia, thereby modulating the amount of accommodation required by the child (Fig. 32.7). Bifocal spectacles may also be necessary for some forms of accommodative esotropia.

Esotropia caused by paralysis of a lateral rectus muscle, a 6th cranial nerve palsy, occurs much more frequently in children than in infancy (Fig. 32.8). Approximately 30% of children will have an intracranial lesion. Other causes include head trauma or a recent viral illness. The 6th nerve palsy may resolve spontaneously if the cause is benign. An older child may present with complaints of diplopia or a face turn or closure of 1 eye to avoid diplopia, whereas a younger child may present with only the esotropia because of rapid development of suppression to eliminate diplopia. Neurologic investigation is indicated if the history does not support a benign etiology or the paralysis does not spontaneously abate in a few weeks (a so-called benign 6th nerve palsy believed to be postviral in origin) or if the child demonstrates other neurologic impairment or has papilledema.

Infantile exotropia is much less common than infantile esotropia. Infantile exotropia presents as a large deviation of the eyes prior to 6 months of age. Infantile exotropia is uncommon in otherwise healthy infants. It is, however, commonly associated with craniofacial disorders or neurologic impairment. Surgery may be done early in life, but these patients are less likely to obtain good binocular vision than infantile esotropes.

Intermittent exotropia is the most common type of exotropia. This usually manifests by 5 years of age. Parents will notice that the eyes deviate out at times and yet not at others. The deviation is most likely to occur when the child is tired or ill. Because the child maintains the ability to keep the eyes aligned part of the time, amblyopia is uncommon. Diplopia is prevented by active cortical suppression of input from the portion of the retina of the deviated eye that overlaps the central view of the fixating eye. When the eyes are straight, the child generally maintains normal binocular function, including stereopsis. The clinical management of intermittent exotropia is not clear. Treatment options include part-time patching, additional minus power spectacles in patients with myopia, orthoptic exercises, and surgery.

Primary vertical strabismus is far less common than horizontal strabismus. A small vertical deviation in association with a larger amount of horizontal strabismus, however, is common, and is managed in conjunction with the horizontal deviation. A common cause of

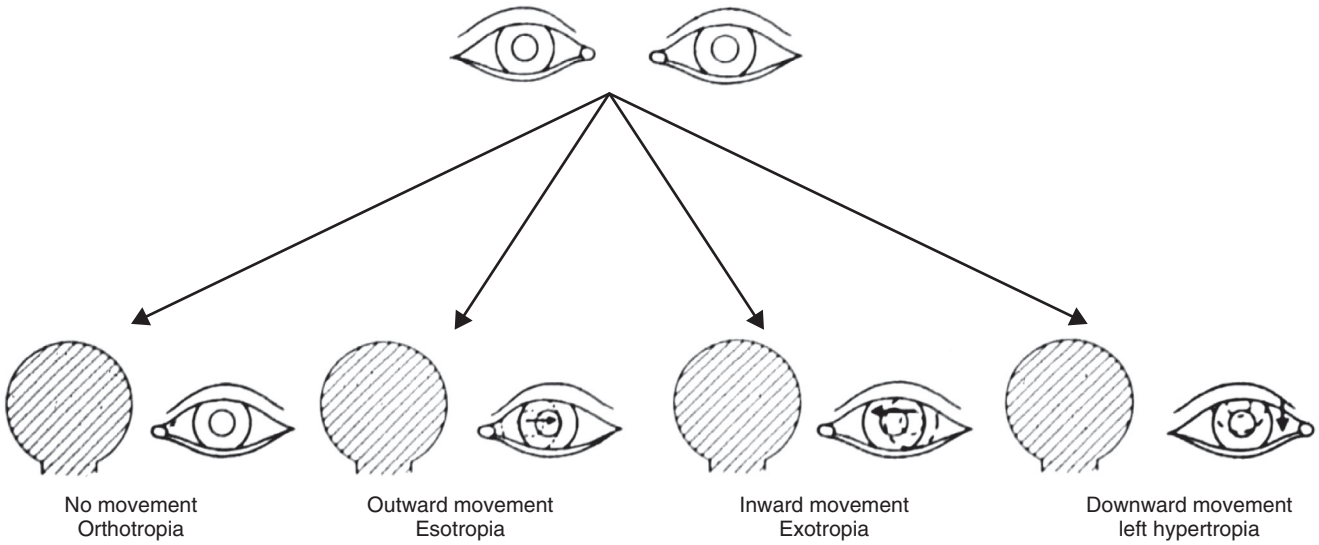

FIGURE 32.6 The cover test. In each instance, the occluder is placed over the right eye while the patient is viewing a fixation target and the examiner is watching for movement of the patient's left eye. If the left eye is not aligned, it will need to move to look at the fixation target. If there is no movement of the left eye, the test needs to be repeated by occluding the left eye and watching for movement of the right eye.

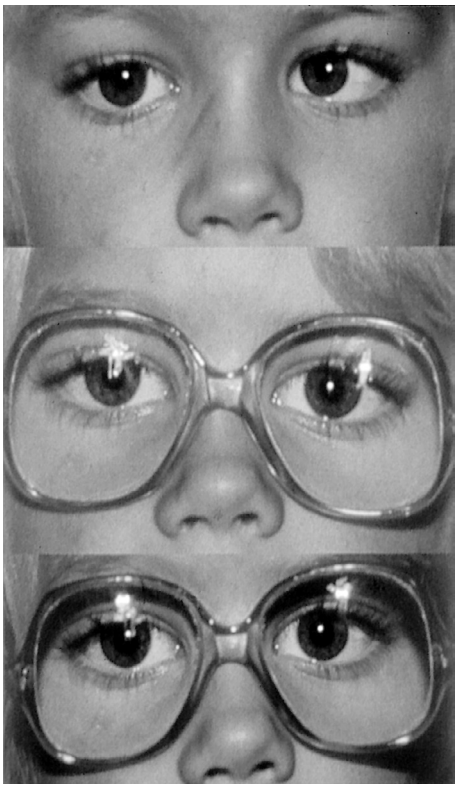

FIGURE 32.7 Accommodative esotropia *(top)*. The deviation is completely controlled with glasses at both distant *(middle)* and near *(bottom)* fixation distances.

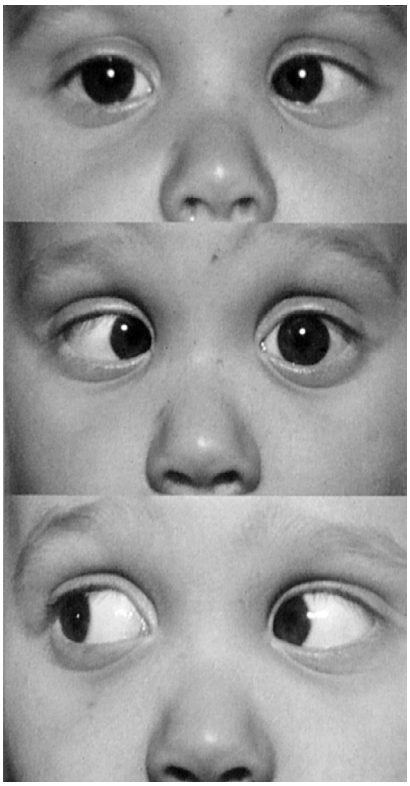

FIGURE 32.8 Left 6th cranial nerve palsy in a 4-year-old. A large manifest esotropia is present when the child looks straight ahead *(top)*. The left eye does not abduct beyond the midline in gaze to the left *(middle)*. Gaze to the right is normal *(bottom)*.

hypertropia in children is congenital paralysis of the superior oblique muscle, a 4th cranial nerve paralysis. In some children, the "paralysis" is actually caused by an anatomic abnormality of the superior oblique tendon. Acquired causes of a superior oblique palsy include trauma, central nervous system abnormalities, or brain tumors. Children with a superior oblique paralysis of any cause frequently present with a head tilt and face turn toward the side opposite the paralyzed superior oblique muscle. If there is a question as to the timing of the onset of the superior oblique palsy, a review of pictures at a younger age may be helpful in determining chronicity. Superior oblique paralysis is 1 of the more common causes of ocular torticollis. An eye muscle disorder needs to be ruled out in any child with a chronic abnormality of head position. The anomalous head position and hypertropia caused by a superior oblique paralysis can be improved by eye muscle surgery in most instances. An approach to the evaluation of strabismus is noted in Fig. 32.9 and less common forms of strabismus are listed in Table 32.3.

REFRACTIVE ERRORS

Refractive errors include myopia (nearsightedness), hyperopia (farsightedness), and astigmatism. Refractive errors may be similar (isometropia) or different (anisometropia) between the 2 eyes. Bilateral amblyopia may result from a high refractive error that is isometropic. Full-time spectacle correction will often correct bilateral amblyopia. Unilateral amblyopia may result from anisometropia. Patching or atropine penalization may be necessary in these children.

Myopia

In patients with myopia, the parallel rays of light in the resting (nonaccommodating) eye are focused in front of the retina. The symptoms of myopia are squinting, holding or viewing an object more closely than normal, and complaining of blurred far vision.

The incidence and degree of myopia increase with age, especially during growth spurts, as in adolescence. There is a complex interaction between genetic and environmental factors in the development of myopia. The incidence of myopia varies with ethnicity and geographic regions and has been increasing in prevalence over the past 50 years. There have been several genetic markers linked to myopia but the increasing frequency among younger generations suggests environment plays an important role. The increase in prevalence from 10-90% in some populations is a public health concern, particularly with high myopia. Myopia can be associated with increased risk of retinal detachment, early cataract, and glaucoma. In very high myopia there can be thinning of the retina and retinal degeneration. This can result in decreased vision even with spectacle or contact lens correction.

Myopia may be associated with other ocular abnormalities, such as keratoconus (central conical protrusion of the cornea), cataracts, ectopia lentis (dislocated lens), spherophakia (overly spherical lens), glaucoma, and medullated (myelinated) nerve fibers. There is an increased prevalence of myopia in premature infants, especially with ROP. Children with high degrees of myopia may have an underlying systemic association, such as Marfan, Stickler, Noonan, or Down syndromes. If myopia is sufficient to produce visual symptoms, spherical concave (minus) lenses in the form of spectacles or contact lenses are prescribed to correct the refractive error. Prescription changes may be needed every 1-2 years and more often during growth spurts.

Hyperopia

In patients with hyperopia (farsightedness), parallel rays of light in the nonaccommodating eye would, if possible, be focused behind the

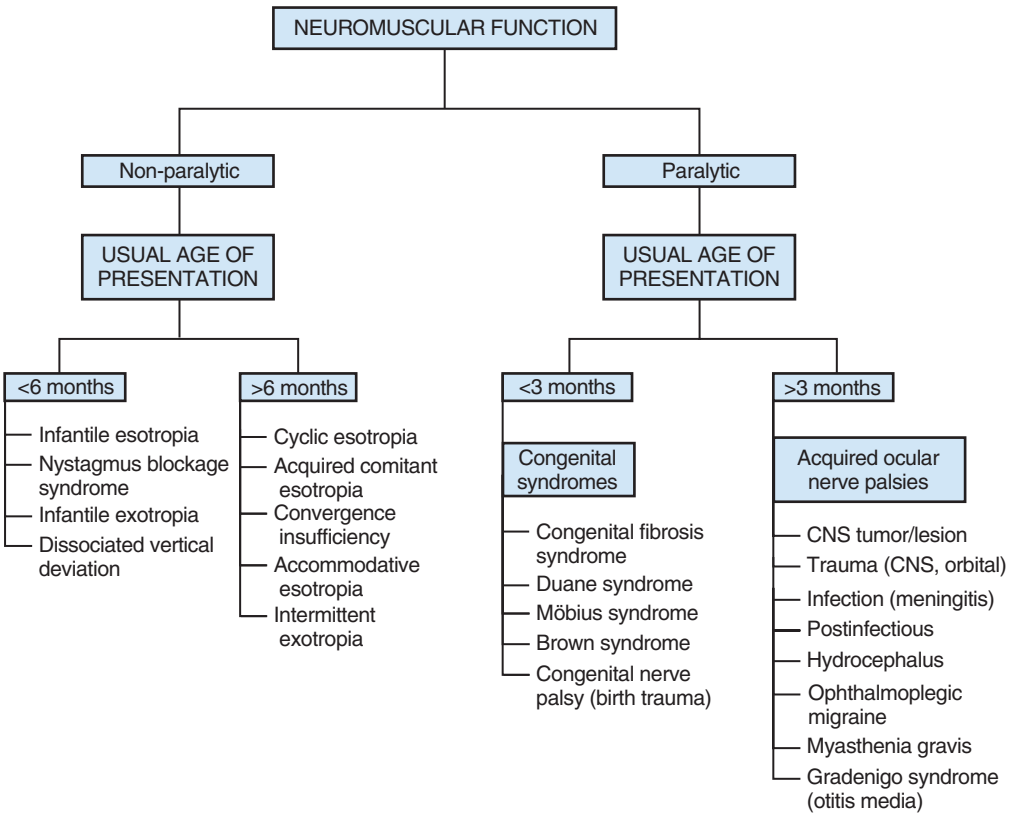

FIGURE 32.9 Evaluation of strabismus. CNS, central nervous system.

TABLE 32.3 Less Common Forms of Strabismus

Type of Strabismus	Presenting Symptoms and Signs	Cause	Treatment
Duane syndrome	Esotropia with deficient abduction or exotropia with deficient adduction of 1 eye; head turn	Absence of 6th nerve nucleus and aberrant innervation of lateral rectus muscle from 3rd cranial nerve	Strabismus surgery for correction of large deviations or abnormal head position
Dissociated vertical deviation	One eye turns up intermittently, especially with fatigue	Eye movement abnormality related most commonly to congenital esotropia	Eye muscle surgery on superior rectus and inferior oblique muscles
Brown syndrome	Head tilt; inability to elevate eye in adduction	Restriction of free passage of superior oblique tendon through trochlea	Observation if not severe; superior oblique tendon surgery if severe
Möbius syndrome	Masklike facies; inability to abduct both eyes; difficulty closing eyes	Bilateral 6th and 7th nerve palsies	Protect corneas from exposure; strabismus surgery
Congenital fibrosis syndrome	Chin-up head position; inability to elevate eyes; ptosis	Autosomal dominant gene on chromosome 16 in some patients; superior division of 3rd nerve in others	Surgical release of tight extraocular muscles
3rd nerve palsy	Exotropia and hypertropia; ptosis; dilated, nonreactive pupil	Congenital absence of 3rd nerve; trauma; or tumor	Ptosis and strabismus surgery
Double elevator palsy	Chin-up head posture; inability to elevate 1 eye	Paresis of superior rectus muscle	Transposition strabismus surgery
Orbital floor fracture	Vertical diplopia; chin-up head position	Entrapment of orbital tissues in fracture	Repair of floor fracture; release of inferior rectus muscle restriction
Myasthenia	Variable ptosis and eye movement abnormalities	Blockage of acetylcholine receptor sites by immune complexes	Treatment of systematic myasthenia; strabismus surgery if patient is stable

retina. The process of accommodation (focusing), which alters the shape of the lens, can compensate for some degrees of hyperopia. Because most children have a tremendous range of accommodation, mildly hyperopic children can see clearly without any visual symptoms. Moderate to severely hyperopic children may be unable to fully compensate through accommodation. The greater accommodative effort may lead to symptoms of "eyestrain," which consist of headaches, fatigue, or eye rubbing. These symptoms may lead to a lack of interest in reading or in prolonged close work. Some children may also develop accommodative esotropia. Some children have a decreased ability to accommodate, or accommodative insufficiency, and are symptomatic even with low degrees of hyperopia. If hyperopia produces symptoms or causes esotropia, spherical convex (plus) lenses usually in the form of glasses are prescribed to correct the refractive error.

Astigmatism

In the patient with astigmatism, the refractive power differs in various meridians of the eye. In most cases, astigmatism is caused by abnormal curvature of the cornea; in rare cases, lens abnormalities may cause astigmatism. Infants and children with corneal distortion secondary to scarring (trauma or infection) or to external compression (ptosis or hemangioma of eyelid) are at an increased risk for astigmatism. Moderate levels of astigmatism may produce blurring of vision (far and near), leading to squinting, fatigue, headaches, and lack of interest in close-up work in older children and amblyopia in younger children. Cylindric or spherocylindric lenses (usually glasses) are used to improve vision and comfort.

Anisometropia

In patients with anisometropia, the refractive error of 1 eye differs significantly from that of the other eye. The difference in refraction can be spherical (hyperopia or myopia) or cylindric (unequal amounts of astigmatism). Mild degrees of anisometropia usually cause no visual symptoms and do not lead to amblyopia. Amblyopia develops with higher degrees of anisometropia because the child uses the less ametropic eye and suppresses vision in the other. Strabismus frequently coexists with anisometropia, and both conditions may be involved in the pathophysiologic mechanisms of amblyopia. Anisometropia may initially be detected by comparison of the red reflex between the 2 eyes (Brückner test). The affected eye has the duller red reflex. Early detection and treatment of anisometropia are essential for the development of optimal visual function.

VISION IMPAIRMENT IN CHILDREN

Vision impairment is formally defined as best-corrected visual acuity of 20/70 or worse in both eyes. Impairment of vision exists as a continuum from 20/70 to no light perception. Unrestricted driver's license has a requirement of best-corrected vision of 20/40 or better in 1 eye in all but 3 states (New Jersey and Wyoming have a requirement of 20/50 best-corrected vision in 1 eye and Georgia has a requirement of 20/60 best-corrected or better in 1 eye). Legal blindness is said to be present when best-corrected visual acuity is 20/200 or less in each eye. Constricted visual fields may also play a role in the diagnosis of vision impairment or legal blindness. An infant or child whose visual acuity and visual field cannot be quantitated may be judged visually impaired on the basis of inability to fixate on and follow movement of the examiner's face or other objects or even, in severe instances, inability to perceive light. Milder vision impairment may be suspected on the basis of associated eye signs but can be difficult to confirm in a preverbal child because of compensatory behavior (holding objects close, a face turn) that allows the child to have relatively normal overall function and development. Observation of the child's behavior in the examination room, examination of the eyes (Table 32.4), and a detailed history (Table 32.5) taken from the parents about the child's visual behavior at home can be important in establishing the degree of impairment. Many visually impaired infants and children have objective signs such as nystagmus, sluggish pupillary light reflexes, or

TABLE 32.4 Red Flags in Inspection and Direct Ophthalmoscopy in Evaluating Visual Impairment

Physical Findings	Possible Pathologic Process
Inspection	
Globe	
Small	High hyperopia, persistent hyperplastic primary vitreous, phthisis bulbi (shrinkage related to deteriorating eye disease)
Large	Glaucoma, high myopia
Red eye	Inflammatory disease (infection, uveitis), trauma, tumor, glaucoma
Protrusion	Retrobulbar or orbital infection/tumor, hyperthyroidism
Sunken	Orbital fracture, Horner syndrome, atrophy, microphthalmia
Misalignment	Impairment of extraocular muscles: congenital weakness, muscle entrapment (tumor/trauma), cranial nerve palsy (infection, tumor, stroke, congenital)
Ophthalmoscopy	
Cloudy cornea	Anterior segment dysgenesis (Peter anomaly), glaucoma, trauma, infection, metabolic storage diseases (mucopolysaccharidoses)
Lens	
Cloudy	Cataracts (congenital vs systemic diseases)
Dislocated	Homocystinuria, Marfan syndrome
Cloudy vitreous	Retinoblastoma, detached retina, endophthalmitis, uveitis, hemorrhage
Optic disk	
Pale	Optic atrophy (congenital, trauma, tumor, hydrocephalus, degenerative neurologic disease)
Swollen	Increased intracranial pressure, optic neuritis
Hemorrhage	Optic neuritis, increased intracranial pressure
Retina/choroid	
Abnormal color	Retinitis pigmentosa (spicule pattern), chorioretinitis (atrophy with hyperpigmentation), Tay–Sachs disease (cherry-red macula)
Exudates	Diabetes mellitus, Coats disease, increased intracranial pressure
Hemorrhage	Hypertension, diabetes mellitus, increased intracranial pressure, trauma, blood disorders
Phakomata	Tuberous sclerosis (yellow plaques, nodules), von Hippel–Lindau disease (reddish globular mass), Sturge–Weber syndrome (choroidal hemangioma), neurofibromatosis (yellow plaques)
Blood vessels	
Constricted	Hypertension
Microaneurysm	Diabetes mellitus

TABLE 32.5 Red Flags in History for Visual Impairment

Manifestation	Possible Pathologic Process
Child's Complaint	
Generalized blurred vision	
Far vision only	Myopia
Near vision only	Hyperopia, disorder of accommodation
Both far and near	Astigmatism or defect of visual pathways
Focal blurred vision (veil, shadow)	
Unilateral	Ipsilateral retinal or optic nerve
Bilateral	Chiasmal, postchiasmal, or bilateral prechiasmal lesion
Ghost/double vision	
With binocular vision	Cranial nerve or extraocular muscle
With monocular vision	Ocular media or macular disease
Changes in special visions	
Poorer color vision	Retinal or optic nerve disease
Poorer night vision	Retinal disease (retinitis pigmentosa)
Visual sensations	
Floaters, spots	Uveitis, retinal detachment, or hemorrhage
Shimmering lines or scotoma	Migraines
Visual hallucinations	Cerebral lesion, psychogenic
Parents' Observations	
Age-appropriate infant does not track	Severe ocular (myopia, cataracts) or systemic (meningitis) pathologic process
Objects viewed too closely	Decreased visual acuity related to refractive error; ocular or neurologic disorder
Squinting	Decreased visual acuity related to refractive error; ocular or neurologic disorder
Roving or wandering eyes	Nystagmus or strabismus; rule out ocular or neurologic disorder
Head tilting	Compensatory posturing for nystagmus, strabismus, astigmatism, or visual field defect
Bumping into objects	Visual field defect, decreased visual acuity
Reading problems	Visual impairment, visual processing disorder

anatomic abnormalities such as optic nerve hypoplasia or chorioretinal scarring.

Visual inattentiveness in an infant deserves special attention because of the possibility that the child has a treatable but not obvious form of vision impairment such as bilateral congenital cataracts. Even if the cause of impairment is not remediable, early diagnosis is important for referral of the infant for physical and occupational therapy for visual impairment since these children have very specific needs. Vision impairment (monocular or binocular) acquired after infancy obligates the physician to search for a cause such as a retinal degeneration because some causes are treatable (Tables 32.6 to 32.8).

TABLE 32.6 Childhood Amaurosis (Blindness): Principal Neurologic Considerations

Congenital Malformations
Optic nerve hypoplasia
Congenital hydrocephalus
Hydranencephaly
Porencephaly
Microencephaly
Encephalocele, particularly occipital type

Phakomatoses
Tuberous sclerosis
Neurofibromatosis (special association with optic glioma)
Sturge–Weber syndrome
von Hippel–Lindau disease

Tumors
Retinoblastoma
Optic glioma
Perioptic meningioma
Craniopharyngioma
Cerebral glioma
Posterior and intraventricular tumors when complicated by hydrocephalus

Neurodegenerative Diseases
Cerebral storage disease
Gangliosidoses, particularly Tay–Sachs disease (infantile amaurotic familial idiocy), Sandhoff variant, generalized gangliosidosis
Other lipidoses and ceroid lipofuscinoses, particularly the late-onset amaurotic familial idiocies such as those of Jansky–Bielschowsky and of Batten–Mayou–Spielmeyer–Vogt
Mucopolysaccharidoses, particularly Hurler syndrome and Hunter syndrome
Leukodystrophies (dysmyelination disorders), particularly metachromatic leukodystrophy and Canavan disease
Demyelinating sclerosis (myelinoclastic diseases), especially Schilder disease and Devic neuromyelitis optica
Special types: Dawson disease, Leigh disease, Bassen–Kornzweig syndrome, Refsum disease
Retinal degenerations: "retinitis pigmentosa" and its variants, and Leber congenital type
Optic atrophies: congenital autosomal recessive type, infantile and congenital autosomal dominant types,
Leber disease, and atrophies associated with hereditary ataxias: the types of Behr, of Marie, and of Sanger–Brown

Infectious Processes
Encephalitis, especially in the prenatal infection syndromes due to *Toxoplasma gondii,* cytomegalovirus, rubella virus, *Treponema pallidum*
Meningitis; arachnoiditis
Optic neuritis
Chorioretinitis

Hematologic Disorders
Leukemia with central nervous system involvement

Vascular and Circulatory Disorders
Collagen vascular diseases
Arteriovenous malformations: intracerebral hemorrhage, subarachnoid hemorrhage

Trauma
Contusion or avulsion of optic nerves or chiasm
Cerebral contusion or laceration
Intracerebral, subarachnoid, or subdural hemorrhage

Drugs and Toxins

RETINOPATHY OF PREMATURITY

Premature infants are at risk for the development of ROP because the retinal vessels have not yet grown out to the periphery of the retina and are susceptible to a variety of postnatal influences, including oxygen that can adversely affect retinal vessel maturation. In advanced stages of ROP, retinal neovascularization and fibrosis may lead to traction on the retina and result in a retinal detachment, the most common cause of blindness in premature infants. In most cases fortunately, ROP spontaneously resolves.

The international classification system for the acute stages of ROP describes the location, extent, and stage of the disease according to the position of the advancing wave of retinal vessels (Fig. 32.10). The retina is divided into zones I, II, and III. Zone I is centered on the optic nerve, from which the retinal arterioles emerge, and zone III exists as a crescent of retina on the temporal side; zone II occupies the midportion of the retina in all 4 quadrants. The severity is indicated by stages 1-5 with stage 1 representing mild ROP and stage 5 representing a total retinal detachment.

The management of ROP begins with a systematic program of eye examinations at well-defined times in infants judged to be at risk for developing ROP. The frequency of examinations is dependent on the findings and progression of the disease. Infants with a birth weight of less than 1500 g are 1st examined 4-6 weeks after birth. Follow-up examinations are performed at regular intervals until the retina is fully vascularized. If treatment is required laser ablation of immature retina or intravitreal injections of anti-vascular endothelial growth factor (VEGF) medication such as bevacizumab are options. The choice of treatment depends on the zone and the rate of progression of disease. Insulin-like growth factor (IGF)-1 supplementation or alterations may be a means to prevent ROP in the future.

LEUKOCORIA AND RETINOBLASTOMA

Leukocoria or "white pupil" is a sign, not a specific disease (Table 32.9). True leukocoria mandates prompt referral to an ophthalmologist as the causes may threaten either vision and/or life. Retinoblastoma is the most feared cause of leukocoria because of its potential to metastasize and cause death. It is the most common malignant ocular tumor of childhood, with an incidence of about 1/15,000. Leukocoria, the most common presenting sign, is caused by light reflection from the tumor's white surface (Fig. 32.11) as opposed to the usual red reflex from the retina. Approximately 25% present with strabismus. Less common presentations include periocular inflammation, glaucoma, and proptosis. Imaging is helpful to evaluate for calcifications that occur in retinoblastoma and to help confirm the diagnosis as well as to evaluate for pinealoblastoma and extension of the tumor into the orbit. Magnetic Resonance Imaging (MRI) should be done since computed tomography (CT) scan poses concern for radiation exposure and the development of secondary cancers for which patients with retinoblastoma are at increased risk. Referral of a patient with suspected retinoblastoma to an ophthalmologist experienced in its diagnosis and management is critical. Genetic counseling is indicated, as is examination of parents and siblings. In about 1% of cases a parent will have a regressed retinoblastoma or retinocytoma. Treatment options include ophthalmic artery chemosurgery, laser photocoagulation, cryotherapy, intravitreal chemotherapy, systemic chemotherapy, and enulcleation depending on laterality, location, extent of tumor, and vision potential. There is concerted effort to save the globes through advances in therapies.

TABLE 32.7 Causes of Monocular Visual Loss

Disorder	Timing	Pattern of Loss	Other Clues	Fundus Appearance	Pupil
Refractive error	Gradual*	Varies	Improves with pinhole	Normal	Normal
Cataract	Very gradual	Tunnel?	Opacity visible	Normal	Normal, but red reflex decreased
Corneal disease	Acute or chronic	Murky	Opacity visible or positive fluorescein	Normal	Normal but red reflex decreased
Iritis	Acute or chronic	Murky	Pain Ciliary flush	Normal	Small Disfigured?
Open-angle glaucoma	Gradual	Varies	Elevated pressures	Normal	Normal
Angle-closure glaucoma	Acute	Varies	Pain Steamy cornea Patient ill	Normal	Dilated Fixed
Central retinal occlusion	Acute	Varied	Painless Abrupt	Pale with cherry-red macula	Normal
Retinal detachment	Acute	Varies	Painless Floaters	Unremarkable or diagnostic	Afferent pupillary defect if extensive
Vitreous hemorrhage	Acute	"Dark"	Cannot see in the eye	Obscured	Normal, but red reflex decreased
Amaurosis fugax	Acute Transient	5-10 min	Carotid or heart disease, migraine	Normal	Normal
Migraine	Acute Transient	5-30 min	Headache History Scintillations	Normal	Normal
Optic neuropathy	Gradual or acute	Central scotoma	Toxins? Multiple sclerosis? Pituitary tumor? Virus?	Normal Pale optic disk?	Afferent defect
Diffuse retinopathy	Gradual	Varies	Genetic? AIDS?	Retinal lesions	Afferent defect?
Papilledema (chronic)	Late	Varies	CNS tumor? Pseudotumor cerebri Hypertensive crisis?	Diagnostic	Normal
Endophthalmitis	Varies	Varies	Corneal infection? Penetrating injury? Systemic injury? Hypopyon	Varies Often obscured	Varies

*Refractive error may be more acute when caused by diabetes mellitus.
AIDS, acquired immunodeficiency syndrome; CNS, central nervous system.
Modified from Reilly BM. *Practical Strategies in Outpatient Medicine.* 2nd ed. Philadelphia: WB Saunders; 1991:60.

CHILDHOOD CATARACTS

Congenital cataracts are a common cause of unilateral or bilateral vision loss in children, usually resulting from irreversible amblyopia in 1 or both eyes and occasionally from other accompanying structural ocular abnormalities (Table 32.10). Many infants with cataracts have leukocoria, but all visually significant cataracts can be detected by careful evaluation of the red reflex (Fig. 32.12). Infants with bilateral, visually significant cataracts may present with visual inattentiveness or nystagmus, signs that significant impairment of vision has already occurred.

Most cases of unilateral cataract are idiopathic in origin or associated with other ocular anomalies (persistent hyperplastic primary vitreous, anterior segment dysgenesis). Bilateral cataracts have a known genetic basis in about 60-70% of the cases but this is increasing as novel mutations continue to be described. Cataracts are commonly inherited in an autosomal dominant manner but may be inherited in an autosomal recessive or X-linked pattern. They can be associated with metabolic disease such as galactosemia or Fabry syndrome. Cataracts found to be a result of a metabolic disease may be reversible by removal of the offending agent; galactosemic cataracts are potentially reversible if lactose is eliminated from the diet promptly. Intrauterine TORCH(S) infections (*T*oxoplasmosis, *R*ubella, *C*ytomegalovirus, *H*erpes simplex and *S*yphilis) can also cause cataracts. Usually these are bilateral but in the case of congenital rubella infection unilateral cataract may occur (Table 32.11). Evaluation for a systemic cause should include a pediatric physical examination, ophthalmologic examination of the infant and family members, urine for reducing substances after lactose-containing milk feeding, labs for TORCH(S) infections, calcium, phosphorus, and glucose. Other metabolic studies, chromosomal evaluation, and genetic consultation may be indicated.

TABLE 32.8 Organic Causes of Vision Loss in Infancy

Condition	Physical Findings	Comments
Corneal Disease		
Corneal forceps injury	Cloudy cornea	May lead to astigmatism and amblyopia; associated with intraocular hemorrhage, retinal detachment
Sclerocornea	Opaque cornea	Scleralization of cornea; familial or sporadic; keratoplasty possibly needed to provide vision
Anterior microphthalmia	Small cornea	Familial inheritance; associated with congenital cataracts, glaucoma, and/or coloboma
Anterior Chamber Diseases		
Peter anomaly	Corneal opacity with iridocorneal/ lenticulocorneal adhesions	Maldevelopment of anterior segment of eye; associated with glaucoma and lens abnormalities
Persistent pupillary membrane	Bands or membranes obscuring pupil	Rupture of vessels in membranes may lead to hyphema; membrane may need to be removed to restore vision
Glaucoma	Tearing, enlarged eye, photophobia, cloudy cornea, pale optic disk	Increased intraocular pressure leading to blindness (optic nerve damage) Causes: anomalies of anterior segment, intraocular hemorrhage, ocular inflammatory disease, intraocular tumors Treatment: surgery
Iris and Lens Disorders		
Aniridia	Large, irregular, unreactive pupil	Hypoplasia of iris – may be heritable or sporadic, which is associated with a deletion of chromosome 11 and Wilms tumor or WAGR syndrome
Cataracts	Lens opacity	Multiple causes, ranging from familial inheritance to drugs
Anterior PHPV	Leukocoria (white pupillary reflex), lens opacity, cloudy cornea, small lens and eye	Persistence of fetal hyaloid vascular system, resulting in fibrovascular plaque on back of lens; as plaque contracts, ciliary process and lens become distorted Complications: glaucoma, cataract, intraocular hemorrhage, rupture of posterior capsule. Treatment: removal of membrane, lens aspiration. Prognosis: poor visual outcome
Retinal and Optic Nerve Disorders		
Posterior PHPV	Fibroglial veils around disk/macula, vitreous opacities (membrane, vessels)	Persistence of posterior fetal hyaloid vascular system; remnants of vascular system may cause traction detachment of retina
Chorioretinitis	Diffuse or local retinal atrophy demarcated by hyperpigmentation	Inflammation of posterior uvea with retinal involvement Causes: toxoplasmosis, histoplasmosis, herpes simplex, cytomegalic inclusion virus, syphilis, tuberculosis, and toxocariasis Other complications: glaucoma, detached retina
Retinoblastoma	Leukocoria	Neoplastic tumor with locus on chromosome 13: high incidence of secondary malignancy: poor prognosis with extraorbital metastasis
Retinopathy of prematurity	Leukocoria, cloudy vitreous; retinal white lines and ridges	Abnormal vascularization of retina: associated with retinal traction and detachment
Leber congenital retinal amaurosis	Normal findings to degeneration of retina	Failure of both rods and cones in retina; reduced or absent response to electroretinography; autosomal recessive
Achromatopsia	Color cannot be detected, photophobia	Failure of cone system in retina; autosomal recessive, or X-linked; diagnosed with ERG
Congenital stationary night blindness	Disk anomalies, poor night vision	Defect in rod system of retina; autosomal recessive, dominant, or X-linked recessive
Optic nerve hypoplasia	Pale, small optic disk; peripapillary halo of pigmentation	Secondary to failure in differentiation or degeneration of retinal ganglion cell axons Some causes: septo-optic dysplasia (hypopituitary, midline CNS defects), chromosomal defects (trisomy 13), albinism, fetal drug exposure (phenytoin, ethanol), infant of diabetic mother, CNS defects (hydrocephalus, anencephaly, encephalocele)

Continued

TABLE 32.8 Organic Causes of Vision Loss in Infancy—cont'd

Condition	Physical Findings	Comments
Optic nerve aplasia	Absence of retinal vessels and optic disk	Maldevelopment of optic nerve; associated with severe eye and CNS anomalies
Morning glory disk anomaly	Enlarged, funnel-shaped disk	Associated with retinal detachments and midline defects (cleft palate, encephalocele, agenesis of corpus callosum)
Coloboma	White, wedge-shaped retinal defect; visual field loss	Malclosure of embryonic fissure that leaves a gap in the retina, hence exposing sclera; defect may extend to lens; associated with many congenital syndromes
Aicardi syndrome	Retinal lacunae, coloboma of optic disk	Occurs mostly in girls and women; associated with agenesis of corpus callosum, seizures, intellectual disability, vertebral anomalies
Albinism	Photophobia; blue–gray to yellow–brown iris; macular hypoplasia	Defect in formation of melanin, resulting in lack of pigment in eyes and sometimes skin; increases risk of skin cancer with hypopigmented skin

CNS, central nervous system; ERG, electroretinogram; PHPV, persistent hyperplastic primary vitreous.

TABLE 32.9 Differential Diagnosis of Leukocoria (White Pupillary Reflex)

Common Causes
Cataracts
Cicatricial retinopathy of prematurity
Exudative retinopathy
Fundus coloboma
Larval granulomatosis (toxocariasis)
Persistent hyperplastic primary vitreous
Retinoblastoma

Other Causes
Atrophic chorioretinal scars
Endophthalmitis
Glioneuroma
Hemangioma
Hamartoma
Leukemic ophthalmopathy
Incontinentia pigmenti
Medullated nerve fibers
Medulloepithelioma
Morning glory disk anomaly
Norrie disease
Organized vitreous hemorrhage
Phakomatoses
Retinal gliosis
Retinal dysplasia
Retinoschisis

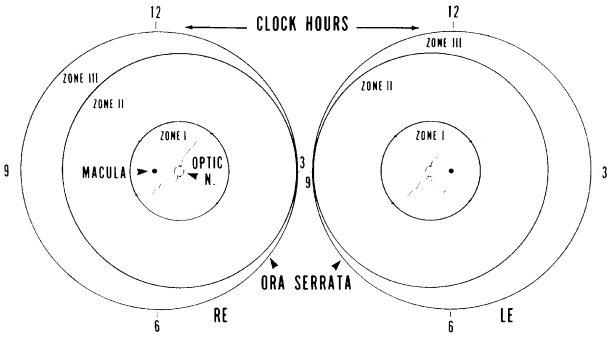

FIGURE 32.10 The international classification of retinopathy of prematurity (ROP). The stage of ROP is determined by the location, extent, and stage of disease according to the position of the advancing waves of retinal vessels. LE, left eye; RE, right eye.

FIGURE 32.11 Infant with leukocoria of right eye caused by retinoblastoma.

Cataracts in older children may be newly acquired due to a metabolic disease, drug exposure such as steroids, or a manifestation of progressive congenital cataracts. Cataract may rarely be the initial manifestation of diabetes type 1 but can occur as a complication particularly in patients with poor glycemic control. Bilateral cataracts are often the presenting sign in patients with unrecognized cerebrotendinous xanthomatosis (CTX). These patients usually have had chronic diarrhea without a known cause. Unfortunately, CTX is often diagnosed late after mental and neurodegeneration has started to occur. Since chenodeoxycholic acid can be used to prevent mental and neurologic deterioration, CTX should be considered in the presence of a juvenile-onset cataract and chronic diarrhea. Occasionally cataracts, unilateral or bilateral, are caused by an underlying congenital lens defect, which develops into a visually significant cataract at a later age. Trauma is a common cause of an acquired unilateral cataract.

Ideally, unilateral cataracts must be removed and amblyopia treatment begun in the 1st or 2nd month of life. Bilateral cataracts judged to be visually significant must be treated in the 1st 3 months of life to facilitate an optimal outcome. After this critical period maximum visual potential is decreased. Aphakic correction in infants younger than 6-12 months with bilateral cataracts is generally provided with extended-wear contact lenses or spectacles. Unilateral aphakia in this age group is best managed with a contact lens. A posterior chamber intraocular lens may be placed in children over the age of 1 year unless the child has an underlying inflammatory condition such as juvenile

TABLE 32.10 Differential Diagnosis of Cataracts

Developmental Variants
Prematurity ("Y" suture vacuoles) with or without retinopathy of prematurity

Genetic Disorders

Simple Mendelian Inheritance
Autosomal dominant (most common)
Autosomal recessive
X-linked

Major Chromosomal Defects
Trisomy disorders (13, 18, 21)
Turner syndrome (45X)
Deletion syndromes (11p13, 18p, 18q)
Duplication syndromes (3q, 20q, 10q)

Multisystem Genetic Disorders
Alport syndrome (hearing loss, renal disease)
Alström disease (nerve deafness, diabetes mellitus)
Apert syndrome (craniosynostosis, syndactyly)
Cockayne syndrome (premature senility, skin photosensitivity)
Conradi syndrome (chondrodysplasia punctata)
Crouzon syndrome (dysostosis craniofacialis)
Hallermann–Streiff syndrome (microphthalmia, small pinched nose, skin atrophy, and hypotrichosis)
Hypohidrotic ectodermal dysplasia (anomalous dentition, hypohidrosis, hypotrichosis)
Ichthyosis (keratinizing disorder with thick, scaly skin)
Incontinentia pigmenti (dental anomalies, intellectual disability, cutaneous lesions)
Lowe syndrome (oculocerebrorenal syndrome: hypotonia, renal disease)
Marfan syndrome
Meckel–Gruber syndrome (renal dysplasia, encephalocele)
Myotonic dystrophy
Nail–patella syndrome (renal dysfunction, dysplastic nails, hypoplastic patella)
Marinesco–Sjögren syndrome (cerebellar ataxia, hypotonia)
Nevoid basal cell carcinoma syndrome (autosomal dominant, basal cell carcinoma erupts in childhood)
Peter anomaly (corneal opacifications with iris–corneal dysgenesis)
Reiger syndrome (iris dysplasia, myotonic dystrophy)
Rothmund–Thomson (poikiloderma: skin atrophy)
Rubinstein–Taybi syndrome (broad great toe, intellectual disabilty)
Smith–Lemli–Opitz syndrome (toe syndactyly, hypospadias, intellectual disability)
Sotos syndrome (cerebral gigantism)
Spondyloepiphyseal dysplasia (dwarfism, short trunk)
Werner syndrome (premature aging in 2nd decade of life)

Inborn Errors of Metabolism
Abetalipoproteinemia (absent chylomicrons, retinal degeneration)
Fabry disease (α-galactosidase A deficiency)
Galactokinase deficiency
Galactosemia (galactose-1-phosphate uridyltransferase deficiency)
Homocystinemia (subluxation of lens, intellectual disability)
Mannosidosis (acid α-mannosidase deficiency)
Niemann–Pick disease (sphingomyelinase deficiency)
Refsum syndrome (phytanic acid α-hydrolase deficiency)
Wilson disease (accumulation of copper leads to cirrhosis and neurologic symptoms)

Endocrinopathies
Hypocalcemia (hypoparathyroidism)
Hypoglycemia
Diabetes mellitus

Congenital Infections
Toxoplasmosis
Cytomegalovirus infection
Syphilis
Rubella
Perinatal herpes simplex infection
Measles (rubeola)
Poliomyelitis
Influenza
Varicella–zoster

Ocular Anomalies
Microphthalmia
Coloboma
Aniridia
Mesodermal dysgenesis
Persistent pupillary membrane
Posterior lenticonus
Persistent hyperplastic primary vitreous
Primitive hyaloid vascular system

Miscellaneous Disorders
Atopic dermatitis
Drugs (corticosteroids)
Radiation
Trauma

Idiopathic

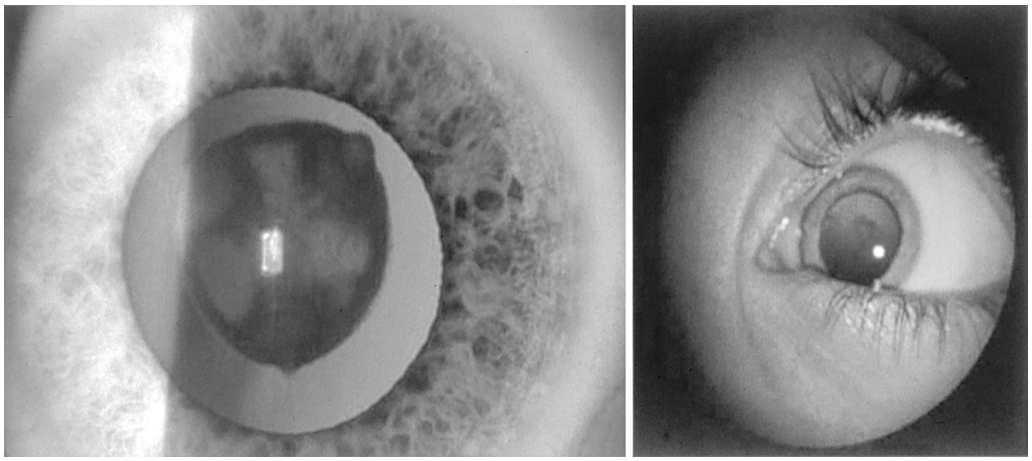

FIGURE 32.12 *Left,* Fundus reflex of an eye with a visually significant congenital cataract. The lens opacity is seen as black against the lighter fundus reflex. *Right,* Fundus reflex of a small, visually insignificant cataract. Nonetheless, this child requires referral for ophthalmologic evaluation.

TABLE 32.11 Childhood Glaucomas

I. Primary Genetically Determined Glaucoma

- A. Congenital open-angle glaucoma
- B. Juvenile glaucoma
- C. Primary angle-closure glaucoma
- D. Primary glaucomas associated with systemic or ocular abnormalities
  - 1. Associated with systemic abnormalities
    - a. Sturge–Weber syndrome
    - b. Neurofibromatosis
    - c. Pierre Robin anomalad
    - d. Oculocerebrorenal syndrome (Lowe syndrome)
    - e. Rieger syndrome
    - f. Hepatocerebrorenal syndrome
    - g. Marfan syndrome
    - h. Rubinstein–Taybi syndrome
    - i. Infantile glaucoma associated with intellectual disabilty and paralysis
    - j. Oculodentodigital syndrome
    - k. Syndrome of microcornea, absent frontal sinuses, and open-angle glaucoma
    - l. Mucopolysaccharidosis
    - m. Trisomy 13
    - n. Hurler disease
    - o. Cutis marmorata telangiectasia
  - 2. Associated with ocular abnormalities
    - a. Aniridia
    - b. Congenital ocular melanosis
    - c. Sclerocornea
    - d. Familial hypoplasia of iris
    - e. Anterior chamber cleavage syndrome
    - f. Iridotrabecular dysgenesis and ectropion uveae
    - g. Posterior polymorphous dystrophy

II. Secondary Glaucoma

- A. Traumatic glaucoma
  - 1. Acute
    - a. Angle concussion
    - b. Hyphema
  - 2. Late onset with angle recession
  - 3. Arteriovenous fistula
- B. Intraocular neoplasm
  - 1. Melanoma
  - 2. Melanocytoma
  - 3. Juvenile xanthogranuloma
  - 4. Retinoblastoma
  - 5. Leukemia
- C. Uveitis
  - 1. Open angle
  - 2. Angle blockage
    - a. Synechial angle-closure
    - b. Iris bombé with pupillary block
- D. Lens-induced glaucoma
  - 1. Subluxation-dislocation and pupillary block
  - 2. Spherophakia and pupillary block
  - 3. Phacolytic glaucoma
- E. Glaucoma after surgery for congenital cataract
  - 1. Lens material blockage of trabecular meshwork
  - 2. Pupillary block
  - 3. Chronic open-angle glaucoma
- F. Steroid glaucoma
- G. Glaucoma secondary to rubeosis
  - 1. Retinoblastoma
  - 2. Coats disease
  - 3. Medulloepithelioma
- H. Secondary angle-closure glaucoma
  - 1. Retinopathy of prematurity
  - 2. Microphthalmos
  - 3. Nanophthalmos
  - 4. Congenital iris–lens membrane
- I. Glaucoma associated with increased venous pressure
  - 1. Idiopathic
  - 2. Orbital disease
- J. Congenital rubella syndrome

From Nelson LB, Calhoun JH, Harley RD. *Pediatric Ophthalmology*. 3rd ed. Philadelphia: WB Saunders; 1991:259.

idiopathic arthritis (JIA). An intraocular lens may be placed in a child with a traumatic cataract if the intraocular structures that support the lens are intact. The management of a cataract goes well beyond cataract surgery. Amblyopia must be treated with occlusion of the sound eye, often for several years, until stable visual acuity can be demonstrated. Children who have had cataract surgery must be monitored indefinitely to evaluate for delayed complications such as glaucoma and retinal detachment.

GLAUCOMA IN CHILDHOOD

Pediatric glaucomas result from abnormalities of the aqueous outflow pathways (primary congenital glaucoma) or abnormalities that affect other parts of the eye (secondary glaucoma). Several genes causing primary congenital glaucoma, usually autosomal recessive, have been identified. Primary congenital glaucoma is bilateral in about 65% of patients. This presents as a classic triad consisting of blepharospasm, photophobia, and epiphora (Fig. 32.13). The cornea may be cloudy due to edema resulting from elevated intraocular pressure. The cornea also enlarges and the axial length of the eye may increase with elevated intraocular pressure. Onset usually occurs in the 1st year of life; only 25% are present at birth. If glaucoma presents after the age of 5 years, it is known as primary juvenile open-angle glaucoma. The natural history of untreated primary congenital glaucoma is blindness resulting from progressive corneal opacification and optic nerve damage. Treatment is surgical although eye pressure lowering medications such as topical β blockers and topical or oral carbonic anhydrase inhibitors may be used as temporizing measures. Even with treatment final visual acuity is worse than 20/50 in more than 50% of the patients.

Secondary glaucoma may present similarly to primary glaucoma but is associated with other factors such as ocular trauma, inflammation, prolonged steroid use, or cataract. Some systemic conditions such

FIGURE 32.13 Bilateral congenital glaucoma in a 4-month-old infant. Note the large corneas and epiphora.

as neurofibromatosis are also associated with secondary glaucoma. The differential diagnosis of congenital glaucoma includes conditions that demonstrate corneal opacities (Table 32.12) or an enlarged cornea (Table 32.13). Epiphora also occurs with conjunctivitis, corneal trauma, and nasolacrimal duct obstruction (NLDO). Photophobia is observed in infants with corneal trauma, corneal deposits, cystinosis, and inflammation (uveitis). Corneal opacification can also be found in infants with corneal dystrophies, metabolic storage diseases such as mucopolysaccharidoses, and forceps-related obstetric trauma.

The diagnosis of primary congenital glaucoma or secondary glaucoma is generally confirmed by performing an examination with the patient under anesthesia. The child needs to be quiet and very cooperative in order to get an accurate intraocular pressure reading and a careful examination of the cornea and anterior segment structures. The diagnosis rests on a constellation of abnormal ocular findings, including elevated intraocular pressure, corneal enlargement, anomalies of the drainage angle, and signs of damage to the optic nerve in conjunction with medical history.

CHILDHOOD UVEITIS

Uveitis is defined as inflammation of the uveal tissue of the eye, which includes the iris, ciliary body, and choroid. Inflammation can involve any or all of these structures, and terms such as iritis, iridocyclitis, choroiditis, and chorioretinitis are used to designate which portion of the uveal tissue is involved. Anatomic location such as anterior, posterior, intermediate, or panuveitis are useful in determining etiology (Table 32.14). JIA is the most common cause of childhood anterior uveitis. JIA uveitis is most common in the pauciarticular form, when the onset occurs before the age of 7 years, and when the antinuclear antibody blood test is positive. Girls are at higher risk than boys; 10-15% of children with JIA develop uveitis and 10% of those who develop uveitis do so prior to the diagnosis of JIA. It is common for children with JIA to have no symptoms of inflammation in the eye. Despite the lack of symptoms, uveitis can cause severe vision loss due to the development of edema or deposition of calcium (band keratopathy) in the cornea or retinal edema (Fig. 32.14). A cataract and/or glaucoma may result from inflammation in the eye or chronic use of steroids used to quiet the inflammation. The pupil may have an irregular shape as a result of adhesions to the underlying lens (posterior synechiae). Visual impairment occurs in up to 40% of children with JIA uveitis and blindness occurs in 10% of affected eyes. For this reason there are screening guidelines for the recommended frequency of eye exams based on the risk factors that predispose patients with JIA to uveitis including category of arthritis (oligoarthritis vs polyarthritis), age of onset of arthritis, presence of ANA positivity, and duration of disease (Table 32.15).

The diagnosis of uveitis can be made from an eye examination. Because uveitis can be caused by infections, trauma, autoimmune disorders, and may be idiopathic, evaluation of the cause of the uveitis requires a thorough pediatric physical examination as well as supplementary radiologic and laboratory testing. A chest radiograph may demonstrate tuberculosis and sarcoidosis. Serologic evaluation may include tests for syphilis, sarcoidosis, JIA, Lyme disease, herpes, measles, and toxoplasmosis. In boys, haplotype testing for human leukocyte antigen B27 may be indicated because of the association between iritis and pauciarticular arthritis that may later evolve into ankylosing spondylitis.

The management of iritis in children is the elimination of intraocular inflammation. In some cases of noninfectious uveitis, local treatment with topical corticosteroid drops or periocular corticosteroid injections may control the inflammation. In many cases, local corticosteroids are not sufficient to control chronic uveitis. Immunomodulatory agents such as oral corticosteroids and corticosteroid-sparing agents, including nonsteroidal antiinflammatory drugs (NSAIDs), antimetabolites, T cell inhibitors, alkylating agents, and antitumor necrosis factor biologic agents are options. Short courses of corticosteroids may be used, but corticosteroid-sparing drugs are the 1st-line therapy for long-term use due to the many side effects of corticosteroids. Mydriatic drops are used to prevent the formation of posterior synechiae.

Toxoplasmosis caused by the intracellular parasite *Toxoplasma gondii* is the most common cause of posterior uveitis in children. Most ocular toxoplasmosis in the pediatric age group is probably acquired from the mother during pregnancy. In some instances, the infection is inactive at birth and goes unrecognized until inflammation occurs. Toxoplasmosis that is active at birth may result in widespread fetal tissue damage or may be associated with chorioretinitis, encephalomyelitis, and visceral disease. The diagnosis of toxoplasmosis is based on clinical findings, intracranial calcification in some children, and laboratory tests for specific immunoglobulin G and immunoglobulin M antibodies. Treatment of isolated ocular toxoplasmosis does not require treatment unless it threatens vision. When treatment is indicated, it involves the use of 1 or more antimicrobial drugs. The most common therapy consists of combination therapy with pyrimethamine and sulfadiazine. Steroids may be given in combination with antibiotics. Intravitreal clindamycin with dexamethasone may be as effective as systemic therapies. Several other entities can simulate uveitis in children and must be considered. These entities include retinoblastoma, leukemia, lymphoma, juvenile xanthogranuloma, and an intraocular foreign body.

NASOLACRIMAL PROBLEMS IN CHILDHOOD

The nasolacrimal system consists of tear-secreting glands and a drainage system. The lacrimal gland, located in the superotemporal orbit, is the primary producer of tears; accessory lacrimal glands in the upper eyelid supplement its output. The lacrimal drainage apparatus begins with puncta on the nasal aspect of the upper and lower eyelid margins. The puncta continue as canaliculi that course nasally to empty into the lacrimal sac. The lacrimal sac in turn drains inferiorly through the nasolacrimal duct just under the inferior turbinate in the nose (Fig. 32.15).

The most common developmental anomaly of the nasolacrimal drainage system is **NLDO**, which occurs in up to 20% of infants. A thin

TABLE 32.12 STUMPED: Differential Diagnosis of Neonatal Corneal Opacities

Diagnosis	Laterality	Opacity	Ocular Pressure	Other Ocular Abnormalities	Natural History	Inheritance
S – Sclerocornea	Unilateral or bilateral	Vascularized, blends with sclera, clearer centrally	Normal (or elevated)	Cornea plana	Nonprogressive	Sporadic
T – Tears in endothelium and Descemet membrane						
Birth trauma	Unilateral	Diffuse edema	Normal	Possible hyphema, periorbital ecchymoses	Spontaneous improvement in 1 mo	Sporadic
Infantile glaucoma	Bilateral	Diffuse edema	Elevated	Megalocornea, photophobia and tearing, abnormal angle	Progressive unless treated	Autosomal recessive
U – Ulcers						
Herpes simplex keratitis	Unilateral	Diffuse with geographic epithelial defect	Normal	None	Progressive	Sporadic
Congenital rubella	Bilateral	Disciform or diffuse edema, no frank ulceration	Normal or elevated	Microphthalmos, cataract, pigment epithelial mottling	Stable, may clear	Sporadic
Neurotrophic – exposure	Unilateral or bilateral	Central ulcer	Normal	Lid anomalies, congenital sensory neuropathy	Progressive	Sporadic
M – Metabolic (rarely present at birth) (mucopolysaccharidoses IH, IS; mucolipidoses type IV)*	Bilateral	Diffuse haze, denser peripherally	Normal	Few	Progressive	Autosomal recessive
P – Posterior corneal defect	Unilateral or bilateral	Central, diffuse haze or vascularized leukoma	Normal or elevated	Anterior chamber cleavage syndrome	Stable; sometimes early clearing or vascularization	Sporadic, autosomal recessive
E – Endothelial dystrophy						
Congenital hereditary endothelial dystrophy	Bilateral	Diffuse corneal edema, marked corneal thickening	Normal	None	Stable	Autosomal dominant or recessive
Posterior polymorphous dystrophy	Bilateral	Diffuse haze, normal corneal thickness	Normal	Occasional peripheral anterior synechiae	Slowly progressive	Autosomal dominant
Congenital Hereditary stromal dystrophy	Bilateral	Flaky, feathery stromal opacities; normal corneal thickness	Normal	None	Stable	Autosomal dominant
D – Dermoid	Unilateral or bilateral	White vascularized mass, hair, lipid arc	Normal	None	Stable	Sporadic

*Mucopolysaccharidosis IH, Hurler syndrome; mucopolysaccharidosis IS, Scheie syndrome.
From Nelson LB, Calhoun JH, Harley RD. *Pediatric Ophthalmology*. 3rd ed. Philadelphia: WB Saunders; 1991:210.

mucosal membrane at the distal end of the duct, the valve of Hasner, is the most common cause of obstruction. Typically, the infant has epiphora and a mucopurulent discharge that causes matting of the eyelids beginning at about 1 month of age. Pressure applied to the lacrimal sac with a finger or cotton swab often results in reflux of cloudy fluid from the puncta. The infection is usually polymicrobial, but a bacteriologic diagnosis is not necessary for clinical management. Eyelash washes with dilute baby shampoo can decrease the frequency of infections. Topical antibiotics can be used to decrease purulence but this likely leads to resistant organisms. Recurrent infections may be considered an indication for early probing. Lacrimal sac massage may push fluid through the mucosal membrane and thereby open the duct, but the pressure applied to the lacrimal sac needs to be forceful. Most NLDOs will spontaneously resolve. If resolution does not occur within the 1st year of life, probing of the duct can be done and is effective in 90% of cases. Effectiveness of nasolacrimal duct probing decreases after the age of 18 months. A silicon stent can be placed to maintain an open duct, which increases the success of long-term patency.

NLDO must be differentiated from atresia of the puncta or canaliculi causing tearing but not infection and lacrimal-cutaneous fistula

TABLE 32.13 Differential Diagnosis of Enlarged Cornea

Anterior	Primary Infantile Simple Megalocornea	Megalophthalmos	Glaucoma with Buphthalmos
Inheritance	Autosomal dominant (?)	X-linked recessive (male preponderance)	Sporadic
Time of appearance	Congenital	Congenital	1st year of life
Bilaterality	Bilateral Symmetric	Bilateral Symmetric	Unilateral or bilateral Asymmetric
Natural history	Nonprogressive	Nonprogressive	Progressive
Symptoms	None	None	Photophobia, epiphora
Corneal clarity	Clear	Clear or mosaic dystrophy	Diffuse edema, tears in Descemet membrane
Intraocular pressure	Normal	Elevated in some adults	Elevated
Corneal diameter	13-18 mm	13-18 mm	13-18 mm
Corneal thickness	Normal	Normal	Thick
Keratometry	Normal	Normal; astigmatism	Flat
Gonioscopy	Normal	Excessive mesenchymal tissue	Excessive mesenchymal tissue
Globe diameter (A scan)	23-26 mm	23-26 mm	27-30 mm
Major ocular complications	None	Lens dislocation; cataract, <40 yr; secondary glaucoma	Optic disk damage, late corneal edema
Associated systemic disorders	None	Occasionally Marfan and other skeletal abnormalities	None consistent

From Nelson LB, Calhoun JH, Harley RD. *Pediatric Ophthalmology*. 3rd ed. Philadelphia: WB Saunders; 1991:201.

TABLE 32.14 Differential Diagnosis of Uveitis

Anterior Uveitis
Juvenile idiopathic arthritis
Trauma
Sarcoidosis
Herpes
Syphilis
Lyme disease
Fuchs heterochromic iridocyclitis
Kawasaki syndrome
Tubulointerstitial nephritis and uveitis syndrome
Behçet disease
Orbital pseudotumor
Idiopathic

Intermediate Uveitis
Pars planitis
Sarcoidosis
Tuberculosis
Juvenile xanthogranuloma
Lyme disease
Idiopathic

Posterior Uveitis and Panuveitis
Toxoplasmosis
Toxocariasis
Herpes, rubella, rubeola, measles
Histoplasmosis
Syphilus
Sympathetic ophthalmia
Sarcoidosis
Bartonella
Candida albicans
Lyme disease
Familial juvenile systemic granulomatosis (Blau syndrome)
Diffuse unilateral subacute neuroretinitis (DUSN)
Tuberous sclerosis
Vogt–Koyanagi–Harada syndrome
Behçet disease
Idiopathic

From Basic and Clinical Science Course, Section 6. *Ophthalmology and Strabismus*. San Francisco: American Academy of Ophthalmology; 2013-2014;268, Table 22-1.

TABLE 32.15 Frequency of Ophthalmic Examination in Patients with Juvenile Idiopathic Arthritis

Type	ANA	Age at Onset	Disease Duration (yr)	Risk Category	Eye Exam Frequency (mo)
Oligoarthritis or polyarthritis	+	≤6	≤4	High	3
	+	≤6	>4	Moderate	6
	+	≤6	>7	Low	12
	+	>6	≤4	Moderate	6
	+	>6	>4	Low	12
	–	≤6	≤4	Moderate	6
	–	≤6	>4	Low	12
	–	>6	NA	Low	12
Systemic disease	NA	NA	NA	Low	12

NA, not applicable.
Modified from Cassidy J, Kivlin J, Lindsley C, et al. Ophthalmologic examinations in children with juvenile rheumatoid arthritis. *Pediatrics*. 2006;117:1843-1845.

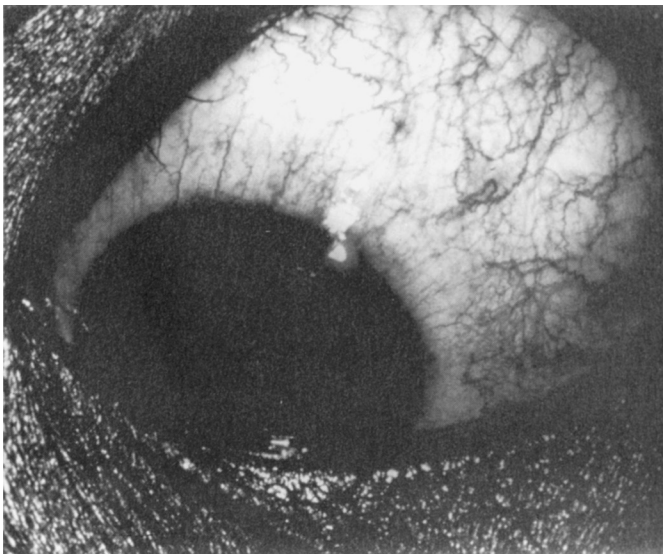

FIGURE 32.14 Ciliary flush associated with iritis. Note the straight, radially oriented vessels extending out from the iris. (From Reilly BM. *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991:41.)

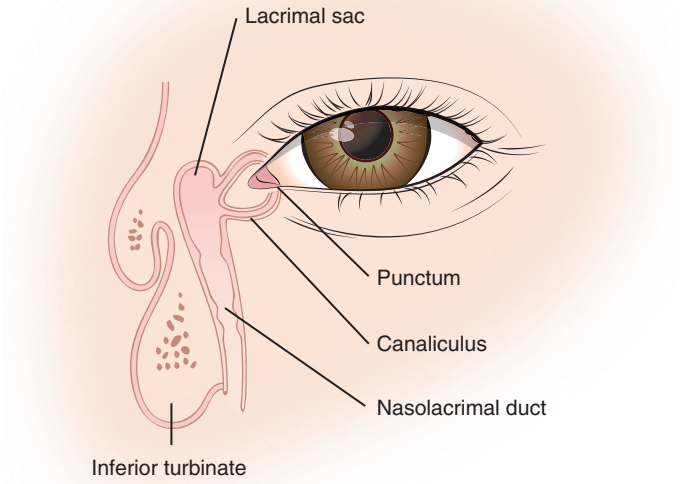

FIGURE 32.15 Anatomy of the nasolacrimal drainage system. (Modified from *Rev Ophthalmol*. 2001;8:122. Reprinted with permission from Jobson Publishing: New York.)

causing tears to drain to the skin surface. These conditions require surgery to re-form the canalicular system and puncta and repair the fistula if present. NLDO should be differentiated from infectious conjunctivitis, especially gonococcal, chlamydial, and herpetic infections. Chronic tearing occurs in congenital glaucoma in addition to blepharospasm and photophobia.

A **dacryocystocele** is a variation of congenital NLDO that occurs in newborns. These infants present with a bluish mass in the nasoorbital region below the medial canthal tendon. This mass is a dilated lacrimal sac that has both distal obstruction from a membrane and proximal obstruction from a 1-way valve effect from an incompetent valve of Rosenmüller (Fig. 32.16). A hemangioma or dermoid cyst may have a bluish hue but hemangiomas typically do not present at birth. An encephalocele or dermoid cyst may also appear to be a bluish mass but will lie above the medial canthus. On occasion, the dilated sac is accompanied by bulging of the nasal mucosa at the distal end of the nasolacrimal duct. The nasal mucocele can compromise the infant's breathing. If the dacryocystocele fails to resolve with topical antibiotics and massage, or if cellulitis develops, systemic antibiotics and surgical decompression must be considered. Decompression is accomplished by relieving the distal obstruction by probing the nasolacrimal duct, removing any nasal cyst, and possibly placing a stent.

RED EYE

The term *red eye* usually refers to inflammation of the conjunctiva that causes the eye to appear red. Much less commonly (and much more seriously), the sclera is injected. Causes of red eye include infection of the ocular surface (cornea, conjunctiva, and sclera), allergy, intraocular inflammation, glaucoma, foreign body, and trauma. Evaluation must be directed toward discerning whether a child's red eye is caused by a benign condition that will spontaneously resolve (viral conjunctivitis) or easily be treated with topical medication (bacterial conjunctivitis) or whether the cause is potentially vision threatening (iritis, corneal

FIGURE 32.16 Dacryocystocele of the left lacrimal sac in a 2-week-old infant. The dacryocystocele resolved with a probing of the left tear duct.

ulceration, glaucoma) and requires urgent ophthalmologic evaluation (Table 32.16). Signs that should raise concerns for a serious etiology of red eye are in an immunocompromised host, severe pain, proptosis, limitation of eye movements, opacified cornea, abnormal pupil response, or lack of response to therapy.

In taking the history, the examiner should inquire about laterality, onset, associated illnesses, contact with others with "pink eye," the presence of pain or itching, the characteristics of any discharge (watery, mucoid, purulent), and blurring of vision. The examination of the child should start with as precise a measurement of visual acuity as possible. The presence and type of discharge should be noted. Inspection of the surface of the eye with a penlight should determine whether the cornea is clear. Fluorescein staining of the cornea to assess for a corneal abrasion should be done. The red reflex should be checked. The presence of foreign bodies should be considered.

The most common cause of a red eye in a child is infectious conjunctivitis (Table 32.17). *Streptococcus pneumoniae* is the most frequent bacterial pathogen, followed by some *Haemophilus* species and *Moraxella*. However, infections from *Haemophilus* species have decreased because of immunization. In hospitalized patients, staphylococcal infections (including methicillin-resistant *Staphylococcus aureus*) are more common. A bacterial culture is not necessary in mild cases of suspected bacterial conjunctivitis because the infection tends to be self-limiting but may last up to 2 weeks. Treatment with a broad-spectrum *topical* antibiotic may relieve symptoms and shorten the course of infection, allowing the child to return to school or daycare. Topical antibiotic options include trimethoprim–polymyxin B, erythromycin, gentamicin or tobramycin, ciprofloxacin, moxifloxacin, gatifloxacin, azithromycin, and sulfacetamide. Sulfacetamide preparations are inexpensive but have a narrower range of effectiveness and cause a great deal of stinging. Sulfa drugs also have an association with Stevens–Johnson syndrome. Gentamicin can cause redness, which can cause difficulty in determining whether or not the conjunctivitis is treated. The aminoglycosides are less effective with gram-positive organisms, particularly streptococcal species. Trimethoprim sulfate/polymyxin B is bacteriostatic and a 7-10 day course of therapy is recommended. The fluoroquinolones are rapidly effective but have different dosing recommendations. Azithromycin has a very short course but can be costly. Steroid-antibiotic combinations should be avoided because of the risk of worsening a bacterial corneal ulcer or an unsuspected herpes simplex infection.

Viral conjunctivitis tends to be associated with a watery or mucoid discharge. Follicles may be visible with low magnification on the palpebral conjunctiva, and a preauricular lymph node can often be palpated. Adenovirus is common pathogen; epidemic outbreaks are frequent. In children as old as 2 years, adenovirus can manifest with severe periorbital edema and erythema that mimics bacterial preseptal or orbital cellulitis; a conjunctival pseudomembrane is common in this setting. Adenoviruses types 8, 19, 35, enterovirus 70, and coxsackie 24 are associated with subconjunctival hemorrhages or hemorrhagic conjunctivitis. Pharyngoconjunctival fever, conjunctivitis accompanied by a sore throat and fever, is associated with adenovirus types 3 and 7. Cultures are not usually necessary but can be performed if there is a question of etiology. Antibiotics are ineffective in adenovirus infections. Treatment is largely supportive, with cool compresses and artificial tears providing symptomatic relief. Adenovirus is highly contagious so careful attention to hygiene should be taken among family members, caregivers, and contacts to prevent the spread of infection.

Less frequent causes of viral conjunctivitis are herpes simplex and varicella. These may be associated with vesicular involvement of the eyelid and face. Treatment with oral antiviral medications can be used if lesions are very near the cornea or there is corneal involvement. Oral antivirals are also considered in individuals who are immunocompromised. Topical antivirals are also used in patients with corneal involvement. Topical corticosteroid medications are contraindicated in herpetic infections because of the potential for worsening the infection. However the ophthalmologist often uses topical steroids to control inflammation after the viral infection has been treated.

The DNA poxvirus *Molluscum contagiosum* can cause a chronic conjunctivitis when lesions are located on the eyelid margin (Fig. 32.17). The conjunctivitis is caused by release of poxvirus particles into the tear film. Additional waxy, umbilicated lesions are oftentimes found elsewhere on the face. The infection may be self-limited but treatment of more severe cases requires incision and debridement of the central core from each lesion.

Allergic conjunctivitis manifests with a bilateral watery or mucoid discharge and must always be considered in the differential diagnosis of bilateral red eyes. The child may rub the eyes because of pruritus; nasal allergic symptoms may also be present. About 80% of individuals with allergies have ocular symptoms and these may occur in isolation. A more severe form of allergic conjunctivitis, **vernal keratoconjunctivitis (VKC)**, tends to occur in males in the first 2 decades of life and is seasonal, occurring in the spring and fall. Ulceration of the cornea can occur. Usually the ulceration is sterile but it can impair vision. Treatment of allergic conjunctivitis includes topical antihistamines, mast cell stabilizers, or a combination of the 2. Systemic treatment of allergies often improves the ocular symptoms. In severe cases of allergic conjunctivitis or VKC, steroids or cyclosporines can be used.

Systemic syndromes must also be considered in a child with a red eye. In the Stevens–Johnson syndrome, conjunctival inflammation is associated with other mucous membrane or cutaneous involvement. This disease can have severe ophthalmic consequences as a result of conjunctival scarring, changes of the eyelid position, and dry eye syndrome. Kawasaki syndrome is a febrile illness of young children who frequently manifest bilateral nonpurulent conjunctival injection and, in rare cases, iritis. Ophthalmic consultation may be indicated to assist in the diagnosis and management of children with Stevens-Johnson and Kawasaki syndromes.

EYELID ABNORMALITIES

Congenital abnormalities of the eyelids can be severe as in the case of cryptophthalmos, in which there is a failure of differentiation of eyelid structures and the skin passes uninterrupted from the forehead to the cheek. This is often associated with corneal abnormalities and systemic

TABLE 32.16 The Red Eye

Condition	Cause	Signs/Symptoms	Treatment
Bacterial conjunctivitis	*Haemophilus influenzae*, *H. influenzae aegyptius*, *Streptococcus pneumoniae*, *Neisseria gonorrhoeae*, *Staphylococcus aureus*, *Yersinia* species, cat-scratch bacillus less common	Mucopurulent unilateral or bilateral discharge, normal vision, photophobia usually absent Conjunctival injection and edema (chemosis); gritty sensation	Topical antibiotics: systemic ceftriaxone for gonococcus, *H. influenzae*
Viral conjunctivitis	Adenovirus, ECHO virus, coxsackievirus	As above; may be hemorrhagic, unilateral enlarged preauricular lymph nodes	Self-limited
Neonatal conjunctivitis	*Chlamydia trachomatis*, gonococcus, chemical (silver nitrate), *S. aureus*	Palpebral conjunctival follicle or papillae; as above	Ceftriaxone for gonococcus and oral erythromycin for *C. trachomatis*
Allergic conjunctivitis	Seasonal pollens or allergen exposure	Itching, incidence of bilateral chemosis (edema) greater than that of erythema, tarsal papillae	Antihistamines, steroids, cromolyn
Keratitis	Herpes simplex, adenovirus, *S. pneumoniae*, *S. aureus*, *Pseudomonas* species, *Acanthamoeba* species, chemicals	Severe pain, corneal swelling, clouding, limbus erythema, hypopyon, cataracts; contact lens history with amebic infection	Specific antibiotics for bacterial/fungal infections; keratoplasty, acyclovir for herpes
Endophthalmitis	*S. aureus*, *S. pneumoniae*, *Candida albicans*, associated surgery or trauma	Acute onset, pain, loss of vision, swelling, chemosis, redness; hypopyon and vitreous haze	Antibiotics
Anterior uveitis (iridocyclitis)	JIA, reactive arthritis, sarcoidosis, Behçet disease, Kawasaki disease, inflammatory bowel disease	Unilateral/bilateral; erythema, ciliary flush (in circumcorneal area), irregular pupil, iris adhesions; pain, marked photophobia, small pupil, poor vision, no discharge	Topical steroids, plus therapy for primary disease
Posterior uveitis (choroiditis)	Toxoplasmosis, histoplasmosis, *Toxocara canis*	No sign of erythema, decreased vision, no discharge	Specific therapy for pathogen
Episcleritis/scleritis	Idiopathic autoimmune disease (e.g., SLE, Henoch–Schönlein purpura)	Localized pain, intense erythema, unilateral; blood vessels bigger than in conjunctivitis; scleritis may cause globe perforation, no discharge	Episcleritis is self-limiting; topical steroids for fast relief
Foreign body	Occupational exposure	Unilateral, red, gritty feeling; visible or microscopic size	Irrigation, removal; check for ulceration
Blepharitis	*S. aureus*, *S. epidermidis*, seborrheic, blocked lacrimal duct: rarely, molluscum contagiosum, *Pthirus pubis, Pediculosis capitis*	Bilateral, irritation, itching, hyperemia, crusting, affecting lid margins	Topical antibiotics, warm compresses
Dacryocystitis	Obstructed lacrimal sac: *S. aureus*, *H. influenzae*, pneumococcus	Pain, tenderness, erythema and exudate in area of lacrimal sac (inferomedial to inner canthus); tearing (epiphora); possible orbital cellulitis	Systemic, topical antibiotics; surgical drainage
Dacryoadenitis	*S. aureus*, *Streptococcus* species, CMV, measles, EBV, enteroviruses, trauma, sarcoidosis, leukemia	Pain, tenderness, edema, erythema over gland area (upper temporal lid); fever, leukocytosis	Systemic antibiotics; drainage of orbital abscesses
Orbital cellulitis	Paranasal sinusitis: *H. influenzae*, *S. aureus*, *S. pneumoniae*, other *Streptococcus* species Trauma: *S. aureus* Fungi: *Aspergillus*, *Mucor* species if immunodeficient	Rhinorrhea, chemosis, vision loss, painful extraocular motion, proptosis, opthalmoplegia, fever, lid edema, leukocytosis *S. aureus*	Systemic antibiotics (postseptal cellulitis), drainage of orbital abscesses
Periorbital cellulitis	Trauma: *S. aureus*, *Streptococcus* species Bacteremia: *H. influenzae*, pneumococci, *S. pyogenes*	Cutaneous erythema, warmth, normal vision, minimal involvement of orbit, fever, leukocytosis, toxic appearance	Systemic antibiotics (preseptal cellulitis)

CMV, cytomegalovirus; EBV, Epstein–Barr virus; ECHO, enteric cytopathogenic human orphan; JIA, juvenile idiopathic arthritis; SLE, systemic lupus erythematosus.

Data from Rosenbaum JT, Nozik RA. Uveitis: Many diseases, one diagnosis. *Am J Med.* 1985;79:545-547; Elkington AR, Khaw PT. The red eye. *BMJ.* 1988;296:1720-1724; Wilhemus KR. The red eye. Infectious conjunctivitis, keratitis, endophthalmitis, and periocular cellulitis. *Infect Dis Clin North Am.* 1988;2:99-116; Forrester JV. Uveitis: Pathogenesis. *Lancet.* 1991;338:1498-1501; Gioliotti F. Acute conjunctivitis of childhood. *Pediatr Ann.* 1993;22:353-356.

Modified from Behrman RE, Kliegman RM. *Nelson Essentials of Pediatrics*. 2nd ed. Philadelphia: WB Saunders; 1994: 357-358.

TABLE 32.17 Conjunctivitis: Differential Diagnosis

	Clinical Findings				
Cause	**Unilateral or Bilateral**	**Discharge**	**Lids**	**Onset/Course**	**Treatment**
Viral* (usually adenovirus)	Bilateral	Thin, mucoid	Follicular	Gradual Upper respiratory tract infection? Preauricular adenopathy	Compresses
Herpes simplex	Unilateral	Thin, mucoid	Follicular	Gradual Keratitis Dendritic ulcer	Acyclovir
Bacterial	Unilateral or bilateral	Purulent	Papillary, purulent	Gradual	Topical antibiotics
Gonococcal	Unilateral	Purulent	Edema, inflamed	Hyperacute	Systemic antibiotics
Chlamydial	Unilateral or bilateral	Thin, mucoid	Follicular	Indolent Persistent Neonatal period Sexually active	Oral erythromycin any age or tetracycline (>10 yr of age)
Allergic	Bilateral	Watery	Papillary	Gradual Seasonal Pruritic	Topical vasoconstrictors Systemic antihistamine Topical steroids
Vernal	Bilateral	Watery	Giant papillary	Adolescence Seasonal	Cromolyn?
Contact lens irritation	Bilateral	Watery	Giant papillary	Lenses	Adjust lens Change solution
Chemical	Unilateral or bilateral	Watery	Variable	Acute	Irrigate Remove irritant

*Undifferentiated viral conjunctivitis, not caused by herpesvirus infection.
Modified from Reilly BM. *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991:46.

FIGURE 32.17 Chronic eczematoid and follicular conjunctivitis in only the left eye, caused by *Molluscum contagiosum,* in a 5-year-old. Note the elevated lesions on the lateral aspect of the left upper eyelid.

abnormalities. Colobomas of the eyelid can occur and are usually on the upper lid and can range in severity from a notch to the entire length of the eyelid. Eyelid colobomas are often associated with Goldenhar and CHARGE syndromes. Surgery can be done to reconstruct the eyelids. More common eyelid abnormalities include entropion (inward turning of the eyelid margin), ectropion (eversion of the eyelid margin), epiblepharon (in which a horizontal fold of skin in the lower eyelid causes the lashes to rub against the cornea), and distichiasis (in which an accessory row of eyelashes is more posterior than the normal ones and can rub against the cornea). All these may resolve spontaneously or, if necessary, can be corrected with eyelid surgery. Epiblepharon tends to be well tolerated by patients. Epicanthus, a crescent-shaped fold of skin, is usually most prominent in the upper eyelid that can make the child appear esotropic by obscuring the underlying sclera.

Congenital ptosis (Fig. 32.18), droopiness of the upper eyelid, is usually caused by abnormal development of the levator muscle. Other causes in children are trauma, congenital 3rd nerve palsy, and congenital Horner syndrome. Acute onset of ptosis in the absence of trauma requires evaluation for new-onset Horner syndrome, which may be associated with neuroblastoma, and evaluation for a 3rd nerve palsy, which may be associated with an intracranial mass. A child with congenital ptosis needs to be monitored for amblyopia. Treatment of ptosis is delayed until the child is several years old unless it is causing amblyopia due to occlusion of the visual axis, an induced astigmatism difficult to treat with glasses, or when severe chin-up head posture is necessary to allow the child to see (Fig. 32.19). Surgical correction consists of resection of the levator muscle or suspension of the upper eyelid to the frontalis muscle with a silicon sling or autogenous or cadaveric fascia lata.

ORBITAL TUMORS

Orbital tumors, either benign or malignant, may occur in children. The space-occupying lesions can present with proptosis, swelling or discoloration of the eyelids, ptosis, or strabismus. Some of the most common benign tumors are vascular lesions. **Hemangiomas** occur in 1-3% of term newborns and are more common in premature infants. Hemangiomas are classified by depth of skin involvement and type of orbital involvement. The natural history involves rapid proliferation over the 1st several months of life. Ulceration, hemorrhage, and occlusion or induced astigmatism of the eye causing amblyopia can occur. After the 1st year of life the lesion begins to regress. Systemic diseases such as

FIGURE 32.18 Congenital ptosis of the right upper eyelid. The child adopted a compensatory chin-up head posture to allow use of both eyes together and did not have amblyopia.

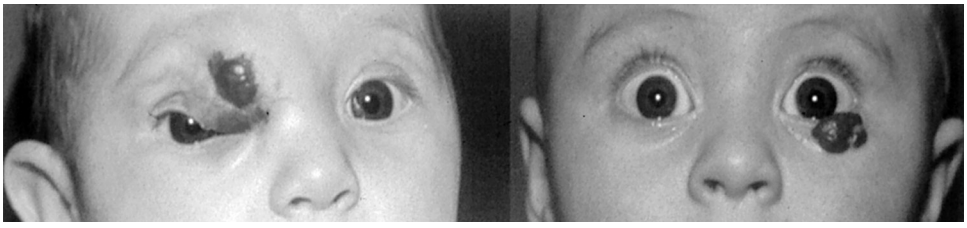

FIGURE 32.19 *Left,* A capillary hemangioma of the right upper eyelid and anterior orbit. This lesion necessitated treatment because it was causing amblyopia from astigmatism as a result of pressure against the globe and by occlusion of the visual axis. *Right,* This capillary hemangioma of the left lower eyelid is not causing amblyopia and does not necessitate treatment unless it grows substantially.

PHACE syndrome (posterior fossa malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, eye abnormalities) and multiple cutaneous hemangiomas with hepatic hemangiomas may have an orbital or eyelid hemangioma as the presenting finding. First-line treatment consists of oral propranolol 1-3 mg/kg/day divided into 3 oral doses. Side effects include bradycardia, hypoglycemia, hypotension, somnolence, bronchospasm, and cough. Treatment initiation is done under medical supervision and care is taken to administer the medicine with feeds to limit the side effects. Topical timolol maleate may be used with minimal side effects for superficial skin lesions but is not effective in deeper or orbital lesions. A pulsed dye laser can also be used to treat the superficial lesions. Propranolol has replaced steroids, vincristine, and interferon alfa-2a due to the unacceptably high side effect profiles of these other medications and the very rapid regression of hemangiomas using propranolol.

Lymphangiomas may cause proptosis. Most commonly these present in the 2nd or 3rd decade but may present in infancy. The size may increase with the onset of an upper respiratory infection. Lymphangiomas are usually managed conservatively but short courses of steroids can be used. Rapid expansion may occur if bleeding into the lesion occurs. This may require surgical intervention if the pressure in the orbit is threatening damage to the optic nerve.

Dermoid cysts are benign choristomas that arise from primitive dermal elements that develop in fetal suture lines. This tissue forms a keratinized epithelium cyst and includes hair follicles, sweat glands, and sebaceous glands. It most commonly occurs superotemporally in the zygomatic frontal suture but may be superonasal in the frontalnasal suture. Imaging can be valuable in confirming the diagnosis and determining if the dermoid extends into the orbit. If the cyst ruptures, a marked inflammatory reaction ensues so removal is recommended prior to the child becoming very active, which increases the chances of the child rupturing the cyst traumatically.

Malignant tumors of the orbit can rapidly enlarge, which make them difficult to differentiate from inflammatory and infectious causes. Rhabdomyosarcomas are the most common primary pediatric orbital tumor. Average age of onset is 5-7 years. Usually the tumor arises in the orbit but it can arise in the conjunctiva, eyelid, or uveal tissue. Patients present with rapidly progressing proptosis. Tumors need to be removed completely and chemotherapy or radiation may also be needed.

Neuroblastoma is the most common metastatic orbital tumor of childhood. It usually arises from the adrenal gland or sympathetic ganglion chain, hence the association with acquired Horner syndrome. Unilateral or bilateral proptosis and eyelid ecchymosis are the classic presentations. **Opsoclonus** (rapid, multidirectional eye movements) is a paraneoplastic syndrome associated with neuroblastoma and is not related to orbital involvement. The mean age of diagnosis of orbital metastasis of neuroblastoma is 2 years.

Other, less common orbital tumors in childhood are Ewing sarcoma, Burkitt lymphoma, leukemia, and Langerhans cell histiocytosis. Ewing sarcoma is the 2nd most common solid tumor metastatic to the orbit (after neuroblastoma). Orbital involvement occurs in 1-2% of children with leukemia and this must be differentiated from orbital infections.

OCULAR MANIFESTATIONS OF SYSTEMIC DISEASE

Neurologic Disease

Ocular abnormalities frequently accompany neurologic disease, and their detection can help in the localization and diagnosis of a specific condition. Abnormal findings of pupillary reaction, decreased visual acuity, or decreased color vision can indicate abnormities of the optic nerve, which can be associated with other neurologic conditions. An afferent pupillary defect is an important finding that may signify unilateral optic nerve disease. The condition may be intrinsic to the optic nerve such as a glioma in neurofibromatosis type 1, extrinsic such as an orbital tumor, applying pressure on the nerve (Fig. 32.20), or inflammation of the optic nerve as seen with **optic neuritis** in multiple sclerosis, neuromyelitis optica, and acute demyelinating

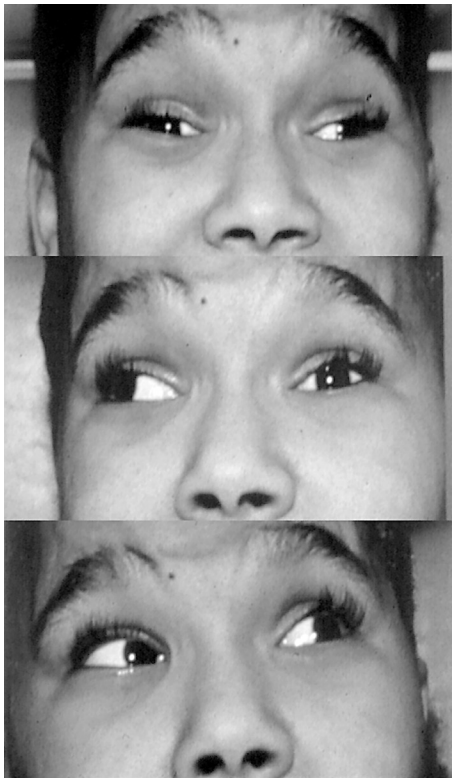

FIGURE 32.20 Left 3rd cranial nerve palsy. The boy has exotropia *(top),* limitation of adduction of his left eye *(middle),* and normal gaze to his left *(bottom).*

FIGURE 32.21 Papilledema of the right optic nerve.

encephalomyelitis (ADEM). Color perception and the visual acuity of the affected eye is usually reduced in comparison with that of the normal eye. The presence of an afferent pupillary defect necessitates a comprehensive eye examination and imaging studies of the orbit and brain.

Optic nerve edema (Fig. 32.21) is a worrisome sign because of its association with conditions that cause increased intracranial pressure. The elevation of the optic nerve and blurring of the disk margins must be differentiated from optic nerve drusen, which can have similar clinical appearances. Papilledema, swelling of the optic nerve as a result of increased intracranial pressure, is almost always bilateral. Visual acuity may be normal initially but decreases with chronic or severe optic nerve swelling.

Strabismus of truly acute onset is most often incomitant and caused by paralysis of extraocular muscles innervated by the 3rd or 6th cranial nerves. Cranial trauma, brain tumors, and viral infections are the most common causes of acute, incomitant strabismus in children. A 6th nerve palsy is of less localizing value than a 3rd nerve palsy because of the more tortuous intracranial course of the 6th nerve. This nerve can be affected by direct pressure from a mass and indirectly by conditions that cause increased intracranial pressure. A patient with an acute 6th nerve paralysis typically has esotropia that increases when he or she gazes toward the affected side (see Fig. 32.8). The patient may have a compensatory face turn toward the side of the lesion to allow fusion and prevent diplopia. A 3rd nerve paralysis usually causes exotropia and hypotropia of the involved eye (see Fig. 32.20). There may also be ipsilateral ptosis and a dilated, nonreactive pupil. A general approach to an acquired diplopia is noted in Fig. 32.22.

The **neurocutaneous syndromes** are a group of inherited disorders featuring multiple, discrete lesions of 2 or more organ systems, most commonly the skin and brain. These include neurofibromatosis, tuberous sclerosis, angiomatosis of the retina and cerebellum (von Hippel–Lindau disease), and encephalofacial or encephalotrigeminal angiomatosis (Sturge–Weber syndrome). Sometimes ataxia-telangiectasia, incontinentia pigmenti, and racemose angioma are included in neurocutaneous syndromes. Ocular involvement is common and may be a site of comorbidity or may serve as a marker for the overall condition. For example, Lisch nodules are benign tan, smooth-surfaced lesions on the iris surface that look somewhat gelatinous seen in **neurofibromatosis** type 1. They are usually not present until 3 years and thereafter about 10% of patients develop Lisch nodules per year. They do not have malignant potential. Other ocular features of neurofibromatosis type 1 (NF-1) are plexiform neurofibromas of the eyelid that give the eyelid margin a sigmoid shape and cause a variable amount of ptosis, astigmatism, and possibly amblyopia. Glaucoma is a significant problem in patients with NF-1. It is usually unilateral and associated with an ipsilateral plexiform neurofibroma of the upper eyelid. This is generally managed surgically. Visual prognosis in patients who develop glaucoma is poor.

Optic gliomas, such as low-grade pilocytic astrocytomas, have the potential to cause severe vision loss in patients with NF-1. The gliomas can involve 1 or both optic nerves as well as the optic chiasm. They are found prospectively in 15% of patients with NF-1 but cause visual symptoms such as vision loss or proptosis in only 1-5% of patients. Treatment of optic gliomas is reserved for lesions that are documented to be growing and causing visual morbidity, although it is difficult to determine which patients require treatment before vision loss occurs. NF-2 is much less common than NF-1 and involves primarily the acoustic nerves. Ocular involvement can consist of posterior lens opacities and hamartomas of the retina.

Tuberous sclerosis is an autosomal dominant disorder localized to chromosome 9. In children with tuberous sclerosis, angiofibromas of the eyelids and retinal lesions known as astrocytic hamartomas can occur but rarely cause significant problems with vision. The retinal lesions are not pathognomonic of tuberous sclerosis, inasmuch as similar lesions have been reported in NF-1 and in unaffected individuals.

Von Hippel–Lindau disease is autosomal dominant. Both benign and malignant tumors can occur in affected individuals as a result of a mutation in a tumor suppressor gene. Hemangioblastomas of the retina can produce a lipid exudate in the retina as a result of leakage from the thin vessel walls. This can lead to vision loss and ultimately a retinal detachment. Symptoms of vision loss do not

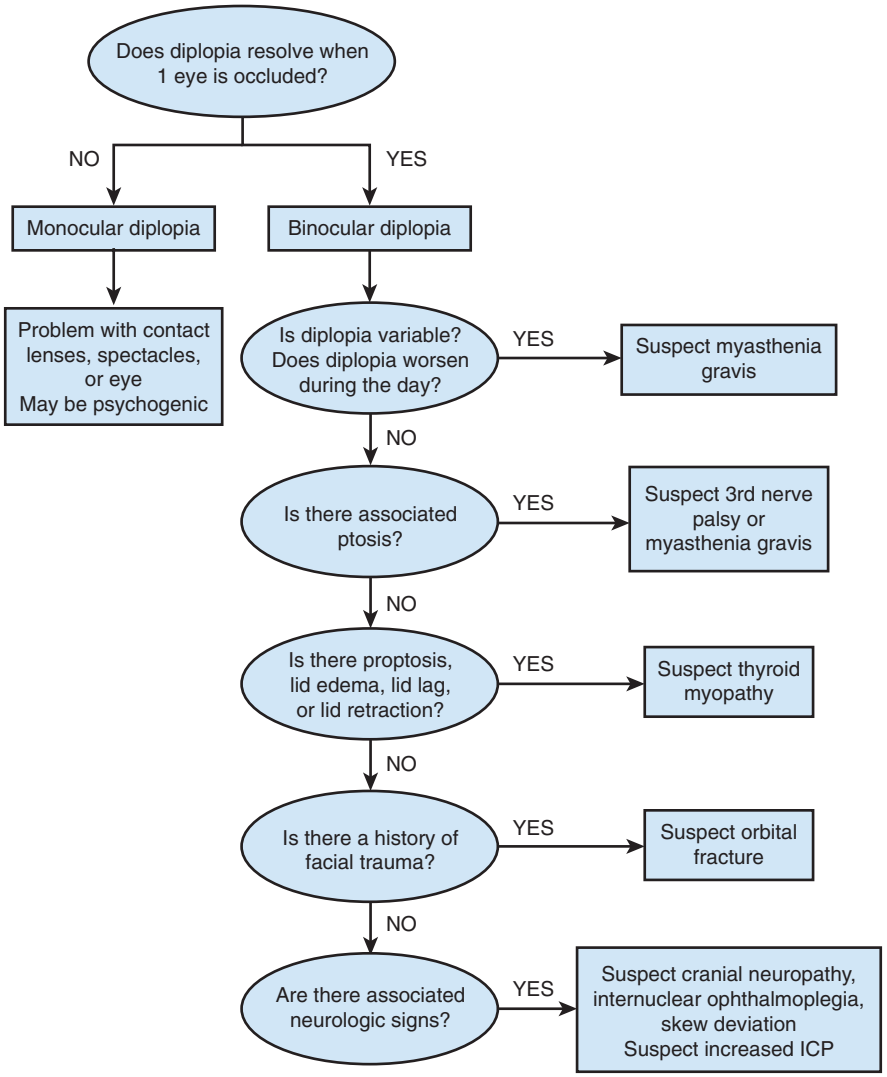

FIGURE 32.22 General approach to diplopia. The clinician should 1st distinguish monocular from binocular diplopia and, in patients with binocular diplopia, address the 5 questions on the right side of the figure. Only then should the clinician identify which muscle is weak, although this is unnecessary if the clinician already suspects myasthenia (from fatigability) or full 3rd nerve palsy (from weakness of the medial rectus, superior rectus, inferior rectus, and inferior oblique muscles, with or without a dilated pupil). Uncommon causes of diplopia and associated ptosis, not presented in the figure, are botulism, the Fisher variant of Guillain-Barré syndrome, and aberrant regeneration of the 3rd nerve. Uncommon causes of diplopia and associated orbital findings (e.g., proptosis) are carotid-cavernous fistula (which causes an orbital bruit), orbital tumor, and pseudotumor. ICP, intracranial pressure. (From McGee S. *Evidence-Based Physical Diagnosis*. 3rd ed. Philadelphia: Elsevier; 2012:522, Fig. 57-1.)

occur until extensive leakage or retinal detachment occurs. More than 65% of lesions can be treated effectively with laser photocoagulation. Because lesions are most effectively treated prior to the development of symptoms, children known to have von Hippel–Lindau disease should have regular eye examinations beginning at the age of 5 years.

Sturge–Weber syndrome is sporadic and ocular involvement is common. Abnormalities of the ocular circulation can occur when the eyelids are affected. These abnormalities range from increased conjunctival vascularity to angiomas of the choroid. Choroidal angiomas usually remain asymptomatic in childhood but can thicken in adolescence and cause degeneration of the overlying retina. Glaucoma is the most serious ocular complication and occurs in 70% of affected patients. Regular eye examinations in infancy are necessary to rule out glaucoma. Treatment of glaucoma associated with Sturge–Weber syndrome may be difficult. Topical drops may be effective in initially lowering eye pressure but the patient may eventually require several surgeries

Ataxia-telangiectasia syndrome is an autosomal recessive disorder. Oculomotor abnormalities may be early manifestations of this syndrome. In 90% of patients, telangiectasia develops in the conjunctiva in children between the ages of 3 and 5 years.

Incontinentia pigmenti syndrome is an X-linked dominant condition in which proliferative retinal vasculopathy develops in about 30% of affected patients. The retinal changes can mimic ROP with incomplete peripheral retinal vascularization. Retinal detachment can occur. Treatment includes laser photocoagulation or cryotherapy but these treatments have varying degrees of success.

In **Wyburn–Mason syndrome,** a racemose angioma can develop in the retina with shunting of blood directly from arteries to veins. Vision can be normal or markedly reduced, depending on the location of the lesion. Treatment is not indicated for primary lesions.

Dermatologic Disease

Albinism is a heterogeneous group of genetic disorders resulting from absence of melanin in the eye, skin, or both. Clinically, albinism is divided into ocular and oculocutaneous forms. Oculocutaneous albinism (OCA) results from mutations in the tyrosinase gene *(TYR)* or *OCA1* gene. There are 2 subtypes and hair color can range from blond to light brown as the most prevalent type of albinism worldwide. Ocular albinism is autosomal recessive or an X-linked mutation in the *OCA1* gene. Ocular albinism mainly affects pigmentation in the visual system and the most common ocular finding is iris transillumination, which may be observable in a darkened room by placing a penlight against the lower eyelid and noting the passage of light from both the pupil and the iris. Other frequent ocular findings are nystagmus, light fundus pigmentation (blonde fundus), and foveal hypoplasia. Visual acuity usually ranges from 20/40 to 20/400. The Chédiak–Higashi and Hermansky–Pudlak syndromes can manifest features of albinism. If either of these conditions is suspected, hematologic consultation is recommended because of the lethal nature of these forms of albinism. All patients with OCA are at an increased risk of skin cancer and should be counseled as such.

Stevens–Johnson syndrome is an acute inflammatory condition affecting skin and mucus membranes. Drugs, particularly sulfonamide medications, are common precipitating factors. Microbial agents, especially *Mycoplasma pneumoniae*, have also been implicated in this condition. Ocular involvement, which occurs in half of the patients, consists of eyelid edema and ulceration, conjunctival injection with vesicle formation and, in severe cases, conjunctival scar formation that may result in adhesions between the palpebral and bulbar conjunctiva (symblepharons). The severity of late ocular complications depends primarily on the extent of conjunctival involvement. Malposition of the eyelids with corneal irritation from inward-turned eyelashes (trichiasis) can occur from severe conjunctival scarring. The most serious complication is dry eye syndrome, caused by damage to the ducts of the lacrimal glands and obliteration of conjunctival mucus-forming cells (goblet cells). Eyelid surgery may be required, and the child with a dry eye may face a lifetime of needing ocular lubrication from artificial tears and ointments. Aggressive lubrication during the acute phase of the disease is recommended to keep tissues moist and prevent conjunctival adhesions. Treatments may include regular debridement of the fornices of the eye or placement of symblepharon rings or amniotic membranes in severe cases.

Hyperkeratotic disorders such as lamellar ichthyosis can cause scaling of the eyelids, ectropion, lagophthalmos, and exposure keratopathy. Although eyelid surgery may be required, the mainstay of treatment is ocular lubrication with artificial tears and ointments. **Connective tissue disorders** such as Marfan syndrome, Stickler syndrome, Ehlers–Danlos syndrome, and pseudoxanthoma elasticum (PXE), are associated with particular ocular abnormalities. Patients with Stickler syndrome, Marfan syndrome, and Ehlers–Danlos syndrome have myopic retinal degeneration and can develop retinal detachment. Lens subluxation is common in Marfan syndrome. Cracks in the Bruch membrane of the retina, known as angioid streaks, occur in 85% of patients with PXE and 70% of these patients experience vision loss from hemorrhage, extension into the macula, choroidal sclerosis and atrophy of the retinal pigment epithelium. Angioid streaks rarely occur before the 2nd decade of life.

Skin disorders causing neoplasia such as juvenile xanthogranuloma can affect the eye, sometimes even in the absence of typical skin lesions. Ocular complications from juvenile xanthogranuloma occur most commonly in infants and consist of nodular tumors of the iris and ciliary body. The iris lesions have thin-walled vessels that are prone to bleeding and to causing a hyphema. Glaucoma and iridocyclitis can also occur. The iris lesions may respond to topical corticosteroids.

Hematologic Disorders

The **hemoglobinopathies** can have direct ocular consequences. Patients with hemoglobin SC or S thalassemia are more prone to retinal vascular occlusive disease because of a higher hematocrit and greater blood viscosity than are patients with hemoglobin SS, but retinal complications are frequently not seen until adolescence or early adulthood. Patients develop hemorrhages, angioid streaks, and arterial occlusions. Patients with sickle cell disease or sickle cell trait are at higher risk of complications of trauma, particularly hyphema. These patients may develop glaucoma, optic nerve damage and artery occlusion in this setting and require close monitoring.

Leukemia in children is usually acute. All ocular structures may be affected by direct infiltration of leukemic cells, hemorrhage, or infection. Conjunctival thickening, hypopyon, corneal ulcers, iris infiltrates, retinal hemorrhages, and neovascularization may occur. Infiltration of the optic nerve can be difficult to distinguish from papilledema secondary to CNS relapse. Infectious processes may present with similar findings as leukemia and can be difficult to discern from leukemic infiltrates. Papilledema and intraocular infection are true emergencies as the findings not only threaten vision but also are highly correlated with CNS involvement. Prompt diagnosis and treatment is necessary.

Congenital Heart Disease

Eye disease can be related to congenital heart disease by association, which is not surprising because there is a temporal relationship between the embryogenesis of the heart and that of the eyes; an embryopathic insult may result in malformations of both systems. CHARGE syndrome, a constellation of *C*oloboma, *H*eart defects, choanal *A*tresia, *R*etardation, and *E*ar abnormalities is a result of a mutation in the CHD7 transcription regulator of tissue-specific genes. The effects are tissue and developmental stage dependent. Colobomas of the eyelid, iris, retina, choroid, and optic nerve occur. They are usually bilateral and the effects on vision are determined by the location of the coloboma. If the macula is involved the visual prognosis is poor. Congenital heart disease can be a cause of eye disease as a direct effect of complications such as cyanosis or systemic hypertension. Severe hypoxia can cause cortical visual impairment or damage to the optic nerve resulting in optic atrophy.

Gastrointestinal Disorders

Ocular manifestations of inherited metabolic abnormalities of the gastrointestinal system occur primarily in the cornea and retina. **Wilson disease** is an autosomal recessive disorder of copper metabolism. The excess copper is deposited in the liver, basal ganglia, cornea, and kidney. Liver damage, neurologic, and psychiatric disorders result at a young age. The deposition of copper in the Descemet membrane of the cornea is the Kayser–Fleischer ring, which is pathognomonic of the disease. Copper may also be deposited in the lens. The corneal deposition of copper is not generally symptomatic but lens deposition may adversely affect vision.

Alagille syndrome, an autosomal dominant condition with intrahepatic bile duct hypoplasia, is associated with a peripheral corneal finding known as posterior embryotoxon. This finding consists of thickening and anterior displacement of the Schwalbe line, which is

the peripheral extent of the Descemet membrane of the cornea. It can best be seen with a slit-lamp biomicroscope. Posterior embryotoxon occurs in more than 90% of patients with Alagille syndrome, but because it also occurs in 15% of normal individuals, it is not pathognomonic for this syndrome.

Inflammatory bowel disease also can be associated with ocular disease. Anterior uveitis occurs in both Crohn disease and ulcerative colitis. Uveitis is diagnosed in almost half of cases of Crohn disease and fewer in ulcerative colitis. In turn, untreated chronic uveitis can lead to cataracts, glaucoma, and retinal edema. Conjunctivitis, keratitis, and retinal vasculitis are less frequent complications of these diseases.

Genitourinary Disease

Oculorenal syndromes may result from chromosomal abnormality syndromes or from inherited metabolic or developmental defects. The **Wilms tumor** gene *WT1* lies near the *PAX6* gene locus on 11p13. A chromosomal deletion of both results in Wilms tumor and aniridia. A larger deletion may result in WAGR syndrome (*W*ilms tumor, sporadic *A*niridia, *G*enitourinary malformations, and mental *R*etardation). Any child with nonfamilial aniridia is at risk for Wilms tumor and needs appropriate genetic evaluation.

The **Bardet–Biedl syndrome** is an autosomal recessive disorder combining retinal dystrophy, polydactyly, obesity, renal abnormalities, and hypogenitalism. An electroretinogram may be the earliest means of detecting the cone-rod dystrophy in suspected cases. Visual acuity and the funduscopic appearance may be normal in early childhood. Vision may then decrease and pigmentary retinopathy, which appears around the age of 8 years, becomes more prominent with age.

Cystinosis is also an autosomal recessive disorder of cystine transport from lysosomes that leads to intracellular accumulation of cystine in many tissues, including the eyes and kidneys. Cystine crystals accumulate in the anterior layer of the cornea beginning in the 1st year of life. This can cause photophobia, which can be severe. Retinal deposits of cystine can lead to focal degeneration of the retinal pigment epithelium. Frequent topical administration of cysteamine drops (6-12 times per day) can clear the cornea of cystine crystals and relieve ocular discomfort.

Alport syndrome is an X-linked syndrome characterized by nephritis, hearing loss, and ocular signs, particularly of the lens. An "oil droplet" appearance can be seen in the pupil with an ophthalmoscope. This represents an abnormality in the anterior capsule of the lens, anterior lenticonus, which can sometimes be associated with a cataract. Perimacular flecks are frequently present in the retina but do not tend to reduce visual acuity.

The **Lowe oculocerebrorenal syndrome** is also an X-linked disorder comprising congenital cataracts, intellectual disability, and renal tubular dysfunction. Glaucoma develops in a high proportion of affected boys and men. The carrier state can frequently be detected in girls and women by the appearance of numerous punctate opacities of the lens.

Endocrine Disease

Optic nerve hypoplasia is the most common congenital optic nerve anomaly. It can involve only a segment of the optic nerve. A superior segmental hypoplasia sometimes occurs in children of diabetic mothers. Optic nerve hypoplasia can occur with other CNS abnormalities. Patients with optic nerve hypoplasia may have septo-optic dysplasia, which denotes the absence of the septum pellucidum and agenesis of the corpus callosum or additional findings including pituitary abnormalities and cerebral hemisphere abnormalities. Evaluation of hypothalamic and pituitary functions is indicated in patients found to have pituitary abnormalities on imaging or if there is clinical suspicion of endocrine abnormalities such as neonatal jaundice, hypoglycemia, or difficulty with temperature control.

Diabetes mellitus results in retinopathy at some point in nearly all persons with insulin-dependent type I diabetes. The prevalence of retinopathy is directly proportional to the duration of disease after puberty. It rarely occurs within 5 years of diagnosis, occurs in about 50% of patients at 7 years after diagnosis, and is seen in 90% at 15 years after diagnosis. Funduscopic signs of diabetic retinopathy are microaneurysms, retinal hemorrhages, cotton wool spots, and hard exudates. Proliferative diabetic retinopathy with neovascularization is uncommon in children. Intensive glucose control as monitored by hemoglobin A_{1c} decreases the incidence and progression of diabetic retinopathy. Diabetic cataracts caused by sorbitol accumulation in the lens are also complications of diabetes mellitus in children. Refractive changes such as myopia can occur with rapid rises in blood sugar because of osmotic changes in the lens.

Thyroid ophthalmopathy related to **Graves disease** occurs in children much less frequently than in adults. It can be a cause of proptosis, lid edema, eyelid retraction, or restrictive strabismus due to lymphocytic infiltration of the muscles.

Infectious Diseases

Intrauterine or maternally transmitted infections can cause tissue damage or malformation. The common types of congenital infections are the **TORCH(S)**. The infectious agent, *T. gondii*, is acquired transplacentally or postnatally and has particular affinity for the central nervous system, including the retina. Chorioretinitis and uveitis may occur and resolution leaves scarring. Reactivation can occur and thus serial eye examinations are necessary. The macula is commonly involved and vision can be quite poor. Intrauterine rubella infection has become a rarity in the United States because of immunization with the measles-mumps-rubella vaccine. A fetus infected transplacentally in the 1st trimester of pregnancy is prone to multiple congenital defects, including heart disease, microcephaly with intellectual disability, and deafness. Ocular sequelae include cataracts, glaucoma, and chorioretinitis. Cataracts may be unilateral. Permanent visual impairment despite cataract surgery is common in these children. **Cytomegalovirus (CMV)** is the most common congenital infection in humans occurring in 1% of infants, although over 90% are asymptomatic and may not require treatment. Ophthalmic manifestations include retinochoroiditis, optic nerve anomalies, microphthalmos, cataract, and uveitis. CMV retinitis can be acquired in children who are immunocompromised.

Herpes simplex virus (HSV) may be acquired during passage through the birth canal or by close contact. Skin lesions on the eyelids (Fig. 32.23), keratoconjunctivitis, uveitis, or retinitis may occur. Acute retinal necrosis may occur in conjunction with CNS involvement. Keratitis is treated with topical antivirals, while systemic disease or retinitis is treated with oral or intravenous antiviral therapy. **Congenital syphilis** may occur following maternal infection. Early eye involvement is rare and symptoms may occur as late as adolescence. Chorioretinitis appears as a salt-and-pepper granularity. Uveitis, glaucoma, or interstitial keratitis may occur. Affected children are treated with intravenous penicillin G and monitored until serologic tests become nonreactive or the titer has decreased 4-fold.

Ophthalmia neonatorum is defined as conjunctival infection or inflammation occurring in the 1st month of life. Almost any bacterial pathogen can cause conjunctivitis in a newborn, but infection with *Neisseria gonorrhoeae* is of particular concern because it produces a hyperacute, profusely purulent conjunctivitis that can lead to corneal perforation and blindness. The US Preventative Services Task Force recommends prophylactic topical 1% tetracycline or 0.5%

FIGURE 32.23 Vesicular eruptions of the right lower eyelid and the right side of the nose, caused by primary herpes simplex infection. The cornea was not involved.

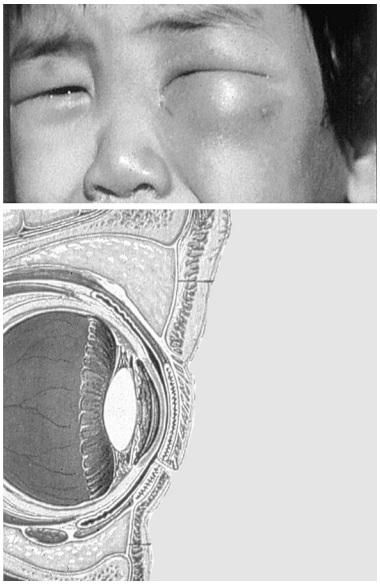

FIGURE 32.24 Preseptal cellulitis in a young girl. The infection is confined to the space anterior to the superior and inferior orbital septa and does not involve the orbit.

erythromycin ointment, administered within 24 hours after birth for prevention of gonococcal neonatorum. A 2.5% solution of povidone-iodine is used effectively and inexpensively in other countries but has not been approved for this use in the United States at this time. *Chlamydia trachomatis* (also known as trachoma–inclusion conjunctivitis or TRIC) is a common cause of neonatal conjunctivitis and is acquired from an infected cervix during delivery. Because this organism can also cause pneumonia, systemic treatment with oral erythromycin is indicated for treatment. In a child presenting with ophthalmia neonatorum it is important to obtain the history of whether prophylaxis has been given, particularly in cases of home births where this is unlikely. Evaluation with Gram and Giemsa stains and bacterial cultures are indicated. Polymerase chain reaction (PCR) testing can be done for suspicion of HSV infection. *Chlamydia* can be diagnosed by culture, fluorescent antibody-staining techniques, or enzyme immunoassays.

Preseptal cellulitis, defined as infection confined to the eyelid tissues anterior to the orbital septum, is a common infection in children and needs to be distinguished from infection involving the orbit (Fig. 32.24). Preseptal infections may result from trauma and insect bites involving the eyelids, severe conjunctivitis, primary bacteremia, upper respiratory infection or they may spread to the eyelids from the paranasal sinuses. The affected eyelids are swollen and red, and the infection can spread further into the eyebrow, forehead, and cheek. Proptosis and limitation of eye movements do not occur in preseptal cellulitis, but confirmation of this can be problematic because of the difficulty of opening the eye. *S. aureus,* group A streptococcus, and *S. pneumoniae* are the most common pathogens. Patients with signs and symptoms of systemic toxicity should be hospitalized for intravenous antibiotics; milder cases of preseptal cellulitis may be managed with oral antibiotics as long as appropriate follow-up is ensured.

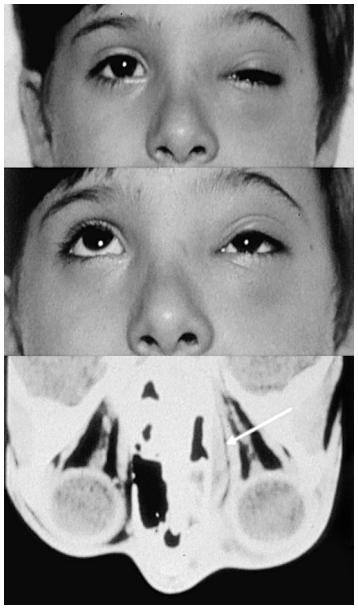

FIGURE 32.25 A subperiosteal abscess of the left orbit *(top image).* Note the limitation of upward movement of the left eye *(middle image).* The computed tomographic scan shows ethmoid sinusitis and a subperiosteal abscess bowing the left medial rectus muscle laterally *(bottom image; arrow).*

Orbital cellulitis is an infection of the orbit that involves the tissues posterior to the orbital septum. Most frequently, this is a result of spread of infection from the ethmoid or frontal sinuses. Ocular signs include eyelid edema and erythema, proptosis, and inferior and lateral displacement of the globe with limited eye movements. Ocular movement is painful; visual activity may be reduced. If orbital cellulitis is suspected, computed tomography of the orbit and sinuses is indicated. Children younger than 9 years are more likely to have an infection caused by a single aerobic pathogen, whereas children older than 9 years may have complex infections with multiple pathogens. Often, orbital cellulitis begins as a subperiosteal abscess that forms in the potential space between the periorbital (analogous to the periosteum of long bones) and the orbital bones (Fig. 32.25). Left untreated, this space-occupying mass can apply pressure to the optic nerve and cause permanent damage to vision. It can also spread into the intracranial space and result in a cavernous sinus thrombosis, a subdural empyema, or cerebral abscess. Systemic toxicity is quite common and severe with orbital cellulitis. Most children younger than 9 years who have small to medium-sized subperiosteal abscesses can be treated successfully with broad-spectrum intravenous antibiotics (ceftriaxone and vancomycin, ampicillin/sulbactam, or piperacillin/tazobactam). Close observation with periodic checks of vision and pupillary function is important in the 1st 24-48 hours of treatment. Older children, those with large subperiosteal abscesses, and children who fail to respond to intravenous antibiotics within 48 hours require surgical drainage of

the abscess. Emergency drainage is indicated in a patient of any age where there is compromise of the optic nerve.

NYSTAGMUS

Nystagmus is defined as an involuntary rhythmic, to-and-fro movement of the eyes. Horizontal nystagmus is the most common form of nystagmus, but vertical nystagmus and torsional nystagmus also occur (Table 32.18). Nystagmus may be congenital or acquired. Gaze positions can affect the eye movement. Congenital nystagmus is somewhat of a misnomer because the abnormal eye movements are generally not noted until an infant is 1 or 2 months of age, when the fixation reflex becomes established. Non-nystagmus eye movements are noted in Table 32.19.

Congenital motor nystagmus is often idiopathic; in this case, visual acuity is only moderately impaired, and the fundus examination findings and the electroretinogram are normal. Usually an affected individual will have a null point or a preferred position in which the eye movements are minimized. This may affect the head position as the patient tries to keep the eyes in the null point. In patients with congenital motor nystagmus there is often dampening or quieting of the nystagmus with convergence. Vision may be quite good (20/40 or better) in the patient's preferred gaze and head position. Sometimes surgery is done on the eye muscles to move them into a position such that the head is straighter. A family history of nystagmus can frequently be ascertained.

Congenital sensory nystagmus occurs with disorders that impair normal image formation (bilateral congenital cataracts) or image processing in both eyes (a retinal dystrophy or bilateral optic nerve atrophy or hypoplasia). Eye movements may be searching and there is no null point. Visual acuity is more severely impaired than in idiopathic congenital nystagmus (20/200 or less), and visual loss may be progressive in some instances. The evaluation of a child with congenital nystagmus entails a thorough health and family history, a general physical examination, and an eye examination by an ophthalmologist with expertise in pediatric eye disorders. A cranial magnetic resonance imaging scan is indicated when the hallmark signs of congenital motor nystagmus such as a null point and dampening of nystagmus on convergence are not yet identifiable and there are no eye findings to suggest a specific pathology such as cataract. Electroretinography, visual evoked potentials (VEPs), or optical coherence tomography (OCT) may be useful in establishing a specific diagnosis.

Acquired nystagmus is less common than congenital nystagmus. Nystagmus that is truly acquired beyond the 1st few months of life is of concern and may represent a significant neurologic abnormality. It may be caused by central nervous system disorders, particularly of the cerebellum, brainstem, or suprasellar region. In children, the most common tumor causing acquired nystagmus is a craniopharyngioma.

TABLE 32.18 Specific Patterns of Nystagmus

Pattern	Description	Associated Conditions
Latent nystagmus	Conjugate jerk nystagmus toward viewing eye	Congenital vision defects, occurs with occlusion of eye
Manifest latent nystagmus	Fast jerk to viewing eye	Strabismus, congenital idiopathic nystagmus
Periodic alternating	Cycles of horizontal and horizontal-rotary movements that change direction	Caused by both visual and neurologic conditions
Seesaw nystagmus	One eye rises and intorts as other eye falls and extorts	Usually associated with optic chiasm defects
Retraction nystagmus	Eyes jerk back into orbit or toward each other	Caused by pressure on mesencephalic tegmentum (Parinaud syndrome)
Gaze-evoked nystagmus	Jerk nystagmus in direction of gaze	Caused by medications, brainstem lesion, or labyrinthine dysfunction
Gaze-paretic nystagmus	Eyes jerk back to maintain eccentric gaze	Cerebellar disease
Downbeat nystagmus	Fast-phase beating downward	Posterior fossa disease, drugs
Upbeat nystagmus	Fast-phase beating upward	Brainstem and cerebellar disease, and some visual conditions
Vestibular nystagmus	Horizontal-torsional or horizontal jerks	Vestibular system dysfunction
Asymmetric or monocular nystagmus	Pendular vertical nystagmus	Disease of retina and visual pathways
Spasmus nutans	Fine, rapid, pendular nystagmus	Torticollis, head nodding; idiopathic or gliomas of visual pathways

TABLE 32.19 Specific Patterns of Non-Nystagmus Eye Movements

Pattern	Description	Associated Conditions
Opsoclonus	Multidirectional conjugate movements of varying rate and amplitude	Hydrocephalus, diseases of brainstem and cerebellum, neuroblastoma
Ocular dysmetria	Overshoot of eyes on rapid fixation	Cerebellar dysfunction
Ocular flutter	Horizontal oscillations with forward gaze and sometimes with blinking	Cerebellar disease, hydrocephalus, or central nervous system neoplasm
Ocular bobbing	Downward jerk of eyes from primary gaze; eyes remain for a few seconds, then drift back	Pontine disease
Ocular myoclonus	Rhythmic to-and-fro pendular oscillations of the eyes, with synchronous nonocular muscle movement	Damage to red nucleus, inferior olivary nucleus and ipsilateral dentate nucleus

Vertically oriented nystagmus is also of concern; it may be associated with the Arnold-Chiari malformation or with pharmacologic agents such as lithium, tranquilizers, or anticonvulsants.

Spasmus nutans is a special form of acquired nystagmus with onset in the 1st 2 years of life. The usual triad of findings consists of nystagmus (often a shimmering type of nystagmus that is frequently asymmetric or even monocular), head nodding, and torticollis. This form of nystagmus is generally benign and disappears by the age of 3-4 years. In some cases, spasmus nutans can be associated with chiasmal or suprachiasmal or retinal dystrophies. Neuroradiologic investigation is indicated.

Opsoclonus is a special form of eye movement abnormality that is not truly nystagmus in that the bizarre, seemingly random oscillations of the eyes are not rhythmic and are frequently multivectorial. The most common cause of opsoclonus in children is acute cerebellar ataxia. The child presents with "dancing eyes and dancing feet." Opsoclonus can occur also with occult neuroblastoma, as a paraneoplastic phenomenon, viral encephalitis, and hydrocephalus.

OCULAR TRAUMA

Trauma is a major cause of acquired visual loss in children. Ninety percent of trauma cases are preventable and 50% occur in the home. The nature of the traumatic injury varies by age but there is a persistent male preponderance. In school-aged children, sports-related injuries are the most common cause of ocular injury accounting for 25% of hospitalizations. There is some effort to reduce injuries by legislation. For instance, the incidence of eye injuries from ice hockey are almost zero since the institution of mandatory face masks in children playing organized hockey. Projectile injuries from firearms, air guns, and fireworks are relatively frequent in the United States, however, these injuries are very rare in countries without easy access to guns or fireworks.

The extent of the eye examination is determined by the child's level of cooperation. If the circumstances of the injury suggest a high likelihood of a perforating injury (from a sharp object that could go through the cornea or sclera), the eye should not be forced open but rather, should be covered with a protective shield to prevent further injury until the child can be seen by an ophthalmologist and an exam under anesthesia can be done if necessary. If a perforating injury is considered unlikely (a blunt or scratching type of injury), a sterile, topical ophthalmic anesthetic agent can be applied to the eye to reduce surface pain, which is a major cause of the child's reluctance to open the eye. The eye can then be inspected for foreign bodies or corneal abrasion. Fluorescein dye may be of help in diagnosing a corneal abrasion. The fluorescein may have linear pattern of staining that suggests a foreign body may be on the tarsal conjunctiva under the upper eyelid and during an eye blink the cornea is being abraded. Lid eversion is needed to investigate this possibility. The inferior fornix should also be inspected for foreign bodies.

Corneal or conjunctival foreign bodies can sometimes be irrigated out of the eye. Otherwise the foreign body may be removed at a slit lamp using topical anesthesia if the patient is cooperative. If not, the patient will require anesthesia. Management of a corneal abrasion entails relief of pain, prevention of infection, and promotion of healing of the corneal epithelium. Ibuprofen or similar analgesics are usually sufficient for pain relief. Topical anesthesia, while used in the office, should not be used at home as it prevents epithelial healing and can be toxic to the cornea with longer-term use. A drop of a cycloplegic agent (cyclopentolate) may provide comfort by relieving ciliary spasm. Application of a topical antibiotic ointment such as erythromycin helps prevent infection and provides lubrication to the ocular surface to allow the new epithelium to form and adhere to the basement membrane of the cornea. Patching the eye has not been shown to be of benefit. Close follow-up is indicated to make sure that the cornea is healing and has not developed an infection that could lead to a corneal ulcer. Most abrasions heal completely within 24-48 hours.

Hyphema

Any child with blunt trauma to the eye should be evaluated for blood in the anterior chamber of the eye, known as a hyphema (Fig. 32.26). The visual acuity of the injured eye should be measured as possible. The anterior segment and pupillary function should be assessed if the hyphema only partially fills the anterior chamber. Funduscopy should be attempted to look for associated retinal hemorrhage, edema (Fig. 32.27), or detachment. The view of the retina may be obscured by

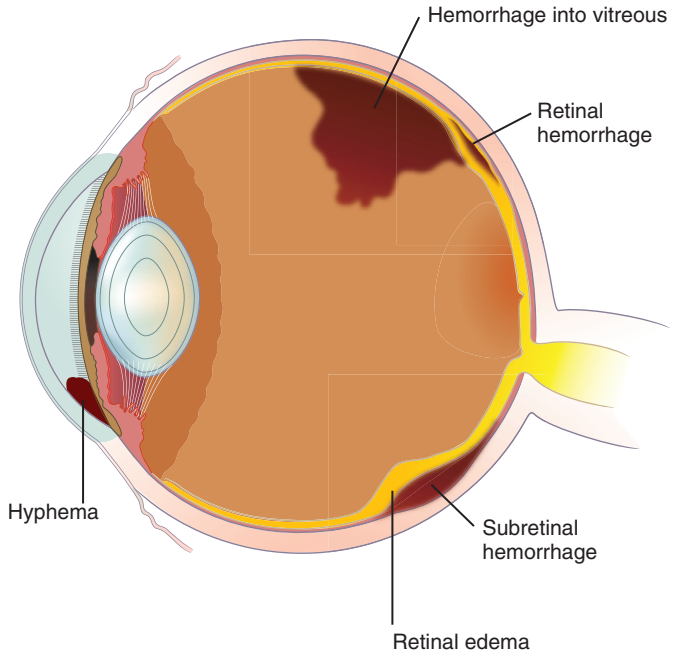

FIGURE 32.26 Various types of ocular hemorrhage after blunt trauma to the globe. (From Reilly BM. *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991:68.)

FIGURE 32.27 Hemorrhage and edema of the retina from blunt ocular trauma (commotio retinae).

blood. If necessary, ultrasound can be used to determine if the retina is attached. Usually the blood will resolve if the patient can limit his or her activity. The complications of hyphema include glaucoma, corneal blood staining, and rebleeding. The glaucoma may be managed initially with topical medications but the blood may need to be washed out of the anterior chamber surgically if the intraocular pressure cannot be controlled, blood is not resolving, or corneal blood staining is severe and threatening vision.

Eye Injuries in Child Abuse

In cases of child abuse, the presenting sign may involve the eye. Ocular injuries are also detected in the course of examining many other child abuse injuries. Blunt injuries to the eyelids and anterior segment of the eye from fingers, fists, or belts may cause eyelid ecchymosis, subconjunctival hemorrhage, hyphema, cataract, and lens dislocation. The finding of such an injury should alert the physician to the possibility of child abuse. Abusive head trauma is caused by forceful acceleration and deceleration motion such as shaking, which results in subdural hemorrhage and retinal or vitreous hemorrhages (Fig. 32.28). The vitreous is adherent to the retina and the traction of the moving vitreous results in multiple retinal hemorrhages, often in all layers of the retina. In severe cases, the optic nerve may be avulsed. Vitreous or retinal hemorrhage may take a long time to resolve and the child is at risk for amblyopia during the time the vision is obscured by blood. In cases of persistent hemorrhage, a vitrectomy may need to be done to clear the blood in the visual axis. Cortical brain damage also has a role in limiting visual function. Fewer than half of the patients diagnosed with abusive head trauma with retinal or vitreous hemorrhage see better than 20/40 after recovery.

Functional Vision Loss

Some patients complain of vision loss or blurring or other visual disturbances (seeing spots, colors, or patterns) while the eye exam is normal. Functional visual disturbances occur most commonly in girls of ages 8-15 years. The key to confirming functional vision loss is to demonstrate objective findings that indicate better vision than the subjective responses. The patient's responses to visual acuity testing are frequently inconsistent. Stereoacuity testing may demonstrate better visual acuity than the patient is reporting. There are several examining techniques that the ophthalmologist can employ to get this information. There are also objective tests available to further delineate etiologies of possible vision loss; however, these are rarely needed. These include imaging tests such as OCT, fluorescein angiogram, electroretinogram (ERG), or VEPs. The relationship of functional vision loss to true psychologic disease is unclear but it is worth keeping in mind that there is a higher incidence of functional vision loss in children who are experiencing psychologic stressors. Some children willfully complain of vision loss because they want glasses. The treatment should consist of reassurance. It may be of benefit to refer the patient to a psychiatrist if the symptoms do not subside.

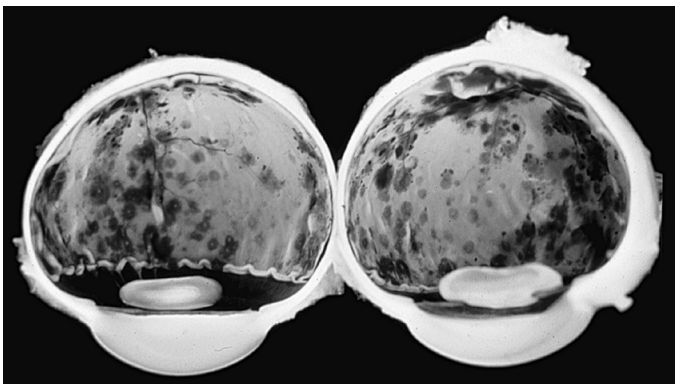

FIGURE 32.28 Gross pathologic specimen from an infant who died of shaken baby syndrome. Note the diffuse retinal hemorrhages.

VISUAL COMPLAINTS FROM CHILDREN

Frequently, a child is brought to the pediatrician because of a subjective visual complaint from the child rather than because of an abnormality observed by a parent. Symptoms associated with reading are common and include seeing blurred print, words "swimming" together, and skipping words or lines. Other children complain primarily of blurred distance vision. Uncommon visual phenomena may include seeing colored lights, objects appearing larger or smaller, seeing spots, and double vision. Eye pain localized to 1 or both eyes is also common. There may be physiologic explanations for each of the complaints, and the child is usually interested in an explanation of the reason proposed for his or her complaint. A careful history of the exact nature of the complaint and any associated concerns should be sought and a screening eye examination performed. Specifically, distance and near visual acuity should be measured in each eye. A cover test or stereopsis test rules out manifest strabismus. An external eye examination may reveal a reason for eye pain (conjunctival injection, tearing, corneal abrasion, foreign body). Pupillary reactions should be assessed. Funduscopy should be done to evaluate optic nerve and retinal status. A color vision test may be helpful. Having the child read an age-appropriate passage may reveal information about the child's reading ability and the

TABLE 32.20 Concerning Symptoms and Signs That Should Raise Red Flags

Symptom or Sign	Most Worrisome or Urgent Cause
Leukocoria	Retinoblastoma
Acute onset of strabismus	Cranial nerve palsy from brain tumor, ↑ICP
Acute vision loss	Compression or infiltration of optic nerve by an orbital or intracranial lesion
Proptosis	Rhabdomyosarcoma
Sudden onset of ptosis	3rd nerve palsy from tumor, ↑ICP
Severe headaches	↑ICP
Black eye	Trauma with associated hyphema
Light sensitivity	Uveitis
Head tilt or turn	Cranial nerve palsy causing strabismus, ↑ICP
Loss of corneal luster	Corneal edema from glaucoma or uveitis
Purulent conjunctivitis in a newborn	Gonococcal infection
Acquired anisocoria	Horner syndrome caused by neuroblastoma, ↑ICP
Bilateral cataracts in a newborn	Galactosemia
Retinal hemorrhage in an infant or toddler	Shaken baby syndrome
Onset of nystagmus after early infancy	Brainstem or posterior fossa tumor

↑ICP, increased intracranial pressure.

severity of the reading complaint. If the examination is normal, simple reassurance may ease the concerns of the child and parent, particularly if combined with an offer to follow up on the complaint if it persists or if the parent notes objective changes in the child's eyes. If difficulty reading persists despite correction of any refractive error and an otherwise normal eye exam, the child may have learning disabilities that warrant further evaluation. Behavioral vision therapy has not been proven to improve reading skills, learning disabilities, or dyslexia.

SUMMARY AND RED FLAGS

Ocular manifestations of vision loss, strabismus, and nystagmus may be caused by isolated ocular pathologic processes or by significant systemic disease. Vision screening and basic evaluations done in the pediatrician's office are important for detection of vision loss. Impaired visual function resulting from strabismus, cataracts, or other conditions may produce amblyopia and blindness. It is important to detect amblyopia because in most cases, amblyopia is reversible if discovered early and treated appropriately. Symptoms and signs that suggest potentially life- or vision-threatening diseases are listed in Table 32.20.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Basic and Clinical Science Course, Section 6. *Pediatric Ophthalmology and Strabismus*. San Francisco: American Academy of Ophthalmology; 2013-2014.

Wright KW, Strube Y, eds. *Pediatric Ophthalmology and Strabismus*. 3rd ed. New York: Oxford University Press; 2012.

Anatomy and Neurophysiology of the Visual System

Livingstone MS. Art, illusion and the visual system. *Sci Am*. 1988;258:78.

Development of the Eye and Visual System

Tripathi BJ, Tripathi RC. Development of the human eye. In: Bron AJ, Tripathi RC, Tripathi BJ, eds. *Wolff's Anatomy of the Eye and Orbit*. 8th ed. London: Chapman & Hall; 1997.

Amblyopia and Vision Screening

Berardi N, Sale A, Maffei L. Brain structural and functional development: genetics and experience. *Dev Med Child Neurol*. 2015;57(suppl 2):4-9.

Dolgin E. The myopia boom. *Nature*. 2015;519:276-278.

Donahue SP, Arthur B, Neely DF, et al; on behalf of the AAPOS vision Screening Committee. Guidelines for automated preschool vision screening: a 10-year, evidence based update. *J AAPOS*. 2013;17:4-8.

Holmes JM, Lazar EL, Melia BM, et al; Pediatric Eye Disease Investigator Group. Effect of age on response to amblyopia treatment in children. *Arch Ophthalmol*. 2011;129:1451-1457.

Repka MX, Kraker RT, Holmes JM, et al; Pediatric Eye Disease Investigator Group. Atropine vs. patching for treatment of moderate amblyopia: follow up at 15 years of age of a randomized clinical trial. *JAMA Ophthalmol*. 2014;132(7):799-805.

Wiesel TN, Hubel DH. Single-cell responses in striate cortex of kittens deprived of vision in one eye. *J Neurophysiol*. 1963;26:1003.

Strabismus

Hug D. Management of infantile esotropia. *Curr Opin Ophthalmol*. 2015;26(5):371-374.

Lavrich JB. Intermittent exotropia: continued controversies and current management. *Curr Opin Ophthalmol*. 2015;26(5):375-381.

Pediatric Eye Disease Investigator Group, Cotter SA, Mohney BG, et al. A randomized trial comparing part time patching with observation for children 3 to 10 years of age with intermittent exotropia. *Ophthalmology*. 2014;121(12):2299-2310.

Pediatric Eye Disease Investigator Group, Mohney BG, Cotter SA, et al. A randomized trial comparing part time patching with observation for intermittent exotropia in children 12 to 35 months of age. *Ophthalmology*. 2015;122(8):1718-1725.

Vision Impairment in Children

Mervis CA, Yeargin-Allsopp M, Winter S, et al. Aetiology of childhood vision impairment, metropolitan Atlanta, 1991-93. *Paediatr Perinat Epidemiol*. 2000;14:70.

Steinkuller PG. Legal vision requirements for drivers in the United States. *AMA J Ethics*. 2010;12(12):938-940.

Retinopathy of Prematurity

Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. *Arch Ophthalmol*. 2003;121:1684-1696.

Good WV, Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the early treatment for retinopathy of prematurity (ETROP) randomized trial. *Trans Am Ophthalmol Soc*. 2004;102:233-248.

Mintz-Hittner HA, Kennedy KA, Chuang AZ, et al; BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. *N Engl J Med*. 2011;364(7):603-615.

Nasolacrimal Problems in Childhood

Becker BB. The treatment of congenital dacryocystocele. *Am J Ophthalmol*. 2006;142(5):835-838.

Lueder GT. Endoscopic treatment of intranasal abnormalities associated with nasolacrimal duct obstruction. *J AAPOS*. 2004;8(2):128-132.

The Red Eye

Fisher MC. Conjunctivitis in children. *Pediatr Clin North Am*. 1987;34:1447.

Matoba A. Ocular viral infections. *Pediatr Infect Dis*. 1984;3:358.

Seth D, Khan FI. Causes and management of red eye in pediatric ophthalmology. *Curr Allergy Asthma Rep*. 2011;11(3):212-219.

Sethuramen U, Kamat D. The red eye: evaluation and management. *Clin Pediatr (Phila)*. 2009;48(6):588-600.

Leukocoria and Retinoblastoma

Abramson DH, Frank CM, Susman M, et al. Presenting signs of retinoblastoma. *J Pediatr*. 1998;132:505.

Ghassemi F, Khodabende A. Risk definition and management strategies in retinoblastoma: current perspectives. *Clin Ophthalmol*. 2015;9:985-994.

Mendoza PR, Grossniklaus HE. The biology of retinoblastoma. *Prog Mol Biol Transl Sci*. 2015;135:503-516.

Childhood Cataracts

Birch EE, Stager DR. The critical period for surgical treatment of dense congenital unilateral cataract. *Invest Ophthalmol Vis Sci*. 1996;37:1532.

Francis PJ, Moore AT. Genetics of childhood cataract. *Curr Opin Ophthalmol*. 2004;15(1):10-15.

Infant Aphakia Treatment Study Group, Lambert SR, Lynn MJ, et al. Comparison of contact lens and intraocular lens correction of monocular aphakia during infancy: a randomized clinical trial of HOTV optotype acuity at age 4.5 years and clinical findings at age 5 years. *JAMA Ophthalmol*. 2014;132(6):676-682.

Infant Aphakia Treatment Study Group, Plager DA, Lynn MJ, et al. Complications, adverse events, and additional intraocular surgery 1 year after cataract surgery in the Infant Aphakia Treatment Study. *Ophthalmology*. 2011;118(12):2330-2334.

Mignarri A, Gallus GN, Dotti MT, et al. A suspicion index for early diagnosis and treatment of cerebrotendinous xanthomatosis. *J Inherit Metab Dis*. 2014;37(3):421-429.

Glaucoma in Childhood

Aponte EP, Diehl N, Mohney BG. Medical and surgical outcomes in childhood glaucoma: a population based study. *J AAPOS*. 2011;15(3):263-267.

Bohnsack BL, Freedman SF. Surgical outcomes in childhood uveitic glaucoma. *Am J Ophthalmol*. 2013;155(1):134-142.

Childhood Uveitis

American Academy of Pediatrics Section on Rheumatology and Section on Ophthalmology, Cassidy J, Kivlin J, et al. Ophthalmologic examinations in children with juvenile rheumatoid arthritis. *Pediatrics*. 2006;117(5):1843-1845.

Harrell M, Carvounis PE. Current treatment of toxoplasma retinochoroiditis: an evidence-based review. *J Ophthalmol*. 2014;2014:273-506.

Levy-Clark G, Jabs DA, Read RW, et al. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. *Ophthalmology*. 2014;121(3):785-796.

Eyelid and Orbital Problems

Drolet BA, Frommelt PC, Chamlin SL, et al. Initiation and use of propanolol for infantil hemangioma: a report of a consensus conference. *Pediatrics*. 2013;131(1):128-140.

Gandhi NG, Lin LK, O'Hara M. Sildenafil for pediatric orbital lymphangioma. *JAMA Ophthalmol*. 2013;131(9):1228-1230.

Gooding C, Meyer D. Intralesional bleomyicin: a potential treatment for refractory orbital lymphangiomas. *Ophthal Plast Reconstr Surg*. 2014;30(3):e65-e67.

Holland KE, Drolet BA. Infantile hemangioma. *Pediatr Clin North Am*. 2010;57:1069-1083.

Holland KE, Drolet BA. Approach to the patient with an infantile hemangioma. *Dermatol Clin*. 2013;31(2):289-301.

Rao AA, Naheedy JH, Chen JY, et al. A clinical update and radiologic review of pediatric orbital and ocular tumors. *J Oncol*. 2013;2013:975908.

Ocular Manifestations of Systemic Disease

Ali Z, Khadije D, Elahe A, et al. Prophylaxis of ophthalmia neonatorum: comparison of betadine, erythromycin and no prophylaxis. *J Trop Pediatr*. 2007;53(6):388-392.

Garcia GH, Harris GJ. Criteria for nonsurgical management of subperiosteal abscess of the orbit: analysis of outcomes, 1988-1998. *Ophthalmology*. 2000;107(8):1454-1458.

Ocular prophylaxis for gonococcal ophthalmia neonatorun. U.S. Preventive Services Task Force reaffirmation recommendation statement. *Am Family Physicasn*. 2012;85:195-196.

Summers CG. Albinism: classification, clinical characteristics, and recent findings. *Optom Vis Sci*. 2009;86(6):659-662.

Virk SA, Donaghue KC, Wong TY, et al. Interventions for diabetic retinopathy in type 1 diabetes: systemic review and meta-analysis. *Am J Ophthalmol*. 2015;160:1055-1064.

Nystagmus

Brodsky MC. *Pediatric Neuro-ophthalmology*. 2nd ed. Springer; 2010.

Ehrt O. Infantile and acquired nystagmus in childhood. *Eur J Paediatr Neurol*. 2012;16(6):567-572.

Ocular Trauma

Kivlin JD, Simons KB, Lazoritz S, et al. Shaken baby syndrome. *Ophthalmology*. 2000;107:1246.

Levin AV. Retinal hemorrhages in abusive head trauma. *Pediatrics*. 2010;126(5):961-970.

SooHoo JR, Davies BW, Braverman RS, et al. Pediatric traumatic hyphema: a review of 138 consecutive cases. *J AAPOS*. 2013;17(6):565-567.

Trief D, Adebona OT, Turalba AV, et al. The pediatric traumatic hyphema. *Int Ophthalmol Clin*. 2013;53(4):43-57.

33

Arthritis

James Nocton and Dominic Co

INTRODUCTION

Although children with musculoskeletal complaints may present with what appears to be an isolated, localized problem, complaints involving the musculoskeletal system (e.g., arthralgia, myalgia, joint swelling, poorly localized extremity pain, limping, refusal to walk) may be associated with a long list of potential illnesses. Children or their parents rarely arrive in the clinic with a complaint of arthritis or patellofemoral syndrome. Instead, they have symptoms such as extremity pain, joint swelling, or limitations of activity and function. These children may have chronic inflammatory arthritis or an associated systemic rheumatic disease, a traumatic condition, a mechanical problem, or a pain syndrome, among other possible explanations.

The differential diagnosis of extremity pain is extensive (Table 33.1). For many of these diagnoses, the history and physical examination are sufficient to confirm a diagnosis; for others, specific laboratory tests or imaging studies will confirm a suspected diagnosis. Musculoskeletal symptoms may indicate pathologic processes localized and restricted to a single extremity or joint, or localized symptoms may be a component of a systemic illness.

Arthritis is a specific sign indicating objective inflammation of the joint, and can be defined as (1) swelling of the joint or (2) limitation of motion combined with 1 of the following: pain on motion, tenderness, or warmth. Arthritis should be distinguished from arthralgia (Table 33.2), bone pain, myalgia, and neuralgia, because if arthritis is present, the diagnostic possibilities are limited to more specific categories of disease (Fig. 33.1). Arthritis is not a specific disease; there are infectious, postinfectious/reactive, hematologic, metabolic, oncologic, and rheumatic causes of arthritis. The precise diagnosis is determined by 1st establishing the characteristics of the arthritis with respect to the number and location of joints involved, severity, degree of disability, and chronicity. The clinician combines these characteristics with the history and the pattern of any associated systemic signs and symptoms to determine the specific cause of arthritis.

◆ History

Although the parents and child are usually the principal historians, it is often helpful to determine whether other adults have seen signs or have been aware of the child's symptoms. Have daycare providers reported problems to the parents? Has the school staff, coach, or physical education teacher noticed any problems similar to those seen at home? Obtaining consistent information from several observers in different settings determines the frequency and consistency of the symptoms, how disabling the symptoms have been, and the reliability of the history. Adolescents have a tendency to either underreport or overreport their symptoms, making the history especially challenging within this age group. If there are inconsistencies, it becomes increasingly difficult to formulate a diagnosis, and information from the physical examination, along with potential laboratory and imaging studies, may be needed to resolve the inconsistencies.

Pain Location

There are several possible sources of extremity pain (Fig. 33.2). Pain directly over a joint or joints may indicate synovial inflammation, arthralgia secondary to viral infection, or mechanical joint problems such as ligament trauma, meniscal tears, or hypermobility. Pain near a joint may represent disease in the muscle, bone, tendon, enthesis (tendon insertion sites), or bursa, or may be referred from a nearby joint. Pain may involve a whole limb or limbs, or isolated regions thereof, in which case it may reflect neuropathy, myalgia, or a regional pain syndrome. On occasion, children complain of pain "all over," which may suggest diffuse myalgia related to a systemic infection, or if chronic, a myofascial pain syndrome. Intense pain localized to a single small area is seen with infection, trauma, fracture, or tumor. Migrating arthritis or arthralgia is more suggestive of diagnoses such as acute rheumatic fever or immune complex–mediated disease, and is less consistent with trauma, tumors, osteomyelitis, or septic arthritis, with the exception of septic arthritis secondary to *Neisseria gonorrhoeae* infection.

Pain Character

Arthritis is an aching discomfort that is usually not severe enough to cause crying or screaming. Some children with arthritis may not complain of pain at all. Very severe pain should increase the suspicion of a pain syndrome or bone disease such as osteomyelitis, leukemia, metastatic neuroblastoma, fracture, or bone tumors. Sporadic episodes of extreme pain interspersed with pain-free intervals are seen with pain syndromes such as growing pains, myofascial pain, and complex regional pain syndrome, or in situations in which psychogenic and behavioral factors contribute to the pain. With some pain syndromes, children often rate their pain as 10 on a scale of 0-10 and also may state that the pain is constant. Some patients may demonstrate "la belle indifference," an incongruity between their affect and their complaint; they may be smiling or laughing while they are describing the presence

(See *Nelson Textbook of Pediatrics,* p. 1162.)

TABLE 33.1 Conditions Causing Arthritis or Extremity Pain

Rheumatic and Inflammatory Diseases
Juvenile idiopathic arthritis
Systemic lupus erythematosus
Juvenile dermatomyositis
Polymyositis
Polyarteritis nodosa
Scleroderma
Sjögren syndrome
Behçet disease
Overlap syndromes
Granulomatosis with polyangiitis
Microscopic polyangiitis
Sarcoidosis
Kawasaki disease
Henoch–Schönlein purpura
Chronic recurrent multifocal osteomyelitis

Infectious Illnesses
Bacterial arthritis (e.g., *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Kingella kingae*, *Neisseria gonorrhoeae*, *Haemophilus influenzae*)
Lyme disease
Viral illness (e.g., parvovirus, rubella, mumps, Epstein–Barr virus, hepatitis B, Chikungunya fever)
Fungal arthritis
Mycobacterial infection

Hematologic Disorders
Hemophilia
Hemoglobinopathies (including sickle cell disease)

Immunodeficiencies
Hypogammaglobulinemia
Immunoglobulin A deficiency
Human immunodeficiency virus
Common variable immunodeficiency

Congenital and Metabolic Disorders
Gout
Pseudogout (calcium pyrophosphate dihydrate crystal deposition disease)
Mucopolysaccharidoses
Glycogen storage diseases
Thyroid disease (hypothyroidism, hyperthyroidism)
Hyperparathyroidism
Vitamin C deficiency (scurvy)
Vitamin D deficiency (rickets)
Hereditary connective tissue disease (Marfan syndrome, Ehlers–Danlos syndrome)
Fabry disease
Farber disease

Orthopedic Disorders
Trauma
Patellofemoral syndrome
Hypermobility syndrome
Osteochondritis dissecans
Avascular necrosis (including Legg–Calvé–Perthes disease)
Hypertrophic osteoarthropathy
Slipped capital femoral epiphysis
Osteolysis
Benign bone tumors (including osteoid osteoma)
Histiocytosis

Neuropathic Disorders
Peripheral neuropathies
Carpal tunnel syndrome
Charcot joints (neuropathic osteoarthropathy)

Neoplastic Disorders
Leukemia
Neuroblastoma
Lymphoma
Bone tumors (osteosarcoma, Ewing sarcoma)
Histiocytic syndromes
Synovial tumors

Reactive Arthritis
Acute rheumatic fever
Postinfectious
Serum sickness
Transient synovitis of the hip
Postimmunization

Pain Syndromes
Fibromyalgia
Growing pains
Depression (with somatization)
Anxiety
Stress
Complex regional pain syndrome
Myofascial pain syndromes

Miscellaneous Disorders
Pigmented villonodular synovitis
Plant-thorn synovitis (foreign body arthritis)
Myositis ossificans
Eosinophilic fasciitis
Tendonitis (overuse injury)
Raynaud phenomenon
Erythromelalgia

TABLE 33.2 Distinguishing Characteristics of Arthritis and Arthralgia

Arthritis	Arthralgia
Prominent swelling	Minimal or no swelling
Morning stiffness	No morning stiffness
Symptoms improve with activity	Symptoms are exacerbated by activity
Stiffness follows rest	Pain constant or improves with rest
Limited range of motion	Normal or excessive range of motion
Warmth of joint	No warmth
Symptoms usually daily, consistent	Symptoms variable, constant, or intermittent

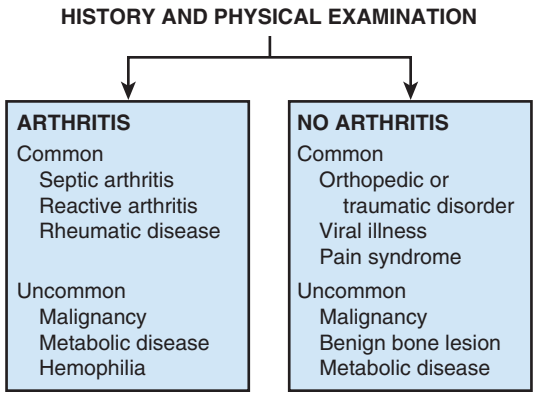

FIGURE 33.1 Algorithm for determining the cause of extremity pain based on the presence or absence of arthritis.

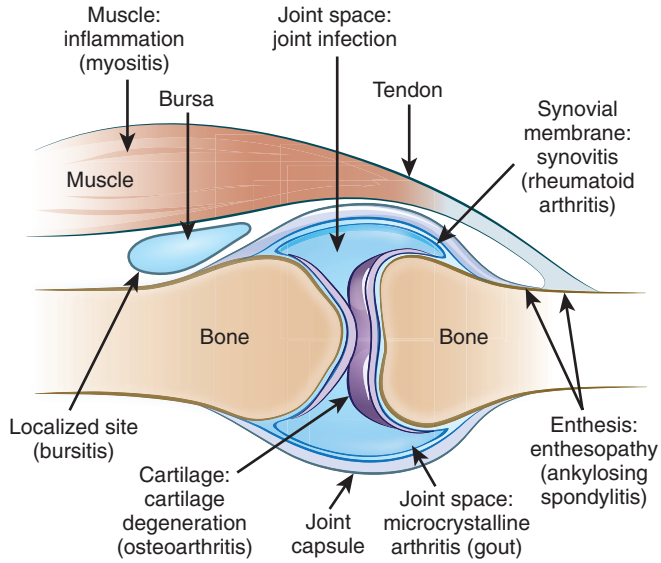

FIGURE 33.2 Location of musculoskeletal disease processes by site, pathophysiologic process, and typical disease *(parentheses)*. (From Fries JF. Approach to the patient with musculoskeletal disease. In: Wyngaarden JB, Smith LH, Bennett JC, eds. *Cecil Textbook of Medicine*. 19th ed. Philadelphia: WB Saunders; 1992:1488.)

of excruciating discomfort. Sharp, radiating, or throbbing pain is very unusual for arthritis and suggests an alternative explanation such as neuropathic pain, trauma, or psychogenic pain.

Pain Timing

Arthritis usually causes consistent patterns of discomfort. Symptoms are present daily, though with day-to-day variability in severity. Stiffness or pain-related discomfort occurs on awakening in the morning or after other periods of inactivity, such as prolonged sitting in class or taking a long car ride. The stiffness may last for hours, but generally improves with activity during the day. Some forms of arthritis, such as Lyme arthritis or enthesitis-related arthritis, may be more episodic. Lyme arthritis classically causes symptoms for days to weeks, usually in a single knee, interspersed with periods of improvement. Enthesitis-related arthritis can cause sudden increases in swelling and discomfort of 1 or more joints for several weeks to months at a time, followed by gradual spontaneous improvement.

Discomfort that occurs with activities and improves with rest is more suggestive of mechanical pain such as that associated with patellofemoral syndrome, hypermobility, tendonitis, overuse, or muscle strain. Affected children do not have significant symptoms in the morning or after naps, and these conditions are generally not associated with signs of significant inflammation such as warmth, prominent swelling, or limited range of motion.

Nocturnal pain that wakes children from sleep may be seen in potentially serious conditions such as leukemia, bone tumors (including benign tumors such as osteoid osteoma), or infections, but may also occur with benign conditions such as growing pains, muscle cramps, or behaviorally mediated pain. Children with benign causes of pain tend to lack systemic symptoms, are well during the day, and have normal physical examination findings, whereas those with more serious illnesses typically have additional symptoms to suggest the diagnosis.

Pain Acuity

Most chronic arthritis is insidious, and affected children often have symptoms for weeks to months before they seek medical attention. If the onset is sudden and severe, the evaluation should focus on excluding diagnoses that require urgent treatment, such as trauma, fracture, septic arthritis, or osteomyelitis. Acute rheumatic fever, reactive arthritis, and viral-associated arthritis or myositis may also manifest suddenly.

Children who describe having extremity pains "for years" often have mechanical causes of their discomfort such as hypermobility syndrome or patellofemoral syndrome, psychogenic or behavioral causes of pain, or other relatively benign conditions such as growing pains. It is very rare for such children to have an unrecognized arthritis.

Signs of Inflammation

The swelling and warmth of arthritis are often apparent to the child and parents. Exceptions may include the shoulder and hip, in which the joints are too deep for these signs to be visible, and the spinal, temporomandibular, and sacroiliac joints, in which the articular surfaces are small in relation to the surrounding soft tissues. In these areas, physical examination may reveal tenderness or limitation of motion in the absence of reported signs of inflammation.

Disability

The chief complaint may often be a disability such as limping, trouble climbing stairs, or difficulty writing. Some children will have associated pain and signs of inflammation, whereas others have little or no discomfort and it may be that they or their family have simply noticed a decrease in functional ability.

If the chief complaint is the disability, it is helpful to localize the source of the disability to the joint, the bones, the muscles, or the nerves. Muscle or nerve disease manifests primarily as weakness, although some children with sensory neuropathies or myositis, particularly acute viral myositis, will also have pain. Dermatomyositis and polymyositis cause symmetric proximal weakness in the upper and lower extremities. The characteristic symptoms are difficulties

climbing stairs, rising from the floor, taking the big step onto a bus or into the family minivan, and washing or combing the hair, as well as fatigue and poor endurance. Isolated lower extremity or asymmetric weakness should increase suspicion of neurologic disease.

Disabilities from arthritis are caused by limited range of motion or discomfort in the joint rather than weakness. Limping, particularly in the mornings, toe-walking because of inability to extend the knee or Achilles tendon, and having difficulty running and jumping are seen with lower extremity arthritis. The child with hand or wrist arthritis has difficulty opening bottles, turning doorknobs, manipulating buttons or snaps on clothing, and gripping pencils or utensils.

Medical History

Numerous genetic syndromes and metabolic diseases are associated with arthritis and arthropathy (see Table 33.1). Endocrine disorders such as diabetes, hyperparathyroidism, and hypothyroidism are associated with arthropathy, periosteal inflammation, and muscle weakness, respectively. Arthritis is more frequent in patients with psoriasis and inflammatory bowel disease. Bone pain is common in hemoglobinopathies such as sickle cell disease. Cystic fibrosis and other chronic pulmonary diseases increase the likelihood of painful hypertrophic osteoarthropathy: the clinical triad of arthritis, digital clubbing, and ossifying periostitis of the long bones. Arthritis or arthralgia may occur after viral diseases or immunization, particularly with immunization against rubella and hepatitis B, presumably secondary to immune complex deposition in the joint.

Medications

Medications may directly cause symptoms, either via serum sickness-like reactions or swelling related to anaphylaxis. Response to medications may also provide further insight into the etiology of arthritis. In most children, an adequate dose of nonsteroidal antiinflammatory drugs (NSAIDs) improves the discomfort of arthritis to some degree. In rheumatic fever, NSAIDs often result in dramatic improvement in symptoms. Conversely, the patient who continues to have severe pain despite adequate doses of antiinflammatory and analgesic medication is more likely to have an infection, a fracture, a tumor, or psychogenic pain.

Family History

For some diseases, a positive family history increases the likelihood that other individuals in the family have that disease, but the genetics of the rheumatic diseases are complex, and none of the genetic associations are strong enough to confirm or eliminate a diagnosis solely on the basis of the family history. Within the rheumatic diseases, the family history is most helpful when diagnostic possibilities include enthesitis-related arthritis, psoriatic arthritis, or lupus. Ankylosing spondylitis, reactive arthritis, or inflammatory bowel disease in the family increases the likelihood that the child's arthritis is related to 1 of these entities. The presence of the human leukocyte antigen (HLA)-B27 in these family members may increase the likelihood of enthesitis-related arthritis in the child. Approximately 30% of patients with lupus will have a 1st-degree relative affected by lupus. Less common familial illnesses that may cause rheumatic complaints include familial Mediterranean fever, mucopolysaccharidoses, hemophilia, and muscular dystrophies. A family history of adults with osteoarthritis or other forms of degenerative arthritis is generally not helpful, since these entities are relatively common and very rarely relevant to a child's joint symptoms.

Social History

Determining the extent to which the problem has limited usual activities helps to gauge the severity of the problem. Has the child missed school because of their symptoms? Has the child been able to participate in physical education, organized sports, or other physical activities such as dancing, swimming, and gymnastics? Is the older child participating in social activities with friends? In some instances, the limitations are directly related to discomfort or disability from arthritis, but school absences and the discontinuation of sports and social activities may also be secondary to depression or psychogenic pain. It is helpful to ask the parents whether the child's mood or personality has changed recently and whether there have been any recent known psychosocial stressors such as problems at school or with friends or discord within the family. Chronic pain syndromes in children are frequently associated with a history of psychosocial stress as well as depression.

Travel history is important in considering Lyme disease because the causative agent, the spirochete *Borrelia burgdorferi*, is transmitted by the bite of a deer tick that has a restricted geographical distribution. Lyme arthritis characteristically causes episodic joint effusions in 1 or several large joints, most commonly the knee. A small percentage of patients develop chronic arthritis. In the United States, endemic regions include the northeast (Connecticut, Rhode Island, and Massachusetts), mid-Atlantic (Long Island, New York City suburbs, New Jersey, southeastern Pennsylvania, Delaware, and Maryland), and the upper Midwest (parts of Minnesota and Wisconsin). Although these endemic areas may be gradually expanding, a child who has not traveled to these areas is unlikely to have Lyme disease. Arthritis may be the only symptom of Lyme disease, and may not appear until up to 2 years after the tick bite; a history of the classic rash (erythema migrans) is helpful but not necessary for a diagnosis of Lyme disease.

Review of Systems

Constitutional Symptoms

Some rheumatic diseases, including several forms of childhood arthritis, are systemic illnesses and cause fevers, poor appetite, weight loss, and fatigue. The absence of these symptoms helps eliminate specific illnesses as diagnostic possibilities. When fevers are present, establishing the pattern of fever is important. Systemic juvenile idiopathic arthritis (JIA) typically produces 1 or 2 high temperature spikes each day, with many afebrile hours in between (Fig. 33.3). More persistent fevers tend to be seen with infections or Kawasaki disease. A periodic fever pattern, in which fevers occur for several days, followed by weeks without fever, is seen in familial Mediterranean fever, cyclical neutropenia, the syndrome of periodic fever, aphthous stomatitis, pharyngitis, and adenopathy (PFAPA), and other autoinflammatory syndromes. Systemic lupus erythematosus (SLE), vasculitis, rheumatic fever, serum sickness, inflammatory bowel disease, sarcoidosis, leukemia, and neuroblastoma may cause fevers associated with arthritis or extremity pains. These illnesses do not cause specific patterns of fever.

A decline in appetite is common in many arthritides, though when associated with documented weight loss may indicate more severe or systemic illness. Although most children with JIA do not have significant appetite changes, those with systemic JIA may have substantial appetite and growth disturbances. Severe polyarticular JIA may cause some appetite changes and mild weight loss. Children with Crohn disease or ulcerative colitis, both of which are often accompanied by abdominal pain and diarrhea, may demonstrate poor appetite and failure to thrive. SLE, vasculitis, scleroderma, malignancies, and chronic infections such as tuberculosis are additional causes of significant weight loss. An increase in weight should raise the suspicion of hypothyroidism or fluid retention.

Fatigue is common with any systemic illness, and it may be present in systemic or polyarticular JIA, SLE, hypothyroidism, rheumatic fever, and chronic pain syndromes. The clinician should attempt to

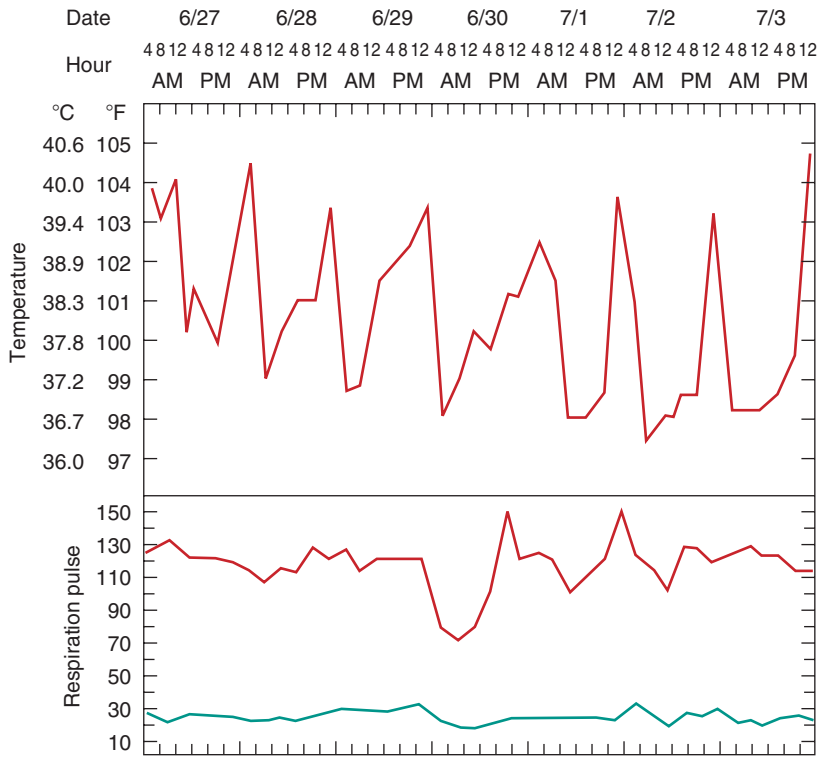

FIGURE 33.3 Pattern of high, intermittent fever in a 3-year-old girl with systemic juvenile idiopathic arthritis (JIA). Most febrile spikes in this patient occurred in the late evening to early morning hours and were accompanied by a systemic JIA rash. (From Cassidy JT, Petty RE, Laxer RM, et al., eds. *Textbook of Pediatric Rheumatology*. 6th ed. Philadelphia: Elsevier; 2011:238.)

distinguish between generalized fatigue and specific muscle weakness. The presence of proximal muscle weakness, often associated with fatigue and poor endurance, is characteristic of polymyositis and dermatomyositis.

Skin Changes

Systemic JIA is nearly always accompanied by evanescent pink or salmon-colored macules, often a few centimeters in diameter or smaller but sometimes coalescing to form larger patches (Fig. 33.4). These may be generalized or localized to the trunk or extremities. The macules are usually not pruritic, appear with the fever spikes, and may resolve completely when the fever is absent. Sometimes parents do not notice the rash because of its fleeting nature. Acute rheumatic fever is associated with a specific rash, **erythema marginatum**, in only approximately 5% of cases. Erythema marginatum is also a fleeting rash, changing in distribution over time, and consists of erythematous patches with serpiginous borders that tend to migrate, usually over the trunk and proximal extremities. Because of their changes in distribution, families often confuse both of these rashes with urticaria. The **malar rash of SLE** is a fixed, erythematous, nonblanching patch over the cheeks and nasal bridge that tends to spare the nasolabial folds. SLE may also cause vasculitic rashes, as well as nonspecific erythematous macular or papular lesions. Vasculitic rashes consist of palpable purpura and can sometimes be ulcerative. The characteristic skin lesions in dermatomyositis are pathognomonic: a **heliotrope rash** is a purpuric discoloration of the upper eyelid, often accompanied by edema (Fig. 33.5); **Gottron papules** are erythematous plaques or papules that appear on the extensor surface of the metacarpophalangeal and proximal interphalangeal joints of the hands (Fig. 33.6). These are sometimes scaly and can be confused with psoriasis or eczema, were it not for the distribution. Lesions similar to the Gottron papules occasionally also appear on the extensor surfaces of the elbows and knees and over the medial malleoli at the ankle. In addition, erythematous patches may appear on the shoulders, chest, or face, where the appearance can cause confusion with the malar rash of SLE.

Erythema migrans occurs in up to 80% of cases of Lyme disease, days to weeks after the tick bite. The lesion expands, beginning as a small papule and then forming a large erythematous, circular patch, usually at least 5 cm in diameter and often with some clearing in the center to produce a target-like appearance (Fig. 33.7). If Lyme disease is left untreated, the lesion usually lasts for several weeks and then gradually resolves. If dissemination occurs, some individuals develop multiple secondary lesions that appear similar to the primary lesion.

The history of other types of rashes or skin lesions may suggest other diagnoses. Measles and parvovirus infections, for example, have characteristic rashes. Petechiae may be seen with SLE, vasculitis, immune thrombocytopenia, or leukemia. Pallor or cyanosis of the digits, hands, and feet in association with cold temperature suggests **Raynaud phenomenon**, which is most often seen in those with no underlying systemic illness, but may be associated with several rheumatic diseases, most notably SLE and scleroderma. **Scleroderma** causes tightening, thickening, and the development of a waxy texture to the skin, and it frequently begins on the hands, feet, and face. A history of photosensitivity is suggestive of SLE.

Additional Symptoms

Questioning the parents about cognitive difficulties, including declining school performance or memory loss, helps screen for the possibility of subtle central nervous system involvement that may be associated

FIGURE 33.4 Systemic juvenile idiopathic arthritis rash, a salmon-colored, macular rash that is nonpruritic. The individual lesions are transient, appear in crops, and may be in a linear distribution after minor trauma such as scratching the surface of the skin (Koebner phenomenon). (From Cassidy JT, Petty RE, Laxer RM, et al., eds. *Textbook of Pediatric Rheumatology*. 6th ed. Philadelphia: Elsevier; 2011:238.)

FIGURE 33.5 Heliotrope discoloration and violaceous suffusion with edema of the upper eyelids in acute dermatomyositis. (From Cassidy JT, Petty RE, Laxer RM, et al., eds. *Textbook of Pediatric Rheumatology*. 6th ed. Philadelphia: Elsevier; 2011:384.)

with SLE or vasculitis. Seizures or frank psychosis may also occur in these illnesses. Alopecia is frequently seen with SLE and may also occur with hypothyroidism. Ocular symptoms, such as pain or redness of the eye, may occur with uveitis. Acute anterior uveitis (involving the iris and/or ciliary body) can be seen with reactive arthritis and enthesitis-related arthritis. Chronic anterior uveitis is most common with oligoarticular JIA and is usually asymptomatic. Sarcoidosis in children is usually associated with posterior uveitis, although anterior uveitis also occurs. Ulcerations of the nose or hard palate may be present with SLE. Aphthous ulcerations can be seen with inflammatory bowel disease

FIGURE 33.6 Symmetric, scaly, erythematous papules over the metacarpopharyngeal and proximal interphalangeal joints of the hand in acute dermatomyositis. (From Cassidy JT, Petty RE, Laxer RM, et al., eds. *Textbook of Pediatric Rheumatology*. 6th ed. Philadelphia: Elsevier; 2011:385.)

FIGURE 33.7 Erythema migrans. Lesions begin as red macules that expand to form large rings that often have a typical "bulls-eye" appearance. (From Cassidy JT, Petty RE, Laxer RM, et al., eds. *Textbook of Pediatric Rheumatology*. 6th ed. Philadelphia: Elsevier; 2011:582.)

and Behçet disease. Frequent sinusitis is often a manifestation of granulomatosis with polyangiitis.

Pleuritic chest pain that is worse when the patient lies supine and improves with sitting up and leaning forward may represent pericarditis, which can be seen in systemic JIA and SLE. Dysphagia suggests esophageal dysmotility, which may occur with inflammatory myopathies and scleroderma. Asking whether the child needs to cut food into small pieces, needs to drink an unusual amount of fluid with meals, or takes a long time to complete a meal are helpful ways of assessing dysphagia. Abdominal pain, vomiting, and diarrhea are nonspecific, but if severe or associated with melena or hematochezia, suggest Henoch–Schönlein purpura (HSP), inflammatory bowel disease, polyarteritis nodosa with vasculitis of the intestine, or the rare intestinal vasculitis associated with dermatomyositis. Testicular pain is seen with some forms of vasculitis, particularly HSP and polyarteritis nodosa. A history of recurrent genital and oral ulcerations is highly suggestive of Behçet disease. Peripheral edema, sacral edema, or periorbital edema may be present with illnesses causing glomerulonephritis, such as SLE and some of the vasculitides.

◆ Physical Examination

Observing the child ambulate or explore the examination room provides a sense of the severity of the illness and the degree of disability. Particularly with young, fearful children, this period of observation may give a better sense of the range of motion or the degree of discomfort in the joints than the formal examination, when the child may be uncooperative.

The examination begins by reviewing the vital signs. Fever, especially in the child with arthritis or localized extremity pain, may suggest an infectious process. Tachycardia may be caused by fever, anxiety, pericarditis, or myocarditis. Tachypnea suggests the presence of cardiac or pulmonary disease and hypertension increases the suspicion of renal disease.

In any child with joint complaints, it is important to examine all of the joints because arthritis may be detected in joints that have not had symptoms. The neck and the joints of the upper extremities are best examined with the child in a sitting position. Children with inflammation in the joints of the cervical spine usually have limitations in extension, lateral flexion, and rotation. This is tested by asking the child to look up at the ceiling, touch each ear to the ipsilateral shoulder, and touch the chin to each shoulder.

Arthritis of the temporomandibular joint is common with polyarticular JIA and might easily be overlooked. Children with chronic arthritis of these joints develop micrognathia and often retrognathia as a result of delayed mandibular growth. The oral opening is often decreased, and there may be pain with opening and closing of the jaw, and tenderness to palpation directly over the joint.

Shoulder arthritis is identified by detecting limited range of motion and pain with motion. With the upper arm abducted to 90 degrees and the elbow flexed to 90 degrees, the clinician can then rotate the upper arm superiorly and inferiorly (external and internal rotation of the humerus, respectively), noting any limitation or pain. Alternatively, the patient can be asked to abduct and extend the arm, reaching behind the head to touch the contralateral scapula, and then to adduct and extend the arm, reaching behind the back and upward, again touching the contralateral scapula. The acromioclavicular joints and the sternoclavicular joints are occasionally affected by arthritis and should be palpated, noting any swelling or tenderness.

In the elbow, arthritis often produces detectable swelling and warmth. Elbow extension and flexion should also be tested, along with supination of the forearm and hand. Many children can normally hyperextend their elbows, and the degree of extension is variable; therefore, it is helpful to compare the range of motion of each elbow to the contralateral side.

The wrists are inspected for swelling and palpated for warmth and tenderness. Many children with wrist arthritis develop swelling on the dorsal aspect of the wrist that may be fairly large but is usually nontender. Extension tends to be more limited than flexion in wrist arthritis, and radial deviation tends to be more limited than ulnar deviation. Children with arthritis frequently complain of pain or withdraw their arm with maneuvers to test flexion and extension of the wrist.

The metacarpophalangeal (MCP) joint and the proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints should be individually palpated, and any swelling, tenderness, or warmth should be noted (Fig. 33.8). The examiner should flex and extend the MCP joints, looking for limitations. To test the range of motion of the PIP and DIP joints, the child should try to supinate the hand and flex all of the digits, attempting to touch the fingertips to the palm. To examine the 1st MCP and thumb interphalangeal joint, the child should try to touch the tip of the thumb to the base of the 5th finger. Grip strength is determined by having the child tightly squeeze 2 of the clinician's fingers. Arthritis of the wrist or any of the small joints of the hand decreases grip strength.

FIGURE 33.8 The joints of the wrists and hands of a 2-year-old boy are swollen, warm, and painful with limited extension of the fingers. (From Cassidy JT, Petty RE, Laxer RM, et al., eds. *Textbook of Pediatric Rheumatology*. 6th ed. Philadelphia: Elsevier; 2011:221.)

The child should next lie in a supine position, either in the parent's lap or on the examination table so that the lower extremities can be examined. Each hip is taken through its range of motion, beginning with flexion by trying to bring the knee as close to the chest as possible. Any pain or limitation is noted. With the hip and knee each flexed to 90 degrees, internal and external rotation are tested by keeping the knee in a fixed position and turning the lower leg laterally and medially, thereby rotating the femur. The hip and knee are extended back to a neutral supine position and abduction is tested. With the child in the prone position, the examiner evaluates hip extension by placing a hand on the child's ipsilateral iliac crest and lifting the child's thigh posteriorly with the knee extended. Hip arthritis most often causes limitations with internal rotation and extension, usually in association with pain in the inguinal area.

The knee is inspected for effusions and other obvious deformities. Palpation of the knee assesses for warmth, a common finding in knee arthritis, synovial swelling, or an effusion. Applying pressure in the suprapatellar area with 1 hand while palpating on either side of the patella with the other allows for the detection of effusions more readily because this forces excessive joint fluid that has accumulated in the suprapatellar area into the synovial space. Small effusions may be detected by eliciting a **bulge sign**. This is done by milking the medial and lateral depressions around the patella superiorly in an effort to push the fluid into the suprapatellar space and then gently pushing either medially or laterally just superior to the patella. This releases the fluid back into the synovial space, causing the area medial to the patella to bulge out. The popliteal fossa should be palpated, because fluid within the knee joint tends to track posteriorly as it accumulates, producing fullness in the popliteal fossa and sometimes a frank cyst, identical to the Baker cysts seen in adults with rheumatoid arthritis.

Palpating around the edges of the patella causes pain in many adolescents with **patellofemoral syndrome** (also known as chondromalacia patellae), a common cause of knee pain in active adolescents. In another maneuver that elicits pain in this syndrome, the patient relaxes the quadriceps muscles while the examiner pushes the patella inferiorly. While the examiner maintains pressure on the patella, the patient contracts the quadriceps. In patients with patellofemoral syndrome, pain elicited by this maneuver is referred to as a positive

patellar apprehension test, while a grinding sensation felt by the examiner constitutes a positive **patellar grind sign**. The tibial tubercle and patellar tendon should be inspected and palpated for swelling and tenderness associated with **Osgood-Schlatter disease** and **patellar tendonitis**, respectively.

Flexing and extending the knee tests range of motion. Most young children can touch their heel to their buttocks and hyperextend the knee. The examiner can detect subtle limitations in extension by standing at the foot of the table and lifting the heels of the child off the table as the child holds his or her legs fully extended. If 1 knee is limited with extension, the patella on that side may be slightly more elevated.

Swelling in the ankles is often best seen when inspecting and palpating the posterior aspect of the ankle, where fullness on either side of the Achilles tendon may be appreciated between the tendon and the malleoli. Warmth is common with ankle arthritis. Testing range of motion in the ankle should include both the tibiotalar ankle joint and the subtalar talocalcaneal joint. Cupping the heel with 1 hand and using the other hand to grasp the forefoot allows the examiner to move the forefoot superiorly (dorsiflexion) and inferiorly (plantar flexion). The hand cupping the heel is rocked laterally and medially to check inversion and eversion associated with motion at the subtalar joint. Holding the heel firmly with a cupped hand and gently rotating the forefoot with the other hand tests the joints of the midfoot. Each of the metatarsophalangeal joints is palpated along with each of the toes. The toes are inspected for the presence of swelling. The plantar fascia and the Achilles tendon are palpated, and any tenderness or swelling is noted.

The child should stand so that the examiner can evaluate the back. The sacroiliac joints are palpated, any tenderness is noted, and the child is asked to keep the knees extended and bend forward, touching the hands to the ground if possible. The lumbar spine should curve forward normally without flattening. The **modified Schober measurement**, which reveals whether the lumbar spine flexes normally, is done by marking the lumbar spine at a point where a horizontal line connecting the dimples of Venus intersects the spine. Then the examiner measures 10 cm above and 5 cm below that spot while the child is standing. When the child bends forward, the distance between the top and bottom marks should increase to at least 21 cm as the vertebral bodies separate during flexion. A shorter distance suggests limitation in mobility of the spine and potential spondylitis. Scoliosis is detected by noting any asymmetric elevation of the shoulder and upper back while the child bends forward.

Hypermobility is a very common cause of pain associated with sports and other activities; it tends to improve with rest. Hypermobility, patellofemoral syndrome, frequent ankle sprains, and pes planus are frequently seen together. The hypermobile child or adolescent can hyperextend the knees and elbows, appose the thumb to the forearm while flexing the wrist, hyperextend the MCP joints so that the digits are parallel to the forearm when the wrist is extended, and easily put the palms flat on the floor while bending forward from a standing position with the knees locked. Extreme hypermobility is seen in some individuals with Ehlers–Danlos syndrome or Marfan syndrome.

Myofascial pain syndromes are associated with the presence of **trigger points**, exquisitely tender, well-localized points often detected in the following locations: the occiput, trapezius muscles, medial borders of the scapula, upper outer quadrant of the buttocks, the 2nd cervical space anteriorly, the 2nd costochondral space just distal to the lateral epicondyle on the forearm, the greater trochanter in the proximal leg, and the medial aspects of the knees. Their presence in the older child with diffuse pain, fatigue, and difficulty sleeping is highly suggestive of a myofascial pain syndrome.

Proximal muscle strength testing should be performed in any patient complaining of weakness or fatigue. The deltoids, biceps, triceps, psoas, quadriceps, and hamstrings are tested. Neck flexor weakness is common in dermatomyositis and polymyositis and is tested by having the child lie supine and lift only his or her head. Most children are able to lift and keep the head elevated, even if asked to resist pressure from the examiner's hand against the forehead. To test proximal leg strength, the child rises from a sitting position on the floor. Muscle atrophy should be noted. Chronic knee arthritis or hip disease leads to atrophy of the ipsilateral quadriceps. Similarly, ankle arthritis causes the gastrocnemius to atrophy; wrist arthritis leads to wasting of the forearm muscles; and elbow contractures cause atrophy of the triceps muscle. Atrophy is easily overlooked, and it is sometimes helpful to measure the circumference of the thigh, calf, or upper arm to detect asymmetry.

The skin and mucous membranes should be examined carefully, as there may be clues to the presence of systemic disease (Table 33.3). Systemic JIA, SLE, acute rheumatic fever, and dermatomyositis are associated with characteristic rashes. Petechiae or palpable purpura suggests vasculitis. Nodules are seen with acute rheumatic fever and some forms of JIA. Thickening and tightening of the skin, particularly over the distal extremities and face, are often present in scleroderma. Nasal or palatal ulcers suggest SLE, whereas aphthous ulceration may be seen with inflammatory bowel disease or Behçet disease. Alopecia,

TABLE 33.3 Skin Manifestations of Rheumatic Disease

Physical Finding	Possible Disease
Petechiae, purpura	Vasculitis (if palpable) Leukemia Meningococcemia Other infections SLE
Erythema nodosum	Inflammatory bowel disease Streptococcal infection Sarcoidosis Drugs Tuberculosis Fungal infection
Gottron papules	Dermatomyositis
Alopecia	SLE, hypothyroidism
Calcification	Dermatomyositis, scleroderma
Subcutaneous nodules	Polyarticular JIA, rheumatic fever
Oral ulcers	SLE, Behçet disease, inflammatory bowel disease, reactive arthritis
Genital ulcers	Behçet disease
Digital ulcers	Vasculitis, SLE, scleroderma
Tight, thickened skin	Scleroderma
Livedo reticularis	Antiphospholipid syndrome, SLE, cutaneous polyarteritis nodosa
Nail dystrophy or pits	Psoriasis
Edema	SLE, vasculitis, scleroderma, eosinophilic fasciitis, serum sickness, Henoch–Schönlein purpura
Desquamation	Kawasaki disease, scarlet fever
Cyanosis	Raynaud phenomenon, hypertrophic osteoarthropathy

JIA, juvenile idiopathic arthritis; SLE, systemic lupus erythematosus.

either localized or diffuse, may be apparent to the examiner without being recognized by the patient. The presence of peripheral or periorbital edema increases the suspicion of glomerulonephritis.

◆ Laboratory Studies

Laboratory testing should be considered when the diagnosis is unclear or when there is a suspicion of life- or limb-threatening disease such as leukemia, septic arthritis, or osteomyelitis. Laboratory testing alone does not establish a diagnosis of JIA. Tests frequently seen in "arthritis panels" such as those for antinuclear antibody (ANA), rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are not specific for arthritis. However, if arthritis is detected on physical examination, laboratory testing aids in classifying the specific type of arthritis that is present.

A complete blood count (CBC) with manual differential is useful as a means of decreasing the suspicion of an acute infection or leukemia, which may manifest with bone or joint pain or even frank arthritis. A normal CBC is reassuring, but it is also helpful to compare the platelet count to the ESR. Because platelets are an acute-phase reactant, their number should increase as the ESR increases. A normal or low platelet count in a child with markedly elevated ESR increases the suspicion of leukemia.

An elevated peripheral white blood cell (WBC) count is often present with septic arthritis or osteomyelitis, but it is neither sensitive nor specific enough to change the diagnostic impression formulated after the history and physical examination. In systemic JIA, the WBC count may be markedly elevated at 20,000 WBCs/mm^3 or greater, the hemoglobin may be as low as 6 or 7 mg/dL, and the platelet count is typically significantly elevated. For many of the other inflammatory diseases that are associated with arthritis or extremity pain, a mild to moderate normocytic anemia as well as a mild thrombocytosis are common. SLE may demonstrate anemia, leukopenia, and thrombocytopenia.

The ESR is helpful when the physical examination is inconclusive regarding the presence or absence of an inflammatory condition. In uncooperative or obese children, it may be difficult to detect small effusions or subtle limitation in the range of motion. In these instances, an elevated ESR increases the suspicion of arthritis, although a normal ESR does not rule it out. In children who clearly have rheumatic disease or infection, the ESR is not diagnostically useful, but it may be used to monitor disease activity over time.

Urinalysis is an excellent screen for glomerulonephritis, which may occur in patients with vasculitis or SLE. Proteinuria or red blood cell casts suggest renal involvement. The creatinine level is elevated with renal insufficiency. Severe proteinuria leads to hypoalbuminemia, though hypoalbuminemia without proteinuria may also be seen in systemic JIA. Kawasaki disease is associated with sterile pyuria.

Serum aminotransferases are elevated in patients with hepatitis and occasionally in patients with SLE. In those with myositis, elevated aminotransferases, usually with the asparate aminotransferase (AST) elevated out of proportion to the alanine aminotransferase (ALT), often occurs concomitantly with increased creatine kinase, lactate dehydrogenase, and aldolase levels.

Antinuclear Antibody

The ANA test is a sensitive screen for SLE because it is positive in more than 95% of patients who also usually have high ANA titers, typically with values of 1:640 or higher. Lower ANA titers, usually in the range of 1:40-1:160, are seen in children with JIA, healthy children, or those with cross-reactive antibodies in the setting of a recent infection. The frequency of ANA positivity varies in the different forms of JIA. The pattern of the ANA is rarely helpful. Homogeneous and speckled patterns are the most common and are not specific for any particular illness. A peripheral or "rim" pattern is usually associated with anti–double-stranded DNA (anti-dsDNA) antibodies and is more specific for SLE. A nucleolar pattern suggests the presence of anti–Scl-70 antibodies, which may be seen in patients with scleroderma.

The ANA test is not specific and should not be ordered unless there is a strong suspicion of SLE or an overlap syndrome. It is not sensitive enough or specific enough to be diagnostically helpful for other diseases. A positive ANA finding is present in many asymptomatic healthy children, and in children with viral illnesses, other infections, other rheumatic and inflammatory diseases, and in relatives of those with autoimmune illnesses.

Rheumatoid Factor

The rheumatoid factor (RF) test is not diagnostic. Only 5% of children with JIA have a positive RF result, and this usually occurs in teenagers with adult-like polyarticular disease. RF is an immunoglobulin M antibody directed against immunoglobulin G. In children with polyarthritis, the presence of RF is a poor prognostic factor; these children have a high likelihood of developing chronic, erosive arthritis. A positive test result for RF can be seen with other illnesses associated with the formation of immune complexes, including rheumatic diseases such as SLE or vasculitis, and with infectious diseases such as bacterial endocarditis, infectious mononucleosis, and hepatitis B or C. It should not be ordered, and will not be helpful diagnostically, in individuals who do not have polyarthritis based on the history and physical examination.

Additional Antibody Testing

If the history and physical examination findings are suggestive of SLE, additional autoantibody testing is helpful (Table 33.4). Anti-dsDNA antibodies and anti-Smith antibodies are highly specific for SLE. Anti-ribonucleoprotein (anti-RNP) antibodies may be seen in patients with SLE, and when present in isolation (without anti-dsDNA and anti-Smith antibodies), suggest mixed connective tissue disease, which has clinical features that are often a combination of those seen with SLE, dermatomyositis, and scleroderma. Anti-Sjögren syndrome type A (anti-SSA [also known as anti-Ro]) and anti-Sjögren syndrome type B (anti-SSB [also known as anti-La]) antibodies are occasionally seen in patients with SLE but are not specific. They are seen in Sjögren syndrome, an illness producing chronic inflammation of the salivary and lacrimal glands and resulting in xerostomia and xerophthalmia.

Anticardiolipin antibodies, 1 of several antiphospholipid antibodies, may be present in SLE, but they are also seen in asymptomatic individuals and in those with the antiphospholipid antibody syndrome, in which clinical manifestations are restricted to the complications of the hypercoagulable state associated with these antibodies. These complications include venous and arterial thromboses and recurrent spontaneous abortions. Many patients with SLE have a false-positive Venereal Disease Research Laboratory (VDRL) test result because this is also a test for antiphospholipid antibodies. A positive direct Coombs test result, indicative of an autoimmune hemolytic anemia, is common in patients with SLE, although rarely is the hemolysis clinically significant.

Granulomatosis with polyangiitis (GPA) and the other antineutrophil cytoplasmic antibody (ANCA) associated vasculitides are the only types of vasculitis that can be diagnosed with confidence on the basis of serologic testing. Antiproteinase 3 antibodies, previously identified as cytoplasmic-staining or c-ANCA, are 95% sensitive and specific for GPA. The antimyeloperoxidase antibody (corresponding to peripheral-staining or p-ANCA) is much less specific; it is present with other vasculitides and a variety of infectious and inflammatory illnesses.

TABLE 33.4 Autoantibodies in Children

Test	Characteristics
Antinuclear antibody (ANA)	99% sensitive in SLE; very nonspecific
Anti–double-stranded DNA (dsDNA)	Up to 80% sensitive for SLE; highly specific (nearly 100%)
Anti-Smith (Sm)	Up to 35% sensitive in SLE; nearly 100% specific
Anti-SSA (Anti-Ro)	50% sensitive in SLE; seen in asymptomatic children; present in Sjögren syndrome and scleroderma; can be associated with neonatal lupus
Anti-SSB (Anti-La)	15% sensitive in SLE; seen in similar conditions as anti-SSA; can be associated with neonatal lupus
Antiribonucleoprotein (RNP)	Up to 40% sensitive in SLE; also seen in mixed connective tissue disease
Antihistone	Drug-induced SLE-like syndromes
Rheumatoid factor (RF)	30% of SLE patients; 5% of JIA; also seen in infections
Antiproteinase 3 (c-ANCA)	90–95% sensitive and specific for granulomatosis with polyangiitis
Antimyeloperoxidase (p-ANCA)	75% sensitive for microscopic polyangiitis; seen in other vasculitides, inflammatory bowel disease, other inflammatory diseases
Anti-RBC membrane (Coombs positive)	Up to 50% sensitive in SLE; nonspecific, seen also in Evan syndrome, isolated hemolytic anemia
Anticardiolipin	Seen in SLE; nonspecific, seen in asymptomatic children and in those with antiphospholipid syndrome

JIA, juvenile idiopathic arthritis; RBC, red blood cell; SLE, systemic lupus erythematosus; SSA and SSB, Sjögren syndrome type A and type B.

TABLE 33.5 Criteria for Diagnosing Lyme Disease

Characteristic clinical presentation
- Early localized disease: erythema migrans at the site of a recent tick bite, possible constitutional symptoms (malaise, headache, mild neck stiffness, myalgia, arthralgia), possible fever
- Early disseminated disease: multiple erythema migrans lesions at sites distinct from initial lesion, cranial nerve palsies (particularly cranial nerve VII), lymphocytic meningitis, polyradiculitis, constitutional symptoms, carditis
- Late disease: arthritis, polyneuropathy, encephalopathy, encephalitis

Exposure in an endemic area*

Positive Lyme ELISA, confirmed by positive Western blot

Western blots are considered positive if the following are present:
For IgM, 2 of the following 3 bands must be present:
23, 39, 41 kD
For IgG, 5 of the following 10 bands must be present:
18, 21, 28, 30, 39, 41, 45, 58, 66, 93 kD

*Mid-Atlantic and southern New England coastal regions, northwestern Wisconsin, and eastern Minnesota are considered the most endemic regions in North America. Even within these regions, the incidence of infection can vary widely.
ELISA, enzyme-linked immunosorbent assay; Ig, immunoglobulin; kD, kilodaltons.

Viral infections such as human parvovirus B19, Epstein–Barr virus, and rubella may be associated with arthralgia or arthritis, and testing for antibodies to these viruses may be helpful in some clinical situations. For diagnosing Lyme disease, the enzyme-linked immunosorbent assay (ELISA) is a very sensitive, but not specific, screening test. A positive ELISA must be confirmed by Western blot (Table 33.5).

Complement

The complement proteins C3 and C4 are often depressed in patients with active SLE, which indicates consumption of C3 and C4 secondary to the formation of immune complexes. Some patients with hereditary complement deficiencies develop SLE. Low levels of complement can be seen occasionally with the vasculitides and in other illnesses with immune complexes such as bacterial endocarditis. The CH_{50} is a functional assay that measures the activity of the entire classical pathway of complement. If any single complement protein is depressed, this may cause a decrease in the CH_{50}. The CH_{50} is less sensitive and less specific than testing for the individual complement components.

◆ Diagnostic Imaging

Radiographs

Plain radiographs of the limbs are helpful as a means of evaluating children for potential infections, trauma, leukemia, or solid bone tumors. Osteomyelitis usually causes periosteal elevation, which may be seen after approximately 1 week of illness. Chronic osteomyelitis causes abscesses that may be visualized on plain radiographs. Fractures, including stress fractures and small avulsion fractures, are occasionally detected even when the clinical information is not strongly suggestive. Leukemia can cause lucency within the metaphyses of the long bones. Solid tumors, including osteosarcomas, Ewing sarcoma, and the benign osteoid osteoma, may all be identified on plain radiographs. Because knee pain may reflect referred pain from the hip, any child with unexplained knee or thigh pain should have pelvis and hip radiographs, including a "frog-leg" view. The young, limping child may have Legg–Calvé–Perthes disease, an avascular necrosis of the femoral head. A slipped capital femoral epiphysis is classically seen in an overweight patient in his or her early teens (see Chapter 34).

In the child with arthritis, soft tissue swelling or effusions within the joint may be identified on plain radiographs. Chronic arthritis may demonstrate bone erosions and juxta-articular osteopenia. Radiographs can be useful in monitoring the course of the disease and can sometimes help guide management.

In children with suspected SLE, a chest radiograph may reveal an enlarged cardiac silhouette, suggestive of a pericardial effusion or the presence of pleural effusions. If GPA is a consideration, a chest radiograph may reveal bilateral cavitating pulmonary nodules. Pulmonary hemorrhage, with bilateral alveolar infiltrates, can be seen with GPA, SLE, microscopic polyangiitis, and rarely HSP.

Magnetic Resonance Imaging (MRI)

MRI is useful when plain radiographs either are unrevealing or have identified a poorly defined abnormality. MRI, a sensitive test for osteomyelitis and avascular necrosis, can also reveal small joint effusions that are not apparent on physical examination. MRI helps distinguish hemarthrosis from other forms of joint swelling and detects ligamentous and meniscal tears. MRI provides better visualization and characterization of tumors than do plain radiographs. If myositis is suspected, MRI may reveal increased signal within the muscle as a result of inflammation and can help determine a potential biopsy site.

(See *Nelson Textbook of Pediatrics,* p. 1483.)

Bone Scan

A bone scan is useful when plain radiographs are unremarkable and when the source of pain cannot be adequately localized. It is a sensitive test for inflammation in the bones and joints, and it can help distinguish arthritis from osteomyelitis, fractures, and tumors. Bone scans, like plain radiographs, are not as sensitive for osteomyelitis if obtained very early in the disease process, and a 2nd scan should be considered if the initial study is negative. A bone scan may detect osteoid osteomas that are not apparent on plain radiographs. Complex regional pain syndrome (CRPS) usually demonstrates asymmetric increased uptake on the affected side.

Additional Imaging Studies

Ultrasonography helps evaluate the hip for transient synovitis with effusion. Ultrasonography may also help to identify synovitis or effusions in other joints and may also be useful when evaluating tendons for tenosynovitis. Echocardiography is useful when acute rheumatic fever is a consideration. Clinically silent valvulitis with resulting insufficiency is detected only by echocardiography and was recently added as a formal diagnostic criterion for rheumatic fever. The echocardiogram can also detect pericardial effusions in patients with SLE and coronary artery aneurysms in patients with Kawasaki disease.

Conventional angiography, computed tomography (CT) with angiography, and magnetic resonance (MR) angiography are useful for the diagnosis of medium- or large-vessel vasculitis such as polyarteritis nodosa or Takayasu arteritis. High-resolution CT of the chest without contrast is helpful in visualizing pulmonary nodules in patients with GPA and in detecting basilar lung fibrosis in those with scleroderma.

Joint Fluid Aspiration

There are few indications for diagnostic joint fluid aspiration in the child with arthritis. Synovial fluid analysis in childhood is most helpful for confirming or excluding 3 possible problems: (1) infectious arthritis, (2) hemarthrosis (either secondary to trauma or a coagulopathy), and very rarely (3) crystal diseases such as gout or pseudogout. A 4th condition, the rare entity of pigmented villonodular synovitis, is suggested by the aspiration of a "chocolate brown" synovial fluid from the knee.

Among these possibilities, only infection is a common consideration in childhood and is typically suspected on the basis of the history and physical examination findings. The child with septic arthritis is usually febrile and has developed acute joint pain, swelling, warmth, and occasionally erythema, most commonly in a single joint (Table 33.6), over a period of hours to days. When septic arthritis is suspected, arthrocentesis is necessary, and the joint fluid is sent for cell count, protein quantification, glucose measurement, Gram stain, and microbiologic studies, including bacterial culture and polymerase chain reaction (PCR) testing for *Kingella kingae*, an increasingly common cause of septic arthritis in children (Table 33.7). Additional microbiologic assays include fungal culture and mycobacterial testing if suspected. Some infectious arthritides develop more indolently, such as gonococcal arthritis, tuberculous arthritis, and opportunistic infections in immunocompromised hosts. Adolescents with monoarticular arthritis (Table 33.8) or acute polyarthritis should undergo joint aspiration, regardless of other symptoms, if they have risk factors for

TABLE 33.6 Distribution of Affected Joints in 1050 Children with Pyogenic Arthritis

Joint	Number	Percentage of Cases
Knee	467	41
Hip	287	25
Ankle	143	13
Elbow	116	10
Shoulder	53	5
Others*	70	6
Total†	1136	100

*Includes sacroiliac joints, joints of the hands and feet, and sternoclavicular joint.
†Some children had more than 1 joint affected.
Modified from Gutierrez KM. Infectious and inflammatory arthritis. In: Long SS, Pickering LK, Prober CG, eds. *Principles and Practice of Pediatric Infectious Diseases*. 3rd ed. Philadelphia: Churchhill Livingstone; 2008:483; Table 81-1.

TABLE 33.7 Characteristics of Synovial Fluid

	Appearance	Viscosity	Cells per mm^3	% PMNs	Crystals	Culture
Normal	Transparent	High	<200	<10%	Negative	Negative
JIA	Translucent	Low	2,000–50,000	Variable	Negative	Negative
Psoriatic arthritis	Translucent	Low	2,000–50,000	Variable	Negative	Negative
Reactive arthritis	Translucent	Low	2,000–50,000	Variable	Negative	Negative
Gout	Translucent to cloudy	Low	200–greater than 50,000	>90%	Needle-shaped, negatively birefringent monosodium urate monohydrate crystals	Negative
Bacterial arthritis*	Cloudy	Variable	2,000–greater than 50,000	>90%	Negative	Usually positive
PVNS	Hemorrhagic or "chocolate brown"	Low	Variable	Variable	Negative	Negative
Hemarthrosis	Hemorrhagic	Low	Variable	Variable	Negative	Negative

*Includes spirochetal, gonococcal, and mycobacterial infections.
JIA, juvenile idiopathic arthritis; PMNs, polymorphonuclear neutrophils; PVNS, pigmented villonodular synovitis.
Modified from El-Gabalawy HS. Synovial fluid analyses, synovial biopsy, and synovial pathology. In: *Kelley's Textbook of Rheumatology*. 9th ed. Philadelphia: Saunders; 2013:755, Table 53-1.

TABLE 33.8 Differential Diagnosis of Monoarticular vs Polyarticular Arthritis and Arthralgia

Usually Monoarticular	Often Polyarticular
Common	
Infectious arthritis	Polyarticular JIA
• Bacterial	Psoriatic arthritis
• Mycobacterial	Reactive arthritis
• Fungal	Enthesitis-related arthritis
Avascular necrosis	• Ulcerative colitis
Hemarthrosis	• Crohn disease
Coagulopathy	Serum sickness
Trauma/overuse	Henoch–Schönlein purpura
Oligoarticular JIA	Systemic lupus erythematosus
Congenital hip dysplasia	Viral arthritis
Osteochondritis dissecans	Immune complex–mediated post-bacteremia (*Neisseria meningitidis*, *Haemophilus influenzae*)
Complex regional pain syndrome	Hypermobility
Stress fracture	Hemoglobinopathies
Osteomyelitis	
Metastatic tumor (neuroblastoma, leukemia)	
Rare	
Pigmented villonodular synovitis	Undifferentiated connective tissue disease
Plant thorn synovitis	Relapsing polychondritis
Familial Mediterranean fever	Whipple disease
Synovioma	Sarcoidosis
Synovial metastasis	Hyperlipidemias types II and IV
Intermittent hydrarthrosis	Systemic JIA
Pancreatic fat necrosis	Pyoderma gangrenosum
Gaucher disease	Pulmonary hypertrophic osteoarthropathy
Behçet disease	Chondrocalcinosis-like syndromes caused by ochronosis, hemochromatosis, Wilson disease
Regional migratory osteoporosis	Acute rheumatic fever
Sea urchin spine	Paraneoplastic syndromes
Amyloidosis (myeloma)	Dialysis arthropathy
Synovial osteochondromatosis	Crystal-induced arthropathies

JIA, juvenile idiopathic arthritis.
Modified from McCune WJ. Monoarticular arthritis. In: Kelley WN, Harris ED, Ruddy S, et al., eds. *Textbook of rheumatology*. 4th ed. Vol 1. Philadelphia: WB Saunders; 1993:369.

TABLE 33.9 Classification of Childhood Vasculitis

- Predominantly large-vessel vasculitis
  - Takayasu arteritis
- Predominantly medium-vessel vasculitis
  - Childhood polyarteritis nodosa
  - Cutaneous polyarteritis
  - Kawasaki disease
- Predominantly small-vessel vasculitis
  - Granulomatous
    - Granulomatosis with polyangiitis
    - Eosinophilic granulomatosis with polyangiitis
  - Nongranulomatous
    - Microscopic polyangiitis
    - Henoch–Schönlein purpura
    - Isolated cutaneous leukocytoclastic vasculitis
    - Hypocomplementemic urticarial vasculitis
- Other vasculitides
  - Behçet disease
  - Vasculitis secondary to infection (including hepatitis B-associated polyarteritis nodosa), malignancy, and medication (including hypersensitivity vasculitis)
  - Vasculitis associated with connective tissue diseases
  - Isolated vasculitis of the central nervous system
  - Cogan syndrome
  - Unclassified

Modified from Ozen S, Ruperto N, Dillon MJ, et al. EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitis. *Ann Rheum Dis*. 2006;65:936-941.

gonococcal disease. Likewise, if there has been exposure to tuberculosis, or if a child is immunocompromised, joint fluid aspiration should be strongly considered.

If the child has sustained trauma and it is unclear from the history and physical examination whether a joint effusion is inflammatory or hemorrhagic, joint fluid analysis may be helpful. Similarly, if there is history of a bleeding disorder in the family or in the child, joint aspiration should be considered (see Table 33.7).

Gout and pseudogout are unusual in childhood. Conditions that result in elevated serum uric acid levels predispose a child to gout, and if children with these conditions develop arthritis, the joint fluid should be analyzed for crystals. These conditions include leukemia, tumor lysis syndrome, renal failure, Down syndrome, Lesch–Nyhan syndrome, and type I glycogen storage disease (von Gierke disease).

Invasive Testing

If weakness is present, an electromyogram (EMG) and a nerve conduction study distinguish myopathies and myositis from neuropathies. Children with inflammatory myositis have a characteristic, albeit nondiagnostic, abnormal EMG. Peripheral neuropathies confirmed by nerve conduction studies may suggest the presence of a vasculitis or SLE.

Biopsies are most helpful in confirming the presence of vasculitis (Table 33.9) and to determine the extent of renal disease in a child with SLE. Kawasaki disease, GPA, Takayasu arteritis, polyarteritis, and HSP are vasculitides that may be diagnosed on the basis of either clinical criteria alone (Kawasaki disease, HSP), a combination of clinical criteria and arteriography (Takayasu arteritis, polyarteritis), or clinical criteria and serologic profiles (antiproteinase 3 antibodies in GPA). Biopsies of affected tissue are often necessary to confirm a diagnosis for many of the vasculitides. The most accessible affected tissue is acquired for biopsy first. In many children with vasculitis, this tissue is the skin and consultation with a dermatologist is helpful to determine which lesions and the location within a lesion that will be most likely to yield a diagnosis. If there is no rash, muscle and nerve samples may be taken for biopsy when EMG and nerve conduction studies reveal the presence of myositis or neuropathy. If neither of these sites

is affected, then the risks and benefits of biopsy of affected organs should be evaluated.

Synovial biopsy is rarely useful in the evaluation of arthritis. Biopsy is necessary to distinguish sarcoid arthropathy from JIA; sarcoid arthropathy is suspected when the young child has erythema nodosum, uveitis, and arthritis, as well as particularly "boggy" synovial effusions. In rare cases, synovial tumors, chronic indolent infections, or foreign bodies are detected by biopsy as well.

JUVENILE IDIOPATHIC ARTHRITIS

To be diagnosed with JIA, a child must have inflammatory arthritis of unknown etiology beginning before age 16 years and persisting for at least 6 weeks. JIA is further classified into different categories (Table 33.10). Specific classification of JIA should be made at 6 months of disease.

Oligoarticular Juvenile Idiopathic Arthritis

This is the most common form of JIA, affecting half of all children with JIA. Oligoarticular JIA can be further classified depending on whether fewer than 4 joints are affected for the entire course of the disease ("persistent") or if more than 4 joints are affected after the 1st 6 months of disease ("extended"). Persistent oligoarticular JIA is the most common form and typically manifests as monoarticular arthritis of the knee. Most affected children have morning stiffness, mild discomfort, swelling, and warmth of the affected joint or joints, but usually remain fairly functional and are systemically well. The arthritis in general has a good prognosis and in some cases may eventually remit on its own. Most such children have a positive ANA test result and are at the highest risk for associated chronic anterior uveitis.

Polyarticular Juvenile Idiopathic Arthritis

There are 2 subtypes of polyarticular JIA: RF-positive and RF-negative. RF-positive disease is most likely identical to adult-onset rheumatoid arthritis, and patients with this tend to have more aggressive, destructive arthritis and associated constitutional symptoms such as fatigue and poor appetite. The arthritis in these subtypes is symmetric and affects both small and large joints. Involvement of the small joints of the hands and feet, as well as the wrists, is very common. Chronic anterior uveitis may occur; it is more common in younger patients, especially if ANA test results are positive.

Enthesitis-Related Arthritis

The older term spondyloarthropathy encompasses a group of diseases that includes ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease-associated arthritis, and reactive arthritis. These diseases are grouped together because they share common clinical features such as male predominance, enthesitis, dactylitis, peripheral oligoarticular disease, axial arthritis, acute symptomatic anterior uveitis, and association with human leukocyte antigen (HLA)-B27. Psoriatic arthritis is classified separately, and the other spondyloarthropathies were redesignated as *enthesitis-related arthritis* (ERA) because of the recognition that these forms of arthritis do not necessarily affect the spine, especially during childhood. In addition to persistent arthritis, patients with ERA must have 2 of the following criteria: persistent sacroiliac joint tenderness and/or inflammatory lumbosacral pain, positive HLA-B27 antigen, acute symptomatic anterior uveitis, presence of symptoms in a male over 6 years of age, and finally, a 1st-degree relative with a history of ankylosing spondylitis, ERA, sacroiliitis with inflammatory bowel disease, reactive arthritis, or acute anterior uveitis.

TABLE 33.10 Classification Criteria for Juvenile Idiopathic Arthritis (JIA)

General Definition of Juvenile Idiopathic Arthritis

- Arthritis that begins before the 16th birthday and persists for at least 6 wk
- Other known causes of arthritis are excluded

Categories

Systemic Arthritis

- Arthritis in 1 or more joints with or preceded by fever of at least 2-wk duration that is documented to be daily ("quotidian") for at least 3 days, and accompanied by 1 or more of the following:
  - Evanescent (nonfixed) erythematous rash
  - Generalized lymph node enlargement
  - Hepatomegaly and/or splenomegaly
  - Serositis

Oligoarthritis

- Arthritis affecting 1–4 joints during the 1st 6 mo of disease
- Subcategories:
  - Persistent oligoarthritis: affecting not more than 4 joints throughout the disease course
  - Extended oligoarthritis: affecting a total of more than 4 joints after the 1st 6 mo of disease

Polyarthritis (Rheumatoid Factor Negative)

- Arthritis affecting 5 or more joints during the 1st 6 mo of disease
- Negative test for RF

Polyarthritis (Rheumatoid Factor Positive)

- Arthritis affecting 5 or more joints during the 1st 6 mo of disease
- 2 or more positive tests for RF, separated by at least 3 mo during the 1st 6 mo of disease

Psoriatic Arthritis

- Arthritis and psoriasis or suspicion of underlying psoriasis as evidenced by
  - Formal diagnosis of psoriasis, or
  - At least 2 of the following:
    - Dactylitis
    - Nail pitting or onycholysis
    - Psoriasis in a 1st-degree relative

Enthesitis-Related Arthritis

- Arthritis and enthesitis, or
- Arthritis or enthesitis with at least 2 of the following:
  - History of sacroiliac joint tenderness and/or inflammatory lumbosacral pain
  - Positive HLA-B27 antigen
  - Onset of arthritis in a male over 6 yr of age
  - Acute (symptomatic) anterior uveitis
  - History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter syndrome, or acute anterior uveitis in a 1st-degree relative

Undifferentiated Arthritis

- Arthritis that fulfills criteria in no category or in 2 or more of the above categories

HLA, human leukocyte antigen; RF, rheumatoid factor.
Criteria from Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol.* 2004;31:391-392.

Psoriatic Arthritis

A diagnosis of psoriatic arthritis can be made when a patient has chronic arthritis accompanied either by a personal diagnosis of psoriasis or by a combination of 2 other clinical criteria (dactylitis, nail pitting/onycholysis, or psoriasis in a 1st-degree relative). Psoriatic arthritis in children has a bimodal distribution with an initial peak between ages 2-3 years that appears clinically similar to oligoarticular JIA and a later peak between ages 10-12 years that appears clinically similar to ERA. The early-onset form of psoriatic arthritis is more likely to affect girls than boys, more often has associated dactylitis and a positive ANA, and is less often associated with a positive HLA-B27. In contrast, the later-onset form is more likely to occur in boys, is more often associated with a negative ANA and positive HLA-B27, and is more likely to manifest with enthesitis and axial arthritis. Psoriasis usually precedes the development of arthritis, but in a sizable minority, arthritis can precede the skin disease, sometimes by many years. Up to 30% of patients with psoriasis also have associated arthritis, with patients that have nail involvement being more likely to develop arthritis. The severity of the arthritis does not typically correlate with the severity of the skin disease.

Systemic Juvenile Idiopathic Arthritis

In systemic JIA (SJIA), any number of joints may be affected, but most patients eventually develop polyarticular involvement. Children with SJIA initially have a characteristic quotidian fever pattern, consisting of 1 or 2 high fever spikes each day with rapid return to normal temperature. An evanescent pink macular rash appears with the fever and may resolve completely as the child's fever abates (see Figs. 33.3 and 33.4). Constitutional symptoms such as fatigue, poor appetite, and weight loss are common. Generalized lymphadenopathy and hepatosplenomegaly are also common; pericarditis or pleural effusions may be seen. These children feel and appear ill during the fever spikes, but they may appear much improved once the fever abates. Peripheral leukocytosis of 20,000 WBCs/mm^3 or greater, anemia, and thrombocytosis are characteristic laboratory findings. Tests of ANA and RF are usually negative, and uveitis is very rare. In many patients, the fevers and rashes subside and polyarticular arthritis persists as an isolated manifestation, while in other patients, the fevers and rashes continue to dominate their clinical picture.

Patients with SJIA are at risk for **macrophage activation syndrome.** This can be a life-threatening complication from uncontrolled immune activation that results in disseminated intravascular coagulation (DIC). Clinically, this is manifested by persistent, unremitting fever, petechial/purpuric rashes from DIC, hepatosplenomegaly, and potentially multiorgan dysfunction. Laboratory examination demonstrates elevated CRP and markedly elevated ferritin with a paradoxically falling ESR due to DIC and consumption of fibrinogen. Cytopenias, particularly thrombocytopenia, are observed, as are hypertriglyceridemia and hypoalbuminemia. Hemophagocytosis is observed in various tissues, most commonly in the bone marrow and cerebrospinal fluid.

◆ Diagnosis

The diagnosis of JIA is based on clinical features, and classification is based on clinical and laboratory criteria (see Table 33.10). Although strict adherence to these inclusion and exclusion criteria is necessary for patients in clinical trials, it is not always helpful or practical when diagnosing individual patients. The differential diagnosis is broad (Tables 33.11 and 33.12; see Table 33.1). Lyme disease should always be considered (Table 33.13). Laboratory tests and imaging studies are used when necessary to exclude other illnesses. The ANA and RF tests are used to classify the subtype of JIA and to determine the risk of uveitis, but they are not diagnostic tests. Ophthalmologic slit-lamp evaluations are necessary at specific intervals to screen for anterior uveitis, because usually the uveitis is asymptomatic and can progress to affect visual acuity before it causes other signs and symptoms. For patients at highest risk—children younger than 7 years of age with a positive ANA test result and oligoarticular or polyarticular JIA—ophthalmologic evaluations should be performed every 3-4 months for at least 4 years after diagnosis, every 6 months for 3 years after that, and then annually. Those with SJIA should have annual examinations since their risk is low. All others should have evaluations at 6-month intervals for the first 4 years after diagnosis, and annually thereafter.

SYSTEMIC LUPUS ERYTHEMATOSUS

In SLE, clinical manifestations are the result of aberrant B cell proliferation and increased production of both specific and nonspecific autoantibodies, with subsequent immune complex formation and deposition throughout the body. The cause of SLE is unknown; it is more common in girls and women, African Americans, and persons with a 1st-degree relative with SLE. In childhood, the peak onset is during the early teen years and rarely occurs in children younger than 5 years. The potential clinical manifestations of SLE are numerous, and the illness demonstrates significant interindividual variability. Children with SLE have more severe disease with a greater incidence of renal involvement and other serious manifestations than adults.

◆ Diagnosis

SLE is suggested by the common manifestations of fever, malar rash (Fig. 33.9), photosensitivity, and arthritis. The arthritis is most often symmetric and polyarticular, and frequently involves the small joints of the hands and feet. In contrast to JIA, the arthritis is typically nondeforming and does not result in erosions or bony remodeling. The Systemic Lupus International Collaborating Clinics (SLICC) criteria were developed for the purpose of research studies and clinical application (Table 33.14). The presence of 4 or more of these criteria is highly sensitive and specific for SLE. Other clinical manifestations of SLE are listed in Table 33.15.

The ANA test is extremely sensitive, positive in more than 95% of children with SLE, and usually in a high titer; however, it is not specific. Testing for anti-dsDNA antibodies, anti-Smith antibodies, anti-RNP antibodies, anti-SSA, and anti-SSB antibodies should be performed in all children suspected of having SLE (see Table 33.4). Anti-dsDNA antibodies and anti-Smith antibodies are highly specific for SLE. Leukopenia, lymphopenia, thrombocytopenia, and autoimmune hemolytic anemia, frequently with a positive direct Coombs test, are common. Urinalysis is mandatory to screen for nephritis; proteinuria indicates disease. The anticardiolipin antibody test identifies antiphospholipid antibodies, a common finding in SLE that results in a hypercoagulable state, placing the patient at risk for thrombotic events. The complement proteins C3 and C4 are low in children with active SLE. Monitoring C3 and C4 levels helps guide therapy; the levels should increase to normal as the illness is better controlled.

DERMATOMYOSITIS

Dermatomyositis is characterized by perivascular inflammation in muscles and skin, occasionally with gut and other organ involvement. Dermatomyositis is more common in girls and can occur at any age; the average age at onset is 8 years. The main manifestations include characteristic skin findings and proximal muscle weakness, specifically involving the neck flexors, deltoids, biceps, triceps, quadriceps, psoas,

(See *Nelson Textbook of Pediatrics,* p. 1176.)

TABLE 33.11 Differential Diagnosis of Juvenile Idiopathic Arthritis: Rheumatic Disease

	Rheumatic Fever	Juvenile Idiopathic Arthritis	Systemic Lupus Erythematosus	Kawasaki Disease	Dermatomyositis
Sex predilection	None	Dependent on subgroup	Girls > boys	None	Girls 3:2
Age at onset	3 yr or older	1 yr or older	Usually > 8 yr	4 yr or younger	2 yr or older
Joint manifestations	Transient migratory arthritis of primarily large joints	Oligoarticular or polyarticular; chronic (≥6 wk)	Arthralgia; transient arthritis; chronic arthritis	Pain and swelling of hands and feet; arthritis occasionally	Joint contractures; arthritis occasionally
Extra-articular manifestations	Fever Cardiac disease Chorea Rash Nodules	Dependent on subgroup: Systemic JIA: fever, rash, lymphadenopathy Oligoarticular JIA: iridocyclitis	Often multisystem disease, including nephritis	Fever Conjunctivitis Oral changes Polymorphous rash Lymphadenopathy Coronary vasculitis	Rash Muscle weakness Myalgia Gut vasculitis Respiratory muscle weakness
Diagnostic studies	Prior streptococcal infection Evidence of carditis on echocardiogram or electrocardiogram	May have ANA, RF	ANA Autoantibodies Low complement Anti-dsDNA antibody	Coronary dilatation or aneurysm on echocardiogram	Elevated muscle enzymes Myopathic electromyography Abnormal muscle biopsy
Pathogenesis	Poststreptococcal	Unknown	Immune complexes	Unknown	Unknown
Diagnosis	Clinical (Jones criteria)	Clinical (JIA criteria)	Clinical plus laboratory (SLICC criteria)	Clinical (Kawasaki criteria)	Clinical: rash plus myositis Muscle biopsy
Natural history	Arthritis–transient. Carditis may cause permanent damage	Chronic: arthritis may be destructive	Chronic or recurrent May be fatal	Self-limited Coronary vasculitis May be fatal	Chronic May be fatal

ANA, antinuclear antibody; Anti-dsDNA, anti–double-stranded DNA; JIA, juvenile idiopathic arthritis; RF, rheumatoid factor; SLICC, Systemic Lupus International Collaborating Clinics.
Modified from Behrman RE, ed. *Nelson Textbook of Pediatrics.* 14th ed. Philadelphia: WB Saunders; 1992:620.

and hamstrings. These symptoms are occasionally accompanied by mild muscle pain, fatigue, or poor endurance. Weakness may be subtle and not recognized for long periods. Frequent early symptoms include difficulties rising from the floor, climbing stairs, climbing in and out of a minivan, and combing the hair.

Skin manifestations include Gottron papules, which are scaly, erythematous plaques or papules that appear over the MCP and PIP joints on the hands (see Fig. 33.6). Similar lesions are seen on the extensor surfaces of the elbows and knees and over the medial malleoli. The distribution of the rash, which may be misdiagnosed as eczema or psoriasis, is an early clue to the diagnosis. The periungual capillaries may become grossly dilated and may develop thromboses that can be visualized either with the naked eye or with mild magnification. Heliotrope rash is a violaceous discoloration of the upper eyelids that is often accompanied by mild edema (see Fig. 33.5) and is pathognomonic for dermatomyositis. Some children develop more extensive erythroderma that may appear over the shoulders, termed the shawl sign, or in a V-neck distribution on the chest. With severe disease, some patients may also develop vasculopathic skin ulcerations.

◆ Diagnosis

The diagnosis is suggested by the rash and proximal muscle weakness detected on physical examination. Muscle enzymes are elevated in most, but not all, children with dermatomyositis. There may be elevations in only 1 or a few enzymes and therefore testing for aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, and aldolase should be performed. The child with a characteristic rash, definite proximal muscle weakness, and elevated muscle enzyme levels may not require additional testing for diagnosis. If weakness is questionable, or if the rash is not characteristic, an EMG can confirm the presence of muscle inflammation. MRI is a sensitive test for muscle inflammation and may be a less invasive method of evaluating the muscle. If there is any doubt regarding the diagnosis, a muscle biopsy is performed. The site for biopsy is determined by weakness on physical examination or localization by EMG or MRI. The quadriceps or the deltoids are the most commonly accessed biopsy sites. Involvement of the muscle may be spotty, and a normal finding on muscle biopsy does not exclude dermatomyositis. Typical findings on biopsy include perivascular inflammation and perifascicular atrophy. The biopsy can help exclude other potential myopathies such as muscular dystrophies and metabolic myopathies.

SCLERODERMA

Scleroderma is classified into systemic sclerosis and localized scleroderma (Table 33.16). Localized scleroderma, which includes morphea and linear scleroderma, is limited to the skin and subcutaneous tissues, is much more common in childhood, and rarely progresses to involve internal organs. Systemic sclerosis can be life threatening, as it has the potential to involve internal organs and cause severe and widespread skin disease.

Morphea

Morphea is a patch of hardened skin that appears spontaneously on any part of the body. The skin becomes firm, stiff, atrophic, and discolored. Hair is absent. Initially, the lesion appears violaceous, but then

(See *Nelson Textbook of Pediatrics,* p. 1186.)

TABLE 33.12 Differential Diagnosis of Juvenile Idiopathic Arthritis: Nonrheumatic Disease

	Septic Arthritis	Lyme Disease	Osteomyelitis	Viral Arthritis	Childhood Malignancy	Structural, Genetic	Growing Pains, Psychogenic
Sex predilection	None	None	None	Girls > boys	None	Dependent on condition	Growing pains: boys > girls; Psychogenic: girls > boys
Age at onset	Any	>2 yr	Any	More common in older children and adults	Any	Any	Growing pains: 2–8 yr; Psychogenic: ≥ 6 yr
Joint manifestations	85% monoarticular; joints swollen, red, hot, painful	Oligoarticular; episodic, recurrent	Sterile joint effusion adjacent to infected bone	Transient arthritis; often polyarticular	Severe bone/joint pain, night pains	Local bone/joint pain or dysfunction	None or features of complex regional pain syndrome
Extra-articular manifestations	Fever SIRS Other signs dependent on causative organism	Flu-like illness Erythema migrans Meningitis Cranial nerve palsies Heart block	Fever SIRS Bone pain	Dependent on causative organism	Signs of underlying malignancy; no high fever, rash, or morning stiffness	Dependent on underlying condition Dysmorphism Structural abnormalities	Growing pains: none Psychogenic: atypical
Diagnostic studies	Cultures: synovial fluid, blood, genital if *Neisseria gonorrhoeae* suspected	Serologic: antibody to *Borrelia burgdorferi*	Blood and bone culture Bone scan	Viral culture/PCR Rise in antibody titers	Hematologic abnormalities Abnormal radiograph or scan	Demonstration of abnormal structure or metabolic abnormality	Normal
Pathogenesis	Direct synovial infection; immune complex deposition in gonococcal and meningococcal arthritis	Synovial and systemic infection with *B. burgdorferi*	Hematogenous infection of bone	Viral infection of synovium; immune complex deposition in some	Primary bone or periarticular tumor; bony metastasis	Idiopathic or genetic	No organic disease
Diagnosis	Demonstration of organisms in joint fluid	Clinical and serologic	Demonstration of organisms in blood/bone; MRI of bone scan (early); plain radiographs (late)	Clinical; serologic; positive viral culture or PCR from synovial fluid	Bone marrow; tissue biopsy	Recognition of condition or syndrome; positive genetic or biochemical assay	Clinical
Natural history	Joint destruction	Self-resolving	Bone/joint destruction	Self-resolving	Joint manifestations may wax/wane	Chronic	Growing pains: benign Psychogenic: may become chronic and disabling

MRI, magnetic resonance imaging; PCR, polymerase chain reaction; SIRS, systemic inflammatory response syndrome.
Modified from Behrman RE, ed. *Nelson Textbook of Pediatrics*. 14th ed. Philadelphia: WB Saunders; 1992:619.

TABLE 33.13 Manifestations of Lyme Disease by Stage

Early Localized Infection (occurs 3–30 days after tick bite)

Erythema migrans (EM) in 80–90% of patients; single lesion, occasionally associated with fever, malaise, neck pain or stiffness, arthralgia, and myalgia

Systemic symptoms noted above in the absence of EM during summer months

Borrelial lymphocytoma (rare, seen primarily in Europe)

Early Disseminated Infection (occurs weeks to months after tick bite)

Profound malaise and fatigue common

Multiple EM lesions with systemic symptoms similar to early localized infection

Migratory polyarthralgia and myalgia

Carditis (<3% of untreated patients)

- Varying degrees of atrioventricular nodal block
- Mild myopericarditis

Neurologic (<10% of untreated patients)

- Cranial neuropathies (especially facial nerve palsy)
- Lymphocytic meningitis
- Radiculoneuropathies
- Encephalomyelitis

Late Disease (occurs months to years after tick bite)

Arthritis (<10% of patients)

- Acute monoarticular or migratory pauciarticular inflammatory arthritis, usually involving the knee
- Chronic antibiotic-refractory arthritis (<10% of patients with arthritis)

Neurologic (rare)

- Peripheral neuropathies
- Mild encephalopathy
- Encephalomyelitis (primarily seen in Europe)

Acrodermatitis chronica atrophicans (primarily seen in Europe)

Modified from Bockenstedt LK. Lyme disease. In: Firestein GS, Budd RC, Gabriel SE, et al., eds. *Kelley's Textbook of Rheumatology*. 9th ed. Philadelphia: Saunders; 2013, Chapter 110, Table 110-1.

TABLE 33.14 Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for Systemic Lupus Erythematosus

4 OR MORE CRITERIA (AT LEAST 1 CLINICAL AND 1 LABORATORY) OR BIOPSY-PROVEN LUPUS NEPHRITIS WITH A POSITIVE ANA OR ANTI-dsDNA

Clinical Criteria	Laboratory Criteria
Acute cutaneous lupus	ANA
Chronic cutaneous lupus	Anti-dsDNA
Oral or nasal ulcers	Anti-Smith
Nonscarring alopecia	Antiphospholipid antibody
Arthritis	Low complement (C3, C4, CH_{50})
Serositis	Positive direct Coombs (does not count if hemolytic anemia already present)
Renal	
Neurologic	
Hemolytic anemia	
Leukopenia	
Thrombocytopenia	

anti-dsDNA, anti–double-stranded DNA; ANA, antinuclear antibody.
From Petri M, Orbai A, Alarcon GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum.* 2012;64: 2677-2686.

it fades to a yellowish-brown or dusky appearance in most individuals. The patches are nontender, and children are otherwise asymptomatic. The natural history of morphea lesions is to gradually fade and soften after an initial period of expansion. Biopsy reveals excessive amounts of collagen in the dermis with absent hair follicles and diminished vascular structures.

Linear Scleroderma

Linear scleroderma is histologically similar to morphea, though lesions consist not of isolated patches, but rather narrow bands that may extend through an entire limb, part of the limb, or across the scalp and face, a finding termed a coup de sabre lesion. Cosmetically and functionally, linear scleroderma is much more severe than morphea, as the impacted areas may involve the face or limit limb use. Growth of the limb may be affected, and involvement of the digits can cause significant functional difficulty. Coup de sabre lesions, particularly with craniofacial involvement, may be associated with neurologic abnormalities and seizures, and these children should have a careful neurologic examination and brain MRI as part of their evaluation.

Systemic Sclerosis

Systemic sclerosis typically begins with severe Raynaud phenomenon, followed by thickening and tightening of the skin over the digits and hands and then the face, and then by varying degrees of progressive skin changes over the extremities and trunk. Difficulty opening the mouth and decreased facial expression are signs of facial involvement. As the skin over the hands tightens and hardens, pigment changes may occur, and flexion contractures of the small joints may develop. Renal disease, pulmonary fibrosis, pulmonary hypertension, esophageal and gut dysmotility, and cardiac disease may all occur. Anti-Scl-70 antibodies (anti-topoisomerase I) are present in approximately 30-40% of patients with systemic sclerosis and are very specific. There are no other helpful serologic tests. High-resolution CT of the chest, esophagography, and echocardiography should be performed to screen for organ involvement and repeated at periodic intervals. The course of systemic sclerosis is variable; patients with rapid progression tend to have a less favorable outcome. A limited variant of scleroderma is known as CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias). Although less severe than systemic sclerosis, these patients can develop life-threatening pulmonary hypertension. CREST syndrome is associated with anticentromere antibodies.

RHEUMATIC FEVER

Acute rheumatic fever is a poststreptococcal illness, resulting from a cross-reactive immune response to group A streptococcal pharyngitis (see Chapters 1 and 8). It is most common in children older than 5 years and occurs more often after infection with certain serotypes of

(See *Nelson Textbook of Pediatrics,* p. 1186.)

FIGURE 33.9 The malar rash of systemic lupus erythematosus crosses the nasal bridge and spares the nasolabial folds, a distribution that is referred to as a "butterfly rash." (From Cassidy JT, Petty RE, Laxer RM, et al., eds. *Textbook of Pediatric Rheumatology*. 6th ed. Philadelphia: Elsevier; 2011:321.)

group A streptococci. There may also be genetic reasons that predispose some children and adults to the illness. Signs and symptoms of rheumatic fever typically develop 1-3 weeks after streptococcal pharyngitis. Clinical manifestations have been grouped according to the Jones criteria, which separate major from minor criteria (Table 33.17).

The arthritis of rheumatic fever is usually very painful and is disproportionate to the degree of swelling on physical examination. It is usually a migratory arthritis of the large joints; it rarely affects the fingers, spine, or toes. It tends to last in 1 joint for several days and then migrates to a different joint. The duration of joint symptoms is rarely longer than 3-4 weeks in untreated patients. If patients are treated with NSAIDs, the arthritis usually responds dramatically within 1-2 days. When rheumatic fever is a consideration and the diagnosis is unclear, it is helpful to avoid NSAID use early in the course to avoid diagnostic confusion.

In the absence of carditis, rheumatic fever may be difficult to distinguish from early SJIA, Kawasaki disease, and viral-induced fever, rash, and joint pain. The diagnosis is clinical. The Jones criteria were developed as a diagnostic aid and include echocardiographic evidence of valvulitis, and in populations with a higher risk of rheumatic fever, monoarthritis or polyarthralgia as less stringent major criteria (see Table 33.17). The presence of 2 of the major criteria or of 1 major and 2 minor criteria plus evidence of recent streptococcal infection is consistent with acute rheumatic fever, though is not specific. Either a positive throat culture or elevations of the antistreptococcal antibodies (antistreptolysin O, anti-DNase B) are the standard indicators of potential recent streptococcal infection. Fulfilling these criteria is not specific for rheumatic fever, especially when the evidence of recent streptococcal infection is based on mildly elevated serologic test results.

TABLE 33.15 Additional Manifestations of Systemic Lupus Erythematosus

Target Organ	Potential Clinical Manifestations
Constitutional	Fatigue, anorexia, weight loss, fever, lymphadenopathy
Musculoskeletal	Arthritis, myositis, tendonitis, arthralgia, myalgia, avascular necrosis, osteoporosis
Skin	Malar rash, discoid (annular) rash, photosensitive rash, cutaneous vasculitis (petechiae, palpable purpura, digit ulcers, gangrene, urticaria), livedo reticularis, periungual capillary abnormalities, Raynaud phenomenon, alopecia, oral and nasal ulcers, panniculitis, chilblains
Renal	Hypertension, proteinuria, hematuria, edema, nephrotic syndrome, renal failure
Cardiovascular	Pericarditis, myocarditis, conduction system abnormalities, Libman–Sacks endocarditis
Neurologic	Seizures, psychosis, cerebritis, stroke, transverse myelitis, depression, cognitive impairment, headaches, migraines, pseudotumor, peripheral neuropathy (mononeuritis multiplex), chorea, optic neuritis, cranial nerve palsies, acute confusional states, dural sinus thrombosis
Pulmonary	Pleuritis, interstitial lung disease, pulmonary hemorrhage, pulmonary hypertension, pulmonary embolism
Hematologic	Immune-mediated cytopenias (hemolytic anemia, thrombocytopenia, or leukopenia), anemia of chronic inflammation, hypercoagulability, thrombotic thrombocytopenic microangiopathy
Gastroenterology	Hepatosplenomegaly, pancreatitis, vasculitis affecting the bowel, protein-losing enteropathy, peritonitis
Ocular	Retinal vasculitis, scleritis, episcleritis, papilledema, dry eyes, optic neuritis

Modified from Sadun RE, Ardoin SP, Schanberg LE. Systemic lupus erythematosus. In: Kliegman RM, Stanton BF, St Geme JW, Schor NF, eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:117, Chapter 158, Table 158-1.

TABLE 33.16 Classification of Scleroderma

Systemic Sclerosis

- Diffuse: systemic fibrosis, including widespread skin involvement (face, trunk, and both proximal and distal extremities) and internal organ involvement (lungs, kidneys, gastrointestinal tract, heart)
- Limited (CREST syndrome): skin fibrosis limited to the distal extremities, face, and neck; internal organ involvement occurs late, if at all, with pulmonary hypertension often being the most significant development

Localized Scleroderma

- Morphea: a single, discrete patch of fibrotic skin; no organ involvement
- Generalized morphea: multiple discrete patches of fibrotic skin; no organ involvement
- Linear scleroderma: band of fibrosis on the face (*coup de sabre*) or along an extremity, sometimes extending the entire length; no organ involvement

CREST, calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias.

TABLE 33.17 Jones Criteria for Diagnosis of Rheumatic Fever

All patient populations must demonstrate evidence of a preceding GAS infection
Initial ARF: 2 major manifestations OR 1 major plus 2 minor manifestations
Recurrent ARF: 2 major OR 1 major and 2 minor OR 3 minor manifestations
Major Criteria
Carditis: clinical (audible murmur) or subclinical (echocardiographic evidence of valvulitis)
Subcutaneous nodules
Erythema marginatum
Chorea
Low-risk populations*: polyarthritis
Moderate- and high-risk populations: polyarthritis, monoarthritis, or polyarthralgia†
Minor Criteria
Fever (≥38.5°C)
Peak ESR ≥30 mm/hr and/or CRP ≥3.0 mg/dL‡
Prolonged P-R interval, after accounting for age variability (unless carditis is a major criterion)
Low-risk populations: polyarthralgia
Moderate- and high-risk populations: monoarthralgia

*Low-risk populations are those with an ARF incidence ≤2/100,000 school-aged children or an all-age rheumatic heart disease prevalence of ≤1/1000 population per yr.
†Polyarthralgia should only be considered as a major manifestation in moderate- to high-risk populations after exclusion of other causes. As in past versions of the criteria, erythema marginatum and subcutaneous nodules are rarely "stand-alone" major criteria. Additionally, joint manifestations can only be considered in either the major or minor categories, but not both in the same patient.
‡The CRP value must be greater than the upper limit of normal for the laboratory. Because ESR may evolve during the course of ARF, peak ESR values should be used.
ARF, acute rheumatic fever; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GAS, group A streptococcal.
Modified from Gewitz MH, Baltimore RS, Tani LY, et al. Revision of the Jones criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography. *Circulation.* 2015;131:1806-1818.

Conversely, there are children with isolated chorea or classic rheumatic carditis who have rheumatic fever without necessarily fulfilling the Jones criteria. When a diagnosis of rheumatic fever is considered in a child with joint symptoms, it is important to distinguish arthritis from arthralgia and to evaluate the nature of the arthritis when present. If the arthritis is nonmigratory and is not exquisitely tender, or if it involves unusual joints such as those in the hands, feet, or spine, or lasts longer than 1 week in a single joint, then alternative diagnoses should be strongly considered.

Careful consideration of the diagnosis is especially important because of future implications regarding prognosis and treatment. Children with rheumatic fever may develop carditis with future episodes of streptococcal pharyngitis; each episode of carditis can produce additional heart valve damage. Therefore, prophylactic antibiotic treatment is recommended to minimize streptococcal infections, even for patients who do not have carditis with the initial attack. For those without carditis, most authorities recommend prophylaxis until age 21 years or for 5 years, whichever is longer. For patients with carditis, this recommendation is extended to 10 years or to age 21, whichever is longer. If there is residual valvular damage, prophylaxis is recommended for 10 years or until age 40, whichever is longer. Prophylaxis is usually either daily oral penicillin or monthly intramuscular injections of long-acting penicillin.

Henoch–Schönlein Purpura

HSP is an acute self-limited systemic vasculitis of children characterized by the classic triad of palpable purpura, arthritis, and nephritis. It occurs most commonly between the ages of 3 and 15 years. The presence of palpable purpura is essential for the diagnosis of HSP. Typically, the rash presents as petechiae that coalesce into larger purpura on dependent areas such as the buttocks and legs. The rash is often edematous and on occasion can become ulcerative. Arthritis occurs in up to 80% of children with HSP, is typically acute with significant pain and limitation of range of motion, and usually resolves within days to a week. Large joints tend to be affected and the arthritis is nonmigratory. In the majority of cases, the rash of HSP precedes the development of arthritis, but occasionally, the arthritis may occur a few days before the rash. Other features that might suggest a diagnosis of HSP are gastrointestinal symptoms, nephritis, or angioedema. Gastrointestinal symptoms result from gut vasculitis causing intestinal edema and potentially ischemia and infarction of the gut. Gastrointestinal disease often presents as episodic abdominal pain from intussusception, or with abdominal angina (postprandial abdominal pain related to intestinal ischemia). Rarely, hematochezia or currant jelly-like stools can result from intestinal necrosis. In up to a third of cases, abdominal pain will precede the rash. Nephritis may occur at any time up to 6 months after the initial presentation, and may manifest with hypertension or with proteinuria, hematuria, or casts on urinalysis. As such, serial urinalysis is recommended until 6 months after the initial presentation to survey for the development of nephritis. Angioedema can occur on the dorsum of the hands or feet, scalp, forehead, eyelids, and scrotum. The acute manifestations of HSP usually resolve in 1-2 weeks, though may recur episodically in less severe form for several weeks after. Nephritis is usually the most concerning complication that requires longer monitoring and prompt referral to a pediatric nephrologist if urinary abnormalities persist.

MYALGIA

In the child with extremity pain, muscle pain needs to be distinguished from joint pain, bone pain, and the less common neuropathic pain. If the complaint is localized to the muscles, the differential diagnosis is narrowed considerably. Intermittent benign bilateral myalgia of the calves or thighs is 1 of the more common muscle pain presentations encountered in young children. These pains occur in an active child who has normal physical examination findings without evidence of weakness or systemic illness. Symptoms typically occur in the evening and resolve with massage or mild analgesics such as acetaminophen or ibuprofen, usually within an hour. The frequency of pain can vary and in some children may escalate periodically. Additional evaluation or treatment is unnecessary in most children, and eventually the pains resolve completely.

As myalgia may accompany polymyositis and dermatomyositis, every child complaining of muscle pain should undergo careful muscle strength testing. Myalgia may also be seen with vasculitis and SJIA. Many children with acute-onset diffuse myalgia have a transient viral illness, and pain usually resolves within several days; however, infection with influenza can cause an exquisitely painful myositis of the gastrocnemius muscles with resultant difficulty ambulating. This condition is usually distinguished easily from a chronic inflammatory muscle disease by the sudden onset and localization to these specific muscles. The creatine kinase level may be very elevated. Myoglobinuria may

ensue and potentially affect renal function; therefore, affected children should undergo urinalysis, in which the presence of myoglobin yields positive results for heme on macroscopic analysis, though no erythrocytes on microscopic examination. The myositis resolves within several days, and treatment is based on symptoms.

Complex Regional Pain Syndrome

CRPS is rare in childhood and is not well understood. After a seemingly minor injury, affected children develop intense pain in an extremity or part of an extremity. Additional symptoms include intermittent autonomic changes such as discoloration, coolness, and localized excessive sweating. The pain leads to progressive disability of the extremity, occasionally resulting in fixed posturing of a hand, foot, or limb. Severely affected children become disabled, are unable to ambulate at times, and are often unable to attend school. Psychosocial comorbidity is common. The treatment is analgesia, intense physical and occupational therapy, education, and psychologic counseling. Some children improve dramatically within a few days of instituting therapy, whereas in others, treatment is difficult and the process lasts indefinitely. In some instances, sympathetic nerve blockade is helpful.

TABLE 33.18 Potential Pitfalls in Diagnosis

Do

1. Examine all joints.
2. Order radiographs of both affected and contralateral joints.
3. Ask parents to photograph swelling and rashes.
4. Explore the complete history including the psychosocial history in all patients.
5. Perform a thorough physical examination.

Do Not

1. Indiscriminately order ANA tests, RF tests, or Lyme antibody tests in patients who do not have clinical features consistent with these conditions.
2. Confuse arthralgia (joint pain) with arthritis (inflammation).
3. Treat with prednisone before a diagnosis is clear.
4. Accept laboratory results at odds with your experience; repeat tests if necessary.
5. Be afraid to say, "I don't know."

ANA, antinuclear antibody; RF, rheumatoid factor.

SUMMARY AND RED FLAGS

The differential diagnosis of arthritis is extensive. Thorough history and physical examination, especially repeated over time, are essential in establishing a diagnosis and initiating a treatment plan. Potential diagnostic pitfalls are noted in Table 33.18. Red flags include manifestations suggestive of septic arthritis (fever, single joint involvement, erythema, extreme tenderness, leukocytosis), malignancy (severe polyarthralgia, night pain, nonarticular bone pain, absence of obvious swelling or stiffness, positive radiographic changes, and abnormal CBC), Lyme disease, and Kawasaki disease. Multiple organ system involvement may be primary (as in SLE and rheumatic fever) or secondary to therapy and must be considered in order to avoid ongoing extraarticular involvement, which may be more life-threatening than the articular process.

In addition, the child with a history of injury and the acute onset of extremity pain may have a fracture or traumatic hemarthrosis and requires prompt evaluation. Any child with extremity pain, including children with arthritis, may have leukemia or neuroblastoma. Systemic symptoms, such as fatigue and poor appetite with weight loss, may accompany the pain and increase suspicion of malignancy. Deep bone pain caused by marrow invasion may not be accompanied by any obvious physical findings. A normal or slightly low platelet count with an elevated ESR increases the suspicion of malignancy. If leukemia is suspected, a CBC should be obtained and a bone marrow aspiration should be performed. This is particularly important if treatment with steroids or other immunosuppressive medications is being considered. Steroids may alleviate a rheumatic condition but may also place a child with leukemia at risk for relapse with steroid-resistant disease.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

General

Cassidy JT, Petty RE, Laxer RM, et al., eds. *Textbook of Pediatric Rheumatology*. 7th ed. Philadelphia: Elsevier; 2016.

Firestein GS, Budd RC, Gabriel SE, et al., eds. *Kelley's Textbook of Rheumatology*. 9th ed. Philadelphia: WB Saunders; 2013.

Hochberg MC, Silman AJ, Smolen JS, et al., eds. *Rheumatology*. 5th ed. Philadelphia: Mosby Elsevier; 2011.

Jacobs JC. *Pediatric Rheumatology for the Practitioner*. 2nd ed. New York: Springer-Verlag; 1993.

Juvenile Idiopathic Arthritis

Grom AA, Mellins ED. Macrophage activation syndrome: advances towards understanding pathogenesis. *Curr Opin Rheumatol*. 2010;22(5):561-566.

Jones OY, Spencer CH, Bowyer SL, et al. A multicenter case-control study on predictive factors distinguishing childhood leukemia from juvenile rheumatoid arthritis. *Pediatrics*. 2006;117(5):e840-e844.

Kahn PJ. Juvenile idiopathic arthritis: what the clinician needs to know. *Bull Hosp Jt Dis*. 2013;71(3):194-199.

Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol*. 2004;31(2):391-392.

Prahalad S, Glass DN. A comprehensive review of the genetics of juvenile idiopathic arthritis. *Pediatr Rheumatol Online J*. 2008;6:11.

Ravelli A, Martini A. Juvenile idiopathic arthritis. *Lancet*. 2007;369(9563):767-778.

Stoll ML, Punaro M. Psoriatic juvenile idiopathic arthritis: a tale of two subgroups. *Curr Opin Rheumatol*. 2011;23(5):437-443.

Systemic Lupus Erythematosus

Lahita RG. *Systemic Lupus Erythematosus*. 5th ed. London: Elsevier; 2011.

Levy DM, Kamphuis S. Systemic lupus erythematosus in children and adolescents. *Pediatr Clin North Am*. 2012;59(2):345-364.

Petri M, Orbai A, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum*. 2012;64(8):2677-2686.

Ruiz-Irastorza G, Khamashta MA, Castellino G, et al. Systemic lupus erythematosus. *Lancet*. 2001;357(9261):1027-1032.

Weiss JE. Pediatric systemic lupus erythematosus: more than a positive antinuclear antibody. *Pediatr Rev*. 2012;33(2):62-74.

Infectious Arthritis

American Academy of Pediatrics. Lyme disease. In: Kimberlin DW, Brady MT, Jackson MA, et al., eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. Elk Grove Village, IL: American Academy of Pediatrics; 2015:516-525.

Gutierrez KM. Infectious and inflammatory arthritis. In: Long SS, Pickering LK, Prober CG, eds. *Principles and Practice of Pediatric Infectious Diseases*. 3rd ed. Philadelphia: Churchill Livingstone; 2008.

Sood SK. Lyme disease in children. *Infect Dis Clin North Am*. 2015;29(2):281-294.

Steere AC. Lyme disease. *N Engl J Med*. 2001;345(2):115-125.

Dermatomyositis

Callen JP. Dermatomyositis. *Lancet*. 2000;355(9197):53-57.

Dimachkie MM, Barohn RJ, Amato A. Idiopathic inflammatory myopathies. *Neurol Clin*. 2014;32(3):595-628.

Rider LG, Katz JD, Jones OY. Developments in the classification and treatment of the juvenile idiopathic inflammatory myopathies. *Rheum Dis Clin North Am*. 2013;39(4):877-904.

Robinson AB, Reed AM. Clinical features, pathogenesis and treatment of juvenile and adult dermatomyositis. *Nat Rev Rheumatol*. 2011;7(11):664-675.

Wedderburn LR, Rider LG. Juvenile dermatomyositis: new developments in pathogenesis, assessment and treatment. *Best Pract Res Clin Rheumatol*. 2009;23(5):665-678.

Scleroderma

Amaral TN, Marques Neto JF, Lapa AT, et al. Neurologic involvement in scleroderma en coup de sabre. *Autoimmune Dis*. 2012;2012:719685.

Other Causes of Arthritis and Extremity Pain

Bruehl S. An update on the pathophysiology of complex regional pain syndrome. *Anesthesiology*. 2010;113(3):713-725.

da Silva NA, Pereira BA. Acute rheumatic fever. Still a challenge. *Rheum Dis Clin North Am*. 1997;23(3):545-568.

Gerber M, Baltimore R, Eaton C, et al. Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis. A scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2009;119(11):1541-1551.

Gewitz MH, Baltimore RS, Tani LY, et al. Revision of the Jones criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography. *Circulation*. 2015;131(20):1806-1818.

Marinus J, Moseley GL, Birklein F, et al. Clinical features and pathophysiology of complex regional pain syndrome. *Lancet Neurol*. 2011;10(7):637-648.

Reid-Adam J. Henoch-Schönlein purpura. *Pediatr Rev*. 2014;35(10):447-449.

Weiss PF. Pediatric vasculitis. *Pediatr Clin North Am*. 2012;59(2):407-423.

34

Gait Disturbances

*Shayne D. Fehr**

Most gait disturbances are benign and resolve with normal growth and development. Others are pathologic in origin and necessitate treatment (Table 34.1).

GAIT CYCLE

The normal gait cycle is described by foot placement. The gait cycle begins with right heel strike, is followed by left toe-off, left heel strike, right toe-off, and ends with right heel strike. These 5 events describe 1 gait cycle and include 2 phases: stance and swing. The **stance phase** is the period of time during which 1 of the 2 feet is on the ground. The **swing phase** is the period during which a limb is being advanced forward without ground contact.

Measuring the duration of the gait cycle makes it possible to calculate the time required for each of the 5 phases. During normal gait, the duration of each phase is as follows: for weight acceptance, 11%; for single limb stance, 39%; for weight release, 11%; and for swing phase, 39%. Velocity, cadence, step length, stride length, and step width may be calculated from the timed and measured gait cycle.

DEVELOPMENT OF GAIT

Central nervous system maturation is necessary for the development of normal gait and accounts for the normal progression of developmental milestones. The typical milestones for locomotion include independent sitting at 6 months of age, crawling at about 9 months, walking without assistance at 12-15 months, and running at 18 months. A normal 1-year-old child has a wide-based stance and a rapid cadence with short steps; the elbows are flexed and reciprocal arm motion is not present. Foot strike occurs without an initial heel strike. A 2-year-old child shows increased velocity, step length, and diminished cadence in comparison with a 1-year-old child. Most of the adult gait patterns are present in children by 3 years, with changes in velocity, stride, and cadence continuing to 7 years of age. The gait characteristics of a 7-year-old child are similar to those of an adult.

CLINICAL EVALUATION OF GAIT DISTURBANCES

◆ History

The clinician should inquire about the pregnancy and delivery, the age at which developmental milestones occurred, the presence of any systemic illnesses (including chronicity, fever, rash, weight loss, and other organ system involvement), and whether there is a family history of any congenital musculoskeletal abnormalities or syndromes. With regard to the gait disturbance, it is important to inquire when it was 1st observed, whether it is unilateral or bilateral, whether it is associated with any injuries or intercurrent systemic illnesses, and whether there has been a history of improvement or worsening with time.

◆ Physical Examination

General Musculoskeletal Examination

Although most of the findings in gait disturbances are confined to the lower extremities, the upper extremities and spine may be involved as part of an underlying disease process. A general assessment of all extremities and the spine should be performed to identify any abnormal motion, tenderness, swelling, deformity, or increased warmth.

The lower extremity musculoskeletal examination should begin with the child ambulating in the examination room or adjacent hallway. The child must be adequately undressed and be observed from a distance while walking so that the trunk and lower extremities can be clearly visualized. The positions of the thighs, knees, lower legs, and feet should be observed during ambulation. Combining gait observation with the history typically allows for diagnosing most of the common gait disturbances such as torsional variations (in-toeing and out-toeing), equinus gait (toe-walking), and limping.

Examination of the lower extremities should include measurement of lower extremity lengths and assessment of the hip, knee, ankle, and subtalar joints. The thighs, lower legs, and feet are inspected for evidence of asymmetry, soft tissue swelling, or injury. Palpation for tenderness or areas of increased warmth is performed. The shape of the foot is assessed for possible intrinsic deformity.

Lower extremity length measurements. The most accurate method of measuring lower extremity length is to have the child stand on a firm, level surface with the examiner standing behind the child and placing index fingers over the lateral aspect of each of the child's iliac crests. The presence or absence of pelvic obliquity is observed, and blocks of various heights are placed beneath the child's foot on the short side until the pelvis is level. The height of the block indicates the amount of lower extremity length discrepancy. Measurements obtained by use of a tape measure can also be performed but are less accurate. The most common method is to measure from the anterior-superior iliac spine to the distal aspect of the medial malleolus. These landmarks are sometimes difficult to palpate accurately, and there can be considerable error using this method.

Joint assessment. The ranges of motion of the hips, knees, ankles, and subtalar joints must be assessed. Hip flexion is measured, as are any flexion contractures. With the hip in extension, the degrees of abduction, adduction, internal rotation, and external rotation are measured, preferably with a goniometer, and are recorded. Hip rotation is most accurately measured with the child in the prone position with the knees flexed. Older children and adolescents are typically more comfortable when measured in the supine position with hips and

*The author would like to acknowledge George H. Thompson, MD, for his contribution to the previous version of this chapter.

TABLE 34.1 Causes of Gait Disturbances

Mechanical
Acute injuries (accidental or nonaccidental)
Overuse conditions (mainly sports-related)
Dysplastic lesions
Limb length discrepancy

Osseous
Legg–Calvé–Perthes disease
Osteochondritis dissecans of knee and talus
Slipped capital femoral epiphysis
Osteomyelitis
Diskitis
Osteoid osteoma or other primary bone tumor

Articular
Developmental hip dysplasia
Septic arthritis
Transient synovitis
Rheumatic disease (JIA, SLE)
Hemophilia-related hemorrhage
Ankylosis of a joint

Neurologic
Guillain–Barré syndrome and other peripheral neuropathies
Intoxication
Cerebellar ataxia
Brain tumor
Lesion occupying spinal cord space
Posterior column spinal cord disorders
Myopathy
Hemiplegia
Complex regional pain syndrome
Cerebral palsy

Hematologic/Oncologic
Sickle cell pain crisis
Leukemia, lymphoma
Metastatic tumor
Langerhans cell histiocytosis

Other
Soft tissue infection
Myositis
Fasciitis
Bursitis
Kawasaki disease
Conversion disorder
Gaucher disease
Phlebitis
Scurvy
Rickets
Peritonitis

JIA, juvenile idiopathic arthritis; SLE, systemic lupus erythematosus.

knees flexed to 90 degrees. Knee flexion and extension, ankle dorsiflexion, and plantar flexion, as well as subtalar motion, must be assessed and recorded.

Spinal evaluation. Spinal mobility should be assessed because abnormalities such as spondylolysis, nerve root impingement, diskitis, and tumors may manifest as a gait disturbance. The child's ability to flex forward and to reverse lumbar lordosis is a sign of normal mobility (see Chapter 35). Areas of vertebral bone tenderness and muscle spasm are determined by direct palpation.

Neurologic Evaluation

Many gait disturbances have a neurologic cause or association. The neurologic examination should include muscle strength testing, sensory assessment (particularly to establish the specific level of any potential sensory deficits), deep tendon reflexes, and pathologic reflexes, such as the Babinski sign. Abnormal rectal tone or bladder distention is concerning for a spinal lesion.

◆ Radiographic Assessment

The need for radiographic evaluation is based on the differential diagnosis. For many gait disturbances, radiographic assessment is not required. When necessary, plain radiographs of the lower extremities, pelvis, or spine are obtained first, followed by special diagnostic studies, such as a teleoroentgenogram to assess for lower extremity length discrepancy, technetium bone scan to localize occult lesions such as avascular necrosis or stress fracture, and computed tomography (CT) to characterize specific lesions. Magnetic resonance imaging (MRI) is helpful in the diagnosis of occult or soft tissue lesions, such as infection, tumors, or metabolic bone disease, as well as other pathologic structural processes of the spine, such as syrinx, tethered cord, or disk anomaly.

◆ Laboratory Tests

Tests such as complete blood cell count with differential, erythrocyte sedimentation rate, and C-reactive protein level are indicated if an infectious, rheumatic, or otherwise inflammatory condition is suspected. Rheumatoid factor and antinuclear antibody determinations are less helpful in the diagnosis of rheumatic causes of gait disturbances (see Chapter 33). Other tests may be indicated for the diagnosis of specific disorders. Electromyography, nerve conduction studies, muscle biopsies, and nerve biopsies are frequently necessary in the diagnosis of myopathic or neuropathic disorders (see Chapter 29). Determinations of creatine phosphokinase, aldolase, and aspartate aminotransferase levels are important in the evaluation of striated muscle function and should be ordered if an underlying myopathy or myositis is suspected.

GAIT DISTURBANCES

The 3 most common categories of gait disturbances of childhood are torsional variations (in-toeing and out-toeing), toe-walking (equinus gait), and limping.

Torsional Variations

The presence of in-toeing or out-toeing does not necessarily imply an abnormality of the foot; rather, it indicates only the direction in which the foot is pointing during ambulation. Torsional variations can be located from the proximal (i.e., the hip) to the distal (i.e., the foot) region in the involved extremity. Some causes, such as clubfeet, are obvious, whereas others are subtle. Most torsional variations resolve with normal growth and development. The common causes of in-toeing and out-toeing are listed in Table 34.2.

Normal Developmental Alignment

In utero positioning affects the alignment of the lower extremities of infants. In the typical in utero position, the hips are flexed, abducted, and externally rotated; the knees are flexed; and the lower legs are

internally rotated. The feet are in a supinated position against the posterolateral aspect of the opposite thigh. The musculoskeletal examination of an infant characteristically shows 20- to 30-degree hip flexion contractures, 50-60 degrees of abduction, 80-90 degrees of external rotation in extension, and minimal or no internal rotation. The knees have 20- to 30-degree flexion contractures, and internal tibial torsion is present. These are normal findings. The increased external rotation of the hip is caused not by femoral retroversion but rather by a posterior hip capsule contracture, which begins to resolve at the time of independent ambulation.

The combination of external rotation at the hip and internal rotation of the lower leg produces a bowed appearance of the lower extremities in the weight-bearing position. This is not true bowing, but rather reflects this torsional combination. After the child attains independent ambulation, this bowed appearance resolves over a 6- to 12-month period.

Physiologic genu valgum ("knock knees") is seen between 3 and 4 years of age. This is true genu valgum and is not the result of torsional variations. This condition resolves with growth and normal adult knee alignment is obtained between 5 and 8 years of age. Newborns have a mean varus alignment of 15 degrees that corrects to neutral alignment between 18 and 20 months of age. The maximum valgus of 12 degrees occurs by 3-4 years of age. By 7 years of age, the valgus alignment corrects to that of a normal adult (8 degrees in females, 7 degrees in males). Overall, 95% of cases of developmental physiologic genu varum and genu valgum resolve with growth, even in children with more pronounced physiologic genu varus or genu valgus. In some children, the condition may not completely correct until adolescence.

TABLE 34.2 Common Causes of In-Toeing and Out-Toeing

In-Toeing	Out-Toeing
Medial (internal) femoral torsion	Lateral (external) femoral torsion
Medial (internal) tibial torsion	Lateral (external) tibial torsion
Metatarsus adductus	Calcaneovalgus feet
Talipes equinovarus (clubfoot)	Hypermobile pes planus

Torsional Profile

The torsional or rotational profile aids in the diagnosis and sequential follow-up of children with torsional variations (Fig. 34.1).

Foot progression angle. The foot progression angle, which is the direction of the long axis of the foot with regard to the direction in which the child is walking (Fig. 34.2), should be measured. Inward

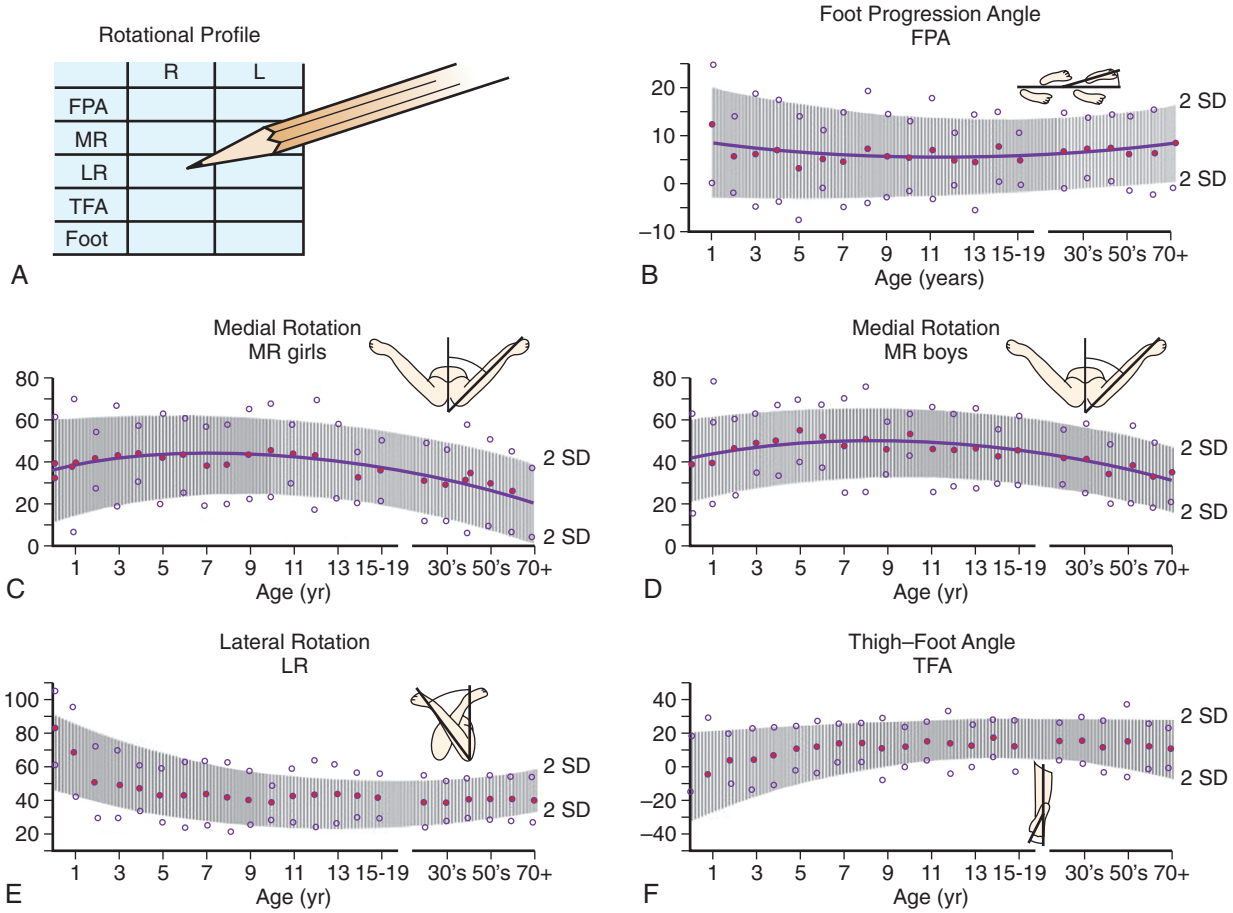

FIGURE 34.1 The torsional or rotational profile from birth to maturity. *A,* The rotational profile is assessed and tracked at each visit. *B,* Mean foot progression angle (FPA) by age. *C,* Mean femoral medial rotation in girls by age. *D,* Mean femoral medial rotation in boys by age. *E,* Mean lateral rotation by age. *F,* Mean thigh-foot angle. All graphs include 2 standard deviations from the mean. (From Morrissey RT, Weinstein SL, eds. *Lovell and Winter's Pediatric Orthopaedics*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 1990.)

rotation is given a negative value and outward rotation a positive value. A normal foot progression angle in children and adolescents is 10 degrees (range, −3 to +20 degrees). The foot progression angle defines whether the gait is normal or if there is an in-toeing or out-toeing gait. The latter is considered abnormal when the foot progression angle exceeds 20 degrees. Recording the angle allows for comparison during follow-up evaluations.

Hip rotation. Measuring hip rotation allows for indirect assessment of femoral version. Typically, the femoral neck creates an anteriorly directed angle with the transcondylar axis of the distal femur (Fig. 34.3). This anterior angulation is known as femoral anteversion and decreases from approximately 40 degrees at birth to 15 degrees by maturity. Increased internal rotation at the hip indicates excessive anteversion, and increased external rotation at the hip indicates retroversion. Hip rotation is assessed with the child in the prone position with the knees together and flexed 90 degrees (Fig. 34.4). In this position, the hip is in neutral alignment. Rotating the lower leg outwardly produces internal rotation of the hip; rotating the lower leg inwardly produces external rotation of the hip. A newborn hip in extension typically rotates externally 80-90 degrees and has a limited internal rotation of 0-10 degrees. By 1 year of age, there is approximately 30-40 degrees of internal rotation. Hip rotation should be bilaterally symmetric. Asymmetric rotation is often indicative of a hip disorder and necessitates radiographs of the pelvis. The mean hip internal rotation in extension in older males is 50 degrees (range, 25-65 degrees), and that in females is 40 degrees (range, 15-60 degrees).

Thigh-foot angle. With the child in the prone position and the knees approximated and flexed 90 degrees, the long axis of the foot in the neutral or simulated weight-bearing position can be compared with the long axis of the thigh (Fig. 34.5). Inward rotation is given a negative value, whereas outward rotation is given a positive value. Inward rotation is indicative of internal tibial torsion, and outward rotation represents external tibial torsion. This angle must be accurately measured and recorded. The mean thigh-foot angle is 10 degrees (range, −5 to +30 degrees) from middle childhood through adult life. Infants have a mean thigh-foot angle of −5 degrees (range, −35 to +40 degrees) as a consequence of the normal in utero position.

Foot shape. With the child again in the prone position, the shape of the foot is easily appreciated, allowing for assessment of children with metatarsus adductus or a calcaneovalgus foot. The mobility of the

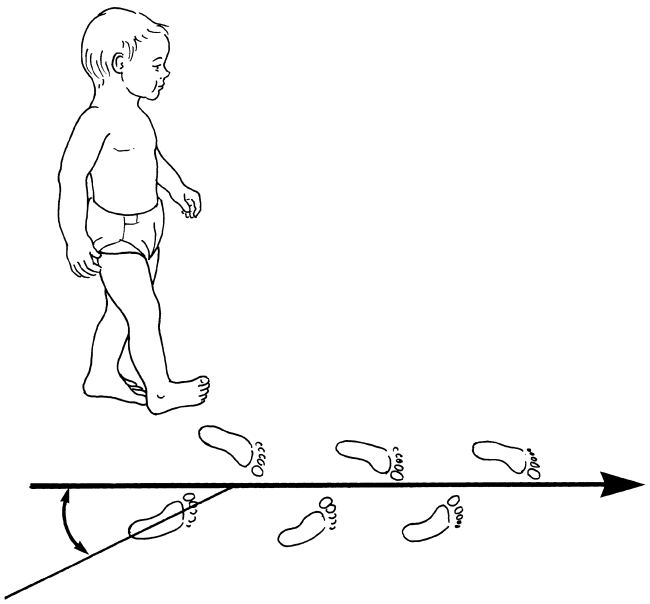

FIGURE 34.2 Foot progression angle. The long axis of the foot is compared with the direction in which the child is walking. If the foot points outward, the angle is positive. If the foot points inward, the angle is negative.

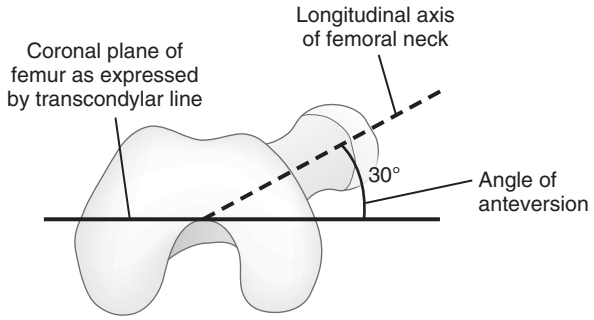

FIGURE 34.3 Femoral version. Typically, the femoral neck creates an anteriorly directed angle with the transcondylar axis of the distal femur.

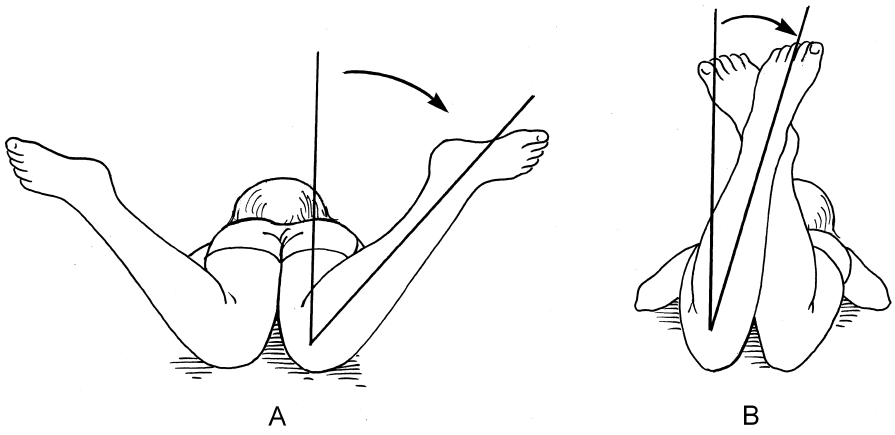

FIGURE 34.4 Hip rotation in extension. The child is in the prone position, with the knees flexed 90 degrees. The lower leg is vertically oriented. This is considered the neutral position. Outward rotation *(A)* of the leg produces internal hip rotation; inward rotation *(B)* produces external hip rotation.

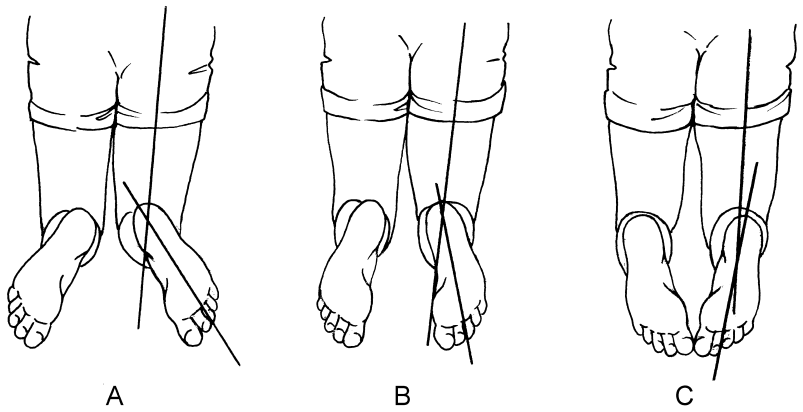

FIGURE 34.5 Thigh-foot angle. With the child in the prone position and the knees flexed and approximated, the long axis of the foot can be compared with the long axis of the thigh. The long axis of the foot bisects the heel and the 3rd or middle toe. External tibial torsion *(A)* produces excessive outward rotation. Normal alignment *(B)* is characterized by slight external rotation. Internal tibial torsion produces inward rotation *(C)*.

FIGURE 34.6 W-sitting is the position of comfort for children with increased femoral anteversion.

ankle and subtalar joint can also be evaluated with the child in this position.

In-Toed Gait

Internal femoral torsion. Increased femoral anteversion, also referred to as internal femoral torsion, is the most common cause of in-toeing in children 3 years of age or older and occurs twice as often in girls as in boys. Many affected children have generalized **ligamentous laxity**. Increased femoral anteversion is secondary to excessive or persistent infantile femoral anteversion and is almost always a benign condition that typically improves by 8-9 years of age. Severe anteversion or lack of progressive improvement by late childhood warrants referral to an orthopedic surgeon.

Children with increased anteversion often run with a circumduction gait secondary to internal rotation at the hip, and the parents may note that the child W-sits rather than sitting cross-legged (Fig. 34.6). W-sitting is of no concern developmentally, is the position of comfort for the child, and does not cause or worsen in-toeing in children. Children will typically stop sitting in this position after sufficient improvement in the internal torsion allows them to sit cross-legged more comfortably. Common femoral anteversion should not be viewed as a reason for decreased athletic ability or as a risk factor for arthritis, bunions, or back pain. A relationship with patellofemoral pain has been reported.

Physical examination. Gait assessment reveals that the entire lower extremity is inwardly rotated during ambulation. Foot progression angle is negative and a circumduction-type gait may be noted. Hip rotation assessment characteristically reveals 80-90 degrees of internal rotation in the prone, extended position (Fig. 34.7). External rotation, as a consequence, is limited to 0-10 degrees. Features of generalized ligamentous laxity are often present, including elbow, wrist, and finger hyperextension, thumb hyperabduction, knee hyperextension, and hypermobile pes planus.

FIGURE 34.7 *A,* Clinical photograph of a 5-year-old girl demonstrating internal femoral torsion. She has approximately 80 degrees of internal rotation bilaterally. *B,* External rotation is limited to approximately 15 degrees, for a total arc of rotation of 90-95 degrees.

Radiographic evaluation. Radiographic evaluation of internal femoral torsion is not necessary. Anteroposterior radiographs of the pelvis are typically normal, but there may be the appearance of a relatively vertical femoral neck angle, or coxa valga. If coxa valga is noted, repeating the radiograph with the hips in 15 degrees of abduction and

30-40 degrees internal rotation will typically reveal a normal femoral neck angle. In more severe cases, MRI, CT, or ultrasonography of the proximal and distal femur can be used to accurately measure the degree of torsion.

Internal tibial torsion. Internal tibial torsion is the most common cause of in-toeing in children younger than 2 years and is secondary to normal in utero positioning. This condition is commonly seen during the 2nd year of life and may be associated with metatarsus adductus. Significant improvement usually does not occur until the child begins to pull up to standing and walk independently. Spontaneous resolution with normal growth and development can be anticipated typically by 4-5 years of age. Rarely, persistent or severe internal tibial torsion in an older child or adolescent may necessitate surgical derotation.

Physical examination. The degree of tibial torsion can be assessed by measuring the thigh-foot angle (see Fig. 34.5). The measurements should be recorded on each visit to the physician to document improvement.

Radiographic evaluation. Radiographic evaluation of internal tibial torsion is not necessary. MRI and CT can assess the degree of tibial torsion, but these are rarely required.

Metatarsus adductus. Metatarsus adductus is the most common congenital foot deformity, occurs equally in boys and girls, and is bilateral in approximately 50% of cases. Metatarsus adductus has hereditary tendencies and is more common in 1st-born children, most likely as a result of increased molding from the more rigid primigravida uterus and abdominal wall. Up to 10% of children with metatarsus adductus have **developmental dysplasia of the hip**. Significant metatarsus adductus persisting or manifesting after 4 years of age may require surgical correction.

Physical examination. In metatarsus adductus, the forefoot is adducted and occasionally supinated, while the hindfoot and midfoot are normal. A visual line bisecting the heel should normally pass through the 2nd toe or 2nd web space; in metatarsus adductus this line intersects the forefoot more laterally. The lateral border of the foot is convex, the base of the 5th metatarsal is prominent, and the medial border of the foot is concave. There is usually an increased interval between the 1st and 2nd toes, with the great toe being held in an inwardly rotated or varus position (Fig. 34.8). Ankle range of motion is normal. Forefoot mobility, assessed by stabilizing the hindfoot and midfoot in a neutral position and applying pressure over the 1st metatarsal head with the opposite hand, can vary from flexible to rigid. Most cases of flexible metatarsus adductus resolve by several months of age; rigid deformities may require surgical correction. In the walking child with an uncorrected or partially corrected metatarsus adductus, there is an in-toed gait, abnormal shoe wear, and possible discomfort from shoe pressure.

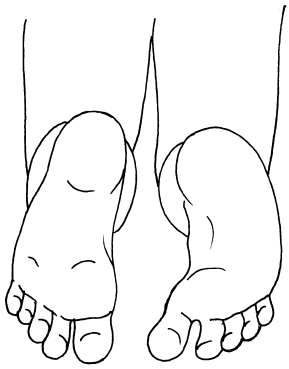

FIGURE 34.8 Foot shape. In the same position as for measurement of the thigh-foot angle, the shape of the foot can also be evaluated. In this illustration, the left foot has normal alignment and the right foot demonstrates metatarsus adductus.

Radiographic evaluation. Radiographs of the foot are not necessary for routine, flexible metatarsus adductus. When obtained, anteroposterior and lateral weight-bearing radiographs demonstrate adduction of the metatarsals at the tarsometatarsal joint and an increased intermetatarsal angle between the 1st and 2nd metatarsals. The midfoot and hindfoot are usually normal. Radiographs should be obtained if the deformity is rigid or if there are any suspected abnormalities of the midfoot or hindfoot.

Talipes equinovarus (clubfoot). Talipes equinovarus is classified as either positional or congenital. **Positional clubfoot** is a normal foot that has been held in the deformed position in utero, and which is flexible on examination in the newborn nursery. **Congenital clubfoot** represents a deformity not only of the foot but also of the entire lower leg and is categorized as either idiopathic or syndromic. There is a spectrum of severity, but clubfoot associated with neuromuscular diagnoses or syndromes is typically rigid and more difficult to treat. Clubfoot is also extremely common in patients with spinal dysraphism, arthrogryposis, and chromosomal syndromes such as trisomy 18 and chromosome 22q11.2 deletion syndrome.

Congenital clubfoot, when diagnosed and treated in infancy with serial casting, typically does not produce a gait disturbance. However, foot contact pressures may remain high, indicating that gait is not entirely normal following correction. In-toeing secondary to persistent internal tibial torsion is common after appropriate treatment. A mild lower extremity length discrepancy of up to 2 cm may be seen in adolescence, but usually does not produce a limp or necessitate treatment. On occasion, residual muscle imbalance may cause the child to walk on the lateral border of the foot, leading to discomfort and an antalgic gait that may require further surgical correction.

Out-Toed Gait

External femoral torsion. Femoral retroversion, also referred to as external femoral torsion, is a rare disorder that usually causes no significant functional impairment unless it is associated with a **slipped capital femoral epiphysis (SCFE)**. If the femoral retroversion is caused by SCFE, the slip is treated surgically. On occasion, persistent femoral retroversion following surgical treatment of SCFE can lead to ongoing functional impairment, such as a severe out-toed gait and difficulty in approximating the knees in the sitting position, and may require further surgical correction.

Physical examination. Children with external femoral torsion demonstrate limited internal rotation and excessive external rotation when the hip is examined in the extended position. The hip externally rotates 70-90 degrees, whereas internal rotation is only 0-20 degrees. Idiopathic external femoral torsion is usually bilateral. If the deformity is unilateral, especially in an obese older child or a young adolescent, SCFE must be considered and evaluated.

Radiographic evaluation. Anteroposterior and frog-leg lateral radiographs of the pelvis are necessary for any child or adolescent presenting with external femoral torsion, especially one who is obese, has atraumatic or referred anterior thigh or knee pain, or has unilateral deformity. Approximately 20% of children with SCFE have simultaneous bilateral involvement. The typical changes of SCFE include widening of the physis and an abnormal relationship between the capital femoral epiphysis (CFE) and the femoral neck. The femoral head appears to be slipped inferiorly and posteriorly, but in actuality, the femoral neck is rotated anteriorly and superiorly.

External tibial torsion. External tibial torsion is common and is secondary to a normal variation of in utero positioning in which the plantar surface of the foot is against the wall of the uterus, forcing it into a hyperdorsiflexed, everted position. This rotated alignment produces external tibial torsion and typically an associated calcaneovalgus foot (Fig. 34.9). When this alignment of the lower leg and foot is combined with the exaggerated external rotation of the normal newborn hip, the lower extremity appears to have severe out-toeing and external rotation. This condition follows the same clinical course as internal tibial torsion in that significant improvement does not occur during the 1st year of life. With the onset of independent ambulation, spontaneous improvement begins and is typically complete by 2-3 years of age.

Physical examination. External tibial torsion results in a positive thigh-foot angle of 30-50 degrees.

Radiographic evaluation. Radiographic assessment for external tibial torsion is not necessary.

Calcaneovalgus foot. The calcaneovalgus foot is common in newborns and is secondary to in utero positioning (see Fig. 34.9). The foot is hyperdorsiflexed with varying degrees of eversion and forefoot abduction. External tibial torsion is usually present. Calcaneovalgus foot is typically unilateral but may occasionally be bilateral. The hyperdorsiflexion of the foot usually resolves during the 1st 3-6 months of life. On occasion, resistant feet may require passive stretching, taping, or casting into a plantar flexed position. Usually, by the time the child begins to pull to standing and walk independently, the calcaneovalgus condition has resolved. The external tibial torsion, however, persists and follows the same natural history as internal tibial torsion.

Physical examination. The involved extremity demonstrates out-toeing, the dorsum of the foot can easily be brought into contact with the anterior aspect of the lower leg, and the forefoot has an abducted appearance. The increased dorsiflexion should not be confused with the increased joint mobility of premature infants. The deformity is flexible, and plantar flexion of the ankle is normal or almost normal. External tibial torsion of 30-50 degrees is a common associated finding.

Calcaneovalgus foot must be distinguished from the following 3 conditions: (1) congenital vertical talus, (2) posteromedial bowing of the tibia, and (3) neuromuscular abnormalities, such as paralysis of the gastrocnemius muscle. Differentiation is typically based on physical examination findings, though radiographs may be required. Congenital vertical talus results in a rocker-bottom appearance to the foot. The deformity is rigid, as opposed to the flexible deformity seen with a calcaneovalgus foot. In posteromedial bowing of the tibia, the apex of the deformity is in the distal tibia, whereas the apex of the deformity in a calcaneovalgus foot is located at the ankle.

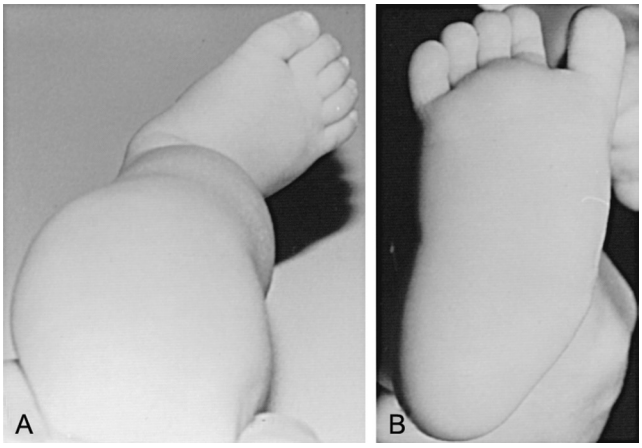

FIGURE 34.9 *A,* A clinical photograph of a 2-month-old girl demonstrating excessive external tibial torsion. This reverse or anterior thigh-foot angle shows approximately 50 degrees of external tibial torsion. *B,* A calcaneovalgus foot with forefoot abduction and increased hindfoot valgus in the same infant. There is also hyperdorsiflexibility of the foot in the ankle.

Radiographic evaluation. Simulated weight-bearing anteroposterior and lateral radiographs of the foot may be necessary to differentiate between the calcaneovalgus foot and a congenital vertical talus. In a calcaneovalgus foot, the radiographs either are normal or reveal an increase in hindfoot valgus. In the congenital vertical talus, the hindfoot is in equinus, whereas the midfoot and the forefoot are dorsally displaced, producing a rocker-bottom appearance. Anteroposterior and lateral radiographs of the tibia and fibula are necessary if there is bowing of the lower leg.

Hypermobile pes planus. Hypermobile, flexible, or pronated feet are **flatfeet**, a common cause of concern to parents. Children with this deformity are usually asymptomatic and have no limitation of activities. An individual may present for concerns of out-toeing because of the overpronation of the midfoot and hindfoot, which may allow the forefoot to become abducted. Flexible flatfeet are also common in neonates and toddlers as a result of the associated laxity in the bone-ligament complexes of the feet and the abundant fat in the area of the medial longitudinal arch. Most children with flatfeet improve by 6 years of age. In the older child, flexible flatfeet are usually secondary to generalized ligamentous laxity. Most older children and adolescents with flexible flatfeet or hypermobile pes planus are asymptomatic, though feet that are symptomatic with vigorous physical activity usually respond readily to the use of commercially available medial longitudinal arch supports. When the child has excessive heel valgus, pronation, or abnormal shoe wear that is unresponsive to a commercially or custom-made arch support, the use of a UCB (University of California, Berkeley) orthosis may be beneficial. Surgery is rarely indicated.

Physical examination. In the non–weight-bearing position in the older child with a flexible flatfoot, the normal medial longitudinal arch is visible, but in the weight-bearing position, the foot becomes pronated with varying degrees of pes planus and hindfoot valgus. Instead of bearing weight over the lateral column of the foot, the weight is shifted medially, producing pronation. Subtalar motion is examined with the ankle in the neutral position and should be normal or slightly increased. Loss of subtalar motion may indicate a rigid flatfoot. Common causes of rigid flatfeet include Achilles tendon contracture, tarsal coalition, and neuromuscular disorders. Rigid flatfeet may also be a familial trait. Other joints, especially the elbows, hands, and knees, usually demonstrate generalized ligamentous laxity in patients with flexible flatfeet. Children with flexible flatfeet should be evaluated for external tibial torsion.

Radiographic evaluation. Radiographs of asymptomatic flexible flatfeet are usually not indicated. Standing, anteroposterior, and lateral weight-bearing radiographs are obtained, if necessary. The most common indication is the presence of pain (Table 34.3). Anteroposterior radiographs reveal an increase in the talocalcaneal angle (>25 degrees) caused by the excessive hindfoot valgus. The lateral view shows distortion of the normal straight-line relationship between the long axis of the talus and the 1st metatarsal and flattening of the normal medial longitudinal arch.

Equinus Gait (Toe-Walking)

Toe-walking can be a normal finding in children up to 3 years of age. Persistent toe-walking thereafter or acquired toe-walking at a later age

TABLE 34.3 Differential Diagnosis of Foot Pain According to Age

Age Group	Diagnostic Considerations
0–6 yr	Poorly fitting shoes Fracture Puncture wound Foreign body Osteomyelitis Cellulitis Juvenile idiopathic arthritis Hair tourniquet Leukemia
6–12 yr	Poorly fitting shoes Trauma (fracture, sprain) Juvenile idiopathic arthritis Puncture wound Sever disease (calcaneal apophysitis) Accessory tarsal navicular bone Hypermobile flatfoot Oncologic (Ewing sarcoma, leukemia)
12–18 yr	Poorly fitting shoes Stress fracture Trauma (fracture, sprain) Foreign body Ingrown toenail Metatarsalgia Plantar fasciitis Achilles tendinopathy Accessory ossicles (navicular, os trigonum) Tarsal coalition Avascular necrosis of metatarsal (Freiberg infarction) or navicular (Kohler disease) bones Plantar warts

From Marcdante K, Kliegman R, eds. *Nelson Essentials of Pediatrics*. 7th ed. Philadelphia: Saunders; 2015.

is considered abnormal and necessitates careful evaluation. The differential diagnosis for persistent or acquired toe-walking includes the following:

1. Neuromuscular disorders, such as cerebral palsy, Duchenne muscular dystrophy, or spinal cord abnormality resulting from a tethered spinal cord or diastematomyelia
2. Congenital Achilles tendon contracture (idiopathic toe-walking)
3. Habitual toe-walking
4. Lower extremity length discrepancy

The differentiation of toe-walking can usually be determined from the history and the physical examination. The examiner should establish the time at onset, the amount of time a child spends walking on his or her toes, whether it can be voluntarily corrected, and whether there has been improvement or worsening over time.

Neuromuscular Disorders

The neuromuscular disorder most likely to produce an equinus gait, either unilateral or bilateral, is **cerebral palsy**. The most common type of cerebral palsy is spastic diplegia, a disorder in which the lower extremities are more involved than the upper extremities. Prematurity is a common risk factor for spastic diplegia. It can be symmetric or asymmetric, with 1 side being slightly more involved than the other. Spastic diplegia tends to produce a bilateral equinus gait. Spastic hemiplegia, in which only 1 side is involved, is usually caused by birth trauma (asphyxia), perinatal stroke, or underlying congenital malformation and results in unilateral toe-walking.

Acquired or late-onset toe-walking is usually a result of a developing neuromuscular disorder, such as Duchenne muscular dystrophy. As fat and fibrous tissues replace muscle, equinus and other contractures occur. There is usually a history of progressive clumsiness and frequent episodes of falling. The diagnosis of muscular dystrophy is usually made when the child is between 3 and 5 years of age. The diagnosis is confirmed by markedly elevated creatine phosphokinase levels, by muscle biopsy, or by genetic testing. In a spastic equinus gait without contracture, physical therapy and orthoses (daytime, nighttime, or both) may be beneficial. If a contracture has developed, serial casting may be performed in young children, whereas surgical lengthening of the Achilles is usually necessary in older children.

Physical examination. The examination of a child with toe-walking secondary to cerebral palsy reveals either an Achilles contracture or a spastic equinus gait without contracture, as well as abnormal neurologic findings. These findings include increased muscle tone, spasticity, hyperactive deep tendon reflexes, and pathologic reflexes, such as a positive Babinski sign. Hamstring tightness, in addition to ankle equinus, may be a subtle sign of underlying mild cerebral palsy.

Children with Duchenne muscular dystrophy typically demonstrate **pseudohypertrophy** of the calves in addition to equinus contracture. They have proximal muscle weakness first, and then generalized weakness, and perhaps decreased or absent upper extremity and patellar tendon reflexes, depending on the stage of progression. Ankle reflexes are usually preserved.

Radiographic evaluation. Radiographic evaluation of a child with toe-walking is rarely necessary. MRI of the brain and spine is occasionally required during the evaluation of a possible neuromuscular disorder.

Other testing. Dynamic electromyography and gait analysis studies can be helpful in distinguishing between toe-walking caused by mild cerebral palsy and that caused by a congenital Achilles contracture. Serum muscle enzyme (creatine phosphokinase, aspartate aminotransferase, and aldolase) levels and muscle biopsies are required for children with suspected Duchenne muscular dystrophy or other myopathies.

Lower Extremity Length Discrepancy

Lower extremity length discrepancy is a common cause for a unilateral equinus gait in older children and adolescents. Usually, mild discrepancies of less than 2 cm can be adequately compensated for during normal gait with minimal, if any, limping or toe-walking. Greater discrepancies may result in toe-walking and may require surgical correction. The differential diagnosis of a lower extremity length discrepancy is extensive (Table 34.4).

Physical examination. Examination of a child with a lower extremity length discrepancy shows shortness of the involved extremity; this can be measured by placing blocks of various heights beneath the foot until the pelvis is level. The range of motion of the joints of the involved extremity, especially of the hips, must be assessed. The neurologic examination is also important. Children with subtle neurologic disorders, such as cerebral palsy, may also have a very mild lower extremity length discrepancy that contributes to an equinus gait.

Radiographic evaluation. Children with a lower extremity length discrepancy require radiographic assessment. Lower extremity lengths are typically measured radiographically by 1 of several methods, including the teleoroentgenogram, orthoroentgenogram, scanogram, and low-dose biplanar radiography. Digital teleoroentgenograms and orthoroentgenograms are currently preferred, but low-dose biplanar

TABLE 34.4 Causes of Lower Extremity Length Discrepancy

Shortening	Lengthening
Congenital	**Congenital**
Hemiatrophy*	Hemihypertrophy*
Skeletal dysplasias	Local vascular malformation
Short femur	
Proximal focal femoral deficiency*	
Fibular, tibial hemimelia	
Developmental dysplasia of the hip*	
Tumor: Developmental	**Tumor: Developmental**
Neurofibromatosis	Neurofibromatosis
Multiple exostosis	Soft tissue hemangioma
Enchondromatosis (Ollier disease)	Arteriovenous malformation
Osteochondromatosis	Hemihypertrophy with Wilms tumor
Fibrous dysplasia (Albright syndrome)	Aneurysm
Punctate epiphyseal dysplasia	
Dysplasia epiphysealis hemimelica (Trevor disease)	
Radiation therapy before skeletal maturity (physeal arrest)*	
Resection of benign or malignant neoplasm	
Infection	**Infection: Inflammation**
Osteomyelitis*	Metaphyseal osteomyelitis
Septic arthritis	Rheumatoid arthritis
Tuberculosis	Hemarthrosis (hemophilia)
Trauma	**Trauma**
Physeal injury*	Metaphyseal, diaphyseal fracture
Failed joint replacement	Diaphyseal operations (bone grafts, osteosynthesis, periosteal stripping)
Osteotomy, atrophic nonunion	
Overlapping, malposition of fracture fragments*	
Burns	
Neuromuscular Disease	
Poliomyelitis	
Cerebral palsy*	
Myelomeningocele	
Peripheral neuropathy	
Focal cerebral lesions (hemiplegia)	
Other	
Legg–Calvé–Perthes disease*	
Slipped capital femoral epiphysis	

*Common.

Modified from Moseley C. Leg-length discrepancy. *Pediatr Clin North Am.* 1986;33(6):1385; Tachdjian M. *Pediatric Orthopedics.* 2nd ed. Philadelphia: WB Saunders; 1990; reprinted and modified from Behrman RE, ed. *Nelson Textbook of Pediatrics.* 14th ed. Philadelphia: WB Saunders; 1992:1702.

radiography is becoming more commonplace at large centers. The teleoroentgenogram is a single radiographic exposure of both lower extremities in the standing position. This can be measured using measurement tools within the digital radiography software. Advantages include single exposure and detection of angular deformities. The orthoroentgenogram consists of overlapping exposures centered on the hips, knees, and ankles on a long cassette. Like the teleoroentgenogram, an advantage of this type of radiograph is that it shows associated angular deformities. A scanogram consists of 3 strip exposures of the hips, knees, and ankles on a standard-sized cassette with a radiographic ruler adjacent to the extremity. This is an accurate method of assessing limb length but does not demonstrate angular deformities. Low-dose biplanar radiography is a 3-dimensional imaging method with superior accuracy and decreased radiation exposure but requires a sophisticated radiologist to correctly align the limbs for computer measurement. CT measurement is accurate but is not commonly used secondary to the amount of radiation exposure required. Radiographs of the left hand and wrist for bone age are also obtained to assess when skeletal maturity will occur.

Habitual Toe-Walking

Habitual toe-walking occurs in a child who is walking on his or her toes voluntarily. Toe-walking occurs relatively commonly in young walkers. Their history and physical examination findings are entirely normal. This is a diagnosis of exclusion. The treatment of habitual toe-walkers is observation. As the child becomes heavier and the central nervous system matures, the toe-walking should resolve.

Physical examination. The findings in the examination of the child with habitual toe-walking are normal. The ankle has a full range of motion, and there is no evidence of an underlying neuromuscular disorder.

Radiographic evaluation. Radiographic evaluation is not indicated.

Idiopathic Toe-Walking

Idiopathic toe-walking is defined as the presence of an equinus gait in a child over 2 years of age with or without Achilles tendon contracture in the absence of other etiologies, including habitual toe-walking. The birth and developmental history and the neurologic findings are usually normal. However, mild developmental delays, especially in speech and in fine and gross motor skills, are seen in some children. Some have suggested possible deficits in sensory processing. A family history positive for Achilles contracture, male predominance, and learning disabilities are common findings. Muscle biopsy samples have shown an increase in type I fibers, suggesting a neuropathic process. Serial casting typically leads to resolution, though in some children, surgical lengthening of the Achilles tendon may be required.

Physical examination. If present, Achilles tendon contracture leads to an inability to dorsiflex the foot to the neutral or plantigrade position. Examination of the ankle shows a 10- to 15-degree fixed equinus contracture. The assessment of an Achilles contracture should be performed with the hindfoot held in a slightly supinated position to bring the calcaneus beneath the talus. If this position is not used, dorsiflexion of the foot produces hindfoot valgus with the appearance of more dorsiflexion than is actually present. In congenital Achilles contractures, no other musculoskeletal or neurologic abnormalities are present.

Radiographic evaluation. Radiographs are not necessary unless an associated abnormality within the foot is thought to be present. Should this occur, anteroposterior and lateral weight-bearing radiographs of the foot should be obtained.

Limping

Limping is categorized as either painful (antalgic gait) or nonpainful (Trendelenburg gait), depending on the length of the stance phase. With an **antalgic gait**, the stance phase is shortened because the child decreases the time spent on the painful extremity. In a **Trendelenburg**

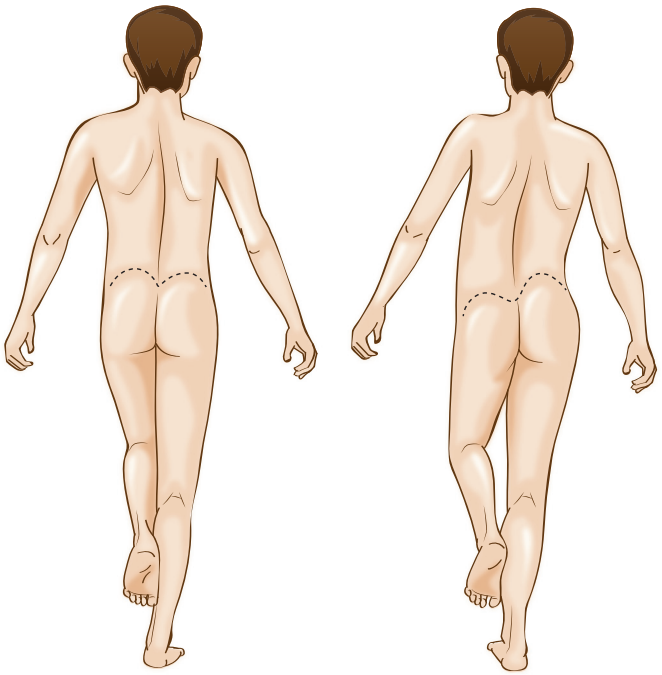

FIGURE 34.10 Trendelenburg gait. With functional weakness of the hip abductor muscles, it is difficult to support the body's weight on the affected side; the pelvis tilts down and away from the weak side, the patient leans toward the affected side.

gait (Fig. 34.10), which indicates underlying proximal muscle weakness (e.g., muscular dystrophy) or hip instability (e.g., developmental hip dysplasia), the stance phase is the same for the involved and uninvolved sides, but the child leans over the involved side to shift the center of gravity for balance. If the disorder is bilateral, it produces a **waddling gait**. The differential diagnosis is extensive (Table 34.5). Most causes involve the lower extremity, but spinal disorders can also produce limping or difficulty walking, especially if there is spinal cord or peripheral nerve involvement. Painful (antalgic) gaits are predominantly caused by trauma, infection, neoplasia, and rheumatic disorders. Trendelenburg gaits are generally caused by congenital, developmental, or neuromuscular disorders. Thus, antalgic gaits result from *acute* disorders, whereas Trendelenburg gaits usually result from *chronic* disorders. The type of gait, the presence or absence of systemic symptoms, and the anatomic location of the symptoms can usually be determined from the history and physical examination findings.

TABLE 34.5 Differential Diagnosis of Limping in Children

Age Group	Diagnostic Considerations
Early walker: 1–3 yr of age	***Painful Limp***
	Septic arthritis and osteomyelitis
	Transient synovitis
	Occult trauma ("toddler's fracture")
	Intervertebral diskitis
	Malignancy
	Painless Limp
	Developmental dysplasia of the hip
	Neuromuscular disorder
	Cerebral palsy
	Lower extremity length inequality
Child: 3–10 yr of age	***Painful Limp***
	Septic arthritis, osteomyelitis, myositis
	Transient synovitis
	Trauma
	Rheumatologic disorders
	Juvenile idiopathic arthritis
	Intervertebral diskitis
	Malignancy
	Painless Limp
	Developmental dysplasia of the hip
	Legg–Calvé–Perthes disease
	Lower extremity length inequality
	Neuromuscular disorder
	Cerebral palsy
	Muscular dystrophy (Duchenne)
Adolescent: 11 yr of age to maturity	***Painful Limp***
	Septic arthritis, osteomyelitis, myositis
	Trauma
	Rheumatologic disorder
	Slipped capital femoral epiphysis: acute; unstable
	Malignancy
	Painless Limp
	Slipped capital femoral epiphysis: chronic; stable
	Developmental dysplasia of the hip: acetabular dysplasia
	Lower extremity length inequality
	Neuromuscular disorder

From Marcdante K, Kliegman R, eds. *Nelson Essentials of Pediatrics*. 7th ed. Philadelphia: Saunders; 2015.

Antalgic Gait

Congenital origin: Tarsal coalition. Tarsal coalition, also called **peroneal spastic flatfoot**, is characterized by a painful, rigid valgus or pronation deformity of the midfoot and hindfoot, in association with peroneal muscle spasm but without true spasticity. This condition represents a congenital fusion or failure of segmentation between 2 or more tarsal bones. However, any condition that alters the normal motion of the subtalar joint may produce the clinical appearance of a tarsal coalition. Thus, congenital malformation, inflammatory disorders, infection, neoplasms, and trauma involving the subtalar joint can manifest with pain, limping, or other symptoms similar to those of a tarsal coalition.

The most common coalitions occur between the calcaneus and navicular (calcaneonavicular) and the middle or medial facet between the talus and calcaneus (talocalcaneal). Coalitions can be fibrous, cartilaginous, or osseous. The incidence of tarsal coalition is approximately 1%, and it appears to be inherited as an autosomal dominant trait. Approximately 60% of calcaneonavicular and 50% of talocalcaneal coalitions are bilateral. Casting and orthotics may provide some relief of symptoms, though surgical repair is typically required.

Physical examination. The onset of symptoms is insidious and usually occurs during late childhood or early adolescence. Although mild limitation of subtalar motion and a valgus or pronated hindfoot may have been present since early childhood, the onset of symptoms varies with the age at which the fibrous or cartilaginous coalition begins to ossify and further decrease motion. The talonavicular coalition ossifies between the ages of 3 and 5 years; the calcaneonavicular coalition, between 8 and 12 years; and the middle facet talocalcaneal coalition, between 12 and 16 years of age. The pain is typically felt laterally in the hindfoot and radiates proximally along the lateral malleolus and distal fibula into the peroneal muscle region. Symptoms are usually

aggravated by sports or other vigorous activities and are relieved by rest. The foot is pronated in both the weight-bearing and the non–weight-bearing positions. Subtalar joint motion is diminished or absent, and attempts at motion produce pain.

Radiographic evaluation. The diagnosis of tarsal coalition is made radiographically. The initial radiographs should include anteroposterior and lateral weight-bearing radiographs of the foot and an oblique radiograph. The latter is necessary in making the diagnosis of a calcaneonavicular coalition. Beaking of the anterior aspect of the talus in the lateral view suggests a talocalcaneal coalition. Axial views of the hindfoot can be useful in the diagnosis of a middle facet talocalcaneal coalition. CT has traditionally been the diagnostic procedure of choice for coalition, but MRI is useful for detecting fibrous coalitions. CT or MRI should be performed on all coalitions for surgical planning because more than 1 coalition can be present.

Developmental origin

Legg–Calvé–Perthes disease. Legg–Calvé–Perthes disease (LCPD) is idiopathic avascular necrosis of the CFE and its associated complications in an immature, growing child. This disorder is caused by an interruption of the blood supply to the CFE, occurs predominantly in males (up to 5:1), and is bilateral in approximately 20% of affected children. Children with LCPD have delayed skeletal or bone age, disproportionate growth, and mildly short stature. Secondary osteonecrosis is seen in patients with sickle cell anemia. LCPD is a local, self-healing disorder. Prevention of femoral head deformity and secondary degenerative osteoarthritis in adulthood is the only indication for treatment.

Physical examination. The symptomatic onset of LCPD typically occurs between 2 and 12 years of age, at a mean age of 7 years. Most of these children present to care with a limp and mild or intermittent pain in the anterior thigh or knee, such that this condition is often referred to as a "painless limp." Pertinent early physical findings include antalgic gait; muscle spasm with mild restriction of hip motion, especially abduction and internal rotation; proximal thigh atrophy; and mild short stature.

Radiographic evaluation. The diagnosis is typically made from anteroposterior and frog-leg lateral radiographs of the pelvis (Fig. 34.11). The radiographic characteristics can be divided into 5 distinct stages, depending on the interval from the onset of symptoms: (1) cessation of CFE growth, (2) subchondral fracture, (3) resorption or fragmentation, (4) reossification, and (5) healed, or residual. The symptoms are usually most pronounced during the phase of the subchondral fracture and fragmentation. A child with LCPD has the potential for collapse and extrusion of the femoral head, which results in a permanent deformity. If plain radiographs do not demonstrate LCPD in suspected cases, a bone scan or MRI is helpful.

Slipped capital femoral epiphysis. SCFE is the most common adolescent hip disorder. It generally occurs in obese adolescents with delayed skeletal maturation, or in tall and thin adolescents who have had a recent growth spurt. SCFE can also occur as a complication of an underlying endocrine disorder, such as hypothyroidism and pituitary disorders. When SCFE occurs before puberty, a hormonal abnormality or systemic disorder should be suspected. The histopathologic features of SCFE indicate that mechanical factors are the ultimate cause of slippage. The initial abnormality is most likely secondary to endocrine changes during early adolescence. Obesity produces high shear forces across a weakened and obliquely oriented CFE, resulting in slippage. Surgical stabilization is required.

Physical examination. The physical findings depend on the degree of slippage and the classification. The disorder is classified as either stable or unstable. In an unstable or acute SCFE, the CFE is separated from the femoral neck. This is extremely painful, and the adolescent is unable to stand or bear weight. In a stable or chronic SCFE, the most common type, the CFE and femoral neck are in continuity, and the slippage is occurring slowly by plastic deformation. The adolescent has an antalgic, out-toed gait. The hip range of motion demonstrates a lack of internal rotation and an increase in external rotation; as the hip is flexed, it becomes progressively more externally rotated. Limitation of flexion and abduction in extension may also be present as a result of the deformity of the proximal femur.

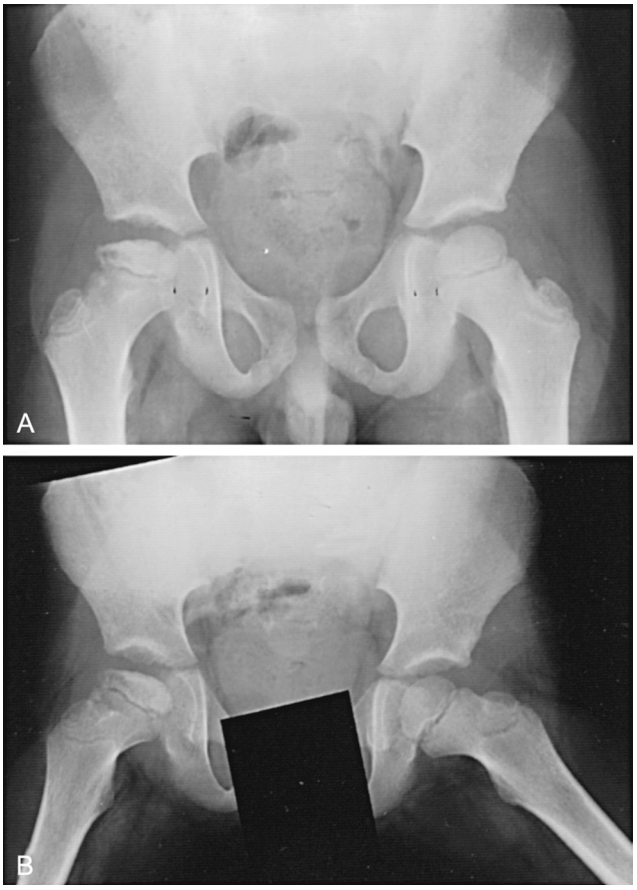

FIGURE 34.11 *A,* An anteroposterior radiograph of the pelvis demonstrating Legg–Calvé–Perthes disease (LCPD) of the right hip. The capital femoral epiphysis (CFE) is collapsing, and there is mild widening of the medial joint space. The left CFE is normal. *B,* A frog-leg lateral radiograph of the pelvis demonstrating limited hip abduction caused by LCPD.

Radiographic evaluation. The diagnosis of SCFE is confirmed radiographically. Anteroposterior and frog-leg lateral radiographs of the pelvis must be obtained (Fig. 34.12). Both hips should be visualized on each radiograph for simultaneous comparison. The earliest sign of SCFE is widening of the physeal plate without slippage, which is considered a pre-slip condition. If slippage occurs, the CFE remains in the acetabulum, whereas the femoral neck rotates anteriorly and superiorly, resulting in varus orientation and retroversion of the femoral head and neck. The severity of slippage can be classified by the degree of displacement of the CFE on the femoral neck.

Trauma

Sprains, strains, and contusions. **Sprains** are ligamentous injuries, whereas **strains** are muscle injuries. **Contusions** are the result of a direct injury and involve the skin and the subcutaneous tissues as well as underlying muscle.

FIGURE 34.12 *A,* An anteroposterior radiograph of the right hip in a 13-year-old obese boy who had been limping and complaining of anterior thigh and knee pain for approximately 2 months. There is a mild stable or chronic slipped capital femoral epiphysis (SCFE). Klein line, a line drawn along the superior aspect of the femoral neck, does not intersect the lateral portion of the capital femoral epiphysis (CFE) and thereby indicates slippage. Also, the physis is wide and irregular. *B,* A frog-leg lateral radiograph clearly demonstrates the slippage of the CFE with respect to the femoral neck. *C,* An anteroposterior radiograph of the pelvis demonstrates an asymptomatic mild stable or chronic left SCFE. It is always important to order radiographs of the pelvis rather than individual views of the right or left hip. *D,* A frog-leg lateral radiograph confirms bilateral SCFE.

Sprains are divided into 3 grades:

1. Grade I: mild with only slight stretching of the ligament
2. Grade II: a moderate injury with partial tearing of the ligament but normal stability
3. Grade III: a severe injury with ligamentous disruption and instability

Sprains, strains, and contusions of the lower extremities are among the most common injuries that produce limping. There is usually a history of trauma, and the location is readily apparent because of soft tissue swelling, ecchymoses, and pain. Most of these injuries occur during athletic activities, but they can also be the result of falls or other minor injuries. In the absence of an associated physeal injury or other fracture, treatment is typically immobilization with a gradual return to activity.

Physical examination. In sprains, the physical examination typically reveals that the involved ligament is tender to direct palpation. There may be soft tissue swelling as well as ecchymoses. The range of motion of the involved joint is typically decreased because of pain. On occasion, a mild joint effusion or hemarthrosis may be present.

Strains involve the muscles, and there is usually tenderness to palpation, soft tissue swelling, and pain with joint motion as a result of stretching of the involved muscle. A palpable defect within the muscle is uncommon except in the most severe injuries. These injuries usually limit the excursion of the muscle and its associated joints.

Radiographic evaluation. In children who sustain sprains, strains, or significant contusions, anteroposterior and lateral radiographs should be obtained. A word of caution regarding sprains is necessary. In children, ligaments are usually stronger than the adjacent physes. Therefore, a **physeal injury** may be present and may have the same clinical features as a sprain (Fig. 34.13; see also Table 34.6). This is especially true with lateral ankle injuries. It is more likely that a Salter–Harris type I separation of the distal fibular epiphysis has occurred, rather than a true ligament injury. This condition should be suspected when there is more tenderness to palpation over the lateral malleolus than over the ligaments. If plain radiographs are normal, stress radiographs may be necessary to establish the diagnosis. This concept also applies to the knee.

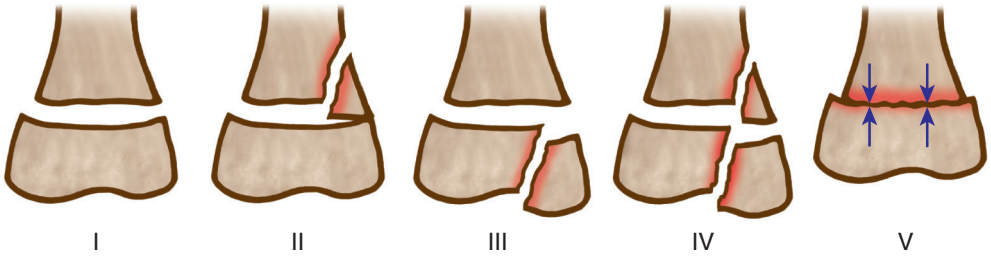

FIGURE 34.13 Salter-Harris classification of physeal fractures, types I-V.

TABLE 34.6 Salter–Harris Classification

Salter–Harris Type	Characteristics
I	Separation through the physis, usually through the zones of hypertrophic and degenerating cartilage cell columns
II	Fracture through a portion of the physis but extending through the metaphysis
III	Fracture through a portion of the physis extending through the epiphysis and into the joint
IV	Fracture across the metaphysis, physis, and epiphysis
V	Crush injury to the physis

From Baldwin KD, Wells L, Dormans JP. Common fractures. In: *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Saunders; 2016:3317, Chapter 683, Table 683-1.

Occult fractures. Occult fractures of the tibia are a relatively common cause of limping or refusal to bear weight in very young children. They can also occur in the femur and fibula. These fractures can be the result of very innocuous trauma, such as tripping while walking, stepping on a toy, or falling from a height. Frequently, the injury may not have been observed, and the child cannot convey to the parents what happened, confounding diagnosis.

The most common occult fracture in early childhood is the **"toddler's fracture"** of the tibia. This is an oblique fracture of the distal third of the tibia without an associated fibula fracture. It most commonly occurs in children younger than 4 years of age. Occult tibia fractures can also occur in the metaphyseal regions, usually distally, but only rarely in the diaphysis. Diaphyseal fractures are more commonly the result of child abuse.

Physical examination. Physical findings in a child with an occult fracture can be subtle. There is usually minimal, if any, soft tissue swelling. There is mild tenderness and perhaps increased warmth on palpation over the fracture. On occasion, the increased warmth may be indicative of osteomyelitis. Stress examination of the involved bone increases discomfort.

Radiographic evaluation. Anteroposterior and lateral radiographs should be obtained (Fig. 34.14). The characteristic finding of a toddler's fracture is a faint oblique fracture line crossing the distal third of the tibia. On occasion, oblique radiographs may be helpful in revealing the fracture. Frequently, initial radiographs reveal no abnormality. If plain radiographs are normal, the child has no systemic symptoms, and an occult fracture of the tibia is suspected, simple immobilization in a long-leg cast is indicated. Another set of radiographs in 1-2 weeks usually reveals the fracture and evidence of healing. If, however, the child has systemic symptoms, such as low-grade fever, and if osteomyelitis is thought to be present, evaluation including a complete blood count with differential, blood culture, C-reactive protein level, erythrocyte sedimentation rate, and an MRI should be obtained.

FIGURE 34.14 *A,* An anteroposterior radiograph of the lower leg of a 2-year-old girl who had been limping on the left lower leg for approximately 1 week. There was no observed trauma. No obvious abnormality is visible in this view. *B,* A lateral radiograph showing a faint oblique fracture line *(arrows).* This is characteristic of the "toddler's fracture." There is already early subperiosteal new bone or callus formation posteriorly.

Neoplasia. Benign and malignant neoplastic lesions that involve bone, cartilage, or soft tissue of the spine, pelvis, and lower extremities can manifest as a mass, can cause pain, and can produce an antalgic gait. Leukemia or metastatic neuroblastoma of the bone marrow may produce deep bone pain and limp without objective findings of swelling or tenderness on physical examination. Night pain is a common characteristic of both benign and malignant primary or metastatic tumors. Osseous lesions can usually be diagnosed on plain radiographs, whereas for those of cartilage or soft tissue, MRI or other special imaging studies may be required for diagnosis.

Benign neoplasms. The most common benign lesions that produce limping include a unicameral (simple) bone cyst and osteoid osteoma (Table 34.7). Other less common benign lesions that can produce pain and limping include eosinophilic granuloma of the bone, osteochondroma, and chondroblastoma. Chondroblastoma typically involves the epiphysis, especially of the proximal humerus.

In **unicameral bone cysts**, the symptoms are usually caused by a nondisplaced pathologic fracture. On occasion, a displaced fracture may occur. The most common location for a unicameral bone cyst is the proximal humerus, followed by the proximal femur. These can occur in any of the bones of the lower extremities, including the foot.

Osteoid osteomas have a highly vascularized nidus, which incites an intense, painful, inflammatory reaction that produces sclerosis of the surrounding bone. The pain is typically worse at night and is characteristically relieved by nonsteroidal antiinflammatory drugs (NSAIDs) and aspirin.

Radiographic evaluation. Most benign neoplasms are visible on anteroposterior and lateral radiographs of the symptomatic area. Characteristics of benign lesions include well-circumscribed lesions without periosteal new bone formation or soft tissue mass. If a lesion is suspected but not visible on plain radiographs, such as may occur in an osteoid osteoma, a technetium bone scan may be helpful. Further evaluation can be achieved with CT or MRI. Diagnosis is further aided by surgical biopsy, which may also allow for surgical treatment.

Malignant neoplasms. Leukemia is the most common childhood malignancy and is frequently accompanied by musculoskeletal complaints, such as limping, fever, bone pain, pallor, bruising, and weight loss (Fig. 34.15). Common malignancies involving the musculoskeletal system include osteogenic sarcoma, Ewing sarcoma, and intraspinal tumors, such as astrocytomas (Table 34.8). Intraspinal tumors tend to produce neurologic symptoms, such as muscle weakness, as the cause of limping. The other lesions may produce a mass, bone weakness, and possible pathologic fractures. Weight loss, fever, and pain are common associated complaints.

Physical examination. A careful musculoskeletal and neurologic examination is necessary for any child with a suspected neoplasm. In many cases, a mass, either in the involved bone or in adjacent soft tissues, may be palpable. These are typically tender and warm. These lesions are frequently adjacent to joints and may result in decreased range of motion. Neurologic evaluation may show evidence of muscle weakness or abnormal reflexes, suggestive of spinal cord or peripheral nerve involvement.

Radiographic evaluation. Anteroposterior and lateral radiographs of the involved area usually reveal the presence of a neoplasm.

TABLE 34.7 Benign Bone Tumors and Cysts

Disease	Characteristics	Radiographic Findings	Treatment	Prognosis
Osteochondroma (osteocartilaginous exostosis)	Common; distal metaphysis of the femur, proximal humerus, proximal tibia; painless, hard, nontender mass	Bony outgrowth; sessile or pedunculated	Excision, if symptomatic	Excellent; malignant transformation rare
Multiple hereditary osteochondromas	Osteochondroma of long bones; bone growth disturbances	As above	As above	Multiple lesions develop until skeletal maturity, after which no new lesions develop; malignant transformation rare
Osteoid osteoma	Pain relieved by aspirin; femur and tibia; found predominantly in boys	Dense sclerosis surrounds small radiolucent nidus <1 cm	As above	Excellent
Osteoblastoma (giant osteoid osteoma)	As above, but more destructive	Osteolytic component; size >1 cm	As above	Excellent
Enchondroma	Tubular bones of hands and feet; pathologic fractures, swollen bone; Ollier disease if multiple lesions are present	Radiolucent diaphyseal or metaphyseal lesion; may calcify	Excision or curettage	Excellent; malignant transformation rare
Nonossifying fibroma	Silent; rare pathologic fracture; late childhood, adolescence	Incidental radiographic finding; thin sclerotic border, radiolucent lesion	None or curettage with fractures	Excellent; heals spontaneously
Eosinophilic granuloma	Age 5–10 yr; skull, jaw, long bones; pathologic fracture; pain	Small, radiolucent without reactive bone; punched-out lytic lesion	Biopsy, excision rare; irradiation	Excellent; may heal spontaneously
Brodie abscess	Insidious local pain; limp; suspected as malignancy	Circumscribed metaphyseal osteomyelitis; lytic lesions with sclerotic rim	Biopsy; antibiotics	Excellent
Unicameral bone cyst (simple bone cyst)	Metaphysis of a long bone (femur, humerus); pain, pathologic fracture	Cyst in medullary canal, expands cortex; fluid-filled unilocular or multilocular cavity	Curettage; steroid injection into lesion	Excellent; some heal spontaneously
Aneurysmal bone cyst	As above; contains blood, fibrous tissue	Expands beyond metaphyseal cartilage	Curettage, bone graft	Excellent

Modified from Marcdante K, Kliegman R, eds. *Nelson Essentials of Pediatrics.* 7th ed. Philadelphia: Saunders; 2015.

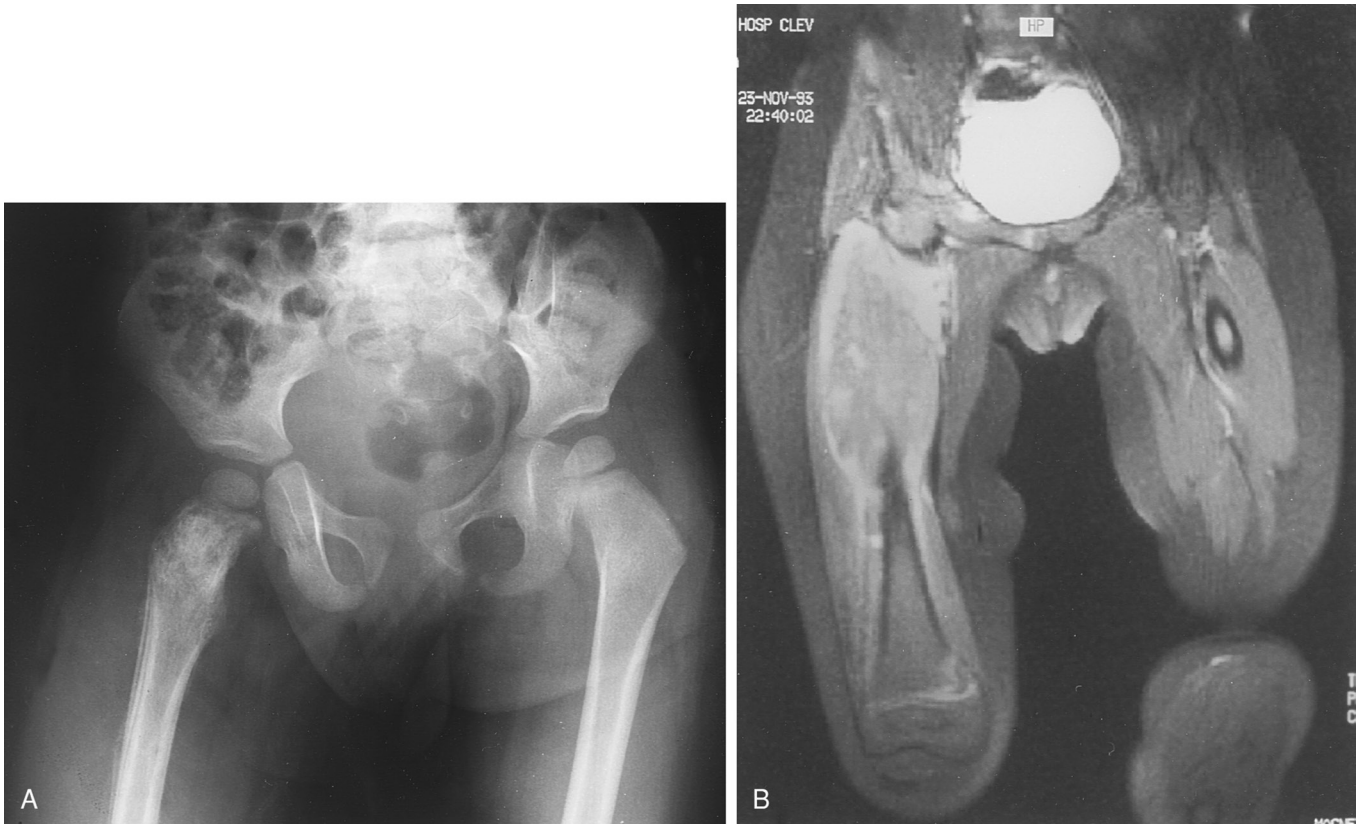

FIGURE 34.15 *A,* Anteroposterior pelvic radiograph of a 2-year-old girl who had been limping for 4 months. There is an extensive destructive lesion on the right proximal femur. *B,* A large soft tissue mass is demonstrated on magnetic resonance imaging scan. The preoperative diagnosis was Ewing sarcoma, but at biopsy the diagnosis was acute lymphoblastic leukemia.

TABLE 34.8 Comparison of Osteogenic and Ewing Sarcoma

	Osteogenic Sarcoma	Ewing Sarcoma
Age	Adolescence	Childhood and adolescence
Racial predilection	All races	Predominantly non-Hispanic white
Sex (M:F ratio)	1.5:1	1.5:1
Cell	Spindle cell, osteoid	Nonosseous, small round cell
Predisposing risk factors	Retinoblastoma Radiotherapy Alkylating agents	None
Site	Metaphysis, epiphysis; distal femur > proximal tibia > proximal humerus	Diaphysis, medullary cavity, cortical bone, soft tissue; femur > pelvis > tibia > humerus
Presentation	Local pain	Pain, fever, increased ESR, FUO, weight loss
Roentgenogram	Lytic, sclerotic Sunburst pattern	Mottled, lytic Onion-skin pattern
Differential diagnosis	Ewing sarcoma, osteomyelitis	Osteomyelitis, eosinophilic granuloma, lymphoma, neuroblastoma, rhabdomyosarcoma
Metastasis	Lung, bones Skip lesions in the same bone	Lung, bones
Treatment	Surgery, chemotherapy Limb salvage if tumor is resectable and the patient is near adult height	Surgery, radiotherapy Chemotherapy
Outcome	50–60% survival	60% survival without metastasis; 5–15% with metastasis, primary site dependent
Poor prognosis	Onset at age <10 yr, large tumor size (>15 cm), symptoms <2 mo, metastasis	Pelvis, soft tissue tumor, increased LDH, metastasis, increased circulating PMNs, decreased circulating lymphocytes

ESR, erythrocyte sedimentation rate; F, female; FUO, fever of unknown origin; LDH, lactate dehydrogenase; M, male; PMN, polymorphonuclear neutrophil.

Modified from Behrman RE, ed. *Nelson Textbook of Pediatrics.* 14th ed. Philadelphia: WB Saunders; 1992:1312.

Characteristics of a malignant osseous lesion include bone destruction, permeative or infiltrative appearance, periosteal new bone formation (Codman triangle), and an associated soft tissue mass (see Table 34.8). Radiographic abnormalities associated with acute leukemia include diffuse osteopenia, metaphyseal bands, periosteal new bone formation, geographic lytic lesions, sclerosis, and permeative distraction. Additional studies, such as a bone scan or MRI, may be helpful in localizing the lesion.

Infection

Septic arthritis and osteomyelitis. Bone and joint infections are common causes of limping in toddlers and children. When the infection is confined to the synovium of a joint, the condition is termed septic arthritis. If the primary focus of the infection is within bone, even if the joint is secondarily involved, the condition is termed osteomyelitis. Bacterial pathogens are the most frequent cause of osteoarticular infections in children, with *Staphylococcus aureus* being the most frequent etiology. In neonates, group B streptococcus and gram-negative bacteria are common. Beyond the neonatal period, *Kingella kingae* is the second most frequent cause in children under 5 years of age. In older children and adolescents with puncture wounds of the foot, *Pseudomonas aeruginosa, S. aureus,* and streptococci are commonly implicated. Sexually active adolescents may develop septic arthritis as a result of gonococcal infections. Patients with sickle cell anemia may develop osteomyelitis as a result of *Salmonella* species or pneumococcal infection.

Acute hematogenous osteomyelitis most commonly involves the femoral neck, the distal femoral metaphysis, and the proximal tibial metaphysis. Acute septic arthritis usually involves the hip, knee, or ankle. Children with these infections may be acutely ill; many may just have fever, limp, and localized pain. Treatment is with surgical drainage as needed and with prolonged antibiotics.

Subacute osteomyelitis, which has very distinct manifestations, occurs most commonly in the knee (Fig. 34.16). These children are usually afebrile and have night pain. Their hematologic studies yield normal findings. Radiographs show sclerotic metaphyseal lesions that occasionally cross the growth plate into the epiphysis. Culture specimens are positive only occasionally, and they typically show *S. aureus*.

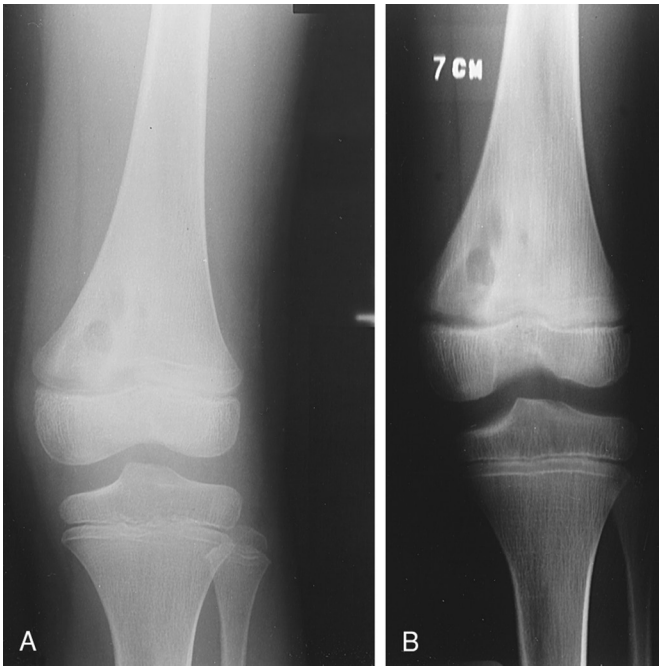

FIGURE 34.16 *A,* Anteroposterior radiograph of the distal femur in a 12-year-old girl with limping and nighttime knee pain for 6 months. There is a lucent lesion with surrounding sclerosis in the metaphysis. The lesion crosses the epiphysis; this is characteristic of a subacute osteomyelitis. *B,* Anteroposterior tomography clearly demonstrates the lucent nature of the lesion and its surrounding sclerosis.

Physical examination. Children with acute bone and joint infections may exhibit the clinical signs of bacteremia and infection, including elevations in temperature, white blood cell count, erythrocyte sedimentation rate, and C-reactive protein level. Some infants present only with **pseudoparalysis** of the affected limb. When the hip joint is involved, the child holds the hip in a position of flexion, abduction, and external rotation. This position unwinds the hip capsule and allows it to hold the greatest volume of intracapsular fluid. This initially decreases pressure, but as the pus continues to accumulate, even this position fails to relieve symptoms. A hip joint effusion is usually not palpable, but there may be overlying soft tissue swelling and tenderness.

Infections of peripheral joints, such as the knee, are more easily diagnosed. There is typically a joint effusion and perhaps soft tissue swelling, erythema, and increased warmth over the metaphysis if osteomyelitis is present. Osteomyelitis typically manifests with point tenderness over the involved site; with continued bone destruction and rupture of pus into the periosteum, tenderness becomes more diffuse. Infections can also occur about the ankle and foot. Infection of the foot is less common except as a sequela to puncture wounds through a tennis shoe, producing the classic *P. aeruginosa* or staphylococcal osteomyelitis-osteochondritis.

Radiographic evaluation. Plain radiographs are not helpful in the first 7-10 days of osteomyelitis, inasmuch as they are usually normal, but must be obtained in the assessment of the child. After 10-14 days of active infection, bone destruction or periosteal bone elevation is seen. MRI, or alternately bone scan, is both sensitive and specific for osteomyelitis and septic arthritis, even early in the course of the disease (Figs. 34.17 and 34.18).

If a septic process about the hip is suspected, an ultrasound study may be beneficial in demonstrating an effusion. If this is present, arthrocentesis or hip aspiration is necessary. The synovial fluid analysis should include a cell count, measurement of protein and glucose levels, Gram stain, cultures, and sensitivity studies. *K. kingae* polymerase chain reaction (PCR) testing should be performed, particularly in younger children. Infections of peripheral joints, such as the knee, are more readily diagnosed by arthrocentesis.

If an osteomyelitis of a metaphyseal region is suspected based on imaging studies, the subperiosteal space and bone may be directly aspirated with a large-bore needle. The material should be sampled for culture and sensitivity, as well as for *K. kingae* PCR testing in younger children. Despite these interventions, microbiologic studies may frequently fail to yield results.

Diskitis. Diskitis, inflammation of the vertebral disk that is often related to infection, may produce refusal to walk and/or limping either, via disk or bone inflammation, referred pain or intraspinal extension (see Chapter 35) (Fig. 34.19).

Rheumatic causes

Transient synovitis. Transient synovitis (also known as toxic synovitis) of the hip is the most common cause of limping in children. It can occur in all age groups, but the mean age at onset is 6 years; most patients are between 3 and 8 years of age. Hip transient synovitis is characterized by acute onset of monoarthritic hip pain, an associated limp, and mild restriction of hip motion, especially abduction and internal rotation. The pain is felt in the groin, anterior thigh, or knee. Any child with atraumatic anterior thigh or knee pain must be

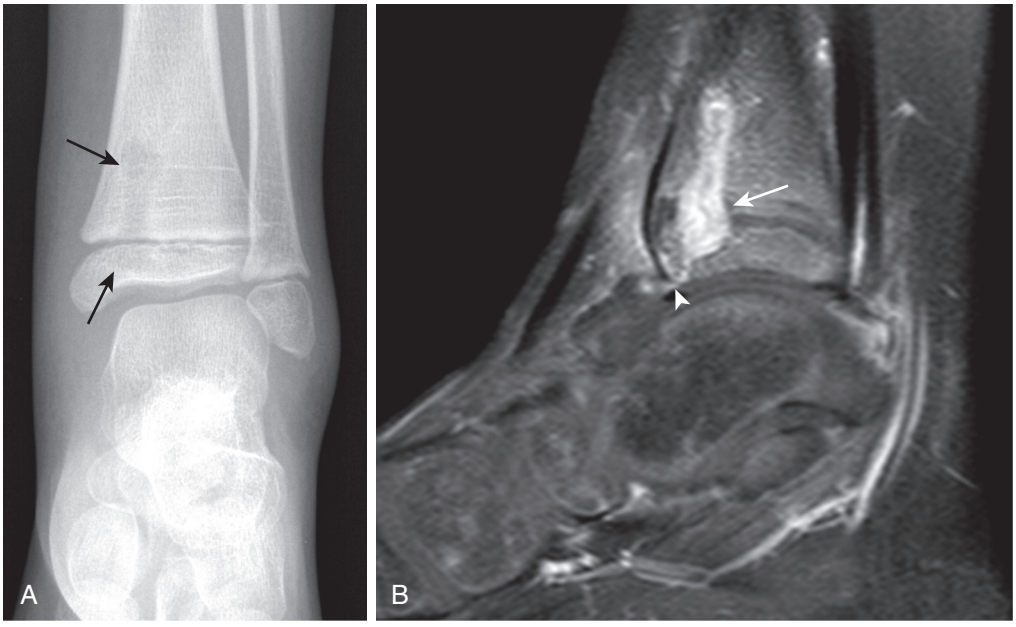

FIGURE 34.17 *A,* A frontal radiograph demonstrates a lytic lesion in the distal tibial metaphysis extending into the epiphysis *(arrows)*. *B,* A T1 weighted fat-saturated postgadolinium sagittal view demonstrates a thick, rim-enhancing lesion with a small amount of nonenhancing fluid consistent with early abscess formation with epiphyseal extension *(arrow)* and a small cloaca *(arrowhead)* extending to the tibiotalar joint. (From Kan JH, Azouz EM. Musculoskeletal infections. In: Coley BD, ed. *Caffey's Pediatric Diagnostic Imaging*. 12th ed. Vol II. Philadelphia: Elsevier; 2013:1472.)

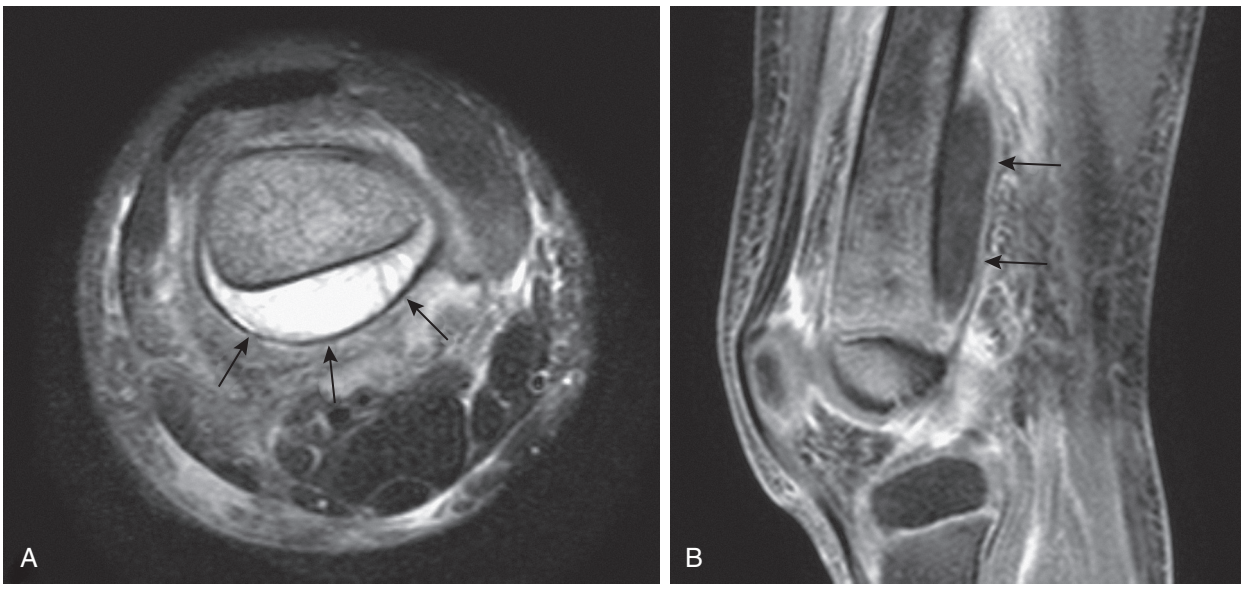

FIGURE 34.18 Acute osteomyelitis of the distal femur in a 5-year-old boy. *A*, T2 weighted fat-saturated axial magnetic resonance imaging (MRI) shows a large subperiosteal abscess *(arrows)* at the posterior aspect of the femur. Increased signal is seen within the bone, and there is adjacent soft tissue edema. *B*, T1 weighted fat-saturated postgadolinium sagittal MRI shows the longitudinal extent of the subperiosteal abscess with an enhancing wall *(arrows)*. (From Kan JH, Azouz EM. Musculoskeletal infections. In: Coley BD, ed. *Caffey's Pediatric Diagnostic Imaging*. 12th ed. Vol II. Philadelphia: Elsevier; 2013:1476.)

carefully evaluated for hip disease because these are the sites of referred pain. Septic arthritis and osteomyelitis must be excluded.

The cause of this disorder remains uncertain. Suspected causes include active or recent systemic viral infection, trauma, and allergic hypersensitivity. Approximately 70% of affected children have had a nonspecific viral upper respiratory infection 7-14 days before the onset of symptoms.

Physical examination. The patient is usually ambulatory, and the hip is not held in a position of flexion, abduction, or external rotation unless a significant effusion has developed. The child walks with an

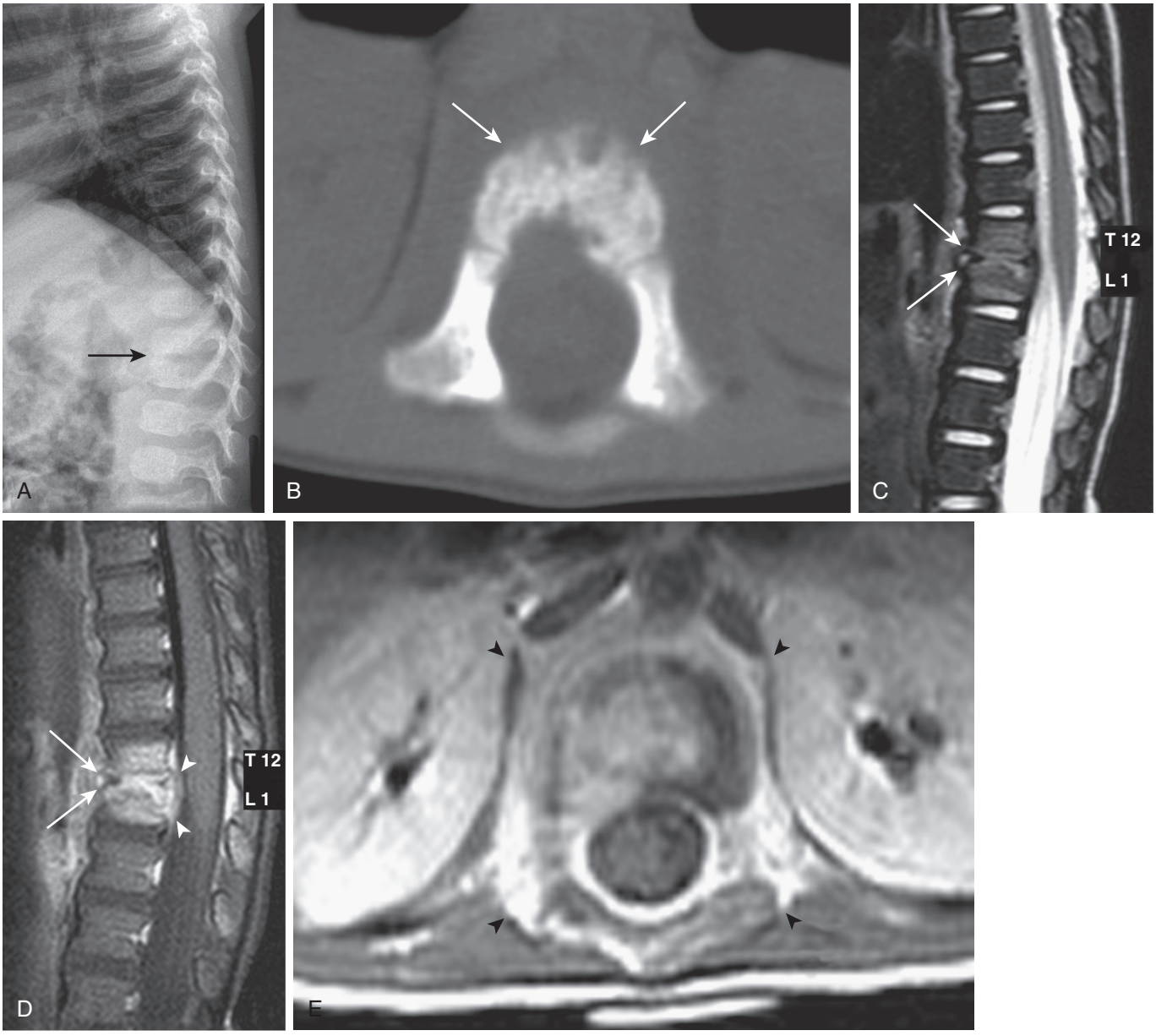

FIGURE 34.19 A 15-month-old girl with an abnormal gait and concern for an intraspinal mass had diskitis/osteomyelitis. Lateral spine radiographs demonstrate narrowing of the T12-L1 intervertebral disk space *(arrow in A)*. An axial bone window from a noncontrast computed tomography scan of the spine demonstrates irregularity to the vertebral end plates *(arrows in B)*. A sagittal T2 weighted image *(C)*, a sagittal fat-saturated T1 weighted postcontrast image *(D)*, and an axial T1 weighted postcontrast image *(E)* of the thoracolumbar junction demonstrate loss of height of the T12-L1 intervertebral disk space with adjacent T2 prolongation of the adjacent end plates *(arrows in C)*, with corresponding abnormal enhancement in the same regions *(arrows in D)*, and surrounding masslike soft tissue enhancement *(arrowheads in E)*. Note the thickening/elevation and enhancement of the posterior longitudinal ligament *(arrowheads in D)*. (From Pollock AN, Henesch SM. Infections of the spine and spinal cord. In: Coley BD, ed. *Caffey's Pediatric Diagnostic Imaging*. 12th ed. Vol I. Philadelphia: Elsevier; 2013:465.)

antalgic gait on the involved side and is usually afebrile. Laboratory findings are usually within normal limits, but occasionally a minimal elevation of the white blood cell count or erythrocyte sedimentation rate may be seen.

Radiographic evaluation. Anteroposterior and frog-leg lateral radiographs of the pelvis are obtained to rule out the presence of other lesions. The radiographs in transient synovitis are normal. On occasion, ultrasonography of the hip may be useful in demonstrating a small joint effusion. MRI is helpful in identifying septic joints or other causes of pain when there is doubt regarding the diagnosis. Bone scans as well may be helpful in difficult or unusual cases; in synovitis, these results are always normal. When the diagnosis of transient synovitis is in doubt, hip arthrocentesis may be necessary. The fluid that is aspirated shows a low white blood cell count (typically well under 25,000 cells/μL), and the cultures are negative.

Trendelenburg Gait

Developmental anomalies

Developmental dysplasia of the hip. Developmental dysplasia of the hip (DDH) refers to the condition of increased laxity of the hip joint and encompasses the following classifications: (1) acetabular dysplasia, (2) hip subluxation, and (3) hip dislocation. Developmental dysplasia of the hip is considered either typical, in which no underlying genetic or syndromic association is identified, or teratologic. Early identification and management improve the functional outcome of surgical repairs. If not identified and appropriately treated, DDH will present with limping, toe-walking, or both. When the problem occurs unilaterally, the child walks with a mild Trendelenburg gait or demonstrates toe-walking. With bilateral involvement, the child stands with an increased lumbar lordosis and has a waddling gait. There is functional impairment resulting from a lack of stability and associated muscle weakness, particularly in the hip abductors.

Physical examination. The most common physical finding in the older child with a developmentally dislocated hip is limited hip abduction on the involved side. There may be a mild hip flexion contracture and apparent shortening of the extremity. The greater trochanter lies above a line between the anterior superior iliac spine and the ischial tuberosity (Nélaton line). In bilateral dislocations, the physical findings are more symmetric but there is still limitation of hip abduction. Positive Trendelenburg signs are present on the involved sides. The normal response to a Trendelenburg test occurs when the patient stands on the uninvolved leg and the abductor muscles are able to maintain balance by elevating the contralateral pelvis. A positive Trendelenburg sign, resulting from weakness, is demonstrated when the abductor muscles are unable to maintain pelvic balance and the patient compensates by leaning to the affected side (see Fig. 34.10).

Radiographic evaluation. The diagnosis can be made from routine anteroposterior and frog-leg lateral radiographs of the pelvis (Fig. 34.20). Specialized studies, such as MRI and CT, are usually not necessary. Ultrasound study is not usually necessary in the older child because the CFE is ossified.

FIGURE 34.20 An anteroposterior radiograph of the pelvis of an 18-month-old girl demonstrating a developmental dislocation of the left hip. The acetabulum is severely dysplastic, there is delayed ossification in the capital femoral epiphysis compared to the normal right hip, and the femoral head is displaced laterally and superiorly.

Lower extremity length discrepancy. Lower extremity length discrepancy in older children and adolescents has been discussed earlier in this chapter.

Neuromuscular Origin

Cerebral palsy. Children with spastic hemiplegia or diplegia may have an associated painless limp caused by muscle spasticity and concomitant weakness of the antagonist muscles. The history should focus on risk factors for cerebral palsy, prematurity, and other congenital anomalies external to the central nervous system, followed by a physical examination, with particular attention to the neurologic system. The neurologic examination reveals evidence of increased muscle tone, spasticity, hyperactive deep tendon reflexes, and pathologic reflexes, such as Babinski signs.

SUMMARY AND RED FLAGS

Conditions associated with limp must be divided into acute, painful lesions and chronic, painless lesions; on occasion, presentations may be mixed. Infection and trauma must be considered emergencies, as should conditions that are joint or limb threatening, such as septic arthritis and osteomyelitis of the hip, avascular necrosis, or SCFE. In addition, signs of spinal cord involvement (see Chapter 35) suggest acute processes that warrant immediate attention to prevent permanent paralysis.

Red flags include acute hip pain, fever with limp, neurologic manifestations (including bowel and bladder dysfunction), point tenderness, the presence of a mass, night pain, and signs of weight loss or hematologic abnormalities such as pallor or bruising.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

General

Badii M, Wade AN, Collins DR, et al. Comparison of lifts versus tape measure in determining leg length discrepancy. *J Rheumatol*. 2014;41(8):1689-1694.

Escott BG, Ravi B, Weathermon AC, et al. EOS low-dose radiography: a reliable and accurate upright assessment of lower-limb lengths. *J Bone Joint Surg Am*. 2013;95(23):e1831-e1837.

Sutherland DH, Olshen R, Cooper L, et al. The development of gait. *J Bone Joint Surg Am*. 1980;62(3):336-353.

Rotational Abnormalities: Femoral/Tibial Torsion

Bruce RW Jr. Torsional and angular deformities. *Pediatr Clin North Am*. 1996;43(4):867-881.

Dodgin DA, DeSwart RJ, Stefko RM, et al. Distal tibial/fibular derotation osteotomy for correction of tibial torsion: review of technique and results in 63 cases. *J Pediatr Orthop*. 1998;18(1):95-101.

Driano A, Staheli L, Staheli LT. Psychosocial development and corrective shoe wear use in childhood. *J Pediatr Orthop*. 1998;18(3):346-349.

Erkocak OF, Altan E, Altintas M, et al. Lower extremity rotational deformities and patellofemoral alignment parameters in patients with anterior knee pain. *Knee Surg Sports Traumatol Arthrosc*. 2016;24:3011-3020.

Karol LA. Rotational deformities in the lower extremities. *Curr Opin Pediatr*. 1997;9(1):77-80.

Koenig JK, Pring ME, Dwek JR. MR evaluation of femoral neck version and tibial torsion. *Pediatr Radiol*. 2012;42(1):113-115.

Lincoln TL, Suen PW. Common rotational variations in children. *J Am Acad Orthop Surg*. 2003;11(5):312-320.

Mooney JF 3rd. Lower extremity rotational and angular issues in children. *Pediatr Clin North Am*. 2014;61(6):1175-1183.

Ruwe PA, Gage JR, Ozonoff MB, et al. Clinical determination of femoral anteversion: a comparison of established techniques. *J Bone Joint Surg Am*. 1992;74(6):820-830.

Strecker W, Keppler P, Gebhard F, et al. Length and torsion of the lower limb. *J Bone Joint Surg Br*. 1997;79(6):1019-1023.

Rotational Abnormalities: Metatarsus Adductus

Asirvatham R, Stevens PM. Idiopathic forefoot-adduction deformity: medial capsulotomy and abductor hallucis lengthening for resistant and severe deformities. *J Pediatr Orthop*. 1997;17(4):496-500.

Bleck EE. Metatarsus adductus: classification and relationship to outcomes of treatment. *J Pediatr Orthop*. 1983;3(1):2-9.

Farsetti P, Weinstein SL, Ponseti IV. The long-term functional and radiographic outcomes of untreated and non-operatively treated metatarsus adductus. *J Bone Joint Surg Am*. 1994;76(2):257-265.

Williams CM, James AM, Tran T. Metatarsus adductus: development of a non-surgical treatment pathway. *J Paediatr Child Health*. 2013;49(9):E428-E433.

Rotational Abnormalities: Talipes Equinovarus (Clubfoot)

Alkjaer T, Pedersen EN, Simonsen EB. Evaluation of the walking pattern in clubfoot patients who received early intensive treatment. *J Pediatr Orthop*. 2000;20(5):642-647.

Cuevas de Alba C, Guille JT, Bowen JR, et al. Computed tomography for femoral and tibial torsion in children with clubfoot. *Clin Orthop*. 1998;353:203-209.

Ezra E, Hayek S, Gilai AN, et al. Tibialis anterior tendon transfer for residual dynamic supination deformity in treated clubfeet. *J Pediatr Orthop B*. 2000;9(3):207-211.

Jeans KA, Erdman AL, Karol LA. Plantar pressures after nonoperative treatment for clubfoot: intermediate follow-up at age 5 years. *J Pediatr Orthop*. 2015;Jul 2[Epub ahead of print].

Karol LA, Concha MC, Johnston CE. Gait analysis and muscle strength in children with surgically treated clubfeet. *J Pediatr Orthop*. 1997;17(6):790-795.

Kuo KN, Hennigan SP, Hastings ME. Anterior tibial tendon transfer in residual dynamic clubfoot deformity. *J Pediatr Orthop*. 2001;21(1):35-41.

Macnicol MF, Nadeem RD, Forness M. Functional results of surgical treatment in congenital talipes equinovarus (clubfoot): A comparison of outcome measurements. *J Pediatr Orthop B*. 2000;9(4):285-292.

Roye BD, Vitale MG, Gelijins AC, et al. Patient-based outcomes after clubfoot surgery. *J Pediatr Orthop*. 2001;21(1):42-49.

Rotational Abnormalities: Calcaneovalgus Foot

Mosca VS. Other conditions of the foot. In: Morrissy RT, Weinstein SL, eds. *Pediatric Orthopaedics*. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2001:1178.

Rotational Abnormalities: Hypermobile Pes Planus

Akrali O, Tiner M, Ozaksoy D. Effects of lower extremity rotation on prognosis of flexible flatfoot in children. *Foot Ankle Int*. 2000;21(9):772-774.

Staheli LT, Chew DE, Corbet M. The longitudinal arch: a survey of 882 feet in normal children and adults. *J Bone Joint Surg Am*. 1987;69(3):426-428.

Sullivan JA. Pediatric flatfoot: evaluation and management. *J Am Acad Orthop Surg*. 1999;7(1):44-53.

Wenger DR, Mauldin D, Speck G, et al. Corrective shoes and inserts as treatment for a flexible flatfoot in infants and children. *J Bone Joint Surg Am*. 1989;71(6):800-810.

Equinus Gait (Toe-Walking)/Neuromuscular Disorders

Kelly IP, Jenkinson A, Stephens M, et al. The kinematic patterns of toe-walkers. *J Pediatr Orthop*. 1997;17(4):478-480.

Rose J, Martin JG, Torburn L, et al. Electromyographic differentiation of diplegic cerebral palsy from idiopathic toe-walking: involuntary coactivation of the quadriceps and gastrocnemius. *J Pediatr Orthop*. 1999;19(5):677-682.

Congenital Achilles Tendon Contracture (Idiopathic Toe-Walking)

Eastwood DM, Dennett X, Shield LK, et al. Muscle abnormalities in idiopathic toe-walkers. *J Pediatr Orthop B*. 1997;6(3):215-218.

Eastwood DM, Menelaus MB, Dickens DR, et al. Idiopathic toe-walking: does treatment alter the natural history? *J Pediatr Orthop B*. 2000;9(1):47-49.

Montgomery P, Gauger J. Sensory dysfunction in children who toe walk. *Phys Ther*. 1978;58(10):1195-1204.

Oetgen ME, Peden S. Idiopathic toe walking. *J Am Acad Orthop Surg*. 2012;20(5):292-300.

Sala DA, Shulman LH, Kennedy RF, et al. Idiopathic toe-walking: a review. *Dev Med Child Neurol*. 1999;41(12):846-848.

Shulman LH, Sala DA, Chu ML, et al. Developmental implications of idiopathic toe-walking. *J Pediatr*. 1997;130(4):541-546.

Stricker SJ, Angulo JC. Idiopathic toe-walking: a comparison of treatment methods. *J Pediatr Orthop*. 1998;18(3):289-293.

Congenital Achilles Tendon Contracture (Idiopathic Toe-Walking): Habitual Toe-Walking

Griffin PP, Wheelhouse WW, Shiavi R, et al. Habitual toe-walkers: a clinical and electromyographic gait analysis. *J Bone Joint Surg Am*. 1977;59(1):97-101.

Congenital Achilles Tendon Contracture (Idiopathic Toe-Walking): Lower Extremity Length Discrepancy

Ballock RT, Wiesner GL, Myers MT, et al. Hemihypertrophy. Concepts and controversies. *J Bone Joint Surg Am*. 1997;79(11):1731-1738.

Dahl MT. Limb length discrepancy. *Pediatr Clin North Am*. 1996;43(4):849-866.

Davidson RS. Leg-length discrepancy. In: Kliegman R, et al., eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Saunders; 2016:3264-3268.

Herzenberg JE, Paley D. Leg lengthening in children. *Curr Opin Pediatr*. 1998;10(1):95-97.

Song KM, Halliday SE, Little DG. The effect of limb-length discrepancy on gait. *J Bone Joint Surg Am*. 1997;79(11):1690-1698.

Stanitski DF. Limb-length inequality: assessment and treatment options. *J Am Acad Orthop Surg*. 1999;7(3):143-153.

Limping/General

Barkin RM, Barkin SZ, Barkin AZ. The limping child. *J Emerg Med*. 2000;18(3):331-339.

Connolly LP, Treves ST. Assessing the limping child with skeletal scintigraphy. *J Nucl Med*. 1998;39(6):1056-1061.

Fischer SU, Beattie TF. The limping child: epidemiology, assessment and outcome. *J Bone Joint Surg Br*. 1999;81(6):1029-1034.

Leet AI, Skaggs DL. Evaluation of the acutely limping child. *Am Fam Physician*. 2000;61(4):1011-1018.

Myers MT, Thompson GH. Imaging the child with a limp. *Pediatr Clin North Am*. 1997;44(3):637-658.

Tarsal Coalition

Blakemore LC, Cooperman DR, Thompson GH. The rigid flatfoot. Tarsal coalitions. *Clin Podiatr Med Surg*. 2000;17:531-555.

Bohne WH. Tarsal coalition. *Curr Opin Pediatr*. 2001;13(1):29-35.

Guignand D, Journeau P, Mainard-Simard L, et al. Child calcaneonavicular coalitions: MRI diagnostic value in a 19-case series. *Orthop Traumatol Surg Res*. 2011;97(1):67-72.

Vincent KA. Tarsal coalition and painful flatfoot. *J Am Acad Orthop Surg*. 1998;6(5):274-281.

Legg–Calvé–Perthes Disease

Guille JT, Lipton GE, Szoke G, et al. Legg-Calvé-Perthes disease in girls. A comparison of the results seen in boys. *J Bone Joint Surg Am*. 1998;80(9):1256-1263.

Herring JA. The treatment of Legg-Calvé-Perthes disease. A critical review of the literature. *J Bone Joint Surg Am*. 1994;76(3):448-458.

Herring JA, Neustadt JB, Williams JJ, et al. The lateral pillar classification of Legg-Calvé-Perthes disease. *J Pediatr Orthop*. 1992;12(2):143-150.

Loder RT, Schwartz EM, Hensinger RN. Behavioral characteristics of children with Legg-Calvé-Perthes disease. *J Pediatr Orthop*. 1993;13(5):598-601.

Martinez AG, Weinstein SL, Dietz FR. The weight-bearing abduction brace for the treatment of Legg-Perthes disease. *J Bone Joint Surg Am*. 1992;74(1):12-21.

Meehan PL, Angel D, Nelson JM. The Scottish Rite abduction orthosis for the treatment of Legg-Perthes disease. *J Bone Joint Surg Am*. 1992;74(1):1-12.

Noonan KJ, Price CT, Kupiszewski SJ, et al. Results of femoral varus osteotomy in children older than nine years with Perthes' disease. *J Pediatr Orthop*. 2001;21:198-204.

Salter RB, Thompson GH. Legg-Calvé-Perthes disease: the prognostic significance of the subchondral fracture and a two-group classification of the femoral head involvement. *J Bone Joint Surg Am*. 1984;66(4):479-499.

Thompson GH, Price CT, Roy D, et al. Legg-Calvé-Perthes disease: current concepts. *Instr Course Lect*. 2002;51:367-384.

Wall EJ. Legg-Calvé-Perthes disease. *Curr Opin Pediatr*. 1999;11(1):76-79.

Weinstein SL. Natural history and treatment outcomes of childhood hip disorders. *Clin Orthop*. 1997;344:222-242.

Slipped Capital Femoral Epiphysis

Carney BT, Weinstein SL, Noble J. Long-term follow-up of slipped capital femoral epiphysis. *J Bone Joint Surg Am*. 1991;73(5):667-674.

Givon U, Bowen JR. Chronic slipped capital femoral epiphysis: treatment by pinning in situ. *J Pediatr Orthop B*. 1999;8(3):216-222.

Kennedy JG, Hresko MT, Kasser JR, et al. Osteonecrosis of the femoral head associated with slipped capital femoral epiphysis. *J Pediatr Orthop*. 2001;21(2):189-193.

Loder RT, Richards BS, Shapiro PS, et al. Acute slipped capital femoral epiphysis: the importance of physeal stability. *J Bone Joint Surg Am*. 1993;75(8):1134-1140.

Matava MJ, Patton CM, Luhmann S, et al. Knee pain as the initial symptom of slipped capital femoral epiphysis: an analysis of initial presentation and treatment. *J Pediatr Orthop*. 1999;19(4):455-460.

Reynolds RA. Diagnosis and treatment of slipped capital femoral epiphysis. *Curr Opin Pediatr*. 1999;11(1):80-83.

Weinstein SL. Natural history and treatment outcomes of childhood hip disorders. *Clin Orthop*. 1997;344:222-242.

Wells D, King JD, Roe TF, et al. Review of slipped capital femoral epiphysis associated with endocrine disease. *J Pediatr Orthop*. 1993;13(5):610-614.

Sprains/Strains

Saperstein AL, Nicholas SJ. Pediatric and adolescent sports medicine. *Pediatr Clin North Am*. 1996;43(5):1013-1034.

Occult Fractures

Aronson J, Garvin K, Seibert J, et al. Efficiency of the bone scan for occult limping toddlers. *J Pediatr Orthop*. 1992;12(1):38-44.

Mellick LB, Reesor K. Spiral tibial fractures of children: a commonly accidental spiral long bone fracture. *Am J Emerg Med*. 1990;8(3):234-237.

Tenenbien M, Reed MH, Black GB. The toddler's fracture revisited. *Am J Emerg Med*. 1990;8(3):208-211.

Neoplasia

Copley L, Dormans JP. Benign pediatric bone tumors. *Pediatr Clin North Am*. 1996;43(4):949-966.

Himelstein BP, Dormans JP. Malignant bone tumors of childhood. *Pediatr Clin North Am*. 1996;43(4):967-984.

Tuten HR, Gabos PG, Keimar SJ, et al. The limping child: a manifestation of acute leukemia. *J Pediatr Orthop*. 1998;18(5):625-629.

Septic Arthritis/Osteomyelitis

Blyth MJ, Kincaid R, Craigen MA, et al. The changing epidemiology of acute and subacute haematogenous osteomyelitis in children. *J Bone Joint Surg Br*. 2001;83(1):99-102.

Kim HK, Alman B, Cole WB. A shortened course of parenteral antibiotic therapy in the management of acute septic arthritis of the hip. *J Pediatr Orthop*. 2000;20(1):44-47.

Luhmann JD, Luhmann SJ. Etiology of septic arthritis in children: an update for the 1990s. *Pediatr Emerg Care*. 1999;15(1):40-42.

Lyon RM, Evanich JD. Culture-negative septic arthritis in children. *J Pediatr Orthop*. 1999;19(5):655-659.

Newton PO, Ballock RT, Bradley JS. Oral antibiotic therapy of bacterial arthritis. *Pediatr Infect Dis J*. 1999;18(12):1102-1103.

Oudjhane K, Ozouz EM. Imaging of osteomyelitis in children. *Radiol Clin North Am*. 2001;39(2):251-266.

Pöyhiä T, Azouz EM. MR imaging evaluation of subacute and chronic bone abscesses in children. *Pediatr Radiol*. 2000;30(11):763-768.

Rasool MN. Primary subacute haematogenous osteomyelitis in children. *J Bone Joint Surg Br*. 2001;83(1):93-98.

Sonnan GM, Henry NK. Pediatric bone and joint infections. Diagnosis and antimicrobial management. *Pediatr Clin North Am*. 1996;43(4):933-947.

Waagner DC. Musculoskeletal infections in adolescents. *Adolesc Med*. 2000;11(2):375-400.

Wall EJ. Childhood osteomyelitis and septic arthritis. *Curr Opin Pediatr*. 1998;10(1):73-76.

Wang MN, Chen WM, Leck S, et al. Tuberculosis osteomyelitis in young children. *J Pediatr Orthop*. 1999;19(2):151-155.

Transient Synovitis

Do TT. Transient synovitis as a cause of painful limps in children. *Curr Opin Pediatr*. 2000;12(1):48-51.

Kocher MS, Zurakowski D, Kasser JR. Differentiating between septic arthritis and transient synovitis of the hip in children: an evidence-based clinical prediction algorithm. *J Bone Joint Surg Am*. 1999;81(12):1662-1670.

McCarthy JJ, Noonan KJ. Toxic synovitis. *Skeletal Radiol*. 2008;37(11):963-965.

Developmental Dysplasia of the Hip

DeKleuver M, Kooijman MA, Pavlov PW, et al. Triple osteotomy of the pelvis for acetabular dysplasia: results at 8 to 15 years. *J Bone Joint Surg Br*. 1997;79(2):225-229.

Kerry RM, Simonds GW. Long-term results of the late non-operative reduction of developmental dysplasia of the hip. *J Bone Joint Surg Br*. 1998;80(1):78-82.

Kim HT, Kim JI, Yoo CI. Diagnosing childhood acetabular dysplasia using the lateral margin of the sourcil. *J Pediatr Orthop*. 2000;20(6):709-717.

Kim HT, Wenger DR. The morphology of residual acetabular deficiency in childhood hip dysplasia: three-dimensional computed tomographic analysis. *J Pediatr Orthop*. 1997;17(5):637-647.

LeBa TB, Carmichael KD, Patton AG. Ultrasound for infants at risk for developmental dysplasia of the hip. *Orthopedics*. 2015;38(8):e722-e726.

Lin CJ, Romanus B, Sutherland DH, et al. Three-dimensional characteristic of cartilaginous and bony components of dysplastic hips in children: three-dimensional computed tomography quantitative analysis. *J Pediatr Orthop*. 1997;17(2):152-157.

Olney B, Latz K, Asher M. Treatment of hip dysplasia in older children with a combined one-stage procedure. *Clin Orthop*. 1998;347:215-223.

Vedantam R, Capelli AM, Schoenecker PL. Pemberton osteotomy for the treatment of developmental dysplasia of the hip in older children. *J Pediatr Orthop*. 1998;18(2):254-258.

Back Pain in Children and Adolescents

John G. Thometz

Persistant back pain in children necessitates a thorough evaluation to rule out disorders that can result in significant morbidity, such as infection or tumor. Back pain in younger children is unusual and suggests significant diseases. The prevalence of complaints of low back pain increases with age, and is as prevalent as 30% by the teenage years. Back pain is frequently mild and often resolves spontaneously in adolescents. The complaints are often related to overactivity in sports, work, or a specific traumatic event. Back pain is not a disease but a symptom and is often associated in adolescents with headaches, emotional problems, daytime tiredness, and behavioral disorders. Activity modification and rehabilitation or exercises for the spine are sufficient to prevent recurrent episodes of back pain. *Severe or persistent back pain necessitates a thorough history, physical examination, and appropriate imaging studies to evaluate the child for potentially serious pathologic processes.*

EVALUATION OF THE PEDIATRIC SPINE

Examination of the spine should be part of the routine physical examination in the healthy child and adolescent. Even in patients who present with back pain as a chief complaint, the most important diagnostic steps are a detailed history and a thorough and systematic examination (Table 35.1).

When findings on screening examinations are abnormal or when a patient presents with complaints of back pain, a more detailed examination is required. The spinal vertebral column, spinal cord, and spinal nerves are intimately related, and disorders affecting any 1 of these elements produce symptoms and signs in the others. Detailed examination of strength in the muscles of the spine and lower extremities (Fig. 35.1), sensation (Fig. 35.2), abdominal and lower extremity reflexes, anal sphincter tone, and perianal sensation should be performed when the primary examination suggests involvement of the neural structures that pass through the spinal column. Persistent or severe back pain is uncommon in young children and may be associated with serious underlying disease.

NORMAL GROWTH AND DEVELOPMENT OF THE SPINE

Vertebral growth occurs in an orderly manner throughout childhood and adolescence. About 50% of vertebral column height is present by the age of 2 years. Acceleration of vertebral growth occurs during the adolescent growth spurt but contributes less to total height than does lower limb growth; the sitting heights of siblings in early and late adolescence are often remarkably similar. Spinal growth slows at menarche in girls and at the time of voice change in boys and is usually complete 2-3 years later. Developmental abnormalities of the column, such as idiopathic scoliosis, most commonly first appear just before the growth spurt. Alterations in spinal configuration caused by congenital deformities of vertebral segments change most rapidly during periods of rapid spinal growth: before the age of 2 and at the time of the adolescent growth spurt.

There is a strong association of genitourinary tract, cardiac, and neural abnormalities in patients with congenital abnormalities of the spine. Warning signs in patients with congenital spine deformities include leg length inequality, foot size asymmetry, high foot arches, hairy patches or hemangiomas or a mass over the spine, sacral dimpling, enuresis, toe-walking, asymmetry or abnormality in the lower extremity deep tendon reflexes, and lower extremity weakness.

NORMAL SPINAL ALIGNMENT

The normal trunk is symmetric when viewed from the front or the back (Fig. 35.3). The shoulders and pelvis are parallel to each other and to the ground. The distance between the right and left elbows and the sides of the trunk is equal. When the trunk is viewed from the side, a series of curves is present (see Fig. 35.3). A convex anterior lordotic curve is present in the cervical region. The spine is concave anteriorly in a kyphotic pattern in the thoracic region. The normal lumbar spine is lordotic, and the sacrum and coccygeal regions are kyphotic. Normal adult sagittal alignment develops gradually; children younger than 10 years typically have less cervical lordosis and more lumbar lordosis than adults. Healthy children are often quite swaybacked. Injuries, infections, tumors, inflammation, and developmental abnormalities of the spine often produce alterations in these expected contours. Range of motion is demonstrated in Fig. 35.4.

BACK PAIN OF BRIEF DURATION

Few children younger than 10 years sustain significant injuries of the spinal column or associated musculature in routine play and organized sports activities; extremity injuries are far more common. When the trunk is involved, contusions and abrasions are much more common than ligament sprains and muscle strains.

When a child presents with back pain of brief duration after a play- or sports-related injury, a careful examination should be performed. If there are no other associated injuries and the screening examination shows no alterations in trunk configuration or lower extremity strength or sensation (see Figs. 35.1 and 35.2), no further work-up is necessary. A brief period of rest for 1-2 days, followed by gradual resumption of activities, is appropriate treatment. Routine imaging is not necessary when the duration of symptoms is short and the physical examination findings are normal. Signs of systemic illness (fever, weight loss) or neurologic deficits warrant an immediate evaluation.

Acute back injuries occur more frequently in adolescence, as the sizes of participants and potential forces generated in recreational

(See *Nelson Textbook of Pediatrics,* p. 3245.)

TABLE 35.1 Guidelines for Primary Examination of the Back

History

Is there a history of back pain? If so, what is the:
- Frequency?
- Duration?
- Relationship to activity?

Antecedent trauma?
Is there associated pain in the legs?
Is there incontinence or enuresis?
Is walking painful?
Have there been systemic signs of chronic illness?
Is there a family history of deformity?
Is there a family history of disk disease?

Physical Examination

General Appearance

Are the right and left sides of the trunk symmetric?
Are there hairy patches, nevi, sinuses, or dimpling over the midline of the spine?
Are the pelvis and shoulders level?
Is there normal kyphosis and lordosis?
On forward bending, is a rib hump present?
Is there localized tenderness?
Is there muscle atrophy?

Motion

Can the patient easily bend forward and touch his or her toes?
Is normal hamstring flexibility present?
Is the gait normal?

Lower Extremities

Are leg lengths equal?
Is strength normal in the major motor groups of the lower limbs?
Is sensation normal in the lower limbs?
Are reflexes normal at the knees and ankles?
Are pathologic reflexes present?
What is the response to straight leg *and* cross straight leg raising maneuvers?

activities increase. If there are no other associated injuries and the screening examination findings are normal, no further imaging work-up is necessary. A period of rest followed by gradual resumption of activities is appropriate treatment. The importance of a comprehensive and balanced conditioning exercise program should be stressed to young athletes. Most sports-related injuries can be prevented by preparticipation conditioning, appropriate warm-up, careful supervision, and resting when fatigued.

Trauma sufficient to cause spine fractures may occur as a result of motor vehicle or bicycle crashes, falls, and diving and gymnastic injuries. The frequency and severity of spine trauma rises in later adolescence as exposure to potentially violent forces in sports and motor vehicles increases. In such cases, there is a clear relationship between the crash and the onset of symptoms. Injury to the spinal column should be suspected in all individuals whose level of consciousness is impaired after an accident, regardless of the presence or absence of symptoms.

Children with suspected acute spinal injury should be immobilized on backboards designed for children until definitive imaging studies can be performed and interpreted. Immobilization of the child's cervical spine on a solid backboard should be avoided. The child's occiput projects farther posteriorly than that of the adult, and flexion of the neck occurs if the child's neck is immobilized on a standard backboard. Spinal immobilization boards for children are readily available and have a cut-out section to accommodate the occiput. When such boards are not available, a blanket or firm mattress should be interposed between the trunk and the backboard to prevent neck flexion.

PERSISTENT BACK PAIN

Persistent or severe back pain is uncommon in young children but is more common in adolescents. Mechanical low back pain is said to be present in the patient with no definable pathology on physical exam or imaging studies. This is the case in over 50% of patients presenting with low back pain. The implications of severe or persistent back pain are more serious in younger patients than in adolescents. Persistent back pain in young children is usually not the result of a congenital spinal deformity or developmental disorders of the spine. As a child enters and passes through the adolescent growth spurt, back pain may

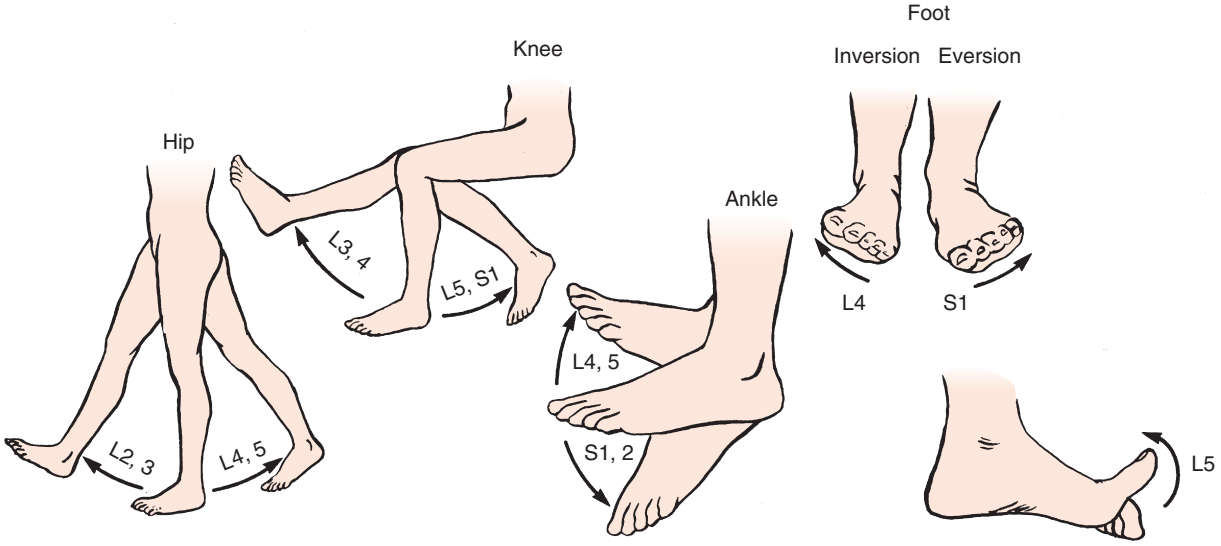

FIGURE 35.1 Motor control of the lower extremity. (From Reilly BM. *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991:926.)

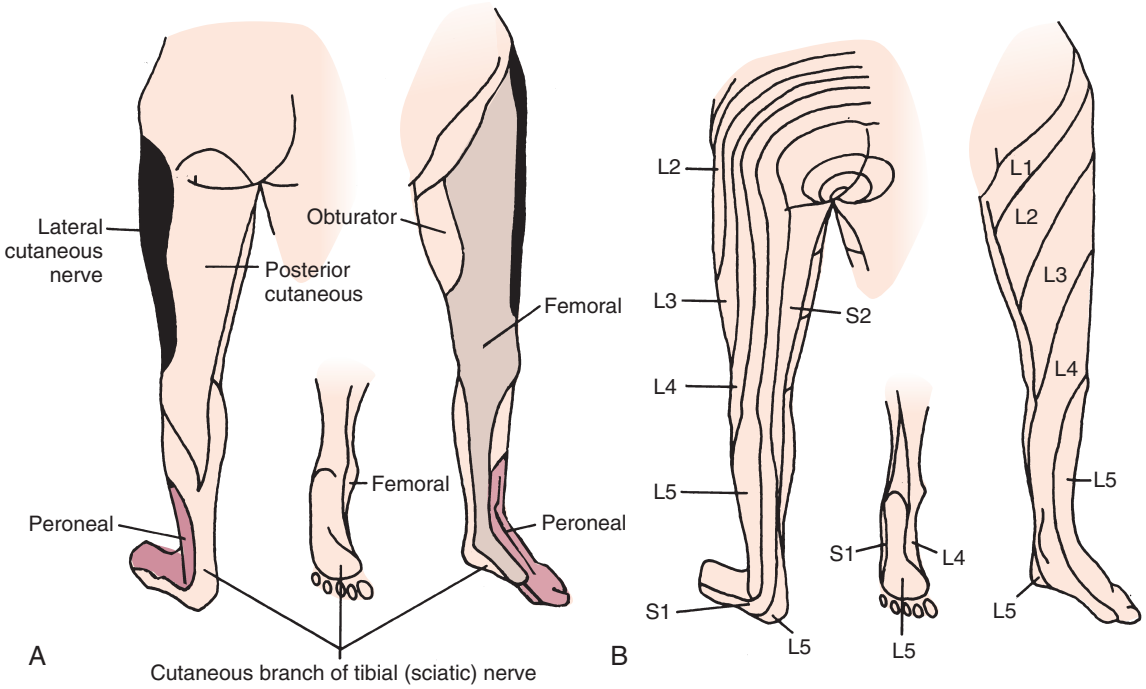

FIGURE 35.2 Sensory innervation of the lower extremity. *A,* Peripheral nerve innervation. *B,* Dermatomal (root) innervation. (From Reilly BM. *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991:927.)

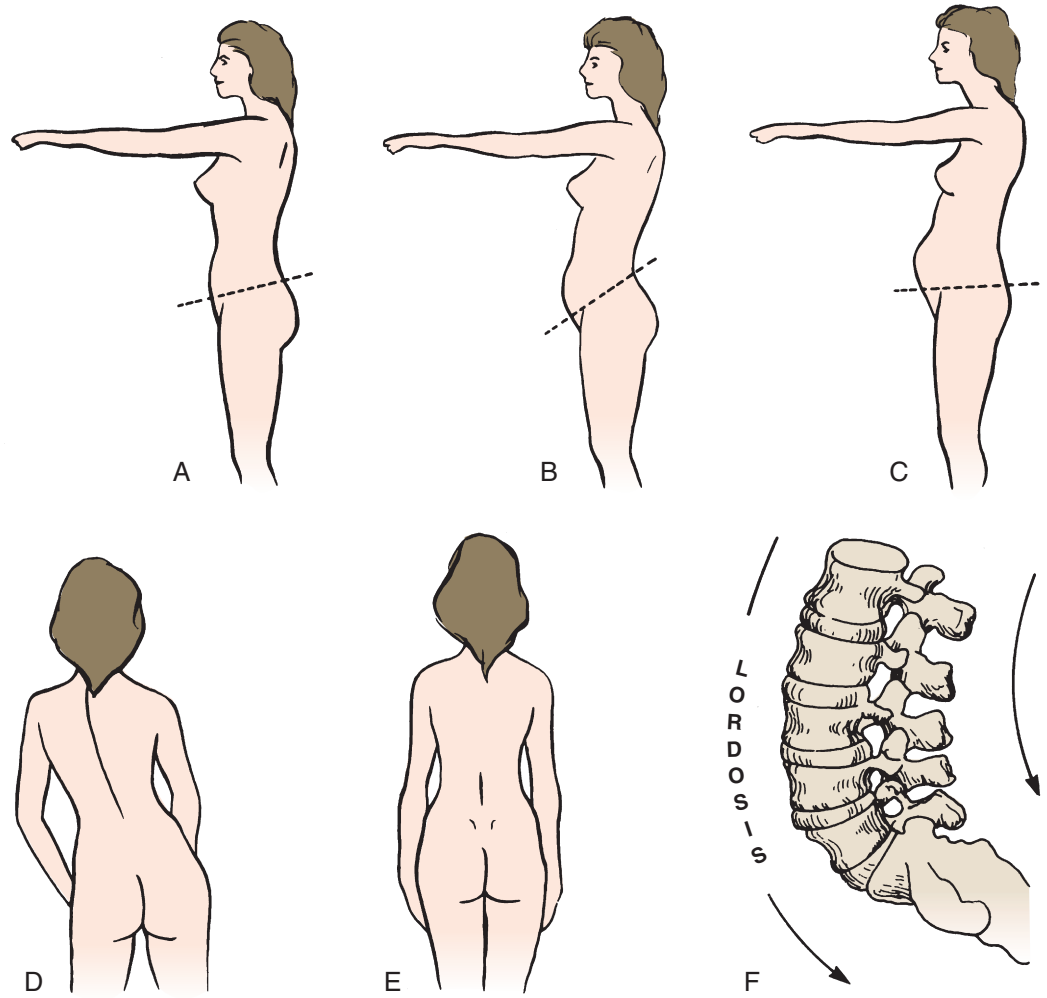

FIGURE 35.3 *A,* Normal posture with normal lumbar lordosis. *B,* Exaggerated lumbar lordosis caused by pelvic tilting. *C,* "Paunchy" posture. *D,* Spastic scoliosis caused by muscle spasm. *E,* Normal posture without scoliosis. *F,* The normal orientation of the lumbar spine is that of mild lordosis. Exaggerated lordosis may predispose the patient to mechanical back pain. (From Reilly BM. *Practical Strategies in Outpatient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991:908.)

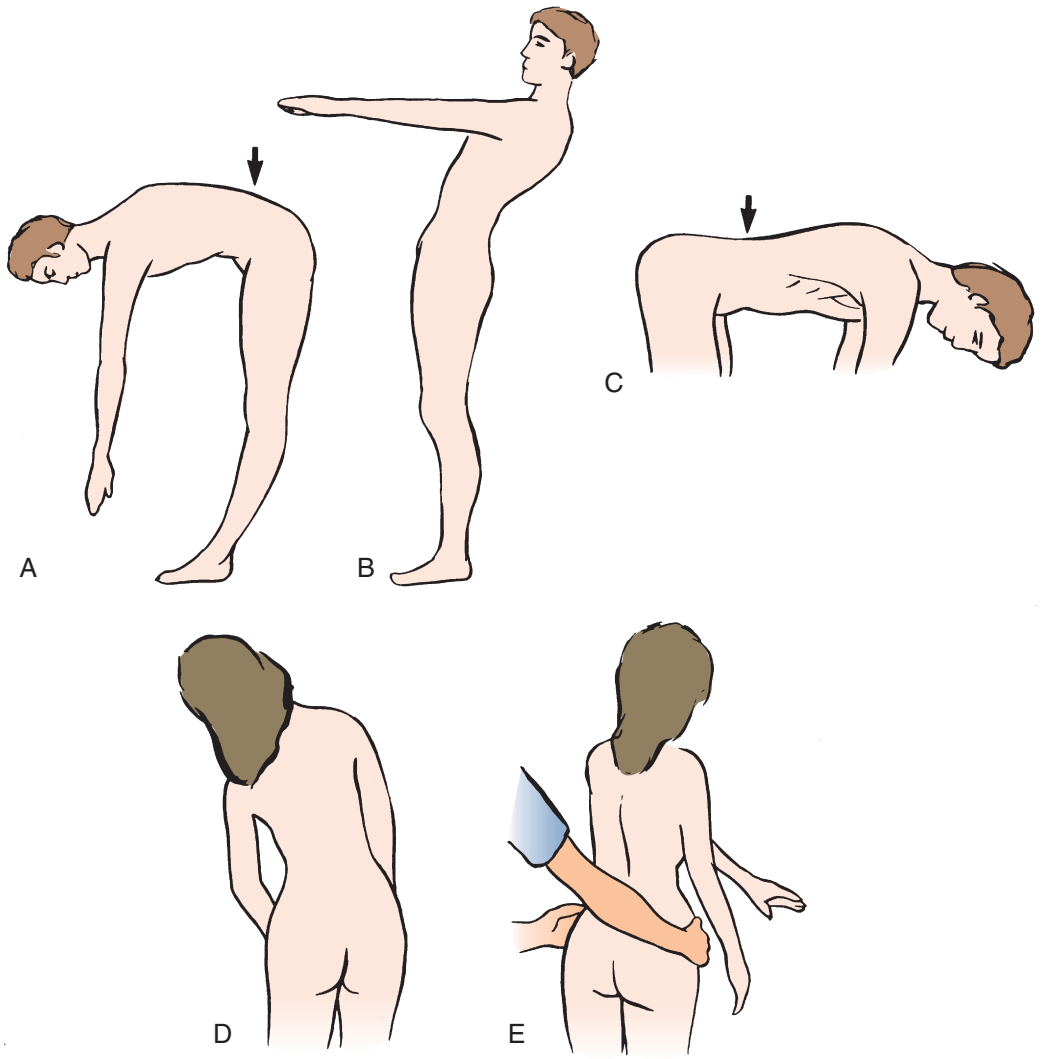

FIGURE 35.4 Back range of motion. *A,* Flexion. Note the normal reversal of lumbar lordosis during flexion *(arrow). B,* Extension. *C,* Persistent lordosis during back flexion as a result of muscle spasm *(arrow). D,* Lateral flexion. *E,* Lateral torsion *(rotation).* (From Reilly BM. *Practical Strategies in Outpatient Medicine.* 2nd ed. Philadelphia: WB Saunders; 1991:909.)

arise from a small number of congenital and developmental disorders of the spinal column. Degenerative disorders of the spine such as intervertebral disk herniation are uncommon causes of back pain in childhood. In evaluating a patient, it is important to try to distinguish musculoskeletal-mechanical disorders from those with more generalized systemic signs or those suggestive of a neoplasia (Fig. 35.5). If the MRI shows no definitive pathology, patients are considered to have mechanical low back pain and have continued conservative treatment. Pediatric multidisciplinary pain clinics also help those who have persistent pain, have no defined pathology, and have failed conservative treatment.

The differential diagnosis of persistent back pain in children younger than 10 years includes intervertebral diskitis and vertebral body osteomyelitis, neoplasia of the vertebrae, primary neoplasia of the spinal cord, and metastatic neoplasia (Table 35.2). In older children and adolescents, congenital variations in the formation of the lower lumbar spine are sometimes responsible for chronic back pain (see Table 35.1). Developmental round back (kyphosis) is occasionally associated with midthoracic back pain in middle and late adolescence. Diskitis, skeletal neoplasia, and tumors of the spinal cord and nerves also occur in adolescence. In documenting the history, special attention must be given to the nature of the onset of symptoms, the presence of radiating pain in the legs, bowel and bladder function, associated abdominal pain, and the presence or absence of fever.

Although this issue is controversial, some authorities believe that school-aged children who carry an excessively heavy backpack are at risk for back pain and alterations of gait or posture. To alleviate this, it is recommended that the backpack be of appropriate size with wide padded straps and back padding. In addition, the weight limit of the pack should not exceed 10-15% of the child's body weight. The pack should be lifted with bending of the knees, and the straps should be adjusted so that the pack fits on the back and not below the waist.

SPECIFIC DIAGNOSIS

Intervertebral Diskitis

Intervertebral diskitis is the term applied to a number of processes that are characterized by back or leg pain and identified radiographically by narrowing of the intervertebral joint space between 2 adjacent vertebral segments (Figs. 35.6 and 35.7). Magnetic resonance imaging

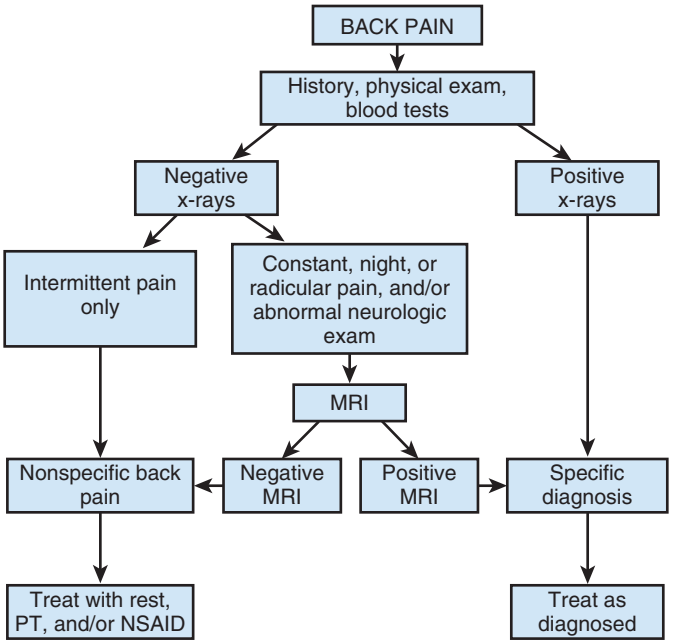

FIGURE 35.5 Pediatric back pain algorithm for children ≥4 years of age. MRI, magnetic resonance imaging; NSAID, nonsteroidal antiinflammatory drug; PT, physical therapy. (From Feldman D, Straight J, Badra M, et al. Evaluation of an algorithmic approach to pediatric back pain. *J Pediatr Orthop.* 2006;26:353-357.)

(MRI) studies suggest that diskitis may begin as a micro abscess within the vertebral body adjacent to the vertebral end plate. The disk becomes infected from perforating vascular channels across the end plate. Vascular channels may also perforate the end plate on the opposite side of the disk, leading to involvement of the opposite vertebral body. In some patients, the symptoms resolve spontaneously without treatment.

Most authorities believe that diskitis is a bacterial infection, usually caused by *Staphylococcus aureus*. Tuberculosis infection of the spine must also be considered in patients who have spent significant time outside the United States or in high-risk patients such as those who are immunocompromised. Surgical drainage, a critical component of effective treatment of other closed space infections of the musculoskeletal system, is not usually required in most patients with intervertebral diskitis.

Clinical Findings

Three age-dependent patterns of presentation have been noted for intervertebral diskitis. Children younger than 3 years (the most common age) often present with irritability and refusal to walk and sit or have apparent dysfunction (limp, antalgic gait) of the lower extremities. Patients may have very tight hamstrings, loss of lumbar lordosis (the lumbar spine is the most common site), and refusal to allow passive motion of the lumbar spine. Patients between the ages of 3 and 8 years often have pain referred to the abdomen, particularly when the disk involves the lower thoracic spine. Adolescents with diskitis often have back pain; the discomfort often radiates into both legs. Additional features at all ages include low-grade fever; refusal to bear weight (sitting or standing); hyperlordosis; and, if intraspinal inflammation is present, decreased lower extremity muscle strength, decreased tone, and alterations of deep tendon reflexes. The erythrocyte sedimentation rate is usually elevated; the white blood cell count is usually normal but may be elevated in late cases. Early in the process, plain radiographs of the spine are often normal. Over a certain period of time, the disk space narrowing develops with subsequent erosion of the vertebral end plates (see Fig. 35.6). Traditionally, a bone scan has been recommended for assessment of diskitis. However, MRI is more sensitive than the bone scan. The MRI reveals the extent of the inflammatory process better and can delineate the degree of bone destruction (if any), the presence of abscess formation, or intraspinal inflammation (see Fig. 35.7).

Treatment

The diagnosis of intervertebral diskitis should be suspected in young children with fever and unexplained back or leg pain and in previously healthy toddlers who become irritable and refuse to walk. Vertebral body osteomyelitis is a major consideration in the differential diagnosis and can usually be diagnosed with radiographs and MRI. After appropriate laboratory studies, including blood cultures, have been performed, treatment should be started. A bacterial cause is likely if fever, leukocytosis, and elevation of the sedimentation rate are present. Antibiotic therapy should be started in such cases, because *S. aureus* is the most commonly responsible organism. Knowing the antibacterial sensitivity patterns of community-acquired *S. aureus* helps the clinician choose the appropriate antibiotic (clindamycin, vancomycin, or methicillin). In immunocompromised hosts, broader spectrum antibiotic coverage is essential. If an organism is recovered, antibiotic coverage can be adjusted appropriately. Initial therapy should be intravenous; oral antibiotics can be considered as pain decreases and laboratory studies return to normal. A total of 4-6 weeks of therapy is recommended for patients with infectious intervertebral diskitis.

Immobilization of the spine is used for persistent symptoms. Patients without systemic signs of infection and in whom laboratory studies show no leukocytosis and only moderate elevation of the sedimentation rate may be occasionally managed by antiinflammatory agents and rest.

Patients who remain ill or worsen after the initiation of rest and antibiotic treatment should undergo surgical biopsy and drainage. Biopsy should also be performed in patients in whom tuberculous intervertebral disk space infection is suspected (positive exposure history, positive purified protein derivative findings; see Chapter 2).

The evolution of plain radiographic findings lags behind clinical findings in intervertebral diskitis. Although patients with intervertebral diskitis may experience disk space narrowing and end plate erosion during the course of treatment, normal radiographs and bone scans at the time of initial evaluation do not preclude the diagnosis. Radiographic changes continue long after the inflammatory process has resolved. Progressive disk space narrowing, intervertebral disk space calcification, and spontaneous intervertebral arthrodesis are potential late findings.

Lack of focal changes on plain films obtained 2-3 weeks after the onset of symptoms significantly lessens the likelihood of intervertebral diskitis. In such patients, careful study for other potential diagnoses is essential. Tumors of the spinal cord may manifest in a similar manner without causing the changes in the vertebral segments necessary to produce alterations on bone scanning. In such patients, MRI is invaluable.

Spondylolysis and Spondylolisthesis

The most common abnormalities of the lower lumbar and lumbosacral spine—spina bifida occulta, at L5 or S1, and spondylolysis, usually at L5 to S1—are often noted as incidental radiologic findings in entirely asymptomatic individuals. A few individuals with spondylolysis (defect in the pars interarticularis without slippage) experience back pain and progressive slippage deformity, known as spondylolisthesis.

(See *Nelson Textbook of Pediatrics,* p. 3293.)

TABLE 35.2 Differential Diagnosis of Back Pain

Inflammatory Diseases
Diskitis*
Vertebral osteomyelitis (pyogenic, tuberculosis)
Spinal epidural abscess
Transverse myelitis
Pyelonephritis*
Perinephric abscess
Pancreatitis
Paraspinal muscle abscess, myositis
Psoas abscess
Endocarditis
Pelvic osteomyelitis or myositis
Pelvic inflammatory disease

Rheumatologic Diseases
Pauciarticular juvenile rheumatoid arthritis*
Reactive arthritis
Ankylosing spondylitis
Psoriatic arthritis
Ulcerative colitis, Crohn disease
Fibrositis, fibromyalgia

Developmental Diseases
Spondylolysis (in adolescence)*
Spondylolisthesis (in adolescence)*
Scheuermann syndrome (in adolescence)*
Scoliosis
Chiari malformation type 1 with or without syringomyelia
Spinal dysraphism

Mechanical Trauma and Abnormalities
Muscle strain/sprain*
Hip/pelvic anomalies
Herniated disk (rare)
Juvenile osteoporosis (rare)
Overuse syndromes (common with athletic training and in gymnasts and dancers)*
Vertebral stress fractures
Lumbosacral sprain*
Seatbelt injury
Trauma (direct injury; e.g., motor vehicle crash)*
Strain from heavy knapsacks

Neoplastic Diseases
Primary vertebral tumors (osteogenic sarcoma, Ewing sarcoma)
Metastatic tumor (neuroblastoma, rhabdomyosarcoma)
Primary spinal tumor (neuroblastoma, lipoma, cysts, astrocytoma, ependymoma)
Malignancy of bone marrow (ALL, lymphoma)
Benign tumors (eosinophilic granuloma, osteoid osteoma, osteoblastoma, bone cyst)

Other
Disk space calcification (idiopathic, S/P diskitis)
Conversion reaction
Sickle cell anemia*
Nephrolithiasis
Hemolysis (acute)
Hematocolpos
S/P lumbar puncture

*Common.
ALL, acute lymphocytic leukemia; S/P, status post.
Modified from Behrman R, Kliegman R, eds. *Nelson Essentials of Pediatrics.* 2nd ed. Philadelphia: WB Saunders; 1994:711.

FIGURE 35.6 Intervertebral diskitis. There is loss of intervertebral disk space height between vertebral segments L3 and L4, with early end plate erosion on the anteroinferior surface of L3 and anterosuperior surface of L4.

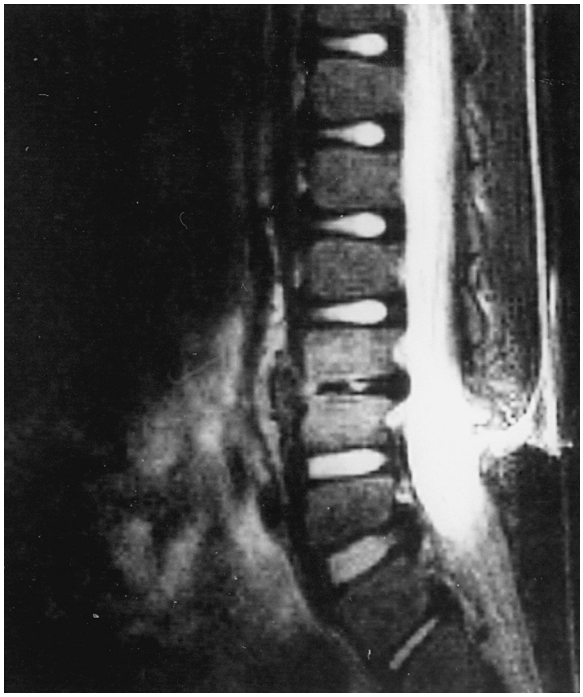

FIGURE 35.7 Intervertebral diskitis, magnetic resonance image. Note the increased marrow signal from the vertebral bodies adjacent to the narrowed L4 intervertebral disk. The normal bright signal is missing from the involved disk itself, and there is evidence of soft tissue abscess formation anterior to the involved disk space.

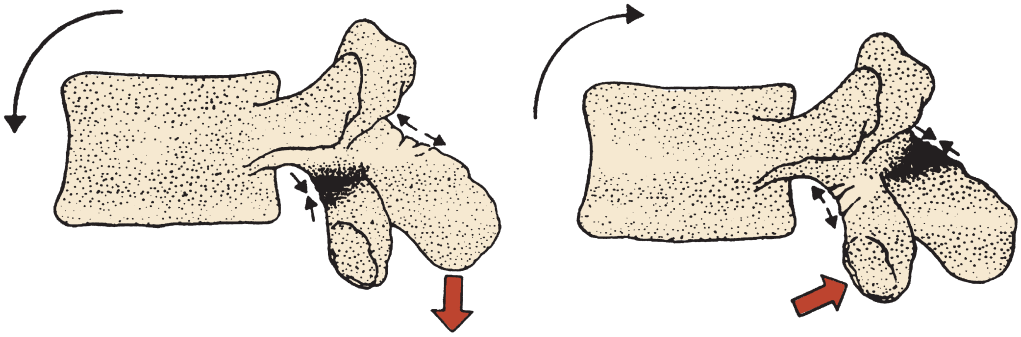

FIGURE 35.8 Stress leading to fracture of the pars interarticularis.

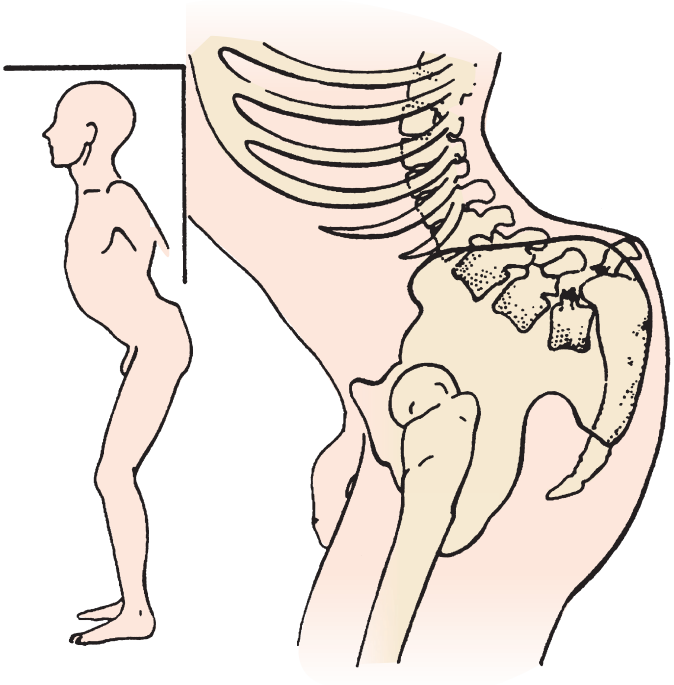

FIGURE 35.9 Clinical picture of severe spondylolisthesis.

As a consequence of the normal lordotic tilt of the lumbar spine, shear forces are generated between the L5 and S1 vertebral segments. Forward displacement of L5 on S1 is normally prevented by the stable articulation of the superior facets of S1 and the inferior facets of L5. Defective formation of the posterior elements of the lumbosacral joint or defects in the bone connection between the body and the arch of the 5th lumbar vertebra render the anterior junction of L5 and S1 unstable and may lead to relative displacement.

Cause

Spondylolysis and spondylolisthesis in children and adolescents usually involve the 5th lumbar and 1st sacral units. Spondylolysis is not present at birth, but with growth and activity, it is seen by age 6 years in about 4% of children and 6% of adults. Spondylolysis appears to be less common in black persons and much more common in some North American Eskimo groups; the lowest incidence has been reported in black females, and the highest in white males. The male to female ratio is 2:1. The disorder appears to be multifactorial; both hereditary and mechanical factors have been implicated. Relatives of patients with spondylolysis are much more likely to be affected than are individuals in the general population, although the degree of slippage is not as well correlated.

Fatigue fracture of the posterior elements of L5 may be responsible for acutely painful spondylolysis in some preadolescent and adolescent athletes (Figs. 35.8, 35.9, and 35.10). Activities that involve repeated trunk flexion and extension have been implicated; adolescent divers and gymnasts are reported to be susceptible to spondylolysis and spondylolisthesis. A high rate of spondylolysis has been reported in Scheuermann disease (thoracic kyphosis), which may be related to compensatory excessive lumbar lordosis. In addition, an increased incidence of spondylolisthesis has been noted among both patients with myelodysplasia and those with cerebral palsy.

Acute fracture-dislocation of vertebral units resulting from violent trauma in a strict sense is 1 form of spondylolisthesis, but because it differs so greatly from other types of spondylolisthesis in cause, presentation, and treatment, it is usually considered as a separate entity.

Presentation

Symptoms in patients with spondylolysis and spondylolisthesis are quite variable; many patients are asymptomatic. Some patients with minimal slips have extreme pain, while others with moderate to severe slips have little or no discomfort. Symptomatic patients complain of aching in the lumbar and lumbosacral regions. Buttock and posterior thigh pain may be present, but radicular symptoms of nerve root compression are usually absent unless the spondylolisthesis is severe. In severe cases, bowel and bladder dysfunction may also be present. Discomfort is usually increased by exercise and relieved by rest.

Signs vary with the severity of spondylolisthesis. Asymptomatic patients with slips of mild severity may have no outward manifestations of vertebral abnormality. Patients with moderate to severe slips usually have tenderness on palpation of the lumbar spine and increased lumbar lordosis. Spasm of the hamstring muscles may extend the sacral spine, causing the buttocks to seem flattened or heart-shaped in appearance. In severe slips, a step-off of L5 on S1 can be palpated. A flexible scoliotic deformity caused by paraspinal muscle spasm may be present.

Neurologic examination findings are usually normal in children with spondylolysis. Symptoms and signs of nerve root compression and mechanical instability are much more common in adult patients with progressive or severe untreated adolescent spondylolisthesis.

Hamstring muscle spasm is a common finding in patients with symptomatic spondylolisthesis and at times may be the chief presenting problem. Affected patients are unable to flex far enough forward to touch their toes without bending their knees. When severe, hamstring spasm results in a loss of normal lumbar lordosis and produces a flattened appearance of the low back. Hamstring muscle spasm also

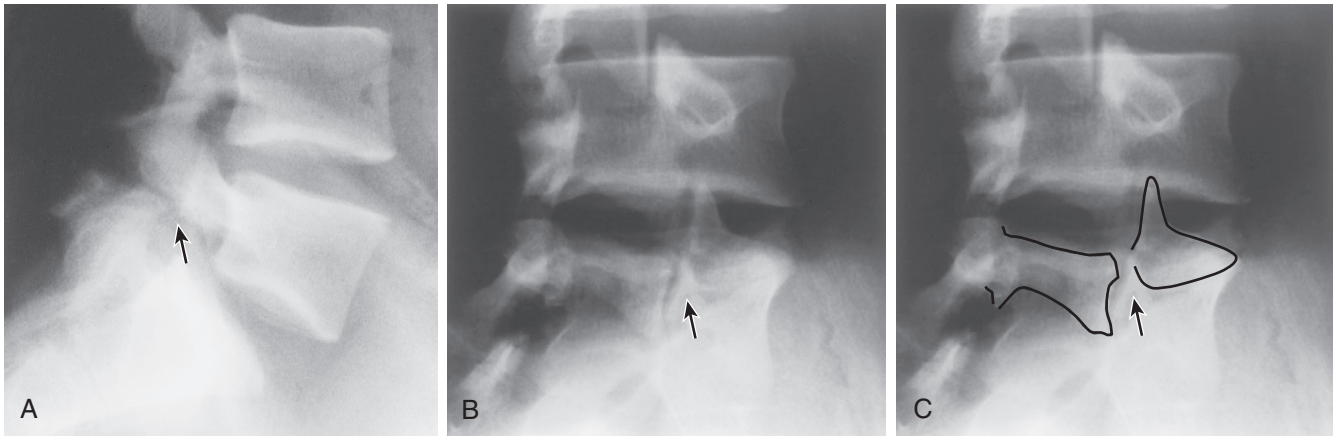

FIGURE 35.10 *A,* Radiograph features of spondylolysis showing lytic defect *(arrow)* in the pars interarticularis. *B,* In isthmic defects, this appears as the collar *(arrow)* of the "Scotty dog" sign. *C,* Collar of the Scotty dog sign outlined on film. (From Rathjen KE. Back pain. In: Herring JA, ed. *Tachdjian's Pediatric Orthopaedics.* 5th ed. Philadelphia: Elsevier; 2014:95.)

interferes with gait; stride length is shortened, and patients run with a peculiar stiff-legged posture. The cause of hamstring spasm in spondylolisthesis is unclear; it does not appear to be caused by compression of spinal nerves, and it is rarely accompanied by other signs of nerve root compromise. Most authorities believe it is a result of abnormal strain on the hamstring muscles caused by mechanical instability of the lumbosacral junction.

Radiographic Assessment

If spondylolysis is suspected, radiographic assessment includes anterior-posterior lateral views of the lumbar spine (Fig. 35.11; see also Fig. 35.10). In cases of unilateral spondylolysis, there may be hypertrophy of the opposite pars or pedicle. A computed tomographic (CT) scan is helpful in determining the anatomy of the defect and can help assess the status of healing during treatment. CT scans also may identify sites of nerve root compression. The bone scan (single photon emission computed tomography scan) is sensitive in identifying the stress fracture before disruption is evident on radiographs. Immobilization at this point may heal the lesion. MRI has been increasingly utilized for assessing spondylolysis due to increasing concern over radiation exposure with CT and bone scan; improved techniques for obtaining MRI images are leading MRI to be the procedure of choice in assessing spondylolysis.

If the clinician suspects an associated herniated disk, MRI is indicated. The plain radiographs illustrate the degree of slippage. This must be documented to see whether progression is occurring over time. The most common classification system notes the position of the posterior border of the L5 vertebral body with regard to the S1 body. When the slip is less than 25% of the width of the 1st sacral body, the slip is considered mild. Slips exceeding 50% are considered severe. These cases are of concern in that the progression may proceed to the point at which L5 dislocates in front of the S1 vertebral body, which is called spondyloptosis.

Treatment

In asymptomatic patients with a mild slip, no treatment is required; likelihood of progression is low. However, if significant progression occurs (even if a patient is asymptomatic), a posterolateral fusion is recommended. When a slip exceeds 50%, the likelihood of continued progression is high, and surgical stabilization should be performed. Both symptomatic and asymptomatic patients with this severe condition should undergo surgical stabilization.

FIGURE 35.11 Spondylolisthesis. Slippage of L5 on the underlying body of S1 has occurred as a consequence of the defective formation of the posterior elements of L5. In this case, slippage is moderate, measuring slightly more than 25% of the width of the S1 vertebral segment.

Initial treatment of patients with symptomatic spondylolysis should be conservative. The examiner must also rule out other causes of back discomfort. Activity restriction with antiinflammatory medication is the initial treatment. When the pain is severe, a brace or corset is helpful. Then abdominal and paraspinal strengthening exercises are instituted to help relieve symptoms. Most patients with symptomatic spondylolysis or mild spondylolisthesis respond to conservative therapy and are able to return to sports. However, a small percentage of patients do not respond to conservative therapy; for these patients, surgical stabilization may be necessary. Patients with a severe slip who have a neurologic deficit that does not respond to conservative management also require surgical intervention. A fusion in situ (L5 to S1) is the most commonly performed surgical procedure for patients with

a slip of less than 50%. Extension of the fusion to L4 is necessary to create a satisfactory fusion in patients with a more significant slip.

Idiopathic Kyphosis

Abnormal increases in expected thoracic kyphosis in children and adolescents produce round back deformities (Fig. 35.12). These may be congenital, neuromuscular, or idiopathic in origin. Mild to moderate increases in kyphosis cause little deformity and few symptoms. Severe kyphosis is disfiguring, often causes back pain, and may lead to spinal cord compromise.

Round back posture is often encountered in otherwise healthy adolescents at school screening examinations. Affected patients are usually asymptomatic, although their parents often report poor posture. A history should be obtained and physical examination performed. Complaints of severe back pain or leg pain, enuresis, and findings of lower extremity weakness or increased reflex tone in patients with round back are ominous findings and warrant referral.

If accentuated kyphosis is present, radiographic follow-up is indicated. Two radiologic patterns are common. The majority of individuals, especially younger adolescents, have thoracic kyphotic curves of 20 to 45 degrees, with no underlying structural vertebral changes. Usually such curves correct easily on passive or active hyperextension. For such children, no treatment except for a thoracic hyperextension exercise program and periodic follow-up examination is necessary.

More severe kyphosis with accompanying structural changes in vertebral bodies at the apex of the deformity is present in a small subset of adolescents with kyphosis. Affected individuals often have kyphotic curves greater than 60 degrees and show little correction with hyperextension. Radiographs show vertebral wedging, end plate irregularity, and kyphosis (Fig. 35.13). **Scheuermann kyphosis** (an osteochondrosis) occurs in approximately 5-8% of the population, affecting males 5-10 times more often than females. The cause remains unclear but may be the result of disruption of growth of the anterior portion of the vertebral body and consequent wedging of multiple vertebral bodies. Back pain is usually mild; many affected patients have no pain at all. The deformity in most affected patients is minimal and only rarely is cosmetically unacceptable. Late neurologic complications are extremely rare.

Treatment depends on the degree of deformity and the age of the patient. Skeletally immature individuals with significant deformity may improve with a program of exercise and use of a Milwaukee or modified Boston brace. Bracing does not reverse a deformity, but it may prevent progression. Older patients with back pain usually respond to a back-strengthening exercise program. Patients with unacceptable deformity who are too old for brace treatment require surgical correction. Often this requires a combination of anterior release and posterior spinal instrumentation and fusion.

Congenital vertebral malformations that produce kyphotic deformities develop during the 1st trimester of gestation and, like other

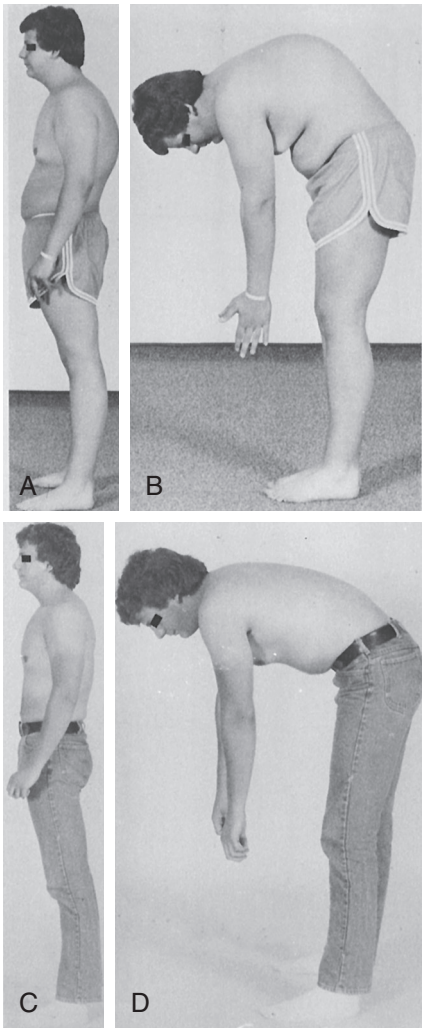

FIGURE 35.12 Preoperative *(A and B)* and postoperative *(C and D)* views of an adolescent boy with severe kyphosis secondary to Scheuermann disease. He required both anterior and posterior spinal fusion. He now has a markedly improved appearance and no further progression of the kyphosis. (From Renshaw TS. *Pediatric Orthopedics*. Philadelphia: WB Saunders; 1986:53.)

FIGURE 35.13 Scheuermann kyphosis. Lateral radiographs of the midthoracic spine in an asymptomatic 16-year-old male with moderately severe kyphosis. There is severe wedging, loss of vertebral height, and end plate irregularity present on these films. His radiographic findings appear far worse than his symptoms and signs. If further collapse was to develop and the kyphosis became more severe, surgical intervention would be necessary.

(See *Nelson Textbook of Pediatrics,* p. 3291.)

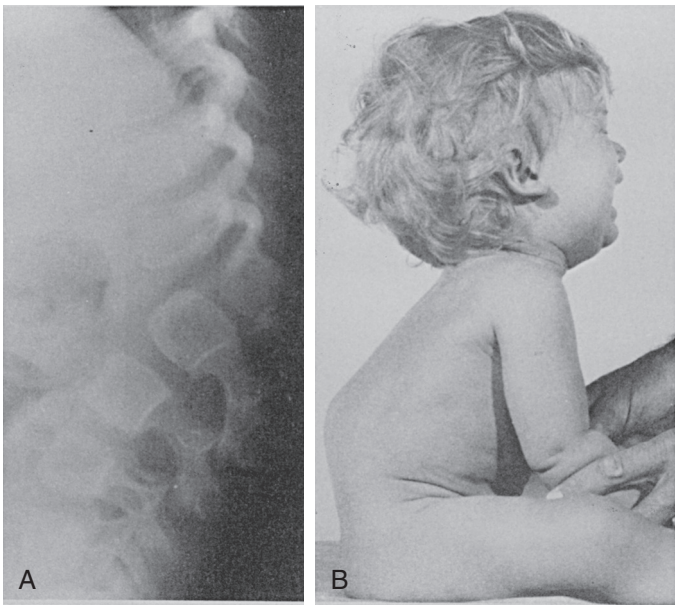

FIGURE 35.14 *A,* Congenital kyphosis secondary to failure of vertebral bodies to form at T12 and L1. *B,* The clinical appearance of the child. Thoracolumbar kyphosis is obvious. (From Renshaw TS. *Pediatric Orthopedics*. Philadelphia: WB Saunders; 1986:44.)

congenital abnormalities of the spine, are often associated with abnormalities of the genitourinary tract or the spinal cord. Kyphosis that results from congenital vertebral deformities is often obvious early in life and may be rapidly progressive (Fig. 35.14). The spinal cord may become tented over the apex of the deformity, producing symptoms and signs of spasticity in the lower extremity and bladder. Progression of deformity is dangerous; congenital kyphosis is the spinal deformity most often associated with paraplegia. Patients should be promptly referred for orthopedic evaluation.

Intervertebral Disk Herniation

Intervertebral disk rupture is much less common in children than in adults. Because most such patients are treated nonoperatively, the absolute incidence of the disorder is not known. In the United States, fewer than 1% of patients undergoing diskectomy are younger than 16 years. The frequency of symptomatic intervertebral disk herniation may be more common in Asian persons than in white persons, perhaps because of the smaller size of the spinal canal.

Some patients have a significant history of trauma. In other patients, congenital anomalies of the lumbar spine, such as transitional vertebra or spina bifida occulta, are noted. There may be a family history of low back pain or herniated disks. An autosomal dominant trait has been linked to the *COL9A2* collagen IX gene.

The symptoms of a herniated lumbar disk in adolescents differ somewhat from those in adults; this may delay recognition. The initial complaint in adolescents is significant low back discomfort; it is only months later that the symptoms of leg discomfort become more noticeable or prominent. Pain is typically aggravated by activity and relieved with rest. Symptoms may be intermittent. The affected adolescent has poor back mobility, often with paravertebral muscle spasm. Lumbar lordosis may diminish, and there is a tendency to walk bent forward. Hamstring tightness with limited straight-leg raising is almost universal. Neurologic signs are less likely to be prominent in the adolescent with herniated disk than in the affected adult. Clues to suggest a lumbosacral radiculopathy include abnormal straight leg or cross straight leg raising responses, weak ankle dorsiflexion, calf wasting, diminished ankle reflex, and decreased sensation. Plain radiographs are needed as an initial study. These are usually normal other than for the loss of lumbar lordosis. The MRI is the procedure of choice for diagnosing a disk herniation. In rare cases, adolescents may develop a lesion that is a fracture of the posterior vertebral apophysis, which displaces posteriorly into the spinal canal and acts like a herniated disk. This is an avulsion fracture that is identified with either a CT scan or MRI. When a patient has severe symptoms, treatment should begin with bed rest, analgesics, and antiinflammatory agents. When the symptoms have begun to abate, physical therapy for lumbar and paraspinal strengthening is helpful. A lumbar corset may be helpful for patients who also have significant symptoms. Patients who present with progressive neurologic deficits require early surgical excision. Similarly, patients who fail to respond to a significant period of nonoperative management also require disk surgery.

The long-term results of a disk excision are good in 70-80% of the patients. Spinal fusion is not required unless the patient shows evidence of instability, which is quite rare.

Scoliosis

Idiopathic scoliosis, a combination of lateral deviation and rotation of vertebral bodies, does not always produce back pain. When painful scoliosis is present, a careful search for the cause of the symptoms must be undertaken. Infection, tumor, a spinal cord syringomyelia or diastematomyelia (more common with left thoracic curves), and occult fractures may produce clinical findings that resemble idiopathic scoliosis but, in contrast to idiopathic scoliosis, cause significant chronic pain as well. Any patient with painful scoliosis should have a careful evaluation for other spinal anomalies causing the pain.

Etiology

Idiopathic scoliosis begins in the immature spine, although progression of preexisting curvatures may occur in adult life. The cause of idiopathic scoliosis remains unknown. Hormonal factors appear to play a role in curve progression, inasmuch as severe curves occur much more often in girls. Some studies have demonstrated abnormalities of proprioception and vibratory sensation in affected patients, which suggests that abnormalities of posterior column function may contribute to the development of curvature. Other investigators have implicated cerebellar or muscular (myopathy) dysfunction as a possible cause of spinal imbalance.

No clear genetic pattern has been established. Curves occur more frequently in individuals with affected 1st-degree relatives, but transmission is not Mendelian. Although curvature is more likely to develop in the daughters of affected mothers than in other children, the magnitude of curvature in an affected individual is not related to the magnitude of curvature in relatives. It appears likely that a combination of genetic predisposition and other undefined factors is responsible for development and progression of idiopathic scoliosis.

Classification

Idiopathic curves are grouped into infantile (birth-3 years), juvenile (4-10 years), and adolescent categories on the basis of age at onset of curvature. The infantile form differs enough from the other varieties to be considered a distinct entity. The distinction between juvenile and adolescent scoliosis is not as sharp.

Infantile idiopathic scoliosis. Infantile idiopathic scoliosis is rare in the United States, probably accounting for fewer than 1% of new cases of idiopathic scoliosis. It is more common in Europe. The majority of patients are males, and most curves are convex toward the left rather than the right, as in the other varieties of idiopathic scoliosis.

Some infants suspected of having idiopathic deformity actually have subtle congenital vertebral abnormalities. The diagnosis of idiopathic deformity is appropriate only when radiographic studies show no evidence of congenital vertebral anomalies (e.g., hemivertebra) and there are no signs of spinal dysraphism or of neuropathic or myopathic disorders.

Although many infantile curves resolve spontaneously, others progress relentlessly and are very difficult to treat effectively. Observation is appropriate until 6 months of age in infants with mild idiopathic scoliosis, but prompt referral should be made if curves persist or increase during the period of observation.

Juvenile idiopathic scoliosis. Juvenile idiopathic scoliosis begins before the adolescent growth spurt. Some curves are probably undetected cases of infantile scoliosis. Others, particularly those that occur in older children, may be early manifestations of adolescent idiopathic scoliosis. Some curves remain small and, in fact, may resolve spontaneously. Others remain stable until the onset of the growth spurt and then progress unless treated. Still others progress steadily throughout childhood and adolescence. Some are associated with intraspinal anomalies (syrinx). There is no reliable method of predicting the behavior of juvenile curves at the time of diagnosis, but, in general, high-magnitude curves in young patients are more likely to increase with growth than are smaller curves in older children.

The majority of patients with juvenile curves greater than 25 degrees at the time of diagnosis require some form of active treatment. Treatment must begin at the time progression is first documented if severe deformity is to be prevented.

Adolescent idiopathic scoliosis. Most cases of idiopathic scoliosis in North America develop around the time of the adolescent growth spurt (Figs. 35.15 and 35.16). Often parents and children are unaware of the presence of curvature at the outset. Nerve root impingement, intervertebral disk disease, and spinal cord compression are uncommon in young patients with idiopathic scoliosis. Large curves are more common in females than in males (7:1 ratio). Pain is so rare that children and adolescents with painful curves must be carefully studied in order to exclude neoplastic and inflammatory processes of the spinal column or neural canal. Idiopathic scoliosis is usually a painless disorder during childhood and adolescence. Severe structural curves may cause no pain until degenerative changes develop in adulthood.

School Screening Programs

School screening for spinal deformity is common in North America. Most programs concentrate on children in the late juvenile and early adolescent periods. The most common screening method employed is the forward-bend test, based anatomically on the vertebral rotation that accompanies lateral spinal deviation (see Fig. 35.15). Associated clinical findings include shoulder asymmetry, unequal distances between the medial borders of the elbows and the flanks, and apparent leg length inequality or pelvic tilt. Breast asymmetry, caused by forward rotation of the chest wall on the side of the curve concavity and backward displacement of the chest wall on the convex side of the curve, is often present in affected girls.

The threshold for "identification" on screening examination is subjective, and it is not surprising that the incidence of spine asymmetry detected by school screening programs varies with the method of screening and the experience of the examiner. A range of 3-20% has been reported. Follow-up radiographic studies of children thought to have abnormal curvatures on school screening examinations indicate an incidence of scoliosis in screened children of less than 15% (range, 0.4-14%). The incidence of curves greater than 20 degrees at the time of primary screening is probably less than 0.5%. Simple devices such as the scoliometer determine spine asymmetry by measuring the angle of trunk rotation at the apex of the rib hump. An angle of more than 7 degrees is an appropriate criterion for referral.

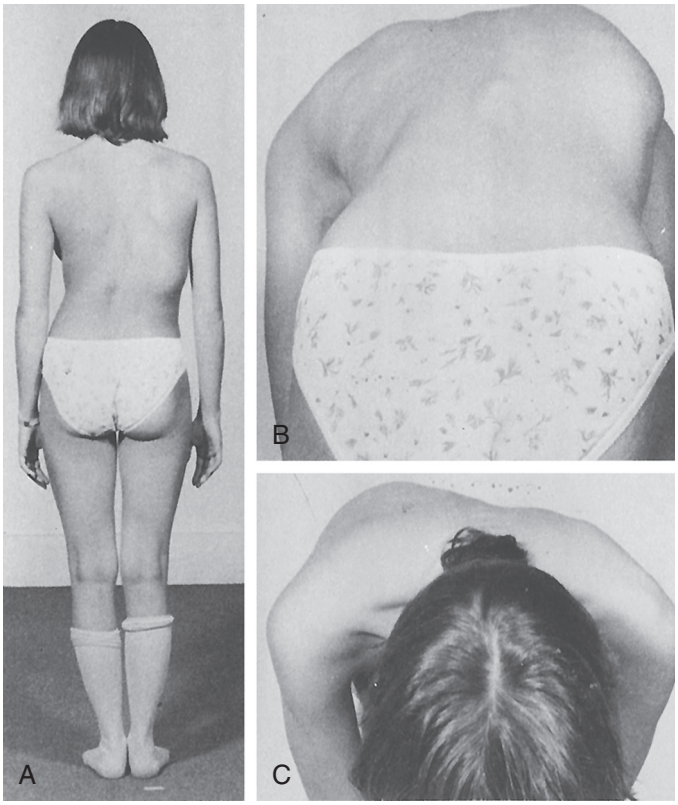

FIGURE 35.15 *A,* Adolescent idiopathic scoliosis, viewed from the back. Note the right-sided thoracic prominence. When the patient bends forward *(B),* the rib prominence is even more apparent. This is secondary to rotation of the ribs and spine. The rib prominence is also quite evident when viewed from the front *(C).* (From Renshaw TS. *Pediatric Orthopedics.* Philadelphia: WB Saunders; 1986:47.)

The 1st response to a positive school screening examination should be a repeated physical examination. If asymmetry is confirmed, a single standing posteroanterior spine film, including vertebral levels T1 to S1, should be obtained. Lateral films, bending films, and oblique views are not necessary. Referral is appropriate for skeletally immature children or adolescents with curves greater than 20 degrees.

Natural History

The natural history of curvature in patients with spine asymmetry is highly variable. Factors that appear to be associated with risk of progression include the magnitude of curvature at the time of detection, the chronological and skeletal age of the patient, the pattern of curvature, and the menarcheal status. Immature patients with large-magnitude curves are far more likely to experience progression than are more mature patients with small curves. Progression of curves after skeletal growth is uncommon in idiopathic thoracic curves of less than 30 degrees at the end of growth but is likely to occur in patients with curves greater than 50 degrees at maturity.

Uncontrolled curve progression causes significant problems in adult life. Unacceptable deformity, back pain, chronic fatigue, and decreased work capacity are common. Premature degenerative arthritis and nerve root impingement caused by deformity and osteophytic spurring occur in patients with lumbar curves or double thoracic-lumbar curves. Asymptomatic decreased vital capacity is common in patients with thoracic curves; symptomatic cardiopulmonary

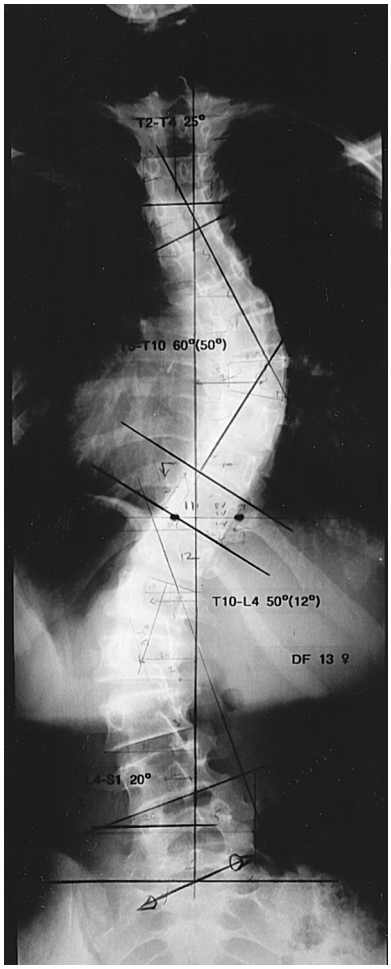

FIGURE 35.16 Adolescent idiopathic scoliosis. The patient, a 13-year-old girl, had a severe double-curve pattern with significant accompanying deformity but no pain. Surgical treatment was warranted to halt progression and restore spinal alignment.

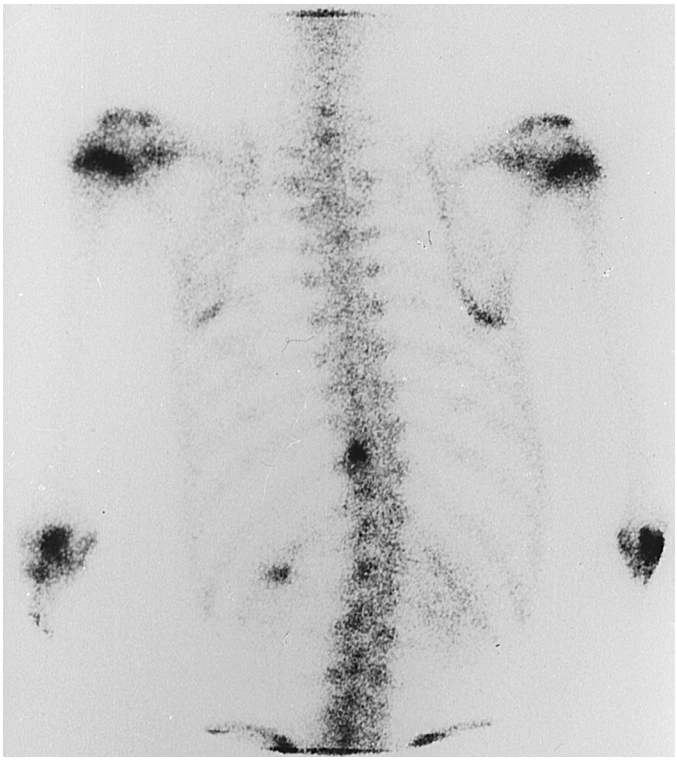

FIGURE 35.17 Osteoid osteoma of the spine. Technetium bone scanning shows increased uptake in the T10 vertebral body in a 15-year-old boy. Note the scoliosis that accompanies this painful lesion. The condition did not respond to antiinflammatory medications, and surgical excision was necessary.

compromise (cor pulmonale) may develop in patients with curves greater than 80 degrees.

Treatment

The goal of treatment in idiopathic scoliosis is to bring a patient to skeletal maturity with a cosmetically acceptable, balanced, and stable curve that is unlikely to progress in adult life. Mature adolescents with curves less than 30 degrees need no treatment beyond initial evaluation. Further progression of curvature is unlikely to occur in these individuals. Patients with juvenile scoliosis and less mature adolescents with curves between 10 and 20 degrees should be monitored at 6-month intervals with single standing posteroanterior spine radiographs. If progression occurs, they should be referred for orthopedic care.

Active treatment is indicated for growing patients with curves greater than 30 degrees. Brace treatment remains the standard method of nonoperative treatment of idiopathic curvature. Surgical treatment is appropriate for patients with curves too severe for brace treatment. Documented progression in spite of nonoperative treatment is another indication for surgical intervention.

Improved instrumentation and internal fixation devices, intraoperative monitoring of spinal cord function, and autologous transfusion have improved the safety and efficacy of surgical correction. In most cases, patients can be out of bed the day after surgery and are discharged within 5 days of surgery. Return to school is usually possible within 3 weeks; most activities of normal life, including sports, can be resumed within 6 months. In many instances, no postoperative immobilization is required; in other cases, a removable lightweight plastic orthosis can be employed. Prolonged periods of immobilization in a plaster cast are uncommon.

Tumors of the Spinal Column

Persistent back pain, muscle spasm, and abnormal trunk posture are ominous findings in children. Neoplastic disease must be considered in patients with no other obvious source of pain (see Table 35.2).

Primary Lesions of Bone

The most common primary bone tumors affecting the spinal column in children are osteoid osteomas (Fig. 35.17), osteoblastomas (Fig. 35.18), eosinophilic granulomas, and aneurysmal bone cysts. Although benign, these lesions may cause considerable back pain and local bone destruction. Osteogenic sarcoma, a malignant lesion of bone, occurs less commonly in the spine than in the long bones of children. Unexplained pain is the hallmark of spinal neoplasia and is usually the presenting complaint. At times, pain may be severe and unresponsive to nonnarcotic analgesics. In other instances, as in osteoid osteoma, the relief of symptoms that occurs with nonsteroidal antiinflammatory agents is so characteristic that it is considered a diagnostic finding. Paraspinal muscle spasm, tenderness in the soft tissues on the side of the spinal column, and alterations in spinal configuration are common. Scoliosis, loss of lumbar lordosis, or accentuations of thoracic kyphosis may be present.

(See *Nelson Textbook of Pediatrics,* p. 2955.)

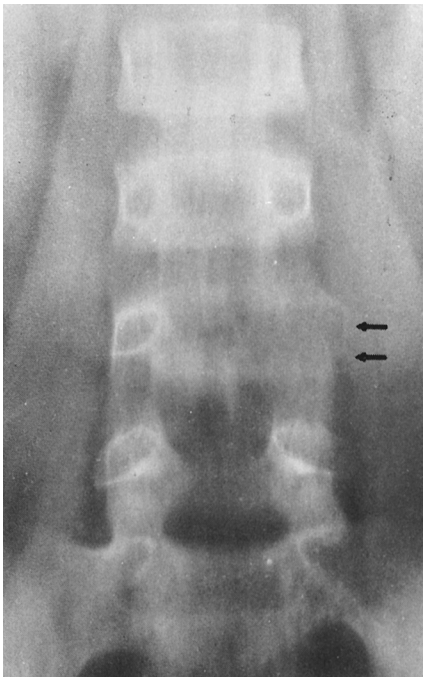

FIGURE 35.18 The patient presented with left-sided lumbar back pain. Note the destruction of the vertebral pedicle at L4 *(arrows)*. This proved to be an osteoblastoma. Children with back pain should be suspected of having a tumor of the spine or spinal cord until it is proven otherwise. (From Renshaw TS. *Pediatric Orthopedics*. Philadelphia: WB Saunders; 1986:57.)

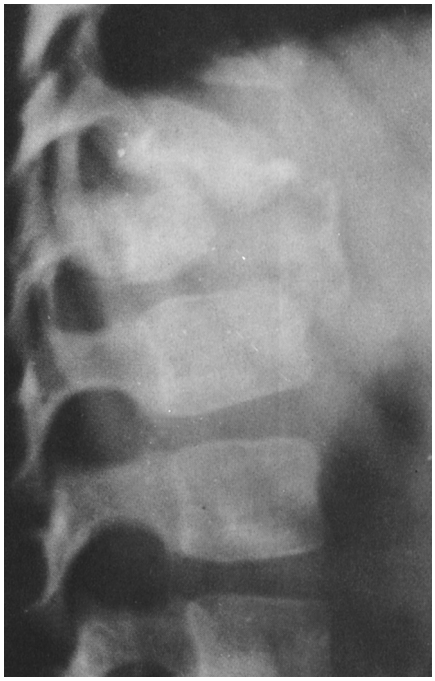

FIGURE 35.19 Osteomyelitis at T11 and T12. Note the destruction of the disk space and vertebral bodies with the beginning of anterior ossification. In this patient, fusion occurred spontaneously, and the patient is now asymptomatic. (From Renshaw TS. *Pediatric Orthopedics*. Philadelphia: WB Saunders; 1986:59.)

Initial evaluation of patients with suspected spinal tumors should include standard anteroposterior and lateral radiographs of the spine (see Fig. 35.18). These may not show small lesions hidden in vertebral pedicles or posterior elements; other studies are often necessary. Technetium bone scanning is particularly useful (see Fig. 35.17). *MRI and CT scans are usually necessary to localize lesions for surgical treatment.* Prompt referral is essential when spinal neoplasia is suspected. The success of treatment depends in large part on early discovery and intervention.

Tumors of Neural Elements

Back pain, lower extremity weakness, and sphincter disturbances are common manifestations of neoplasms of the spinal cord. Although such lesions are rare, they must be suspected in children with unexplained back or leg pain, weakness, sensory or reflex abnormalities, bowel or bladder incontinence, or unexplained gait abnormalities. Neuroblastoma is the most common lesion, but sarcomas (including Ewing sarcoma, rhabdomyosarcoma, and hemangiosarcoma) and astrocytomas or ependymomas also occur in the neural contents of the spinal canal.

In such patients, standard radiography often shows only loss of lordosis or scoliosis secondary to muscle spasm. MRI demonstrates the abnormality, but definitive diagnosis usually requires biopsy. The success of treatment is often related to promptness of diagnosis. Early referral of patients with unexplained back pain is essential for appropriate treatment.

Leukemia

Skeletal involvement is common in patients with leukemia; back pain or limb pain may be the presenting symptom in some children. Proliferation of abnormal hematopoietic tissue in the marrow of long bones or vertebral bodies causes pain and weakens their structure.

Clinical symptoms and signs in children with leukemic skeletal involvement may be confusing. Fever, localized pain and swelling, and elevations of the white blood cell count and erythrocyte sedimentation rate may be mistaken as signs of septic arthritis, osteomyelitis, or intervertebral disk space infection. The presence of abnormal white blood cells on the peripheral blood cell count or of thrombocytopenia increases the likelihood of bone marrow tumor rather than infection.

Osteopenia, periosteal elevation, and metaphyseal lucencies are common radiographic findings in leukemic involvement of long bones. These may be difficult to detect in patients with spinal involvement. Vertebral compression and wedging are sometimes present and may mimic acute fracture or, on occasion, osteomyelitis (Fig. 35.19). The absence of a history of trauma should alert the examiner to search for other causes of the radiographic abnormality. Preservation of intervertebral disk space height with collapse of adjacent vertebral segments is an indication that the vertebral bodies rather than the intervertebral disk are the sites of the abnormality. Technetium bone scanning is useful for detecting other areas of involvement, although it is not as reliable in leukemia as in other spinal lesions. MRI is useful for detecting areas of spinal involvement not visible on plain radiographs and for assessing the extent of intraspinal infiltrate or spinal cord compression present.

The diagnosis of leukemia can be established by bone marrow aspiration. Biopsy of involved vertebral segments is rarely necessary. Support of the spine in a custom-fabricated orthosis is useful for relieving pain and preventing further vertebral collapse during the initial phases of treatment. Prolonged brace treatment may be necessary to prevent vertebral compression fractures that may accompany the osteopenia resulting from steroid therapy. Surgical decompression and fusion may be required in rare cases of acute vertebral compression and spinal cord compromise.

TABLE 35.3 Red Flags: Most Common Indications From History and Examination for Pathologic Findings Needing Special Attention and Sometimes Immediate Action

- Children <18 yr old with considerable pain
- History of violent trauma
- Nonmechanical nature of pain (i.e., constant pain not affected by movement, pain at night)
- History of cancer
- Systemic steroid use
- Drug abuse
- HIV infection or other immunocompromised patients
- Unintentional weight loss
- Systemically ill, particularly signs of infections such as fever or night sweats
- Persisting severe restriction of motion or intense pain with minimal motion
- Structural deformity
- Difficulty with micturition
- Loss of anal sphinter tone or fecal incontinence, saddle anesthesia
- Progressive motor weakness or gait disturbance
- Marked morning stiffness
- Peripheral joint involvement
- Iritis, skin rashes, colitis, urethral discharge, or other symptoms of rheumatologic disease
- Inflammatory disorder such as ankylosing spondylitis suspected
- Family history of rheumatologic disease or structiral abnormality

HIV, human immunodeficiency virus.
Modified from Nachemson A, Vingard E. Assessment of patients with neck and back pain: a best-evidence synthesis. In: Nachemson AL, Johnsson B, eds. *Neck and Back Pain: The Scientific Evidence of Causes, Diagnosis, and Treatment*. Philadelphia: Lippincott Williams & Wilkins; 2001.

SUMMARY AND RED FLAGS

Back pain in children may be referred pain from intraabdominal or retroperitoneal disease (see Table 35.2) or may represent direct involvement of the spinal cord, vertebral bodies, or paraspinal musculature. In most children with normal examination findings, back pain is benign, short-lived, and responsive to rest or nonsteroidal antiinflammatory agents.

Chronic persistent back pain, pain associated with lower extremity or bowel and bladder neurologic deficits, cutaneous lesions over the lumbar spine, systemic signs (as in inflammatory bowel disease, leukemia, osteomyelitis), acute pain, and tenderness with neurologic dysfunction after trauma are red flags (Table 35.3). Signs of cord involvement are particularly ominous and are emergencies. Spinal cord involvement above T10 produces symmetric weakness, increased deep tendon reflexes, up-going toes, and an appropriate sensory loss; conus medullaris involvement (T10 to L2) produces symmetric weakness, increased knee and decreased ankle deep tendon reflexes, a saddle-type anesthesia, and up- or down-going toes on Babinski testing; and cauda equina involvement (below L2) produces asymmetric weakness, loss of deep tendon reflexes, and down-going toes. Such findings represent an acute emergency that warrants immediate imaging (MRI) and therapy, which may include high-dose corticosteroids, radiation therapy, or laminectomy to prevent permanent paralysis.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Aartun E, Degerfalk A, Kentsdotter L, et al. Screening of the spine in adolescents: inter-and intra-rater reliability and measurements error of commonly used clinical tests. *BMC Musculoskelet Disord*. 2014;15:37.

Altaf F, Heran MK, Wilson LF. Back pain in children and adolescents. *Bone Joint J*. 2014;96-B(6):717-723.

Balagué F, Dudler J, Nordin M. Low-back pain in children. *Lancet*. 2003;361:1403-1404.

Bell DF, Erlich MG, Zaleske DJ. Brace treatment for symptomatic spondylolisthesis. *Clin Orthop*. 1988;236:192-198.

Brown R, Hussain M, McHugh K, et al. Discitis in young children. *J Bone Joint Surg Br*. 2001;83:106-111.

Calvo-Munoz I, Gomez-Conesa A, Sanchez-Meca J. Prevalence of low back pain in children and adolescents: a meta-analysis. *BMC Pediatr*. 2013;13:14.

Cassar-Pullicino VN, Eisenstein SM. Imaging in scoliosis: what, why and how? *Clin Radiol*. 2002;57:543-562.

Conrad EU, Olszewki AD, Berger M, et al. Pediatric spinal cord tumors with spinal cord compromise. *J Pediatr Orthop*. 1992;12:454-460.

Deyo RA, Weinstein JN. Low back pain. *N Engl J Med*. 2001;344:363-370.

Edgar M. A new classification of adolescent idiopathic scoliosis. *Lancet*. 2002;360:270-271.

Feldman D, Straight J, Badra M, et al. Evaluation of an algorithmic approach to pediatric back pain. *J Pediatr Orthop*. 2006;26:353-357.

Fernandez M, Carrol CL, Baker CJ. Discitis and vertebral osteomyelitis in children: An 18-year review. *Pediatrics*. 2000;105:1299-1304.

Frennerd AK, Danielson BI, Nachemson AL. Natural history of symptomatic isthmic low-grade spondylolisthesis in children and adolescents: A seven year follow up study. *J Pediatr Orthop*. 1991;11:209-213.

Hadley MN. Management of pediatric cervical spine and spinal cord injuries. *Neurosurgery*. 2002;50:S85-S99.

Harvey BS, Brooks G, Hergenroeder A. Lumbar injuries of the pediatric population. *Prim Care*. 2013;40(2):289-311.

Letts MH, Haasbeek J. Hematocolpos as a cause of back pain in premenarchal adolescents. *J Pediatr Orthop*. 1990;10:731-732.

Lowe TG. Scheuermann disease. *J Bone Joint Surg Am*. 1990;72:940-945.

Michaleff ZA, Kamper SJ, Maher CG, et al. Low back pain in children and adolescents: a systematic review and meta-analysis evaluating the effectiveness of conservative interventions. *Eur Spine J*. 2014;23(10):2046-2058.

Miller R, Beck NA, Sampson NR, et al. Imaging modalities for low back pain in children: a review of spondylosis and undiagnosed mechanical back pain. *J Pediatr Orthop*. 2013;33(3):282-288.

Nussinovitch M, Sokolover N, Volovitz B, et al. Neurologic abnormalities in children presenting with diskitis. *Arch Pediatr Adolesc Med*. 2002;156:1052-1104.

Paassilta P, Lohinvia J, Goring HHH, et al. Identification of a novel common genetic risk factor for lumbar disk disease. *JAMA*. 2001;285:1843-1849.

Pizzutillo PD, Hummer CD. Nonoperative treatment of painful adolescent spondylolysis or spondylolisthesis. *J Pediatr Orthop*. 1989;9:538-540.

Prahinski JR, Polly DW Jr, McHale KA, et al. Occult intraspinal anomalies in congenital scoliosis. *J Pediatr Orthop*. 2000;20:59-63.

Ramirez N, Flynn JM, Hill BW, et al. Evaluation of a systematic approach to pediatric back pain: the utility of magnetic resonance imaging. *J Pediatr Orthop*. 2015;35(1):28-32.

Rogalsky RJ, Black GB, Reed MH. Orthopedic manifestations of leukemia in children. *J Bone Joint Surg Am*. 1986;68:494-501.

Sachs B, Bradford D, Winter RB, et al. Scheuermann kyphosis. Follow-up of Milwaukee brace treatment. *J Bone Joint Surg Am*. 1987;69:50-57.

Seitsalo SK, Osterman H, Hyvarinen K, et al. Progression of spondylolisthesis in children and adolescents. A long term follow-up of 272 patients. *Spine*. 1991;16:417-421.

Sponseller PD. Sizing up scoliosis. *JAMA*. 2003;289:608-609.

Watson KD, Papageorgiou AC, Jones GT, et al. Low back pain in schoolroom children: The role of mechanical and psychosocial factors. *Arch Dis Child*. 2003;88:12-17.

Weinstein SL, Dolan LA, Spratt KF, et al. Health and function of patients with untreated idiopathic scoliosis. *JAMA*. 2003;289:559-566.

36

Lymphadenopathy and Neck Masses

Brett J. Bordini

Given the role of the lymphatic system in developing adaptive responses to numerous antigenic challenges and the rate at which the immune system is exposed to novel antigens early in life, enlarged lymph nodes are regularly encountered both incidentally and within the context of many childhood illnesses. The challenge for the clinician is determining when a change in the size or quality of a lymph node is physiologic and when such a change represents pathology. A thorough history, physical examination, and recognition of the anatomic drainage patterns of the lymphatic system will oftentimes sufficiently narrow the differential diagnosis of lymphadenopathy such that complicated or invasive diagnostic evaluations are unnecessary.

MECHANISM OF LYMPHADENOPATHY

The lymphatic system is a network of vessels and tissues that collects excess fluid from the cellular interstitium and returns it to the peripheral circulation. This interstitial fluid is similar in composition to plasma, though it may contain additional proteins, pathogens, other antigens, and antigen-presenting cells. The collected fluid, termed **lymph**, enters the lymphatic system via specialized lymphatic capillaries and passes into nearby lymph nodes via afferent lymphatic vessels. The lymph nodes contain both B and T lymphocytes lying in a supportive framework within a connective tissue capsule (Fig. 36.1). Additional lymphocytes may enter lymph nodes from the peripheral venous circulation via postcapillary high endothelial venules. Antigens, antigen-presenting cells, and pathogens present within the lymph interact with the lymphocytes, allowing for the production of B- and/or T-cell immune responses in an effort to clear the antigen or pathogen. Efferent lymphatic vessels then carry lymph and antigen-sensitized lymphocytes from the nodes back to the peripheral circulation via the thoracic duct.

Enlargement of lymph nodes can come about via several mechanisms. First, **physiologic hyperplasia** can occur as nodal and circulating lymphocytes proliferate within nodes in response to antigenic stimulation. Second, bacteria that have been transported to the nodes may stimulate the recruitment of polymorphonuclear cells and the elaboration of inflammatory mediators that can lead to the edema, erythema, and tenderness characteristic of **bacterial lymphadenitis** or to suppuration and abscess formation. Third, **malignant cells** may arise within the node itself and proliferate, causing enlargement, or arrive from distant cancerous sites and infiltrate the nodal tissue. Fourth, certain **medications** can cause lymphadenopathy either directly or as part of a serum sickness-like reaction. Finally, in rare **genetic storage diseases** (Niemann–Pick, Gaucher diseases), macrophages laden with abnormally metabolized lipids may lodge within lymph nodes, causing enlargement.

The regional drainage pattern of each lymph node group is important in determining the cause of lymphadenopathy, particularly when localized to an individual node or contiguous group of nodes (Fig. 36.2 and Tables 36.1 and 36.2). The cervical lymph nodes drain lymph from distinct areas of the head, neck, and throat and may enlarge if a local infection is present. Consequently, because otitis media and pharyngitis are common infections in children, head and neck lymphadenopathy is one of the more frequently encountered regional lymphadenopathy patterns in small children. The axillary nodes drain lymph from the arms, lateral breasts, and superficial chest and upper abdomen, and isolated enlargement of these nodes may suggest pathology in these areas. The inguinal nodes drain the lower extremities, genitourinary system, and perineum, which may indicate lower extremity pathology or the presence of a sexually transmitted infection in patients with an exposure history. Supraclavicular lymphadenopathy is a concerning finding and should prompt concern for an underlying neoplasm, fungal infection, tuberculosis, or sarcoidosis. **Generalized lymphadenopathy**, defined as the presence of enlarged or abnormal lymph nodes in 2 or more noncontiguous lymph node groups (with or without hepatosplenomegaly), is often indicative of a systemic response to an infectious or otherwise inflammatory process but may also indicate malignant proliferation of lymphocytes (Table 36.3).

◆ History

History should be aimed at establishing the time course of the development of lymphadenopathy, whether the lymphadenopathy is restricted to a particular anatomic region or is generalized, and if there are any associated signs, symptoms, or exposures that may suggest an etiology.

Lymphadenopathy that develops rapidly over several days is more suggestive of an acutely inflammatory, often infectious process, whereas more indolently developing lymphadenopathy may suggest malignancy, chronic disease, or an atypical infection. The sudden onset of unilateral inguinal adenopathy shortly following lower extremity trauma suggests an infection in the traumatized extremity. In contrast, progressive enlargement of multiple noncontiguous nodal groups over the course of weeks or months that is accompanied by

(See *Nelson Textbook of Pediatrics,* p. 2413.)

weight loss, fevers, or night sweats, suggests a systemic illness such as lymphoma or tuberculosis. When establishing the time period over which the lymphadenopathy developed, the clinician should clarify both when the node was first noted to be abnormal, as well as the last time the node was felt to be normal. This information is particularly essential if associated symptoms, overlying skin changes, and tenderness are absent, since more slowly developing lymphadenopathy may not be noticed until the node or nodes are quite enlarged, or if lymphadenopathy was noted only incidentally when dressing, grooming, or bathing.

The age of the child with lymphadenopathy is similarly important in the consideration of the cause (see Table 36.3). Neonatal lymphadenopathy is typically indicative of exposure to an infectious agent in utero, such as cytomegalovirus (CMV), syphilis, human immunodeficiency virus (HIV), rubella, or toxoplasmosis, though may less frequently be associated with congenital malignancy or storage diseases. In contrast, toddlers and children with adenopathy tend to have either focal infections that drain into the affected nodal chain, or systemic viral infections, resulting in diffusely enlarged nodes. Adolescents may acquire exposures that place them at risk for sexually transmitted infections and inguinal adenopathy. Just as exposure to certain infectious agents may vary with age, the risk of hematologic malignancy varies as well: acute leukemias are more common in toddlers and young children; non-Hodgkin lymphoma is more common is school-aged children, and Hodgkin lymphoma is more common in adolescents.

The past medical history and review of systems should be explored for conditions that may either cause lymphadenopathy directly or place the patient at increased risk for opportunistic infections, such as congenital or acquired immunodeficiency. The clinician should inquire about any signs or symptoms that would suggest an acute infectious process or more slowly progressive constitutional symptoms that may suggest malignancy or indolent infection. The quality of oral hygiene practices and dentition should be assessed as **odontogenic infections** may not readily be appreciated as a source of cervical lymphadenopathy. The use of any prescription medications, over-the-counter medicines, or traditional remedies should be ascertained. In addition to medications that may directly cause lymphadenopathy, other substances may provoke lymphadenopathy as a component of a serum sickness-like reaction or be associated with autoimmune or rheuma-

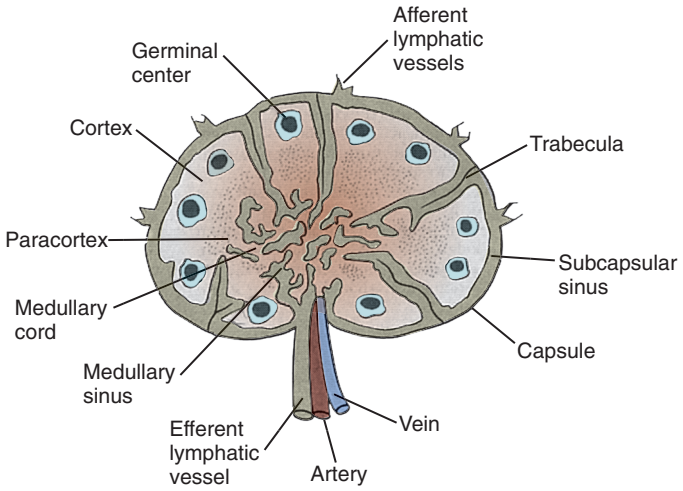

FIGURE 36.1 Diagrammatic representation of the structure of a lymph node. (From Faller DV. Diseases of the lymph nodes and spleen. In: Wyngaarden JB, Smith LH, Bennett JC, eds. *Cecil Textbook of Medicine*. 19th ed. Philadelphia: WB Saunders; 1992:979.)

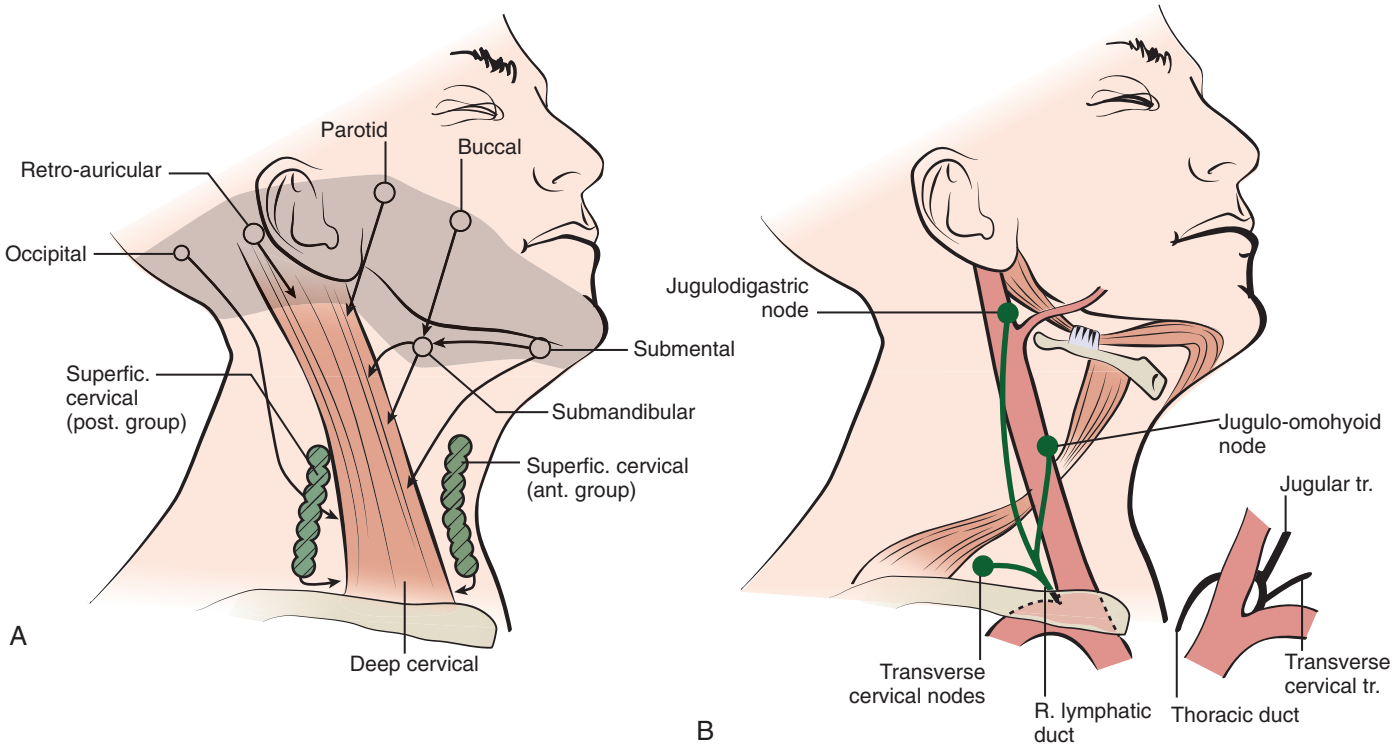

FIGURE 36.2 The superficial *(A)* and deep cervical *(B)* lymph nodes that drain the head and neck. Ant., anterior; post., posterior; R, right; superfic., superficial; tr., tributary. (From O'Rahilly RO. *Gardner-Gray-O'Rahilly Anatomy: A Regional Study of Human Structure*. 5th ed. Philadelphia: WB Saunders; 1986:719)

TABLE 36.1 Drainage Areas of Regional Nodes

Abdominal and Pelvic
Abdomen, lower extremity, pelvic organs

Axillary
Arm, breast, chest wall, hand, upper and lateral abdominal wall

Cervical
External ear, larynx, parotid, superficial tissues of the scalp, head, and neck, thyroid, tongue, trachea

Epitrochlear
Forearm, hand

Iliac
Bladder, lower abdomen, part of the genitalia, urethra

Inguinal
Gluteal region, lower anal canal, lower extremity, perineum, vulva and vagina in females, scrotum and penis in males, skin of the lower abdomen

Mediastinal
Thoracic viscera

Occipital
Posterior scalp

Popliteal
Knee joint, skin of the lateral lower leg and foot

Preauricular
Cheek, conjunctivae, eyelid, temporal scalp

Submaxillary/Submental
Buccal mucosa, gums, teeth, tongue

Supraclavicular
Abdomen, arms, head, lungs, mediastinum, neck, superficial thorax
Left supraclavicular adenopathy is usually due to an intraabdominal problem.
Right supraclavicular adenopathy is usually due to an intrathoracic problem.

TABLE 36.2 Sites of Regional Lymphadenopathy and Associated Diseases

Cervical
Oropharyngeal infection (viral, group A streptococcal, or staphylococcal)
Scalp infection (tinea)
Mycobacterial lymphadenitis (tuberculous and nontuberculous mycobacteria)
Viral infection (EBV, CMV, HHV-6, measles)
Cat-scratch disease
Kawasaki disease
Thyroid disease
Kimura disease
Periodic fever, aphthous stomatitis, pharyngitis, cervical adenopathy (PFAPA) syndrome
Kikuchi-Fujimoto disease

Anterior Auricular
Conjunctivitis or other eye infections
Oculoglandular tularemia, cat-scratch disease, EBV, adenovirus

Posterior Auricular
Otitis media
Viral infection (especially rubella, parvovirus)

Supraclavicular
Malignancy or infection in the mediastinum (right)
Metastatic malignancy from abdomen (left)
Lymphoma
Tuberculosis

Epitrochlear
Hand infection, arm infection*
Lymphoma†
Sarcoidosis
Syphilis
EBV
HIV

Inguinal
Urinary tract infection
Sexually transmitted infection (especially syphilis or lymphogranuloma venereum)
Lower extremity suppurative infection
Plague

Hilar (Not Palpable, Found on Chest Radiograph or CT) (see Table 36.4)
Tuberculosis†
Histoplasmosis†
Blastomycosis†
Coccidioidomycosis†
Leukemia/lymphoma†
Hodgkin disease†
Metastatic malignancy*
Sarcoidosis†
Castleman disease

Axillary
Cat-scratch disease
Arm infection
Malignancy of chest wall
Leukemia/lymphoma
Brucellosis

*Unilateral.
†Bilateral.
CMV, cytomegalovirus; CT, computed tomography; EBV, Epstein–Barr virus; HHV-6, human herpesvirus 6; HIV, human immunodeficiency virus.

tologic conditions that cause generalized lymphadenopathy (see Table 36.3).

After determining the timing and distribution of the lymphadenopathy and placing these findings within the context of the child's age and past medical history, the clinician should inquire about any exposures that may have led to the development of lymphadenopathy, focusing in particular on diet, travel history, and contact with individuals, animals, or environments that may pose a risk for disease transmission. Contact with or consumption of raw or undercooked meats, particularly pork, lamb, and venison, may transmit *Toxoplasma gondii*, leading to toxoplasmosis. Similarly, contact with agricultural animals or ingestion of unpasteurized dairy products may place patients at risk for acquiring certain pathogens, such as *Brucella* species or *Mycobacterium bovis*; infection with either of which may lead to generalized lymphadenopathy. Potential exposures in the home environment should be assessed, including the risk of contaminated drinking water and whether there are concerns for mold exposure, particularly in immunocompromised patients. The presence of pets, either within the home or in the area, should be determined. Cats or kittens that may scratch the child and transmit *Bartonella henselae*, the etiologic agent of **cat-scratch disease**, are often omitted from the history unless such questions are specifically asked. Furthermore, some families may deny the presence of household pets but forget to mention that the child plays with a pet present in a barn or around the neighborhood. Travel history should determine whether the child is from or has been exposed to geographic areas associated with a higher risk for acquiring certain infections, such as tuberculosis in developing nations or histoplasmosis in the Ohio River valley. The clinician should inquire whether any family members or close contacts are ill or taking medications, whether any have recently traveled to or immigrated from other countries, and whether any have recently been incarcerated. Adolescents should be questioned about risk factors for HIV and sexually transmitted infections, such as syphilis or lymphogranuloma venereum, which may cause generalized or inguinal lymphadenopathy, respectively.

The family history should also focus on potentially heritable conditions, such as autoimmune or rheumatologic disorders, certain

TABLE 36.3 Differential Diagnosis of Generalized Lymphadenopathy

Neonate	Child	Adolescent
Common Causes		
CMV	Nonspecific viral infections	Viral Infections
HIV	EBV	EBV
Syphilis	CMV	CMV
Toxoplasmosis	HIV	HIV
	Toxoplasmosis	Measles
	Measles	Toxoplasmosis
		Syphilis
Rare Causes		
Chagas disease (congenital)	Serum sickness	Serum sickness
Congenital leukemia	SLE, JIA	SLE, JIA
Congenital tuberculosis	Leukemia/lymphoma	Leukemia/lymphoma
Reticuloendotheliosis	Tuberculosis (miliary)	Tuberculosis
Metabolic storage disease	Sarcoidosis	Sarcoidosis
Histiocytic disorders	Fungal infections	Fungal infections
Listeria sepsis	Plague	Plague
	Leptospirosis	Leptospirosis
	Brucellosis	Brucellosis
	Langerhans cell histiocytosis	Drug reaction (immune)
	Macrophage activating syndrome	Castleman disease
	Hemophagocytic lymphohistiocytosis	Rickettsial infection
	Castleman disease (very rare in the this age group)	
	Chronic granulomatous disease	
	Sinus histiocytosis (Rosai–Dorfman disease)	
	Kikuchi-Fujimoto disease	
	Autoimmune lymphoproliferative disease (ALP)	
	Rickettsial infection	

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HIV, human immunodeficiency virus; JIA, juvenile idiopathic arthritis (as Still disease); SLE, systemic lupus erythematosus.

hematologic and soft tissue malignancies as well as storage diseases that may be associated with noninfectious forms of lymphadenopathy.

◆ Physical Examination

Physical examination should assess general appearance and look for signs or symptoms that may reveal the underlying cause of lymphadenopathy. Examination of the lymphatic system should establish the size, quality, and distribution of any abnormal lymph nodes and should assess for the presence of tenderness or changes in the overlying skin or surrounding tissues.

Size

The threshold beyond which a particular node is considered enlarged varies by nodal group. In general, nodes over 1 cm in diameter are considered enlarged; exceptions include epitrochlear nodes greater than 0.5 cm in diameter and inguinal nodes greater than 1.5 cm in diameter.

Quality

The quality of the nodes often yields some clues as to the cause of the adenopathy. The clinician should assess consistency, mobility, shape, tenderness, and whether any changes to the overlying skin or soft tissues are present. The following general patterns are worth noting:

- Erythematous, tender, and warm: acute bacterial infection with suppurative adenitis
- Tender, nonerythematous, and soft: viral infection or other systemic infection
- Firm, hard, rubbery, and nontender: lymphoma or other infiltrating tumor
- Hard, matted, immobile, and nontender: tumor, metastatic or local; fibrosis that follows acute infection

Distribution

All areas in which lymphadenopathy is commonly present should be palpated, including the cervical, auricular, axillary, epitrochlear, inguinal, and supraclavicular areas, because lymphadenopathy in certain regions is linked to systemic or local illness. If more than 2 noncontiguous nodal groups are abnormal, without evidence of distinct focal infections inciting the lymphadenopathy within each group, the lymphadenopathy is generalized.

Regional lymphadenopathy usually reflects pathologic processes within the lymphatic drainage distribution of that particular nodal chain (see Table 36.2). Several patterns of regional lymphadenopathy should prompt further evaluation. The presence of palpable supraclavicular nodes is often a red flag for a serious illness such as malignancy. **Supraclavicular nodes** that are palpated on the right side often reflect a mediastinal tumor or invasive mediastinal infection, such as histoplasmosis. Supraclavicular nodes on the left side are often the result of metastatic spread of an abdominal tumor. The presence of either type of node mandates an urgent evaluation, including computed tomography (CT) or magnetic resonance imaging. **Epitrochlear nodes**, if unilateral, commonly indicate the hand or arm as a source of distal infection; however, palpable bilateral epitrochlear lymph nodes usually reflect systemic illness, such as syphilis, sarcoidosis, or lymphoma. **Inguinal** node enlargement is common and is usually caused by the frequent occurrence of minor trauma and infections in a child's legs and feet. Significantly enlarged inguinal nodes may also be present with sexually transmitted infections, such as syphilis, chlamydial urethritis, lymphogranuloma venereum, or with urinary tract infection, lymphoma, or abdominal tumors.

Mediastinal adenopathy (or mass) may be detected incidentally, or secondary to chest symptoms, or during the evaluation of peripheral but generalized lymphadenopathy. The differential diagnosis is noted in Table 36.4.

◆ Differential Diagnosis

The differential diagnosis of lymphadenopathy is developed in a stepwise fashion, first by determining whether the lymphadenopathy is regional or generalized. Next, the time course of the lymphadenopathy should be defined as acute or as chronic, defined as being present for a period of more than 4 weeks. Finally, the quality of the nodes and

TABLE 36.4 Differential Diagnosis of Mediastinal Masses

Anterior Mediastinum
Lymphoma
Thymic cyst
Thymic "hyperplasia"
Benign teratoma
Malignant germ-cell tumor
Thymoma
Middle Mediastinum
Lymphoma
Tuberculosis
Histoplasmosis
Sarcoidosis
Posterior Mediastinum
Neuroblastoma
Ganglioneuroma
Neurofibroma
Sarcoma
Duplication cyst

From Alexander S, Ferrando AA. Pediatric lymphoma. In: Orkin SH, et al, eds. *Nathan and Oski's Hematology and Oncology of Infancy and Childhood.* 8th ed. Philadelphia: Elsevier; 2015;2:1627; Box 53-2.

the presence of any associated signs or symptoms should be ascertained. Using this approach, a comprehensive differential diagnosis and evaluation plan can then be developed (Figs. 36.3 and 36.4).

Differential Diagnosis of Head and Neck Lymphadenopathy: Head and Neck Masses

Several congenital and acquired lesions of other head and neck structures, many of which are benign, may mimic lymphadenopathy and deserve consideration. History and physical examination should provide sufficient information to arrive at an appropriate differential diagnosis and evaluation strategy of these mimics. Important factors in distinguishing lymphadenopathy from nonnodal congenital or acquired lesions of the head and neck include the age of the child, anatomic position, presence of signs of inflammation, associated symptoms, and the time course of the development of symptoms (Figs. 36.5 and 36.6).

◆ Evaluation and Management Strategies

Many previously healthy children with acute lymphadenopathy require few, if any, laboratory or imaging studies. No laboratory testing may be required for well-appearing children whose acute, localized adenopathy can be attributed to an infection in the vicinity of the node. Patients with localized cutaneous bacterial infections causing adenopathy also may not need laboratory investigations before the initiation of empiric antimicrobial therapy unless there is suspicion of bacteremia or invasive spread of the infection to underlying tissues.

Acute cervical adenopathy accompanying pharyngitis in children older than 18 months may necessitate a throat culture for group A *Streptococcus*. The additional presence of hepatomegaly or splenomegaly should raise suspicion of Epstein-Barr virus (EBV)–related infectious mononucleosis. The clinician could obtain a complete blood cell count with white blood cell differential (to identify lymphocytosis and atypical lymphocytes) and EBV titers (or a monospot heterophile antibody test in older children).

Supraclavicular adenopathy, acute cervical adenopathy accompanied by respiratory distress, or prolonged cervical adenopathy warrants anteroposterior and lateral radiographs of the neck and/or chest, a complete blood cell count with white blood cell differential, and interferon gamma release assay or placement of a purified protein derivative (PPD) tuberculin skin test. CT with contrast is necessary in certain situations to fully delineate cervical adenopathy that is excessively large or that impinges on the airway, or to determine whether mediastinal adenopathy is also present.

Children presenting with prolonged diffuse lymphadenopathy, hepatomegaly or splenomegaly, weight loss, night sweats, fevers, recurrent infections, or failure to thrive must be more thoroughly studied. Only after the complete blood cell count and differential and chest radiograph are analyzed should other diagnostic studies be considered. HIV, EBV, and CMV studies (culture, polymerase chain reaction [PCR], and serologic profiles) may be obtained for some children. Because the diagnoses of leukemia (through bone marrow aspiration, biopsy), lymphoma (through bone marrow aspiration, biopsy), systemic lupus erythematosus (through antinuclear antibody, double-stranded DNA antibodies), and cat-scratch disease (through biopsy and/or *B. henselae* serologic profile) require more invasive and expensive tests, the physician should first consider all aspects of the history and physical examination before ordering laboratory studies.

Regional Lymphadenopathy

The typical child with acute regional lymphadenopathy presents with enlarged nodes, commonly in the cervical region. A thorough history and careful physical examination should reveal whether nodes are definitively involved, as opposed to other nonnodal structures, such as the parotid gland. In many cases, no other abnormalities are found on examination, and systemic signs are minimal. Laboratory tests should include a complete blood cell count and differential as well as measurement of the erythrocyte sedimentation rate and the C-reactive protein. In the child with fever and a tender cervical lymph node, oral antibiotics (with activity against mouth flora, streptococci, and staphylococci) should be started; if the lymphadenopathy persists or worsens, intravenous antibiotics are indicated. A PPD or interferon gamma release assay should be undertaken, and if the results are negative and symptoms resolve, it is reasonable to complete the antimicrobial course orally.

In contrast, if the lymphadenopathy continues or becomes frank lymphadenitis with erythema and tenderness despite antimicrobial therapy, further work-up is indicated. Imaging the involved area is helpful but not always necessary. Although ultrasonography can reveal enlarged nodes or a fluid-filled abscess or cyst, contrast-enhanced computed tomography of the area is the best method for defining the extent of inflamed nodes and whether an abscess is present (Fig. 36.7). If an abscess is found, incision and drainage, followed by appropriate bacterial and mycobacterial cultures and stains, are appropriate. If atypical mycobacteria are suspected on the basis of a borderline positive PPD result or clinical presentation, fine-needle aspiration or excisional biopsy is preferred because incision and drainage often leads to draining sinus tracts that are difficult to heal. Enlarged nodes that do not recede in several weeks with appropriate antimicrobial therapy and without explanation (such as acute EBV infection) should also raise the suspicion of malignancy.

Generalized Lymphadenopathy

In the child with generalized lymphadenopathy, the cause may be infectious, immunologic, or malignant. Infectious causes, such as HIV, EBV, toxoplasmosis, secondary syphilis, and CMV infections, can generally be determined quickly through serologic testing. Noninfectious causes, such as systemic lupus erythematosus and serum sickness, can

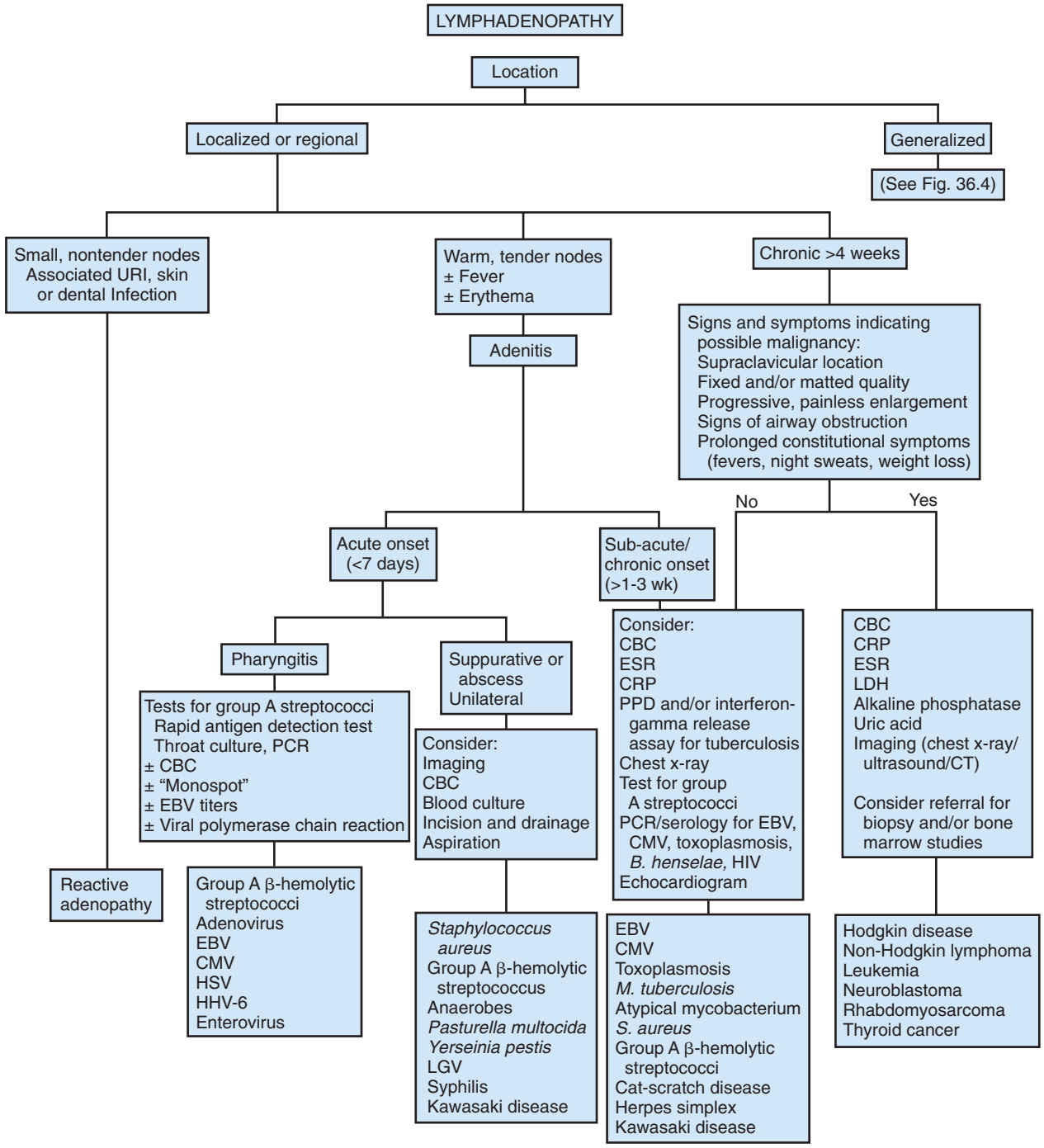

FIGURE 36.3 Diagnostic algorithm for the evaluation of regional lymphadenopathy. CBC, complete blood count; CMV, cytomegalovirus; CRP, C-reactive protein; CT, computed tomography; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; HHV, human herpesvirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; LDH, lactate dehydrogenase; LGV, lymphogranuloma venereum; PCR, polymerase chain reaction; PPD, purified protein derivative (tuberculosis skin test); RPR, rapid plasma reagin; URI, upper respiratory infection; VDRL, Venereal Disease Research Laboratory. (Modified from Pomeranz AJ, Sabnis S, Busey SL, Kliegman RM. *Pediatric Decision-Making Strategies*. 2nd ed. Philadelphia: Elsevier; 2016:229.)

also generally be excluded by a thorough history and serologic studies when indicated. Drugs may cause serum sickness but may also produce hypersensitivity reactions with resulting generalized lymphadenopathy. Medications associated with drug-induced lymphadenopathy include allopurinol, atenolol, captopril, carbamazepine, gold, hydralazine, penicillins, phenytoin, primidone, procainamide, pyrimethamine, quinidine, sulfonamides, sulindac, and tetracyclines. If the generalized lymphadenopathy cannot be attributed to an infectious or other cause, if the nodes fail to recede within several weeks, and especially if there are systemic symptoms, malignancy must be considered. An abnormal complete blood cell count demonstrating anemia, leukopenia, or thrombocytopenia, or radiologic evidence of mediastinal adenopathy or pleural disease is highly suggestive of malignancy. Because serious disseminated infections, such as tuberculosis and histoplasmosis, can

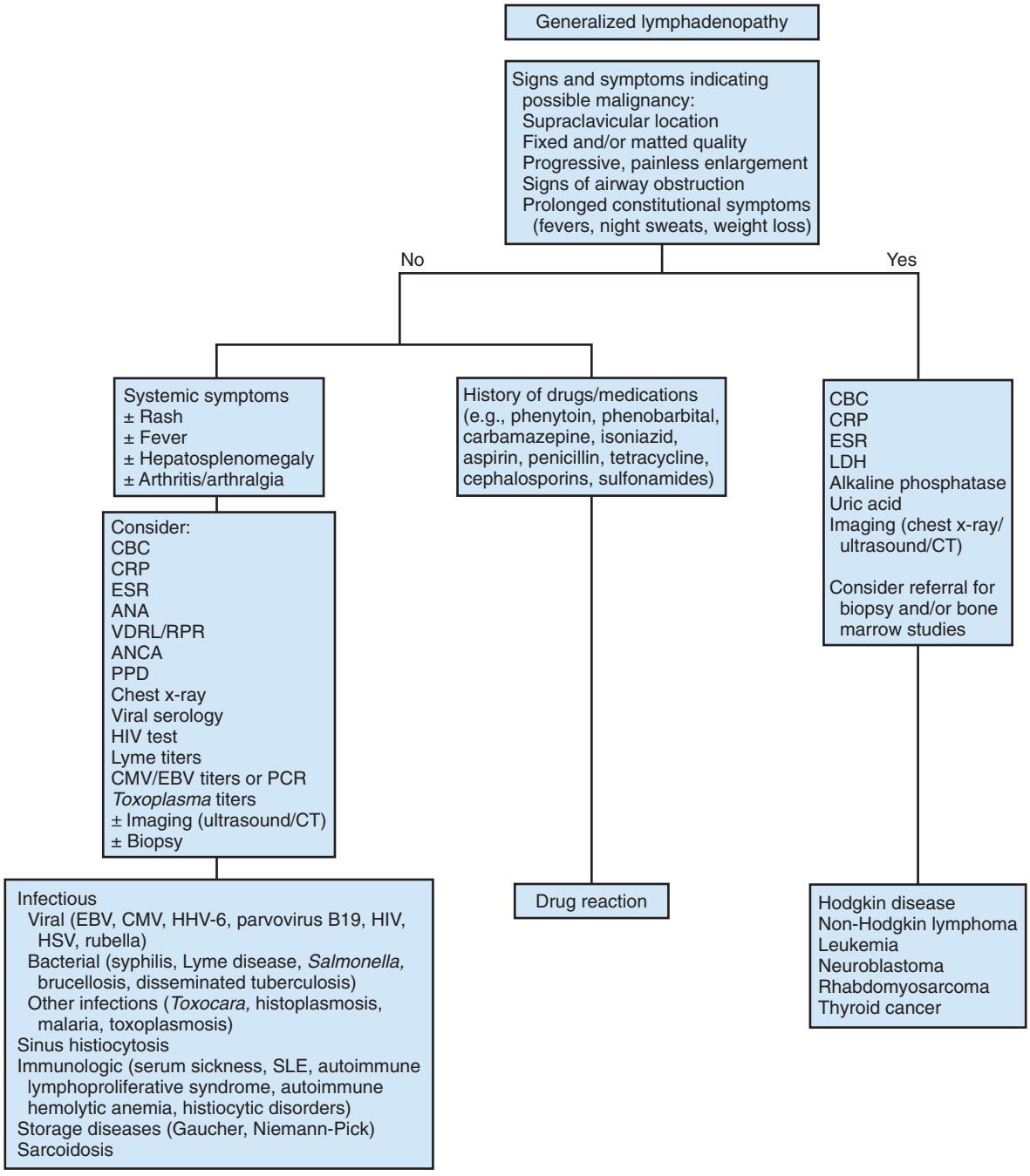

FIGURE 36.4 Diagnostic algorithm for generalized lymphadenopathy. ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; CBC, complete blood count; CMV, cytomegalovirus; CRP, C-reactive protein; CT, computed tomography; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; HHV-6, human herpesvirus 6; HSV, herpes simplex virus; LDH, lactate dehydrogenase; PCR, polymerase chain reaction; PPD, purified protein derivative (tuberculosis skin test); RPR, rapid plasma reagin; SLE, systemic lupus erythematosus; VDRL, Venereal Disease Research Laboratory. (Modified from Pomeranz AJ, Sabnis S, Busey SL, Kliegman RM. *Pediatric Decision-Making Strategies*. 2nd ed. Philadelphia: Elsevier; 2016:231.)

manifest in a similar manner, fine-needle aspiration or biopsy of an involved node or bone marrow aspiration is crucial. Excision of a node is preferred in some cases in order to obtain adequate tissue for pathologic study, stains, or cultures.

Lymphadenopathy Patterns

Several patterns of lymphadenopathy and their underlying causes deserve special mention, due either to the frequency with which they are encountered in pediatric practice, or to the potential severity of the underlying cause.

Infections of the oropharynx. Pharyngeal infection is the most common cause of regional lymphadenopathy in children (see Chapter 1). Many of these pharyngeal infections are associated with cervical lymphadenopathy and are viral in origin. Frequent viral causes include adenovirus, parainfluenza, influenza, rhinovirus, and enterovirus. EBV and CMV also commonly cause exudative pharyngitis and cervical

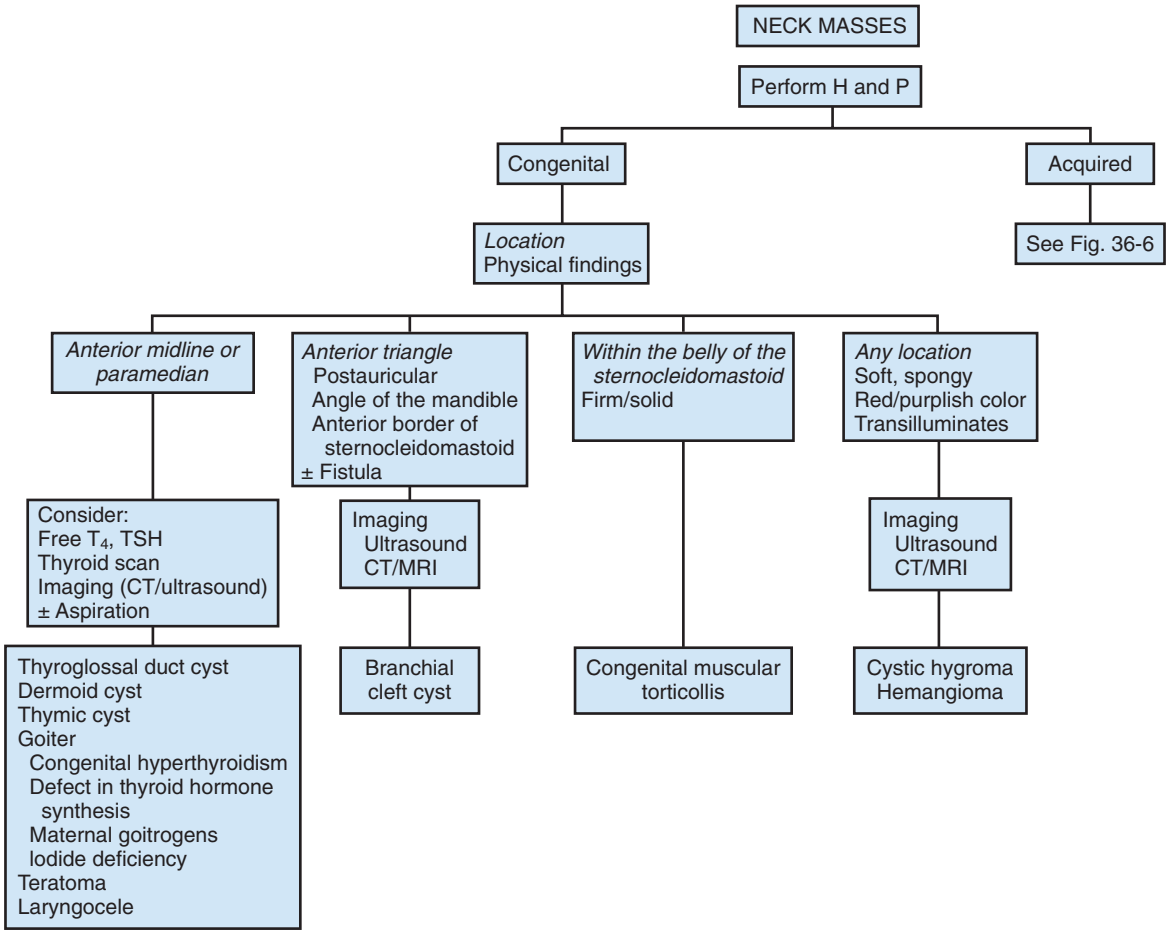

FIGURE 36.5 Diagnostic algorithm for congenital neck masses. CT, computed tomography; H and P, history and physical examination; MRI, magnetic resonance imaging; T_4, thyroxine; TSH, thyroid-stimulating hormone. (Modified from Pomeranz AJ, Sabnis S, Busey SL, Kliegman RM. *Pediatric Decision-Making Strategies*. 2nd ed. Philadelphia: Elsevier; 2016:9.)

lymphadenopathy. The chief complaint usually includes pain with swallowing and with talking, as well as tender, enlarged lymph nodes in the neck. Systemic manifestations, such as fever, myalgia, chills, and rhinorrhea may also be present. An examination of the throat typically reveals a symmetrically erythematous posterior oropharynx with enlarged tonsils that often contain exudates. Exudates can be seen with both viral and bacterial causes of pharyngitis and adenopathy, and thus do not reliably enable the examiner to discriminate between the 2 causes. Herpes stomatitis with mucocutaneous involvement and herpes pharyngitis with oropharyngeal vesicles are also associated with bilaterally enlarged, tender, non-erythematous cervical nodes.

Bacterial infection of the pharynx is also commonly associated with enlarged, tender cervical lymph nodes. Strains of group A β-hemolytic streptococci are the most common causes of such infections and are difficult to differentiate clinically from viral causes of pharyngitis and lymphadenopathy; thus, throat culture, PCR, or rapid antigen detection is necessary. An associated sandpapery rash and beefy-red tonsils with palatal petechiae are not usually seen with viral pathogens and should make the examiner consider group A streptococci and toxin-mediated scarlet fever as a likely cause. Other bacteria can cause pharyngitis and cervical adenopathy, including non–group A streptococci and anaerobic organisms, such as *Fusobacterium* species. Anaerobic organisms can lead to painful oral gingivitis or stomatitis and pharyngitis (Vincent angina) that may progress to peritonsillar abscess. Asymmetry in the tonsils and surrounding tissues, as well as deviation of the uvula away from the affected side may be seen with peritonsillar abscesses, along with unilateral tender, enlarged cervical lymph nodes ipsilateral to the abscess. Complications of acute bacterial pharyngitis may also include **Lemierre syndrome**, the findings of which include high fever and unilateral, lateral neck swelling that may be confused with adenopathy. Lemierre syndrome is due to septic thrombosis of the internal jugular vein (and pulmonary septic emboli), usually caused by invasion of the bloodstream by *Fusobacterium* organisms, and should lead to prompt hospitalization, blood cultures, treatment with intravenous antibiotics, and imaging of the internal jugular vein via Doppler flow ultrasonography or contrast-enhanced computed tomography.

Acute cervical lymphadenitis—inflammation of the cervical lymph nodes with tender enlargement—is most likely to occur with group A streptococcal or *Staphylococcus aureus* infection. There may or may not be a history of sore throat or pharyngeal inflammation on examination. Infection with other oral bacteria, including non–group A streptococci and anaerobes such as *Fusobacterium* or *Arcanobacterium* species may also occur, presumably with the pharynx as the portal of entry. Other common sites for acute lymphadenitis are the submandibular nodes. Usually, these nodes quickly diminish in size after institution of appropriate antibiotic therapy, providing some degree of retrospective diagnosis while simultaneously being therapeutic.

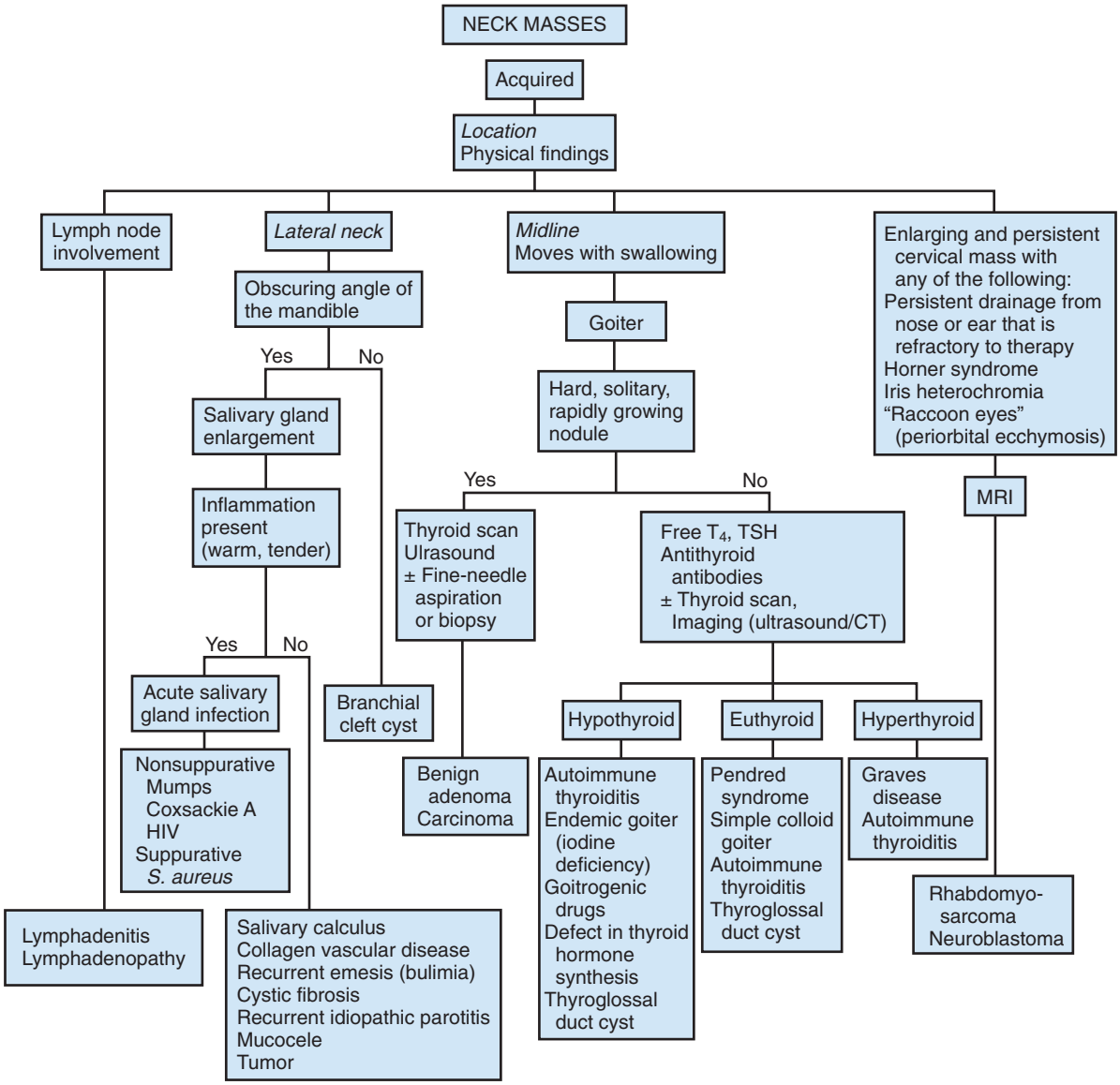

FIGURE 36.6 Diagnostic algorithm for acquired neck masses. CT, computed tomography; MRI, magnetic resonance imaging; T_4, thyroxine; TSH, thyroid-stimulating hormone. (Modified from Pomeranz AJ, Sabnis S, Busey SL, Kliegman RM. *Pediatric Decision-Making Strategies*. 2nd ed. Philadelphia: Elsevier; 2016:11.)

Suppuration and spontaneous drainage of the nodes is less common than adenitis and is not typically seen in the setting of viral infections. Acute suppurative cervical adenitis can be seen in infections of the face and scalp and is usually caused by infection with group A streptococci or *S. aureus*. Management of suppuration includes incision and drainage or excision of the suppurative node. Gram stain and bacterial, fungal, and mycobacterial cultures of the drainage should be obtained. If there is concern for mycobacterial disease, a tuberculin skin test should be placed and/or interferon-gamma release assay should be performed. Total excision should be performed if atypical mycobacterial infection is suspected, because draining fistulas may form if a needle biopsy or partial resection is performed. Fine-needle aspiration may reduce the risk of sinus formation.

Infections of the extremities. Bacterial infections of the skin and soft tissues are common causes of localized lymphadenopathy and adenitis, and can lead to axillary or inguinal adenopathy if these infections originate in the extremities. These infections, primarily caused by group A β-hemolytic streptococci or *S. aureus*, may drain into and inflame single or multiple regional lymph nodes. Any laceration or insect bite that becomes infected may yield adenopathy upstream in the nodal drainage basin of the infected site. Occasionally, penetrating injuries to the feet occurring through damp shoes or in wet areas may yield infections with other bacteria, such as *Pseudomonas aeruginosa*. These penetrating infections usually manifest with cellulitis or osteomyelitis; lymphadenopathy is noted during the physical examination. The most common sites of infection include the foot or leg, leading to unilateral inguinal lymphadenitis, and the hand or arm, causing axillary lymphadenitis or unilateral inflammation of the epitrochlear nodes.

Epstein–barr virus infection. Infection with EBV is a common cause of both regional (bilateral cervical) and diffuse lymphadenopathy. This virus classically causes a mononucleosis syndrome in adolescents (Fig. 36.8), consisting of acute pharyngitis that may have a prolonged course, with tender and firm cervical adenopathy, malaise, fever, weight loss, and anorexia. Nearly half of patients will have generalized lymphadenopathy as well. More than 80% of patients have

mild hepatitis that is clinically silent but can be documented with liver enzyme studies; approximately 10% become jaundiced. Splenomegaly is present in more than 50% of patients and, in rare cases, progresses to splenic rupture. A small number of patients also have parapharyngeal and tonsillar lymphoid hyperplasia, which causes difficulty swallowing or breathing and can produce significant problems, leading to dehydration or airway obstruction. Small children with EBV infection often present with atypical symptoms or may be completely asymptomatic. In these children, fever and mild cervical adenopathy may be the major symptoms on presentation, or the child may be significantly ill with high fever and pharyngitis. In some, a nonspecific rash, appearing often after beginning empiric antibiotic therapy with penicillins, will suggest the diagnosis. Young children with acute EBV infection are more likely to have hepatosplenomegaly, rash, and eyelid edema than are young adults.

The diagnosis of EBV infection in older children focuses on the characteristic clinical syndrome and a relative lymphocytosis of 40-50% seen in the differential white blood cell count, with up to 10-20% atypical lymphocytes. Heterophile immunoglobulin M (IgM) antibodies, which are non-EBV directed and agglutinate sheep and horse red blood cells, are found in more than 80% of young adults with EBV and are at maximal titer 3-4 weeks after infection. Heterophile antibodies are rarely found in children younger than 5 years with EBV infections. In young children, antibody titers directed to specific EBV antigens are necessary to confirm the diagnosis (Table 36.5). IgM antibodies against viral capsid antigen (VCA) followed by immunoglobulin G (IgG) directed to VCA and early antigens (EAs) are the most common antibody profile. Antibodies to nuclear antigens develop

FIGURE 36.7 Suppurative lymphadenitis in a 5-year-old female with neck swelling and redness. Contrast-enhanced computed tomography image reveals a group of enlarged nodes in the right posterior triangle with central hypoattenuating necrosis *(arrow)*. Also, note the enlarged tonsils (T) in this child with recurrent tonsillitis. (From Lowe LH, Smith CJ. Infection and inflammation. In: Coley BD, ed. *Caffey's Pediatric Diagnostic Imaging*. 12th ed. Philadelphia: Elsevier; 2013;1:139.)

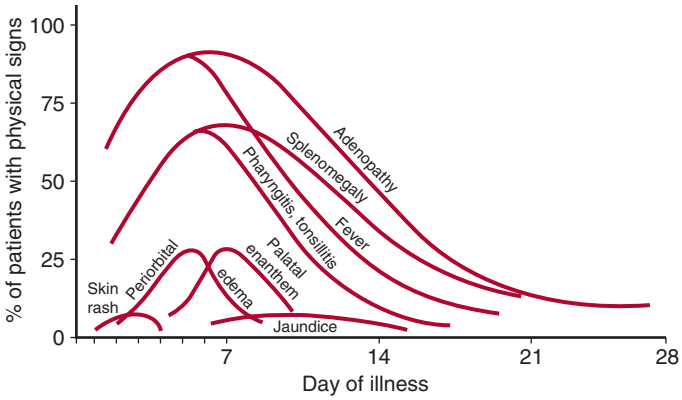

FIGURE 36.8 The clinical course of acute Epstein-Barr mononucleosis. Adenopathy occurs early in the infection and can persist for weeks. (Modified from Rapp CE, Hewston JF. Infectious mononucleosis and the Epstein-Barr virus. *Am J Dis Child*. 1978;132:78.)

TABLE 36.5 Frequently Determined EBV-Specific Antibodies

Antibody Specificity	Positive in IM (%)	Time of Appearance in IM	Persistence	Comments
Viral Capsid Antigen				
VCA-IgM	100	At clinical presentation	4–8 wk	Highly sensitive and specific; of major diagnostic utility
VCA-IgG	100	At clinical presentation	Lifelong	Useful for documentation of past EBV infection
Early Antigen				
Anti-Diffuse	70	Peaks 3–4 wk after onset	3–6 mo	Correlates with disease severity; seen in NPC patients
Anti-Restricted	Low	2 wk to several months after onset	2 mo to >3 yr	Occasionally seen with unusually severe cases; seen in African Burkitt lymphoma patients
EBNA	100	3–4 wk after onset	Lifelong	Presence excludes primary EBV infection

EBNA, EBV nuclear antigen; EBV, Epstein–Barr virus; IM, infectious mononucleosis; NPC, nasopharyngeal carcinoma; VCA, viral capsid antigen. Modified from Schooley RT. Epstein-Barr virus (infectious mononucleosis). In: Mandell GL, et al., eds. *Principles and Practice of Infectious Diseases*. Philadelphia: Churchill Livingstone; 2010.

weeks later and, if present with EA IgG, are indicative of infection in the recent past. Approximately 20% of children present after the VCA IgM has already declined. In these children, VCA and EA IgG are present.

Organ transplant and other immunosuppressed patients may develop a **lymphoproliferative syndrome** due to EBV that presents with generalized lymphadenopathy, hepatosplenomegaly, and fever. Diagnosis is based on the EBV viral load determined by PCR on blood.

Because group A streptococcal infection can present in a similar manner, or be present simultaneously with EBV infection, and because other viruses can cause pharyngitis and tender, enlarged cervical lymph nodes, differentiating these various causes of pharyngitis and lymphadenopathy is important. Acute streptococcal pharyngitis improves after institution of penicillin therapy; EBV infections do not, and they also have a more prolonged clinical course. In addition, severe malaise and splenomegaly do not occur with most bacterial or viral causes of pharyngitis and cervical lymphadenopathy. These findings prompt the clinician to consider EBV infection. Similarly, most viral causes of cervical adenopathy and pharyngitis, with the exception of CMV, are not associated with the brisk atypical lymphocytosis commonly seen with EBV infections, and they are not usually associated with abnormal liver function results.

Cytomegalovirus infection. Infection with CMV in children can be associated with a mononucleosis-like syndrome and lymphadenopathy. CMV mononucleosis is associated with fever and malaise similar to that seen in EBV; however, in contrast to EBV, CMV mononucleosis does not usually cause severe, exudative tonsillopharyngitis or the production of heterophile-specific or EBV-specific antibodies. CMV mononucleosis can be associated with an atypical lymphocytosis and diffuse lymphadenopathy in the immunocompetent host. Women who are pregnant when they have primary CMV infections are at risk of delivering a child with congenital CMV infection through transplacental infection; approximately 10% of these neonates will have severe systemic findings. Lymphadenopathy may be present in congenital CMV but is not a common finding. Intrapartum transmission via cervical secretions or postpartum transmission via breast milk typically does not result in clinically apparent infection. Identifying CMV in the urine of the neonate in the 1st week of life confirms congenital infection.

The diagnosis in older children is usually made serologically, in tests measuring both IgM and IgG antibodies directed to CMV. Viral culture and nucleic acid amplification assays can also identify CMV from blood, throat swab, and urine specimens. Although CMV culture (especially from the urine) is frequently positive in children with CMV infection, many children, especially those in daycare, are silently infected and excrete CMV in absence of clinical signs and symptoms. Therefore, CMV culture is less useful in the toddler age group.

Cat-scratch disease. Cat-scratch disease is caused by a small gram-negative bacillus, *B. henselae*, which can also cause bacillary angiomatosis in patients with HIV infection. Cat-scratch disease occurs several days after the scratch or bite of an infected cat or kitten. A papule at the site of the trauma usually develops, followed 1-3 weeks later by regional lymphadenopathy; there is no lymphangitis. Most patients with cat-scratch disease have a single enlarged, usually nonsuppurative lymph node. Nodes may be tender, particularly in the 10-30% that suppurate. Axillary nodes are the most common to be enlarged, likely secondary to the upper extremities being the part of the body most frequently scratched or bitten. The next most common sites for adenopathy are the neck and jaw, followed by the inguinal region. Although single nodes are most commonly affected, regional adenopathy may also occur. Generalized lymphadenopathy is unusual in the immunocompetent host.

Approximately half the patients have low-grade fever and malaise, but a small number have high fevers (>39.5°C) and more severe systemic symptoms. In most patients, the swollen, inflamed nodes regress spontaneously within several weeks; approximately 10-30% progress to have purulent fluid drainage that is culture-negative by standard techniques. Uncommon complications include a spontaneously resolving encephalopathy, erythema nodosum, oculoglandular syndrome of Parinaud (in which *B. henselae* is inoculated into the eye and causes conjunctivitis and preauricular adenopathy), thrombocytopenia, hepatitis or splenitis with granulomas, transverse myelitis, and in rare cases osteolytic bone lesions. Other causes of **oculoglandular syndrome** include tularemia, adenoviruses, and enteroviruses.

The diagnosis is based on the history of contact with kittens or cats and the classic clinical manifestations, including a careful search for an entrance site papule. Confirmatory testing is difficult, as *B. henselae* is a fastidious organism and is difficult to isolate via conventional culture techniques. Acute and convalescent antibody titers are typically employed, though the clinician should exercise caution in interpretation given the high rate of seroprevalence in the general population and the potential for cross-reactivity with other infections. Pathologic samples of tissue from the involved node may provide further evidence if they demonstrate granulomas, central necrosis, and organisms on Warthin–Starry silver stain. The decision to perform a biopsy is usually reached when there is no clear history of a preceding contact with a cat or kitten, or when the presentation is atypical and cannot be differentiated from other, more serious illness, such as mycobacterial adenitis.

Chronic granulomatous disease. Chronic granulomatous disease (see Chapter 41) comprises a group of rare inherited disorders of neutrophil function, characterized by recurrent pyogenic infections that are often accompanied by lymphadenopathy and/or abscess formation. Most cases are inherited in an X-linked manner; 30% are autosomal recessive. Chronic granulomatous disease should be considered in a young child (often a boy) who presents with recurrent fevers and infection, pneumonia, adenopathy, and abdominal pain. Family history often reveals another relative with the disease or recalls a death from an infection in a young child. Common pathogens contain catalase and include *S. aureus* and *Aspergillus* species.

The diagnosis is made by performing neutrophil function tests, such as dihydrorhodamine or nitroblue tetrazolium testing, which demonstrate the defective neutrophil oxidation. Positive findings on neutrophil function tests are confirmed via immunoblot or genetic assays.

Human immunodeficiency virus. Initial infection with HIV may manifest as a heterophile-negative mononucleosis-like syndrome that is an acute retroviral syndrome consisting of diffuse lymphadenopathy, fever, sore throat, rash, myalgias, diarrhea, leukopenia, thrombocytopenia, and general malaise. Many patients with HIV infection go on to have weight loss or poor weight gain and a history of thrush and opportunistic infections, such as pneumonia caused by *Pneumocystis jirovecii*. HIV-infected children are also more likely than immunocompetent hosts to have other infectious causes of lymphadenopathy, such as tuberculosis, atypical mycobacterium, CMV, fungi, or noninfectious causes, such as lymphoma or Kaposi sarcoma (human herpesvirus type 8 [HHV-8]). *Regional* lymphadenopathy is not a common manifestation of HIV infections unless the regional adenopathy represents a distinct focal infection. HIV infection is typically established via a rapid antibody assay that if positive is confirmed via Western blot; the early, acute, retroviral syndrome is diagnosed by viral RNA or DNA load because antibodies may not be present with early infection.

Mycobacterial infections. Tubercular cervical adenitis is not common in the United States, though can be associated with ingestion

(See *Nelson Textbook of Pediatrics,* p. 1590.)

(See *Nelson Textbook of Pediatrics,* p. 1423.)

of raw, contaminated milk and infection with *M. bovis*. Regional or diffuse lymphadenopathy caused by infection with *M. tuberculosis* is also unusual in developed countries; it is increasing in frequency in children in the United States as a result of an increase in the number of adults actively infected with tuberculosis. This increase is attributable to several issues, including immigration from endemic areas, reduction in tuberculosis control programs, the likelihood of HIV-infected individuals to have a high mycobacterial burden, noncompliance by infected individuals with multidrug treatment regimens, and drug resistance by the organism. Most adenitis caused by mycobacteria in the United States is caused by atypical strains that are not serious pathogens in the immunocompetent host.

Several historical and clinical criteria can be used to differentiate tuberculous adenitis from atypical mycobacterial infections. Most children with tuberculosis have a history of exposure to an adult with active tuberculosis. Infection with atypical mycobacteria is more common in the southern parts of the United States. Children with tuberculous adenitis may have hilar lymphadenopathy because the lungs are usually the source of primary infection. Evidence of extralymphatic disease is also common in children with tuberculosis; such disease includes pneumonia, pleural effusions, bone marrow suppression, liver function abnormalities, and miliary disease. Disseminated (miliary) tuberculosis may manifest with diffuse lymphadenopathy and should be considered if pulmonary infiltrates and systemic symptoms are present. Such extralymphatic disease and diffuse lymphadenopathy are rare in immunocompetent children with adenitis caused by atypical mycobacteria but may occur in the setting of HIV infection.

The most common mycobacterial infection in children in the United States is the infection of the lymph nodes with the atypical mycobacteria, primarily *M. avium-intracellulare* complex, *M. kansasii*, *M. scrofulaceum*, and *M. marinum*. The lymph nodes involved are usually tender, unilateral and cervical in most infections, presumably because the organism enters via the oropharynx. Most frequently, a previously healthy child presents with a mass that is really unilateral lymphadenitis or adenopathy in the cervical, submandibular, or submaxillary region (Fig. 36.9). Although fever may be present, other significant systemic symptoms are usually not present. In a small number of patients, the affected node spontaneously ruptures and drains before the visit to the physician. The drainage is not usually grossly purulent and may be a clue that atypical mycobacteria are the cause of the infected node. Regional adenopathy may also be seen after immunization with bacille Calmette-Guérin (BCG) vaccine.

The gold standard for diagnosis of lymphadenitis caused by atypical mycobacteria is acid-fast staining and culture of the excised node. Incision and drainage or needle aspiration of these nodes may lead to chronically draining sinus tracts, which may leave scars; thus, this method is contraindicated. Fine-needle aspiration may be beneficial. The usual scenario involves a young, preschool-aged child with an enlarged cervical node that responds poorly to antibiotics. The child has no history of contact with cats and is otherwise well. A tuberculin skin test often yields 5-9 mm of induration because atypical mycobacteria have antigens cross-reactive to those of tuberculosis. This amount of induration is considered indeterminate for tuberculosis in low-risk patients and suggests that the adenopathy is caused by an atypical mycobacterium. Skin tests with antigens from the various atypical mycobacteria are very sensitive and specific for infection; however, these antigens are not consistently available. In rare cases, infection with atypical mycobacteria yields skin test results in the positive range of more than 15-mm induration, which mandates a more extensive work-up that focuses on the possibility that the adenitis is caused by

FIGURE 36.9 Nontuberculous mycobacterial infection in a 10-year-old male with left neck swelling. Axial contrast-enhanced computed tomography image shows a cluster of enlarged nodes in the left neck containing low-attenuation necrotic centers *(arrow)*. (From Lowe LH, Smith CJ. Infection and inflammation. In: Coley BD, ed. *Caffey's Pediatric Diagnostic Imaging*. 12th ed. Philadelphia: Elsevier; 2013;1:139.)

M. tuberculosis infection. **Interferon gamma release assays** will be positive for *M. tuberculosis*, *M. bovis*, and some atypical mycobacterium (*M. marinum*, *M. kansasii*) but will be negative for BCG and infection with *M. avium* complex. Gradual resolution of lymphadenitis sometimes occurs in children with atypical mycobacterial infections. Excisional biopsy is not necessary if the diagnosis is made presumptively from skin test results of less than 10-mm induration, if other infections are ruled out, if resolution occurs, and if the child is at low risk for infection with *M. tuberculosis* (see Chapter 2). If the node does not improve, continues to enlarge, or spontaneously drains, excision is recommended and is usually curative. Fine-needle aspiration (for culture and acid-fast staining) may also be used, if the node is in an area where excision is impractical.

Toxoplasmosis. *T. gondii* is a protozoan organism that is a parasite of cats. Many other animals, including humans, can be incidentally and chronically infected hosts in which the parasite cannot complete its life cycle. Human acquisition of toxoplasmosis can result from contact with cat feces or soil that contains oocysts, which infect the host upon ingestion. Alternatively, the ingestion of raw or undercooked meat containing tissue cysts, particularly lamb or pork, may lead to infection. Adults in the United States are more likely to be infected from ingestion of raw meat than from contact with oocysts in cat feces or soil. Finally, infection can be transmitted to the fetus, especially when a pregnant woman is acutely infected with toxoplasmosis. Although many fetal infections are asymptomatic, transplacental infection with toxoplasmosis can result in severe neurologic damage, chorioretinitis, aseptic meningitis, and significant systemic illness manifesting with the classic triad of hepatosplenomegaly, intracranial calcifications, and hydrocephalus. Although lymphadenopathy can occur in the newborn

with congenital toxoplasmosis, it is a more common symptom of acute toxoplasmosis in older children and young adults.

The most common symptoms in children who acquire toxoplasmosis are lymphadenopathy, fever, malaise, myalgia, and pharyngitis. The most commonly affected nodes include the anterior and posterior cervical and axillary, which may be tender; involvement is usually bilateral. The lymph node enlargement seen in toxoplasmosis is caused by reticular hyperplasia and inflammation. Most laboratory results are normal, but the white blood cell count may show an absolute lymphocytosis with atypical lymphocytes, which can cause confusion with EBV, HIV, or CMV mononucleosis.

The diagnosis is made primarily with serologic studies. Various diagnostic techniques can be used on the patient's serum, including indirect immunofluorescence, complement fixation, and enzyme-linked immunosorbent assay. A 4-fold rise in IgG titer or the presence of IgM antibodies is diagnostic. In neonatal infections, tests measuring IgM have become more sensitive and specific. If biopsy is performed, actual parasite forms can sometimes be demonstrated. Antigen tests and cultures that grow the parasite are also available but primarily on an investigational level.

Syphilis. Syphilis, caused by the spirochete *Treponema pallidum*, is common in the United States (see Chapter 18). The natural course of noncongenital syphilis includes 3 major clinical manifestations:

- Primary syphilis, in which the individual develops a painless chancre at the site of inoculation
- Secondary syphilis, in which the organism disseminates hematogenously to many organs
- Tertiary syphilis, in which gummatous lesions develop in end organs, such as the brain, heart, and bones

Lymphadenopathy can be seen as 1 of the manifestations of syphilis in several situations. In primary syphilis, in which the inoculation site is usually the genital area, regional lymphadenopathy with painless, firm nodes occurs at the time that a chancre is observed. Thus, inguinal adenopathy in an adolescent who is sexually active mandates further examination and work-up for sexually transmitted infections such as syphilis. In secondary syphilis, the organism has disseminated, causing multiple organs to be involved. The classic manifestations are protean and usually include nonvesicular rashes. Lymphadenopathy, regional or generalized, is common and often includes epitrochlear nodes. Systemic symptoms may include fever, malaise, anorexia, and weight loss. Syphilis therefore should be at the top of the differential diagnosis in sexually active adolescents with rash and lymphadenopathy.

Pregnant women with syphilis who are untreated readily transmit the disease to the fetus, causing congenital syphilis, often with significant sequelae. Infants with congenital syphilis may also have generalized lymphadenopathy, although this finding is less common than other systemic symptoms, such as hepatosplenomegaly, snuffles, and periosteal reactive disease.

The diagnosis has been complicated by the inability to grow the organism in vitro. Dark-field examination of tissue from chancres or mucous lesions shows numerous spirochetes, but dark-field methods are often unavailable to routine laboratories. Serologic study continues to be the primary mode of diagnosis. Nontreponemal serologic studies rely on host production of antibodies to nonspecific lipoidal host tissue antigens that arise as a result of infection with the spirochete. These tests include the Venereal Disease Research Laboratory (VDRL) test, the serologic test for syphilis, and the rapid plasma reagin (RPR) test. Levels of these antibodies decline after adequate treatment and are useful in confirming eradication of the infection. False-positive reactions can occur, particularly in individuals with connective tissue disorders or mononucleosis. In contrast, the fluorescent treponemal antibody absorption test (FTA-ABS) measures antibodies directed specifically to *T. pallidum* and can be used as a confirmatory test in individuals with positive results on screening tests. These antibodies usually remain present for the life of the infected individual, even if the patient receives adequate therapy. Thus, in contrast to the VDRL test, the FTA-ABS has little use in monitoring the efficacy of treatment.

Acute leukemia, lymphoma, and other malignancies. Lymphadenopathy is frequently among the presenting findings in patients with leukemia or lymphoma. Enlarged lymph nodes may be noted in an isolated, regional, or generalized distribution, with or without classic systemic symptoms, such as fever, malaise, night sweats, weight loss, and anorexia. Malignant nodes are usually firm, rubbery, fixed, and nontender, and may be matted. Unlike many of the acute lymphadenopathies caused by infectious agents, most lymph nodes that are malignant increase in size gradually. Additional findings suggestive of malignancy include age >10 years, size >2.5 cm, duration >6 weeks (and increasing in size), and supraclavicular location.

Approximately 50% of children with acute **lymphoblastic leukemia** have adenopathy at the time of diagnosis. Nodal disease may be either generalized or localized to regional nodal groups, often the cervical chains. Nodal disease is frequently accompanied by other signs and symptoms, including fevers, malaise, weight loss, pallor, bone pain, petechiae and bruising, splenomegaly, or hepatomegaly. The complete blood count usually demonstrates anemia, thrombocytopenia, leukocytosis or leukopenia, circulating blasts, or some combination thereof. Some patients may have normal peripheral blood laboratory results on initial evaluation. Acute myelogenous leukemia is less common in children but may manifest in a similar manner. Bone marrow biopsy and aspiration must be performed, and the findings are diagnostic.

Non-Hodgkin lymphoma is a relatively common childhood malignancy and often manifests with mediastinal or pleural disease. Adenopathy in the supraclavicular, cervical, or axillary regions is usually present and may occur in the absence of chest involvement. Systemic symptoms are variable at the time of diagnosis. Lymph nodes, as with other malignancies, tend to be firm, nontender, and rubbery. Their size may increase relatively rapidly over several weeks. Because lymphoblastic lymphoma may represent a variant of acute lymphoblastic leukemia, the signs and symptoms of leukemia and lymphoma may merge. Non-Hodgkin lymphoma of B cell origin (Burkitt and non-Burkitt lymphoma) in children in the United States usually originates in an intraabdominal site, and regional adenopathy, if present, is then in the inguinal or iliac regions. The African variety of Burkitt lymphoma often manifests as an expanding jaw mass.

Hodgkin disease often manifests with painless cervical or supraclavicular lymphadenopathy in older school-aged children and adolescents. Nodes are firmer than those seen in patients whose nodes are enlarged in reaction to infections. In a small number of children with Hodgkin disease, the size of the nodes may wax and wane for several months before a definitive diagnosis is made. Supraclavicular nodes usually indicate intrathoracic disease, which is present in 60-70% of patients at the time of diagnosis. Axillary or inguinal nodes may also be the sites of presenting lymphadenopathy. Approximately 30% of patients with Hodgkin disease have systemic symptoms at presentation, including fatigue, weight loss, fevers, night sweats, and poor appetite. Some patients with Hodgkin disease also have unusual symptoms, such as pruritus, hemolytic anemia, and chest pain after alcohol ingestion. Such systemic symptoms with lymphadenopathy are red flags for immediate work-up for malignancy. Diagnosis is confirmed by biopsy of involved nodes and/or bone marrow aspiration, if the tumor has spread to the bone marrow.

Disseminated neuroblastoma may manifest as diffuse adenopathy in younger children. Such children often have primary adrenal or

TABLE 36.6 Ulceroglandular Disorders

Anthrax
Tularemia
Herpes simplex
Pasturella multocida (dog or cat bite)
Rickettsialpox
Tick-borne lymphadenopathy syndrome
Mediterranean spotted fever
African tick bite fever
Typhus
Cat-scratch disease
BCG immunization
Spirillary rate-bite fever
Plague
Nocardiosis
Cutaneous diphtheria
Cutaneous coccidioidomycosis
Cutaneous histoplasmosis
Cutaneous leishmaniasis
Monkeypox

BCG, bacille Calmette-Guérin.

paraspinal masses with bone metastasis and have nonspecific systemic symptoms, abdominal mass, bone pain, and sometimes, symptoms of spinal cord compression. Other tumors, such as rhabdomyosarcoma and thyroid cancer, manifest in rare cases with lymphadenopathy caused by local or disseminated metastasis.

Ulceroglandular disorders. Ulceroglandular (lymphocutaneous) disorders usually involve an initial injury or bite to an extremity with a resulting cutaneous lesion (ulcer, eschar, papule) and enlarged regional nodes, with or without lymphangitis (Table 36.6). In some, the cutaneous lesion is secondary to hematogenous spread; in these circumstances the lymph node enlargement may then be generalized (monkeypox).

Kimura disease. Asymptomatic, unilateral, chronic, cervical lymphadenopathy in Asian boys is suspect for Kimura disease. This benign condition is characterized by peripheral eosinophilia and elevated immunoglobulin E levels. Biopsies should be performed to rule out malignancy. Histologic specimens show a massive eosinophilic infiltration of the nodal architecture. This benign condition necessitates no therapy unless the adenopathy creates functional disability.

Kikuchi-Fujimoto disease (histiocytic necrotizing lymphadenitis). Kikuchi-Fujimoto disease (KFD) is a rare, usually self-limiting disease that was originally reported in patients of Asian heritage. Cases are now described in all ethnic groups. KFD occurs in children 11-16 years of age usually as firm unilateral posterior cervical adenitis, fever (30-50%), malaise, elevated erythrocyte sedimentation rate, atypical lymphocytosis, and leukopenia. Nodes range in size from 1-3 cm, are painful or tender in only 50% of cases, may be multiple, and must be differentiated from lymphoma. Node involvement may occasionally be bilateral or present in axillary or supraclavicular regions.

The etiology is unknown, but evidence supports an abnormal immune response; the diagnosis is made by lymph node biopsy. Histologic features include necrosis with karyorrhexis, a histiocytic infiltrate, crescentic plasmacytoid monocytes, and an absence of neutrophils. The disease is self-limiting and usually spontaneously resolves within 6 months, although relapses may occur. Therapy with systemic steroids is reserved for cases with severe symptoms. Many autoimmune diseases have been associated with Kikuchi-Fujimoto disease, most commonly systemic lupus erythematosus.

Sinus histiocytosis with massive lymphadenopathy (Rosai–Dorfman disease). This usually self-limited disease is most common in Africa and the Caribbean. Patients have massive bilateral painless and mobile cervical lymphadenopathy with associated fever, leukocytosis, and elevated erythrocyte sedimentation rate; polyclonal elevation of IgG may be present. Night sweats and weight loss are common. Autoimmune hemolytic anemia is an uncommon associated finding.

Other nodal chains may be involved; extranodal involvement occurs in 40% of cases. The most common sites are the skin, followed by the nasal cavity and sinuses, palate, orbit, bone, and central nervous system. Histology demonstrates pale histiocytes containing engulfed lymphocytes, and immunoreactivity to S100 protein in large histiocytes, in conjunction with expected clinical features, is diagnostic.

Castleman disease. Castleman disease is an uncommon lymphoproliferative disease that is also called *angiofollicular lymph node hyperplasia*. There is an association with human herpesvirus 8, which is thought to stimulate excessive production of interleukin 6 (IL-6). The disease is usually seen in adolescents or young adults. Enlargement of a single node, most often in the mediastinum or abdomen, is the most common localized presentation. Some patients may have fever, night sweats, weight loss, and fatigue. Management includes surgery and/or radiation therapy.

Multicentric Castleman disease is a systemic lymphoproliferative disorder that causes lymphadenopathy, hepatosplenomegaly, fever, anemia, overexpression of IL-6, and polyclonal hypergammaglobulinemia. Multicentric Castleman disease may be associated with HIV infection and autoimmune disease–associated lymphadenopathy.

SUMMARY AND RED FLAGS

Lymphadenopathy is a common manifestation of many childhood illnesses. Most often, regional adenopathy is associated with a bacterial infection in the vicinity of the node or with a viral pharyngitis. Generalized adenopathy does not always indicate a serious underlying disease. Adenopathy usually resolves either spontaneously or after appropriate antibiotic therapy. When adenopathy is accompanied by weight loss, recurrent fevers, night sweats, or other systemic signs or symptoms, a more serious cause must be vigorously sought. The presence of supraclavicular nodes is usually a red flag for serious illness. Adenopathy associated with hepatomegaly, splenomegaly, or an abdominal mass must be quickly investigated. Furthermore, if the adenopathy does not diminish or resolve after antibiotic therapy or after 3 weeks, a more thorough evaluation is necessary. In children with known immunodeficiency, the cause of the adenopathy may be far more serious. These children are more prone to opportunistic infections; malignancies also occur at a higher frequency in immunosuppressed children than in the general population.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

General References

Grossman M, Shiramizu B. Evaluation of lymphadenopathy in children. *Curr Opin Pediatr*. 1994;6:68.

Kelly CS, Kelly RE Jr. Lymphadenopathy in children. *Pediatr Clin North Am*. 1998;45:875.

Medication-Related Causes of Lymphadenopathy

Pangalis GA, Vassilakopoulos TP, Boussiotis VA, et al. Clinical approach to lymphadenopathy. *Semin Oncol*. 1993;20:570-582.

Cervical Adenopathy

Alvarez A, Schreiber J. Lemierre's syndrome in adolescent children—Anaerobic sepsis with internal jugular vein thrombophlebitis following pharyngitis. *Pediatrics*. 1995;96:354.

Barton LL, Feigin RD. Childhood cervical lymphadenitis: a reappraisal. *J Pediatr*. 1974;84:846.

Brook I. Aerobic and anaerobic bacteriology of cervical adenitis in children. *Clin Pediatr*. 1980;19:693.

Peters TR, Edwards KM. Cervical lymphadenopathy and adenitis. *Pediatr Rev*. 2000;21:399.

Epstein–Barr Viral Infections

Case Records of the Massachusetts General Hospital. Case 24-1994. *N Engl J Med*. 1994;330:1739.

Cohen JI. Epstein-Barr virus infection. *N Engl J Med*. 2000;343:481.

Rapp CE, Heweston JF. Infectious mononucleosis and the Epstein-Barr virus. *Am J Dis Child*. 1978;132:78.

Sumaya CV, Ench Y. Epstein-Barr virus infectious mononucleosis in children: I. Clinical and general laboratory findings. *Pediatrics*. 1985;75:1003.

Cat-Scratch Disease

Bass JW, Freitas BC, Freitas AD, et al. Prospective randomized double blind placebo-controlled evaluation of azithromycin for treatment of cat-scratch diseases. *Pediatr Infect Dis J*. 1998;17:447.

Bass JW, Vincent JM, Person DA. The expanding spectrum of *Bartonella* infections: II. Cat scratch disease. *Pediatr Infect Dis J*. 1997;16:163.

Carithers HA. Cat-scratch diseases: an overview based on a study of 1,200 patients. *Am J Dis Child*. 1985;139:1124.

Schutze GE. Diagnosis and treatment of *Bartonella henselae* infections. *Pediatr Infect Dis J*. 2000;19:1185.

Human Immunodeficiency Virus

Baroni CD, Uccini S. The lymphadenopathy of HIV infection. *Am J Clin Pathol*. 1993;99:397.

Mycobacterial Infections

Huebner RE, Schein MF, Cauthen GM, et al. Usefulness of skin testing with mycobacterial antigens in children with cervical adenopathy. *Pediatr Infect Dis J*. 1992;11:450.

Wolinsky E. Mycobacterial lymphadenitis in children: a prospective study of 105 nontuberculous cases with long term follow-up. *Clin Infect Dis*. 1995;20:954.

Toxoplasmosis

Frenkel JK. Toxoplasmosis. *Pediatr Clin North Am*. 1985;32:917.

Montoya JG, Remington JS. Studies on the serodiagnosis of toxoplasmic lymphadenitis. *Clin Infect Dis*. 1995;20:781.

Sexually Transmitted Diseases

1998 Guidelines for treatment of sexually transmitted diseases. Centers for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep*. 1998;47(RR–1):1.

Other Disorders

Bower M, Newsom-Davis T, Naresh K, et al. Clinical features and outcome in HIV-associated multicentric Castleman's disease. *J Clin Oncol*. 2011;29:2481-2486.

Lee BC, Patel R. Kikuchi-Fujimoto disease: a 15-year analysis at a children's hospital in United States. *Clin Pediatr*. 2013;52(1):92-95.

Leroy S, Moshous D, Cassar O, et al. Multicentric Castleman disease in an HHV-8-infected child born to consanguineous parents. *Pediatrics*. 2012;129(1):e199-e203.

Muskardin TW, Peterson BA, Molitor JA. Castleman disease and associated autoimmune disease. *Curr Opin Rheumatol*. 2012;24:76-83.

Shad A, Magrath I. Non-Hodgkin's lymphoma. *Pediatr Clin North Am*. 1997;44:863.

Stones DK, Havenga C. Sinus histiocytosis with massive lymphadenopathy. *Arch Dis Child*. 1992;67:521.

Unadkat RJ, Khubchandani SR, Gurjar AS. Kikuchi-Fujimoto disease. *Pediatr Infect Dis*. 2015;7:13-16.

Weitzman S, Jaffe R. Uncommon histiocytic disorders: the non-Langerhans cell histiocytoses. *Pediatr Blood Cancer*. 2005;45:256-264.

Zhu F, Zhang J, Xing X, et al. Rosai-Dorfman disease: a retrospective analysis of 13 cases. *Am J Med Sci*. 2013;345:200-210.

37

Pallor and Anemia

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INTRODUCTION

Pallor, a perceptible reduction in the usual color and tone of the skin and/or mucosa, may result from alterations of cutaneous blood flow, anemia, or unknown mechanisms. Under normal circumstances the pink appearance of the lips, mucosa, and skin is influenced by the nature and character of these tissues, the adequacy of vascular perfusion, and the level of hemoglobin. Pallor is a highly nonspecific finding that may be a manifestation of a diversity of diseases or it may be normal for a given individual. Parental perception of pallor frequently generates considerable anxiety. Although pallor is most often intuitively associated with anemia by families and physicians, a broad diagnostic perspective is appropriate (Table 37.1). Anemia is the condition in which hemoglobin level (or hematocrit) is more than 2 standard deviations below the mean for age. Anemia is clinically relevant only when the low hemoglobin level results in decreased oxygen-carrying capacity of the blood. By definition, 2.5% of the general population has a hemoglobin or hematocrit level below the defined limits of normal. This fact must be kept in mind when evaluating children with mild anemia for which no explanation can be identified. Hemoglobin level varies considerably with age and sex (Table 37.2). Newborns have relatively high levels of circulating hemoglobin due to intrauterine adaptation to a relatively hypoxic environment. During the 1st 2 months of life, hemoglobin production markedly diminishes and a physiologic nadir occurs. The mean hemoglobin level rises gradually during childhood equally for both boys and girls until puberty when boys achieve a level approximately 20% higher than that of girls. Anemia occurs as the result of 1 or a combination of 3 pathophysiologic mechanisms:

- Acute blood loss
- Impaired bone marrow production of red blood cells (RBCs)
- Increased peripheral destruction of RBCs (hemolysis)

Under normal conditions, the body's RBC mass is maintained at a level appropriate to support tissue oxygen needs through the oxygen-sensing regulatory feedback stimulus of the hormone erythropoietin. Produced in the kidney, erythropoietin stimulates the production of mature RBCs within the bone marrow. Over a 3- to 5-day period, RBC precursors mature into reticulocytes that are released into the peripheral blood. In 24-48 hours, reticulocytes become mature RBCs that circulate in the peripheral blood for approximately 120 days. Senescent RBCs are removed from the circulation by reticuloendothelial cells within the spleen, liver, and bone marrow. A metabolic by-product of hemoglobin catabolism is bilirubin.

◆ History

There are several important aspects of the history that can assist in the evaluation of a patient with pallor and suspected anemia. A child with pallor is not necessarily anemic. Assessment of sun exposure and familial patterns of complexion are crucial because many patients are intrinsically pale. A careful evaluation of the medical history is fundamental in the assessment of a patient with suspected pallor (Table 37.3).

Obtaining a dietary history is very important when evaluating a patient for anemia. Infants delivered prematurely or exclusively breast-fed infants without adequate iron supplementation from infant foods in the 2nd half of their 1st year of life are at risk for iron or iron deficiency anemia. Toddlers who consume large amounts of cow's milk and children and adolescents who consume little meat are also at risk for iron deficiency anemia. In addition, patients and breast-fed infants of mothers who follow a strict vegan diet may become deficient in vitamin B_{12}.

A neonatal history of hyperbilirubinemia supports a possible diagnosis of congenital hemolytic anemia such as hereditary spherocytosis. This can be further supported by a family history of anemia, blood transfusions, splenectomy, and/or cholecystectomy.

Medication history is pertinent because certain drugs, including antimalarial agents and sulfonamide antibiotics, can induce oxidant-associated hemolysis in the patient deficient in glucose-6-phosphate dehydrogenase (G6PD), whereas other medications may cause immune hemolysis (penicillin) or decreased RBC production (chloramphenicol). Travel history may suggest exposure to infections such as malaria.

◆ Physical Examination

The general appearance of the child can provide clues to the severity and chronicity of the problem. Severe anemia that develops slowly over weeks or months is often well tolerated. Vital signs (including orthostatic blood pressure), height, weight, and growth offer further insight into the severity of the problem. Isolated pallor in a well-appearing child who does not have evidence of systemic disease is usually much less ominous than pallor noted in a child who is ill-appearing, has bruising, petechiae, lymphadenopathy, hepatosplenomegaly, or abdominal mass. Pallor at any site increases the likelihood of anemia; pallor of the face, nail beds, tongue, palms and palmar creases as well as conjunctival pallor enhance the likelihood of anemia. Conjunctival rim pallor when compared to the usually more fleshlike pallor of the deeper posterior region of the palpebral conjunctiva is highly specific in adult patients with anemia. Table 37.4 outlines physical examination findings that may provide clues to the underlying cause of the anemia.

Prominent cheekbones, dental malocclusion, and frontal bossing may occur in patients with chronic hemolytic anemias (i.e., thalassemia major) because of the expansion of bone marrow space. Tortuosity of conjunctival vessels occurs in sickle cell disease. Splenomegaly is often present in children with congenital hemolytic anemia. Lymphadenopathy and hepatosplenomegaly may indicate the presence of infiltrative disease of the bone marrow and visceral organs such as

leukemia. Purpura in the anemic child is suggestive of associated thrombocytopenia that may accompany aplastic anemia or leukemia.

Many congenital anomalies and/or dysmorphic features have been associated with hematologic syndromes. Patients with Fanconi anemia are often short, have hyperpigmentation, hypoplastic "finger-like" thumbs, radial bone anomalies, and structural renal abnormalities. Patients with Diamond–Blackfan anemia are often short and have a "curious, intellectual" facial expression.

When pallor and anemia are seen in the context of other signs that suggest chronic inflammation, infection or systemic disease, a diligent general physical examination may yield substantive information. Hypertension and short stature may suggest chronic renal disease. Joint swelling and/or pain may suggest rheumatologic disorders. Digital clubbing may suggest advanced cyanotic cardiopulmonary diseases. Abdominal pain, diarrhea, and poor growth may suggest inflammatory bowel disease.

Recent onset of pallor is suggestive of anemia. The child who has always appeared somewhat pale but is otherwise well with normal growth and development likely has an intrinsic constitutional characteristic. In such instances, the child and other family members often have light hair and skin complexion. An unremarkable general medical history and physical examination support a physiologic explanation for pallor. Some children may appear pale as a result of limited sun exposure as might occur during the winter in cooler climates.

Children with malignant disease or chronic illness (e.g., rheumatologic disorders, inflammatory bowel disease, chronic cardiopulmonary disorders, diabetes) may have a pale appearance that is unrelated or out of proportion to the degree of associated anemia. Atopic children often have distinctly pale mucosa as a result of local edema. Children with generalized edema caused by hypoproteinemia, congestive heart failure, or vasculitis often appear pale as a result of excess interstitial fluid within the mucosal or cutaneous tissues. Patients with hypothyroidism are pale because of myxedematous changes in the skin, subcutaneous tissue, and mucosa.

TABLE 37.1 Causes of Pallor in Children Based on Etiologic Mechanism

I. Anemia
II. Decreased Tendency of the Skin to Pigment
  A. Physiologic (fair-skinned individuals)
  B. Limited sun exposure
III. Alteration of the Consistency of the Subcutaneous Tissue
  A. Edematous states, increased intravascular hydrostatic pressure (e.g., congestive heart failure), decreased intravascular oncotic pressure (hypoproteinemia), increased vascular permeability (e.g., vasculitis)
  B. Hypothyroidism
IV. Decreased Perfusion of the Cutaneous/Mucosal Vasculature
  A. Hypotension, cardiogenic shock (pump failure or rhythm disturbance), hypovolemia (blood loss, dehydration), anaphylaxis, sepsis, acute adrenal insufficiency, vasovagal syncope
  B. Vasoconstriction, increased sympathetic activity (hypoglycemia, pheochromocytoma), neurologic complications (head trauma, seizures, migraine)
V. Chronic Medical Conditions
  A. Malignant disease
  B. Atopy
  C. Chronic inflammatory disease, juvenile idiopathic arthritis, inflammatory bowel disease
  D. Cardiopulmonary disease (including cystic fibrosis)
  E. Diabetes mellitus
  F. Congenital and acquired immunodeficiencies

From Reece RM. *Manual of Emergency Pediatrics*. 4th ed. Philadelphia: WB Saunders; 1992.

◆ Laboratory Evaluation

The initial laboratory test in a child with pallor should be a complete blood cell count (CBC) including a manual white blood cell (WBC) differential. Significant pallor from anemia usually does not occur until the hemoglobin level falls below 8 g/dL. "False anemia" (resulting from laboratory error, sampling difficulty, or "statistical anemia") should be

TABLE 37.2 Values (Normal Mean and Lower Limits of Normal) for Hemoglobin, Hematocrit, and MCV Determination

	HEMOGLOBIN (g/dL)		HEMATOCRIT (%)		MCV (fL)	
Age (yr)	Mean	Lower Limit	Mean	Lower Limit	Mean	Lower Limit
0.5–1.9	12.5	11.0	37	33	77	70
2–4	12.5	11.0	38	34	79	73
5–7	13.0	11.5	39	35	81	75
8–11	13.5	12.0	40	36	83	76
12–14						
Female	13.5	12.0	41	36	85	78
Male	14.0	12.5	43	37	84	77
15–17						
Female	14.0	12.0	41	36	87	79
Male	15.0	13.0	46	38	86	78
18–49						
Female	14.0	12.0	42	37	90	80
Male	16.0	14.0	47	40	90	89

MCV, mean corpuscular volume.
From Nathan DC, Oski F. *Hematology of Infancy and Childhood*. 4th ed. Philadelphia: WB Saunders; 1993.

TABLE 37.3 Historical Clues in Evaluation of Anemia

Variable	Comments
Age	Iron deficiency rare in the absence of blood loss before 6 mo in term or before doubling birth weight in preterm infants Neonatal anemia with reticulocytosis suggests hemolysis or blood loss: with reticulocytopenia it suggests bone marrow failure Sickle cell anemia and β-thalassemia appear as fetal hemoglobin disappears (4–8 mo of age)
Family history and genetic considerations	X linked: G6PD deficiency Autosomal dominant: spherocytosis Autosomal recessive: sickle cell, Fanconi anemia Family member with early age of cholecystectomy (bilirubin stones) or splenectomy: hemolysis Ethnicity: (thalassemia with Mediterranean origin), (G6PD deficiency in blacks, Greeks, and Sephardic Jews) Race: (β-thalassemia in whites; α-thalassemia in blacks and Asians; SC and SS in blacks)
Nutrition	Cow's milk diet and iron deficiency Strict vegetarian and vitamin B_{12} or iron deficiency Goat's milk and folate deficiency Pica: plumbism and iron deficiency Cholestasis: malabsorption and vitamin E deficiency
Drugs	G6PD-susceptible agents Immune-mediated hemolysis (e.g., penicillin) Bone marrow suppression Phenytoin: increases folate requirements
Diarrhea	Malabsorption of vitamins B_{12} and E and iron Inflammatory bowel disease and anemia of chronic disease or blood loss Milk protein allergy-induced blood loss Intestinal resection and vitamin B_{12} deficiency
Infection	*Giardia* and iron malabsorption Intestinal bacterial overgrowth (blind loop) and vitamin B_{12} deficiency Fish tapeworm and vitamin B_{12} deficiency Epstein–Barr virus, cytomegalovirus and bone marrow suppression *Mycoplasma* and hemolysis Parvovirus and bone marrow suppression Chronic infection Endocarditis Malaria and hemolysis Hepatitis and aplastic anemia

G6PD, glucose-6-phosphate dehydrogenase.

considered whenever a child is said to be anemic and laboratory findings are not consistent with clinical impressions. Capillary blood sampling can be associated with substantial error, depending on the difficulty in performing the procedure and the use of mechanical force necessary to promote blood flow. When laboratory or sampling errors are suspected, a venipuncture sample should be obtained for confirmation. By definition, 2.5% of the general population has hemoglobin levels below the lower limit of normal, which is termed "statistical anemia." This phenomenon should be considered when mild, unexplained normocytic anemia is identified in a healthy child.

Almost all laboratories perform CBCs with automated technology systems. Hemoglobin level (grams per deciliter), RBC count (cells per cubic millimeter), and mean corpuscular volume (MCV) (expressed in femtoliters [fL]) are directly measured. Hematocrit value, mean corpuscular hemoglobin (MCH), and MCH concentration (MCHC) are derived values and therefore are less accurate. Other important information reported includes RBC distribution width (RDW), WBC count (cells per cubic millimeter), and platelet count. In addition to the hemoglobin values, careful attention should be given to the MCV, RDW, RBC morphology, platelet count, and WBC count.

CLASSIFICATION OF ANEMIA

Reticulocyte Count

The reticulocyte count, reported as a percentage of total RBCs, is essential in categorizing anemia. An elevated reticulocyte count implies a bone marrow response to either increased RBC destruction (hemolysis) or acute or chronic blood loss. In cases of acute blood loss, there is an average delay in bone marrow response of 3-4 days. Thus, in the setting of acute blood loss, the reticulocyte count is most helpful when the bleeding and subsequent anemia have been present for more than a few days.

Anemias are categorized on the basis of the adequacy of the reticulocyte response. The reticulocyte count is expressed as a percentage of the total number of RBCs. In the setting of a normal hemoglobin, the reticulocyte count is about 1-2%. In patients with moderate or severe anemia, the reticulocyte count may appear elevated, but in absolute terms, it may be insufficient for the degree of anemia. Therefore, the reticulocyte count must be corrected using the following formula:

$$\text{Corrected reticulocyte count} = \frac{\text{reticulocyte count} \times \text{hemoglobin}}{\text{(normal hemoglobin for age)}}$$

If the corrected reticulocyte count is greater than 2%, then the bone marrow is producing RBCs at an accelerated pace (Fig. 37.1).

Red Blood Cell Size

The MCV is vital to the classification of anemia. High MCV is termed *macrocytosis*, and low MCV is termed *microcytosis*. Normal standards for MCV are age related; a simple guideline is that the lower normal limit of MCV for children older than 6 months is 70 fL plus the patient's age in years until the adult standard of 80-100 fL is reached (Table 37.2). The MCV must always be interpreted in conjunction with a review of the peripheral blood smear, RDW, and reticulocyte count. A varied population of both smaller and larger RBCs (e.g., reticulocytes) may yield a falsely normal MCV and be diagnostically misleading. A high RDW in the setting of a normal MCV is a clue that 2 populations of RBCs exist. Microcytosis is associated with iron deficiency, thalassemia, and long-standing anemia of inflammation (Table 37.5). Macrocytosis, an unusual finding in children, is associated with vitamin B_{12} or folate deficiency, bone marrow failure syndromes (Fanconi anemia, Diamond–Blackfan anemia), and some cases of hypothyroidism (Table 37.5).

An individual with small RBCs may have a normal or near-normal hemoglobin level if the RBC count is increased as occurs in patients with thalassemia minor who often have RBC counts of more than 5×10^6. The MCHC reflects the level of hemoglobin per cell and would be expected to be low in patients with anemias in which RBCs are "underhemoglobinized," such as the hypochromic anemia of iron deficiency.

The RDW is derived from the histogram of RBC volumes. A normal RDW (11.5-14.5%) implies a uniform population of RBCs that are similar in size. In α-thalassemia trait or β-thalassemia trait, a uniform population of small cells exists; hence, the MCV is low and

TABLE 37.4 Physical Findings in the Evaluation of Anemia

System	Observation	Significance
Skin	Hyperpigmentation	Fanconi anemia, dyskeratosis congenita
	Café-au-lait spots	Fanconi anemia
	Vitiligo	Vitamin B_{12} deficiency
	Partial oculocutaneous albinism	Chèdiak–Higashi syndrome
	Jaundice	Hemolysis, hepatitis
	Petechiae, purpura	Bone marrow infiltration, autoimmune hemolysis with autoimmune thrombocytopenia, hemolytic uremic syndrome
	Erythematous rash	Parvovirus, Epstein–Barr virus
	Butterfly rash	SLE
Head	Frontal bossing	Thalassemia major, severe iron deficiency, chronic subdural hematoma
	Microcephaly	Fanconi anemia
Eyes	Microphthalmia	Fanconi anemia
	Retinopathy	Hemoglobin SS, SC disease
	Optic atrophy, blindness	Osteopetrosis
	Blocked lacrimal gland	Dyskeratosis congenita
	Kayser–Fleischer ring	Wilson disease
	Blue sclera	Iron deficiency
Ears	Deafness	Osteopetrosis
Mouth	Glossitis	Vitamin B_{12} deficiency; iron deficiency
	Angular stomatitis	Iron deficiency
	Cleft lip	Diamond–Blackfan syndrome
	Pigmentation	Peutz–Jeghers syndrome (intestinal blood loss)
	Telangiectasia	Osler–Weber–Rendu syndrome (blood loss)
	Leukoplakia	Dyskeratosis congenita
Chest	Shield chest or widespread nipples	Diamond–Blackfan syndrome
	Murmur	Endocarditis; prosthetic valve hemolysis
Abdomen	Hepatomegaly	Hemolysis, infiltrative tumor, chronic disease, hemangioma, cholecystitis
	Splenomegaly	Hemolysis, sickle cell disease (early), thalassemia, malaria, lymphoma Epstein–Barr virus, portal hypertension, hemophagocytic syndromes
	Nephromegaly	Fanconi anemia
	Absent kidney	Fanconi anemia
Extremities	Absent thumbs	Fanconi anemia
	Thenar eminence hypoplasia; triphalangeal thumb	Diamond–Blackfan syndrome
	Spoon nails	Iron deficiency
	Beau line (nails)	Heavy metal intoxication, severe illness
	Mees line (nails)	Heavy metals, severe illness, sickle cell anemia
	Dystrophic nails	Dyskeratosis congenita
	Edema	Milk-induced protein-losing enteropathy with iron deficiency, renal failure
Rectal	Hemorrhoids	Portal hypertension
	Heme-positive stool	Intestinal hemorrhage
Nerves	Irritable, apathy	Iron deficiency
	Peripheral neuropathy	Deficiency of vitamins B_1, B_{12}, and lead poisoning
	Dementia	Deficiency of vitamins B_{12} and E
	Ataxia, posterior column signs	Vitamins B_{12} and E deficiency
	Stroke	Sickle cell anemia, paroxysmal nocturnal hemoglobinuria

SLE, systemic lupus erythematosus.
Modified from Scott JP. Hematology. In: Behrman RE, Kliegman RM, eds. *Nelson Essentials of Pediatrics*. 2nd ed. Philadelphia: WB Saunders; 1994:520.

the RDW is normal or minimally elevated. An elevated RDW is seen in iron deficiency where the population of small cells is variably sized; hence, the MCV is low and the RDW is elevated. In some hemolytic anemias the RDW is elevated because of the presence of large reticulocytes (Table 37.6). An elevated RDW in the setting of a normocytic anemia suggests 2 populations of RBCs, namely large cells (elevated MCV) and small cells (low MCV) and is concerning for a combined anemia (i.e., concomitant iron deficiency and vitamin B_{12} or folate deficiency).

Red Blood Cell Morphology

Abnormalities of RBC structure may be readily apparent on inspection of the peripheral blood smear and provide helpful diagnostic hints (Table 37.7 and Fig. 37.2).

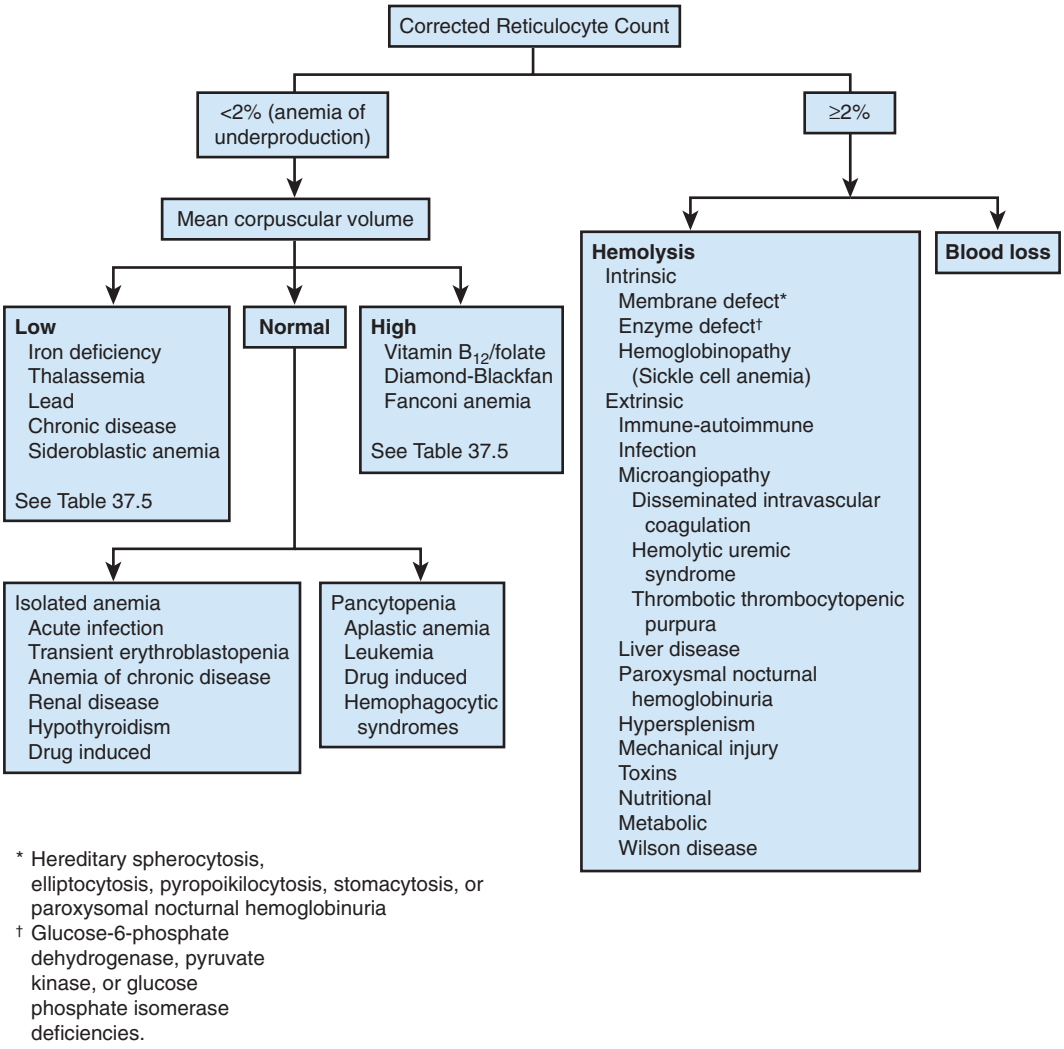


FIGURE 37.1 Diagnostic approach to anemia.

Other Laboratory Abnormalities Associated with Anemia

Evaluation of the WBC count, differential, and platelet count is imperative in the setting of anemia. For example, leukopenia, neutropenia, and/or thrombocytopenia occurring in a patient with anemia of underproduction are suggestive of aplastic anemia or infiltrative bone marrow disease such as leukemia. The presence of immature leukocytes on a smear associated with either a high or a low WBC count is suggestive of leukemia. Thrombocytosis may be present in patients with iron deficiency, blood loss, inflammatory disease, infection, malignancy, or asplenia.

Elevated serum indirect bilirubin, lactate dehydrogenase, and urinary urobilinogen levels occur in patients with increased rates of RBC destruction (hemolysis). Immune-mediated hemolytic anemia should be suspected when anemia, jaundice, reticulocytosis, splenomegaly, and microspherocytes are noted. To investigate the underlying cause of the hemolysis, a direct Coombs test should be performed to detect the presence of an autoantibody on the RBC surface. A low serum iron level, elevated total iron-binding capacity, and a low percentage of iron saturation (% saturation = serum iron/total iron-binding capacity × 100) and/or decreased serum ferritin level are helpful in establishing a diagnosis of iron deficiency. Hemoglobin identification via electrophoresis or high-performance liquid chromatography is necessary to identify hemoglobinopathies such as sickle cell disease or thalassemia. Assessment of RBC enzyme levels (e.g., G6PD) may be necessary when infection- or medication-related hemolytic anemia is suspected in a male of Mediterranean or African descent. True macrocytic anemia should prompt assessment for vitamin B_{12} or folate deficiency. Bone marrow aspirate and biopsy should strongly be considered when other cytopenias exist such as thrombocytopenia or neutropenia.

DIAGNOSTIC WORK-UP

From a clinical perspective, it is best to consider the differential diagnosis of pallor in the context of the acuity and severity of the clinical findings (Fig. 37.3). The well-appearing child may only need a CBC to confirm normal counts and provide reassurance. The pale child who appears mildly or moderately ill requires a CBC and other potential studies to detect any suspected underlying disease. The pale child who appears seriously ill requires urgent evaluation and appropriate therapeutic intervention. A CBC should be obtained for all children with other laboratory assessments dictated on the basis of the suspected diagnosis. If hemorrhage or severe anemia is suspected, a type and cross-match must be sent to the blood bank, 2 large intravenous lines

TABLE 37.5 Causes of High or Low Mean Corpuscular Volume

Low Mean Corpuscular Volume
Iron deficiency
Thalassemias
Lead toxicity
Anemia of chronic disease
Copper deficiency
Sideroblastic anemia
Hemoglobin E
Hereditary pyropoikilocytosis

High Mean Corpuscular Volume
Normal newborn
Elevated reticulocyte count
Vitamin B_{12} or folate deficiency
Diamond–Blackfan anemia (congenital hypoplastic anemia)
Fanconi anemia
Aplastic anemia
Down syndrome
Hypothyroidism (occasionally)
Orotic aciduria
Lesch–Nyhan syndrome
Drugs (zidovudine, chemotherapy)
Chronic liver disease
Paroxysmal nocturnal hemoglobinuria
Thiamine-responsive megaloblastic anemia
Myelodysplasias
Dyserythropoietic anemias

TABLE 37.6 Red Blood Cell Distribution Width (RDW) in Common Anemias of Childhood

Anemia	MCV
Elevated RDW (Nonuniform Population of RBCs)	
Hemolytic anemia with elevated reticulocyte count	High
Iron deficiency anemia	Low
Anemias due to red blood cell fragmentation: DIC, HUS, TTP	Low
Megaloblastic anemias: vitamin B_{12} or folate deficiency	High
Normal RDW (Uniform Population of RBCs)	
Thalassemias	Low
Acute hemorrhage	Normal
Fanconi anemia	High
Aplastic anemia	High

DIC, disseminated intravascular coagulation; HUS, hemolytic uremic syndrome; MCV, mean corpuscular volume; RBC, red blood cell; TTP, thrombotic thrombocytopenic purpura.

TABLE 37.7 Peripheral Blood Morphologic Findings in Various Anemias

Microcytes
Iron deficiency
Thalassemias
Lead toxicity
Anemia of chronic disease

Macrocytes
Newborns
Vitamin B_{12} or folate deficiency
Diamond–Blackfan anemia
Fanconi anemia
Aplastic anemia
Liver disease
Down syndrome
Hypothyroidism

Spherocytes
Hereditary spherocytosis
Immune hemolytic anemia (newborn or acquired)
Hypersplenism

Sickled Cells
Sickle cell anemias (SS disease, SC disease, $S\beta^{+}$thalassemia, $S\beta^{0}$thalassemia)

Elliptocytes
Hereditary elliptocytosis
Iron deficiency
Megaloblastic anemia

Target Cells
Hemoglobinopathies (especially hemoglobin C, SC, and thalassemia)
Liver disease
Xerocytosis

Basophil Stippling
Thalassemia
Lead intoxication
Myelodysplasia

Red Blood Cell Fragments, Helmet Cells, Burr Cells
Disseminated intravascular coagulation
Hemolytic uremic syndrome
Thrombotic thrombocytopenic purpura
Kasabach–Merritt syndrome
Waring blender syndrome
Uremia
Liver disease

Hypersegmented Neutrophils
Vitamin B_{12} or folate deficiency

Blasts
Leukemia (ALL or AML)
Severe infection (rarely)

Leukopenia/Thrombocytopenia
Fanconi anemia
Aplastic anemia
Leukemia
Hemophagocytic histiocytosis

Howell-Jolly Bodies
Asplenia, hyposplenia
Severe iron deficiency

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia.

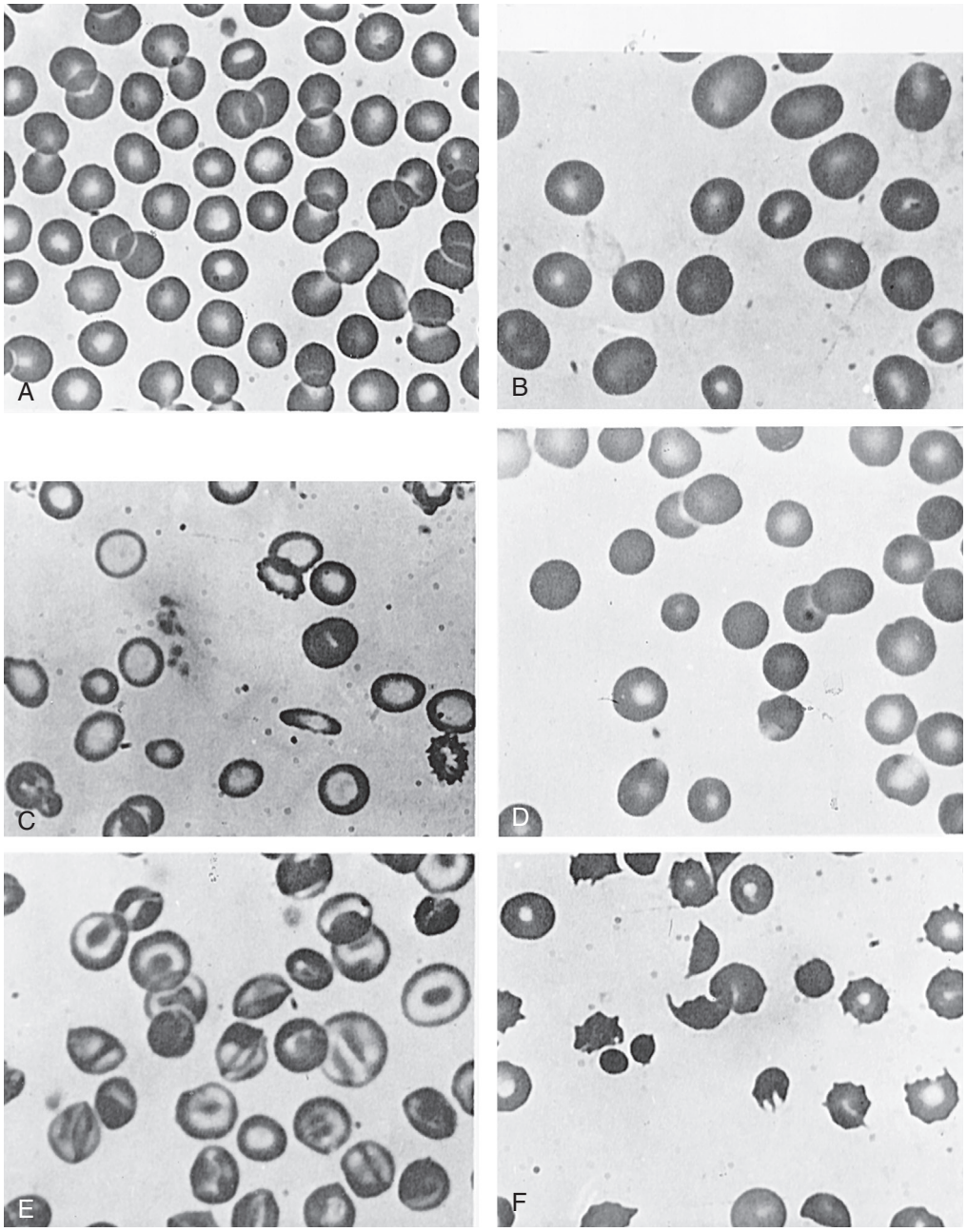


FIGURE 37.2 Morphologic abnormalities of the red blood cell. *A,* Normal. *B,* Macrocytes (folic acid deficiency). *C,* Hypochromic microcytes (iron deficiency). *D,* Spherocytes (hereditary spherocytosis). *E,* Target cells (hemoglobin CC disease). *F,* Schistocytes (hemolytic uremic syndrome). (From Behrman RE, Kliegman RM, eds. *Nelson Essentials of Pediatrics*. 2nd ed. Philadelphia: WB Saunders; 1994:521.)

must be secured, and frequent serial evaluations of hemoglobin, blood pressure, pulse, perfusion, and end-organ function must be performed.

DIFFERENTIAL DIAGNOSIS OF ANEMIA

The classification of anemia is presented in Figs. 37.1 and 37.4.

Anemia Secondary to Acute Blood Loss

Significant blood loss on an acute or subacute basis results in anemia. In subacute bleeding, the fall in hemoglobin occurs gradually and a period of about 24 hours may be required for full intravascular equilibration after acute blood loss. When severe acute blood loss occurs, intravascular volume depletion is the primary concern, which cannot be assessed by hemoglobin level. Therefore, in the setting of severe blood loss, blood pressure, heart rate, adequacy of peripheral perfusion, and mental status are the best ways to assess patients. In most instances, an obvious history of blood loss is apparent (epistaxis, hematemesis, lower gastrointestinal bleeding, trauma). In some cases, intraabdominal bleeding can occur that is not clinically apparent. Large amounts of blood may accumulate in the gastrointestinal tract before the development of hematemesis, hematochezia, or melena. Intraabdominal bleeding may occur after trauma or may result from an ulcer (see Chapter 13) and may be associated with progressive anemia in the absence of an obvious source of bleeding. The clinical

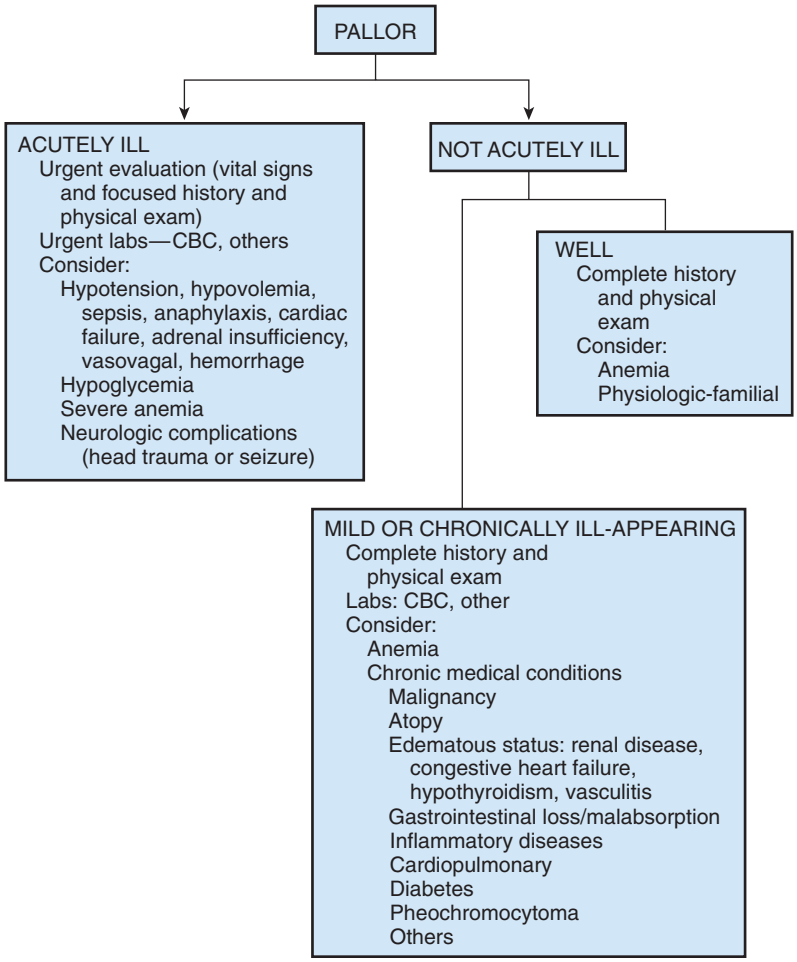


FIGURE 37.3 Approach to the pale child. CBC, complete blood count.

history coupled with the physical examination (including rectal examination) and tests for occult blood in the stool generally define the source of blood loss.

In anemia associated with blood loss, the RBC size and morphology are normal and appropriate reticulocytosis should occur within 3-5 days from the start of the blood loss. If hemorrhage has ceased, the hemoglobin level should gradually increase unless supervening factors such as iron deficiency exist.

Severe hemorrhage associated with intravascular volume depletion warrants immediate intervention to avoid shock. RBC transfusions are necessary until hemorrhage has ceased. Less severe hemorrhage that is not associated with intravascular volume depletion will likely manifest with moderate to severe anemia. Transfusions may be necessary when the oxygen-carrying capacity of the blood is diminished to the point of impending tissue hypoxia. In these cases, the need for transfusion therapy is based on clinical symptoms including tachycardia, dyspnea, heart failure, fatigue, or lightheadedness. If hemorrhage has ceased, intravascular volume is replete, and if the patient is not manifesting signs of cardiorespiratory compromise, transfusion therapy can often be avoided. In such instances, it is appropriate to supply therapeutic doses of iron to ensure adequacy of the reticulocyte response (Table 37.8).

TABLE 37.8 Therapy for Iron Deficiency

Infants and Children

3–6 mg/kg of elemental iron/day, given in divided doses 2 or 3 times/day (mild nutritional anemia deficiency in infants may be treated with a single daily dose of 3 mg/kg before breakfast)

Adolescents

3–6 mg/kg/day of elemental iron (maximum, 200 mg) given in divided doses 2 or 3 times/day

Duration of Prescription

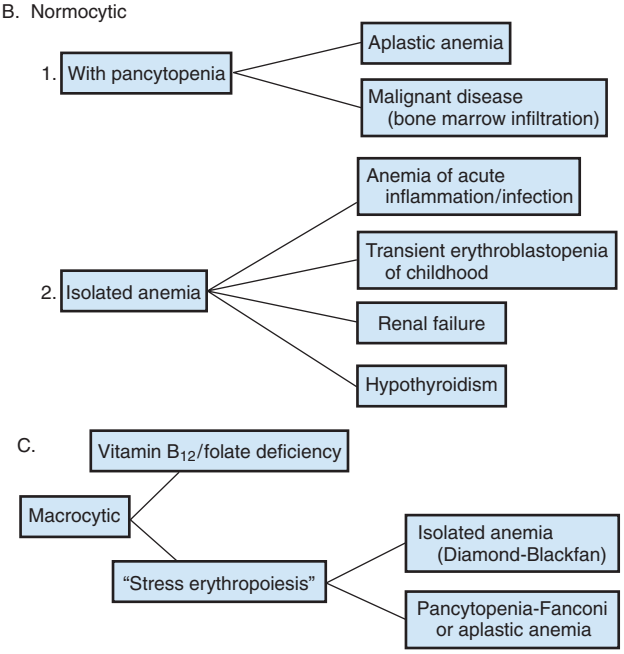
Continue *therapeutic dose* of iron for 2–3 mo after hemoglobin level has been corrected (to replete stores), after which maintenance nutritional needs must be met.

Anemia Secondary to Underproduction

Anemia caused by the underproduction of RBCs (see Figs. 37.1 and 37.4) is characterized by a suboptimal bone marrow response to the anemia reflected by a corrected reticulocyte count of less than 2%. Associated clinical symptoms can provide clues to the etiology of underproduction, especially for nonhematologic causes of anemia. Common nonhematologic causes of underproduction include chronic renal disease, chronic inflammation, or infection. Hematologic causes of underproduction are outlined in subsequent text. Anemia due to underproduction of RBCs should be evaluated in the context of RBC size: microcytic, normocytic, or macrocytic.

I. Acute blood loss with hemodilution

II. Anemia of RBC underproduction (i.e., inadequate reticulocyte count)
  A. Microcytic
    1. Iron deficiency
    2. Lead intoxication
    3. Thalassemia syndromes
    4. Anemia of chronic diseases
  B. Normocytic



  C. Macrocytic
    - Vitamin B_{12}/folate deficiency
    - "Stress erythropoiesis"
      - Isolated anemia (Diamond-Blackfan)
      - Pancytopenia-Fanconi or aplastic anemia

III. Anemia due to increased destruction = hemolysis (i.e., adequate reticulocyte count)
  A. Intrinsic RBC defect
    1. Hemoglobinopathies (sickle cell anemia, unstable hemoglobins)
    2. Membrane defects (hereditary spherocytosis, elliptocytosis)
    3. Enzymopathies (G6PD, pyruvate kinase deficiency)
  B. Extrinsic defects
    1. Immune hemolysis
    2. Infection (bacterial, viral, other)
    3. Microangiopathy (disseminated intravascular coagulation, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura)
    4. Liver disease
    5. Paroxysmal nocturnal hemoglobinuria
    6. Hypersplenism
    7. Mechanical injury (e.g., burns)
    8. Toxins
    9. Nutritional (vitamin E deficiency)
    10. Metabolic (galactosemia)
    11. Wilson disease

FIGURE 37.4 Differential diagnosis of anemia. G6PD, glucose-6-phosphate dehydrogenase; RBC, red blood cell.

Microcytic Anemias

Hemoglobin, the chief intracellular component of the RBC, is composed of heme (iron and protoporphyrin IX) and globin chains (α and β). Any factor that diminishes the availability or utilization of these components results in microcytic anemia. The automated MCV represents the mean RBC volume and does not address variations in cell size. The RDW, however, describes variation in RBC size and if normal defines a relatively uniform population of cells. Review of the peripheral blood smear also provides additional evidence regarding variability in cell size and shape. It is important to note that MCV is age related (Table 37.2). Common hematologic causes of microcytic anemia are discussed in subsequent text. When the diagnosis is not immediately apparent, it is helpful to carefully select from a variety of available laboratory studies to further differentiate the cause of the microcytic anemia (Table 37.9).

TABLE 37.9 Laboratory Findings in Microcytic Anemia

	FEP	Fe	TIBC	Pb	HbA_2	Ferritin
Iron deficiency	↑	↓	↑	nl	nl	↓
α-Thalassemia	nl	nl	nl	nl	nl	nl
β-Thalassemia	nl	nl	nl	nl	↑	nl
Lead poisoning	↑	nl	nl	↑	nl	nl
Anemia of chronic disease	↑	↓	↓	nl	nl	nl or ↑

Fe, iron; FEP, free erythrocyte protoporphyrin; HbA_2, hemoglobin A_2; nl, normal; Pb, lead; TIBC, total iron-binding capacity.
Modified from Reece RM. *Manual of Emergency Pediatrics*. 4th ed. Philadelphia: WB Saunders; 1992.

Iron deficiency anemia. Iron deficiency is the most common nutritional deficiency that causes anemia. Iron deficiency results when nutritional intake is insufficient to meet demands associated with growth and/or blood loss. Iron is a key component of the hemoglobin molecule; its deficiency leads to anemia associated with reduced hemoglobin production (hypochromia) and small RBCs (microcytosis). Infants are at particular risk for the development of iron deficiency since their rapid growth and expanding blood volume impose considerable iron demands. Premature infants are at the highest risk because most in utero iron is transferred to the fetus during the last trimester of pregnancy and postnatal growth rate is rapid. In addition, exclusively breast-fed infants are also susceptible to iron deficiency in the later months of their 1st year of life if sufficient solid food intake high in iron does not keep up with iron demands. Toddlers are also at high risk for the development of iron deficiency due to excessive cow's milk intake leading to poor iron absorption, decreased intake of dietary sources of iron, and gastrointestinal blood loss from milk protein sensitivity. Thus, appropriate counseling should be provided to the family to ensure that cow's milk is limited to no more than 24 oz/day. Adolescent females are at very high risk due to menstrual blood loss and inadequate nutrition. Risk for iron deficiency is high in adolescent females especially during the 1st year after menarche. *When iron deficiency occurs outside of the setting of infancy, toddlers, or adolescent females a pathologic source of blood loss must be strongly considered and occult gastrointestinal bleeding is an important source to consider as iron deficiency anemia can be the first clue to the presence of inflammatory bowel disease.*

Nutritional sources of iron include iron-fortified infant formula (12 mg/L), iron-fortified infant cereal, beef, fish, and fowl. Ascorbic acid (vitamin C) enhances the absorption of iron. The American Academy of Pediatrics recommends iron-fortified infant formula or breast milk until the age of 1 year and the introduction of iron-rich foods after 6 months of age. Cow's milk is a very poor source of nutritional iron and should not be given to infants less than 1 year of age. After 1 year of age, infants should consume no more than 24 oz/day. Iron supplementation is necessary for preterm infants, most adolescent females, and pregnant women and should be strongly considered for all exclusively breast-fed infants regardless of diet. Iron deficiency must be viewed as a systemic deficiency disorder, only 1 manifestation of which is anemia (Table 37.10).

Iron deficiency is usually detected by routine hemoglobin screening. This should be performed initially in children between 9-12 months of age and again between 18-24 months of age as toddlers are especially vulnerable to iron deficiency anemia during the transition from

TABLE 37.10 Nonhematologic Consequences of Iron Deficiency

Impairment of cognitive development
Pica
Epithelial abnormalities (gastrointestinal mucosal lesion, glossitis; spoon-shaped nails)
Exercise intolerance (muscle weakness)
Behavioral manifestations
Growth retardation
Impaired collagen synthesis (blue sclera)

formula to cow's milk. Adolescent females should be screened 1-2 years after menarche. Laboratory confirmatory studies are necessary when iron deficiency anemia is suspected in patients who are not at high risk for nutritional deficiency or in those in whom anemia is moderately severe (Table 37.9). A serum ferritin level of less than 12 ng/dL or an iron saturation of less than 10% confirms the diagnosis.

Symptomatic iron deficiency is infrequent, but when it occurs, it is generally noted in infants who consume large amounts of cow's milk and have intestinal blood loss as a result of asymptomatic milk protein–induced enterocolitis. Such children may have pallor, irritability, fatigue, glossitis, blue sclera, and in extreme cases signs and symptoms of high-output cardiac failure (dyspnea, diaphoresis, pallor, tachycardia, gallop rhythm, and hepatomegaly). Blood loss may be intermittent; a negative stool test for blood does not rule out the diagnosis. Mild anemia in otherwise well infants between 6-24 months of age, particularly in association with ingestion of large amounts of cow's milk, is most likely caused by iron deficiency.

When mild anemia is detected in the healthy, menstruating adolescent female, chronic blood loss is usually the etiology. Empirical iron therapy is often prescribed in such circumstances (Table 37.8). If the hemoglobin level has normalized after 1 month of therapy, a presumptive diagnosis has been established and the patient should receive an additional 2-3 months of therapeutic doses of iron to replete stores. An appropriate response to iron therapy is the diagnostic "gold standard."

Recurrent iron deficiency anemia in infants and children, despite limitation of cow's milk intake and compliance with supplemental iron, should raise the suspicion for **pulmonary hemorrhage** as a source of chronic blood loss. This condition is called Heiner syndrome and is due to severe cow's milk protein hypersensitivity. Heiner syndrome should be considered when chronic iron deficiency anemia exists with associated cough, wheeze, or diagnosis of "asthma." Chest radiograph reveals pulmonary infiltrates consistent with hemorrhage.

The treatment of iron deficiency anemia is outlined in Table 37.8. Intravenous iron therapy is rarely necessary, although it may be useful in certain situations (iron malabsorption in patients with celiac disease, intestinal bacterial overgrowth syndrome, inflammatory bowel disease, and genetic causes affecting iron absorption; children receiving hemodialysis). The optimal approach to iron deficiency anemia in infants and children is prevention.

Thalassemia syndromes. The thalassemia syndromes represent a heterogeneous group of inherited disorders of decreased globin production that lead to microcytic anemia, which can be mistaken for iron deficiency. The child with microcytic anemia, without evidence of iron deficiency, should be evaluated for thalassemia.

Two genes, one inherited from each parent, code for the production of the β-globin chains of hemoglobin. When 1 gene is affected by the β-thalassemia mutation, a moderate diminution in the production of the β-globin chain occurs, resulting in mild microcytic anemia of underproduction. β-Thalassemia occurs most commonly in individuals of Mediterranean, Asian, or African descent. Patients with **β-thalassemia trait** are asymptomatic and the diagnosis is frequently made when anemia and microcytosis are noted at the time of routine screening for iron deficiency or incidentally when a CBC is obtained for the assessment of acute or chronic symptoms. Typically patients have mild anemia and a low MCV. For an equivalent degree of anemia, the MCV is substantially lower than that seen in iron deficiency.

This phenomenon is reflected in the Mentzer index calculated by dividing the MCV by the RBC count (in millions). The RBC count is usually elevated in thalassemia. Thus, an index of less than 13 is suggestive of thalassemia trait, whereas an index of more than 13 is generally suggestive of iron deficiency anemia. A normal MCV virtually excludes a diagnosis of β-thalassemia. A normal or mildly elevated RDW is usually seen in thalassemia and reflects a relatively uniform population of microcytic RBCs. This is in contrast to iron deficiency wherein the RDW is uniformly elevated reflecting variation in cell size.

The peripheral blood smear demonstrates microcytosis, hypochromia, and target cells. Occasional fragments may be seen. The significance of diagnosing β-thalassemia trait is twofold: (1) its confusion with iron deficiency (hence, patients may be treated unnecessarily with repeated courses of iron and undergo repeated unnecessary blood studies) and (2) its genetic implications. A mating between 2 individuals with β-thalassemia trait carries a 25% risk per pregnancy of offspring with homozygous β-thalassemia (thalassemia major), a severe hematologic disorder. Parents and siblings of a child with a diagnosis of β-thalassemia trait should be appropriately screened and counseled. For purposes of screening, a normal, age-adjusted MCV essentially excludes a diagnosis of β-thalassemia trait.

Homozygous β-Thalassemia, also known as β-thalassemia major or Cooley anemia, results from the inheritance of the β-thalassemia trait mutation from each parent. This results in a severe deficiency of β-globin chain production. Excess α-globin chains precipitate within developing erythroid elements in the marrow and lead to brisk intramarrow destruction of developing erythroid elements (ineffective erythropoiesis). As a result, patients with β-thalassemia major present during infancy at 6-12 months of age with severe anemia and an inadequate reticulocyte count during the time when transition from fetal hemoglobin to adult hemoglobin occurs. The child with β-thalassemia major typically presents with fatigue, irritability, pallor, jaundice, and marked hepatosplenomegaly that is caused by extramedullary hematopoiesis. Frontal bossing and prominent cheek bones (maxillary hyperplasia) may be noted and result from expansion of the marrow space in an attempt to compensate for the severe anemia. Most patients are of Mediterranean or Asian descent.

Laboratory findings include severe anemia and a decreased age-adjusted MCV. The peripheral blood smear is markedly abnormal, demonstrating severely underhemoglobinized RBCs, target cells, and wide variability in cell shape and size (increased RDW). Long-term transfusion therapy sufficient to suppress ineffective erythropoiesis (maintaining hemoglobin level >10 g/dL) may be associated with relatively normal growth, development, and functional capabilities. Long-term iron chelation to prevent iron overload allows for prolonged survival and avoidance of transfusional hemosiderosis (hepatic, endocrine, and cardiac dysfunction). Bone marrow transplantation is curative and a potential treatment option for younger patients who have a human leukocyte antigen–identical healthy sibling or matched unrelated donor.

Four genes code for the α-globin chains of hemoglobin: 2 genes on each chromosome 16. Deletions of 1, 2, 3, or 4 of these genes account

for the variable laboratory and clinical findings associated with the **α-thalassemia syndromes**. Decreased α-globin chain production leads to an excess of β-globin chains, which tend to precipitate within developing RBCs in the bone marrow leading to destruction. Mature RBCs are mildly hypochromic and microcytic and may appear to be targeted.

Deletion of 1 α-thalassemia gene is known as the "silent carrier" state because it is not associated with anemia or microcytosis. This occurs in about 30% of African-Americans as well as individuals of Asian descent.

Deletion of 2 genes represents **α-thalassemia trait**. Such patients manifest mild anemia and microcytosis with MCVs generally in the mildly decreased range (less microcytosis than is generally seen in β-thalassemia trait).

A 3-gene deletion leads to **hemoglobin H disease**, which is associated with moderate hemolytic anemia, microcytosis, reticulocytosis, and splenomegaly.

A 4-gene deletion represents **α-thalassemia major** or hemoglobin Bart's disease, in which the fetus is unable to produce any α-chains. Hence, nearly all in utero hemoglobin is Bart's type (composed of 4 β-chains). Hemoglobin Bart's has an extremely high oxygen affinity and leads to severe tissue hypoxemia and resultant fetal hydrops and death. On occasion, babies with hemoglobin Bart's disease have been saved by extraordinary measures (intrauterine transfusion and early delivery), but they are then committed to lifelong transfusion support and/or bone marrow transplantation.

Hemoglobin H disease and α-thalassemia major occur almost exclusively in individuals of Asian descent. This is because Asians and Africans have different chromosomal arrangements of the abnormal genes. When α-thalassemia minor (2-gene deletion) occurs in the Asian population, deletions may be *cis* (both genes deleted from the same chromosome) or *trans* (each chromosome missing 1 gene). In individuals of African descent, α-thalassemia minor (2-gene deletion) occurs only on the basis of a *trans* distribution; hence, a mating between 2 individuals with the African variety of α-thalassemia trait produces offspring with only 2 α genes deleted (α-thalassemia minor). A mating between 2 individuals of Asian descent who have α-thalassemia minor may produce an offspring with all 4 genes deleted (α-thalassemia major). The implication of a diagnosis of α-thalassemia trait in individuals of African descent usually relates primarily to its confusion with iron deficiency. Individuals of Asian descent must be appropriately counseled regarding the potential for transmission of serious hematologic disease if a mating between 2 individuals with α-thalassemia trait occurs.

Lead poisoning. The occurrence of elevated serum and total body burdens of lead is a major public health problem. This is of particular importance for infants and young children from lower socioeconomic families living in old housing with lead-based paint. Elevated lead levels may decrease erythropoiesis because lead inhibits several enzymes along the path of protoporphyrin synthesis. Lead may also produce hemolysis.

Anemia is usually seen in association with lead levels of 60-70 μg/dL or higher. Anemia is mild, variably microcytic, and associated with prominent basophilic stippling of RBCs. Coexistent iron deficiency is common because iron deficiency promotes increased lead absorption. The presence of mild microcytic anemia in children with mild to moderate lead burdens is usually due to concomitant iron deficiency. Lead chelation therapy is appropriate when lead levels are higher than 40-45 μg/dL. Additional features of marked lead toxicity include intestinal colic, lead lines in long bone radiographs, behavioral changes, renal tubular defects, and lead encephalopathy associated with increased intracranial pressure.

Anemia of inflammation. In a wide variety of chronic inflammatory or infectious disorders, mild to moderate anemia, termed **anemia of inflammation** (previously known as anemia of chronic disease), may be present. The MCV is usually normal to mildly decreased. Chronic inflammation or infection impairs the transfer of iron from reticuloendothelial cells within the marrow to developing erythroid elements. This results in some degree of iron-deficient erythropoiesis despite adequate marrow stores of iron. This impaired transfer of iron is thought to be due in part to the molecule hepcidin that is elevated during times of inflammation. Often the history and physical examination findings point to chronic illness, but occasionally patients have no obvious manifestations of systemic disease. The presence of unexplained normocytic or mild microcytic anemia should alert the clinician to the possibility of occult systemic disease. An elevated erythrocyte sedimentation rate is usually noted in patients with chronic inflammatory or infectious states. Anemia of inflammation is characterized by no specific abnormalities on peripheral smear other than mild hypochromia and microcytosis. Serum ferritin level is often elevated as a result of the inflammatory state and is thus a poor reflection of iron status. Serum iron level and total iron-binding capacity are generally decreased, but the percentage of iron saturation is often within the low to normal range distinguishing it from iron deficiency anemia.

Rare causes of microcytic anemia. **Sideroblastic anemias** are a group of very rare congenital (often X linked) inherited diseases associated with impairment of protoporphyrin synthesis and variable microcytic anemia. The bone marrow examination demonstrates evidence of developing erythroid cells with excess iron deposited in mitochondria that tend to form a circular appearance around the nucleus; hence, the term *ringed sideroblast.* **Copper deficiency** is another rare cause of microcytic anemia. Associated features include neutropenia and scurvy-like bone changes (periosteal elevation). Only under unusual circumstances, when prominent microcytic anemia is otherwise unexplained, should these rare disorders be considered.

Normocytic Anemia Secondary to Underproduction

When normocytic anemia secondary to underproduction is identified in a patient, the key issue is whether anemia is occurring in isolation or is associated with other cytopenias (Table 37.11 and Fig. 37.5; Fig. 37.4). Normocytic anemia with an inadequate reticulocyte response and pancytopenia raises the possibility of serious primary or secondary bone marrow disease (Table 37.11) including malignancy. The history and physical examination findings are often predictive of the presence of thrombocytopenia (easy bruising, petechiae, ecchymosis) and/or neutropenia (fever, signs of infection). Adenopathy and hepatosplenomegaly are suggestive of bone marrow infiltration caused by malignancy.

Acquired aplastic anemia is a rare disorder of childhood characterized by pancytopenia (neutropenia, anemia, thrombocytopenia) and a markedly hypoplastic bone marrow. Clinical manifestations may include pallor, fatigue, purpura, bleeding (cutaneous petechiae and ecchymosis, epistaxis, gingival oozing), and/or recurrent infection. The physical examination may reveal purpura and pale mucosa and skin. Adenopathy and hepatosplenomegaly are not features of this condition. The cause is often obscure but may be related to prior infection (hepatitis, Epstein–Barr virus), toxin exposure (benzene, other volatile compounds), or medications (chloramphenicol, anticonvulsants). Postinfectious, drug-related, or idiopathic acquired aplastic anemia is most likely mediated by immunologic mechanisms. The peripheral blood smear demonstrates normal-appearing RBCs, an absence of polychromasia, and few leukocytes and platelets. The MCV may be elevated. A bone marrow biopsy demonstrates hypoplasia involving all cell lines. Severe acquired aplastic anemia is most appropriately treated by bone

TABLE 37.11 Differentiation of Red Blood Cell Aplasias and Aplastic Anemias

Disorder	Age at Onset	Characteristics	Treatment
Congenital			
Diamond–Blackfan syndrome (congenital hypoplastic anemia)	Newborn–1 mo 90% <1 yr age	Pure red cell aplasia, autosomal recessive, autosomal dominant or sporadic, elevated fetal hemoglobin, fetal i antigen present, macrocytic; some have thrombosis, short stature, webbed neck, cleft lip, triphalangeal thumb; late-onset leukemia	Prednisone, transfusion
Acquired			
Transient erythroblastopenia	6 mo–5 yr 85% >1 yr age	Pure red blood cell defect; no anomalies, fetal hemoglobin or i antigen; spontaneous recovery; normal MCV	Transfusion for symptomatic anemia
Idiopathic aplastic anemia (S/P hepatitis, drugs, unknown)	All ages	All cell lines involved; chloramphenicol, phenylbutazone, radiation	Bone marrow transplantation, antithymocyte globulin, cyclosporine, androgen
Familial			
Fanconi anemia	Before 10 yr; mean, 8 yr	Absent thumbs, cafè-au-lait spots, cutaneous hyperpigmentation, short stature; chromosomal breaks, high MCV and hemoglobin F; horseshoe or absent kidney, leukemic transformation; autosomal recessive trait	Androgens, corticosteroids, bone marrow transplantation
Paroxysmal nocturnal hemoglobinuria	After 5 yr	Initial hemolysis followed by aplastic anemia; increased complement-mediated hemolysis; thrombosis, iron deficiency	Iron, bone marrow transplantation, androgens, steroids
Dyskeratosis congenita	Mean for skin, 10 yr; mean for anemia, 17 yr	Pancytopenia; hyperpigmentation, dystrophic nails, leukoplakia; X-linked recessive; lacrimal duct stenosis; high MCV and fetal hemoglobin	Androgens, splenectomy, bone marrow transplantation
Familial hemophagocytic lymphohistiocytosis	Before 2 yr	Pancytopenia; fever, hepatosplenomegaly, hypertriglyceridemia, CSF pleocytosis	Transfusion (often lethal), VP-16, bone marrow transplantation
Infections			
Parvovirus	Any age	Superimposed on any chronic hemolytic anemia, typically sickle cell; new-onset reticulocytopenia	Transfusion
Epstein–Barr virus (EBV)	Any age; usually <5 yr	X-linked immunodeficiency syndrome, pancytopenia	Transfusion; bone marrow transplantation
Virus-associated hemophagocytic syndrome (CMV, HHV-6, EBV)	Any age	Pancytopenia; hemophagocytosis present in marrow	Transfusion, antiviral therapy, intravenous immunoglobulin

CMV, cytomegalovirus; CSF, cerebrospinal fluid; HHV-6, human herpesvirus-6; MCV, mean corpuscular volume; S/P, status post; VP-16, etoposide. Modified from Scott JP. Hematology. In: Behrman RE, Kliegman RM, eds. *Nelson Essentials of Pediatrics*. 2nd ed. Philadelphia: WB Saunders; 1994:525.

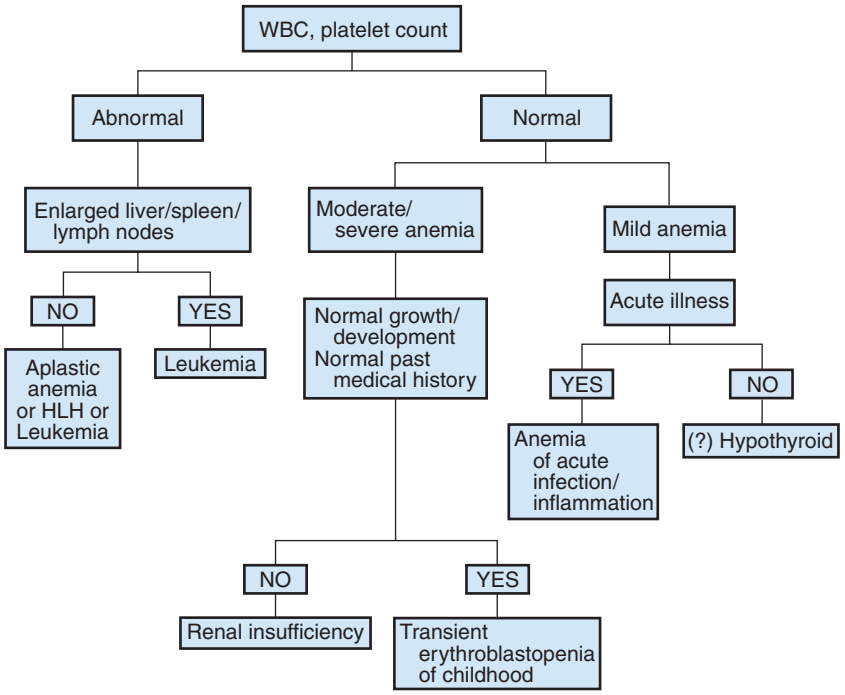


FIGURE 37.5 Diagnostic scheme of normochromocytic anemia of underproduction. HLH, hemophagocytic lymphohistiocytosis; WBC, white blood cell.

marrow transplantation when a human leukocyte antigen–matched sibling marrow donor is available. Unrelated matched donors offer another possibility for bone marrow transplantation. If marrow transplantation is not feasible, immunosuppressive therapies, including antilymphocyte globulin, corticosteroids, and cyclosporine, have been used with variable success. Aplastic anemia should always be considered when anemia occurs in association with thrombocytopenia and neutropenia in the absence of adenopathy and hepatosplenomegaly.

Disorders associated with bone marrow infiltration including **leukemia** and **metastatic malignancy** often manifest with normocytic anemia secondary to underproduction, thrombocytopenia, and either neutropenia, or leukocytosis. Teardrop erythrocytes may be present in the peripheral smear. The MCV may be elevated. Many children with leukemia come to medical attention because of pallor, fatigue, and purpura. Limping and skeletal pain are also common with childhood leukemia. Pallor, purpura, adenopathy, and hepatosplenomegaly are often seen on physical examination. Peripheral blood smear may show leukemic blasts. Bone marrow examination findings are diagnostic.

When normocytic anemia secondary to underproduction is isolated without associated thrombocytopenia or neutropenia, several diagnostic entities must be considered. Mild anemia commonly accompanies **acute infections** and inflammatory illness. Children are often incidentally found to be anemic several days to a few weeks after having childhood infectious illnesses including viral upper respiratory tract infections, gastroenteritis, or undifferentiated febrile illnesses. Anemia reflects impaired erythrocyte production as a result of the bone marrow–suppressive mediators of the immune/inflammatory response including interleukins, interferons, and tumor necrosis factor. Cessation of RBC production leads to a fall in hemoglobin level of about 1 g/dL/wk. Mild anemia discovered during or shortly after acute illness does not necessitate an extensive evaluation; rather a follow-up hemoglobin determination should be obtained several weeks later. Persistent anemia necessitates further evaluation.

Transient erythroblastopenia of childhood, occurring predominantly in infants and toddlers, represents a temporary arrest of erythropoiesis that is likely secondary to IgG antibodies that cross-react with early erythroid precursor cells. Infection is thought to be 1 impetus for the development of this condition. Patients present with pallor and fatigue that occurs gradually over several weeks to months. Because of the very gradual fall in hemoglobin, most affected children are remarkably well compensated. Physical examination usually shows only marked pallor and mild tachycardia. Adenopathy and hepatosplenomegaly are not present. Congestive heart failure occurs only if anemia is very severe. The CBC demonstrates a normocytic anemia and profound reticulocytopenia. The WBC and platelet counts are normal in most patients; however, 25% of patients have mild neutropenia at the time of presentation. The peripheral blood smear is unremarkable. Recovery is spontaneous. Blood transfusion is indicated only for patients with severe, symptomatic anemia. Transient erythroblastopenia of childhood may be difficult to differentiate from congenital hypoplastic anemia (Diamond–Blackfan anemia), particularly in children younger than 1 year (Table 37.11). In Diamond–Blackfan anemia, a constitutional RBC aplasia syndrome, MCV and fetal hemoglobin levels are usually elevated for the patient's age providing clues to the diagnosis.

The patient with previously undiagnosed chronic hemolytic anemia (sickle cell anemia, hereditary spherocytosis) may present with normocytic anemia and severe reticulocytopenia if transient RBC hypoplasia occurs on the basis of a viral infection such as commonly seen with parvovirus B19. Because of a shortened RBC life span in patients with chronic hemolysis, a transient arrest of RBC production can cause severe anemia that evolves over several days. Patients may have a history of neonatal jaundice and/or intermittent icterus, and they often have splenomegaly and an abnormal peripheral smear related to the underlying hemolytic disease.

Isolated anemia secondary to underproduction occurs in children with **chronic renal disease** as a result of erythropoietin deficiency. Clinical and laboratory findings often suggest a diagnosis of renal insufficiency such as poor growth, hypertension, edema, abnormal urinalysis, and elevated serum urea nitrogen and creatinine levels. The anemia of chronic renal disease can be successfully treated by recombinant human erythropoietin.

Macrocytic Anemia (Figs. 37.1 and 37.4)

Diamond–Blackfan anemia is a constitutional pure RBC aplasia syndrome that manifests during the 1st year of life with isolated severe anemia and reticulocytopenia (Table 37.11). The remainder of the CBC is unremarkable. Because synthesis of RBCs containing adult hemoglobin is markedly impaired, RBCs generally manifest fetal characteristics, including elevated MCV, increased levels of fetal hemoglobin, and the "i" surface antigen. Bone marrow aspirate demonstrates pure RBC aplasia. Two-thirds of patients with Diamond–Blackfan anemia initially respond to corticosteroid treatment; the remaining patients require long-term transfusion therapy. In patients who initially respond to steroid therapy, the anemia may become refractory over time. Bone marrow transplantation has been curative in selected steroid-resistant patients.

Fanconi anemia usually manifests with macrocytic anemia secondary to underproduction and pancytopenia. It is a constitutional disorder frequently, but not invariably, associated with physical stigmata (Table 37.11). Most patients do not present with overt hematologic manifestations until 4 or 5 years of age. Thumb and radial anomalies should alert the clinician to possible Fanconi anemia even in the absence of cytopenias. RBCs tend to have fetal characteristics including increased MCV and elevated fetal hemoglobin level. Patients usually initially respond to androgen therapy, however, mortality rates are high due to evolving resistance to treatment over time in addition to predisposition to myeloid leukemia and other malignancies. Bone marrow transplantation can be curative based on the hematologic manifestations. Fanconi anemia is among the chromosomal breakage disorders wherein DNA is unusually fragile and susceptible to injury. Thus, the diagnostic laboratory abnormality is an increased chromosomal breakage when cells are cultured in the presence of a clastogenic agent, such as diepoxybutane, commonly known as the DEB test. There are at least 15 genes responsible for Fanconi anemia; sequencing may confirm the diagnosis.

Megaloblastic anemia (vitamin B_{12} deficiency or folate deficiency). Megaloblastic anemia, characterized by macrocytic RBCs with variable abnormalities of WBCs and platelets, is usually caused by vitamin B_{12} deficiency or folate deficiency. Albeit rare in children, it can occur secondary to nutritional or congenital etiologies. If severe, associated pancytopenia can occur. In addition to large ovoid RBCs, hypersegmented neutrophils (more than 5 lobes/cell) are often seen on the peripheral smear (Fig. 37.6); large platelets can be present. It is appropriate to suspect vitamin B_{12} deficiency or folate deficiency in patients with otherwise unexplained macrocytic anemia. Documenting the presence of vitamin B_{12} deficiency or folate deficiency requires an exhaustive etiologic search, including assessment of nutrition and gastrointestinal absorption. Prompt diagnosis of vitamin B_{12} deficiency is imperative due to the associated neurologic manifestations that can occur. Importantly, the degree of anemia can be inversely proportional to the neurologic symptoms; thus, a high index of suspicion is needed in order to not miss the diagnosis. The diagnosis of vitamin B_{12} deficiency and folate deficiency cannot be made solely on the levels of

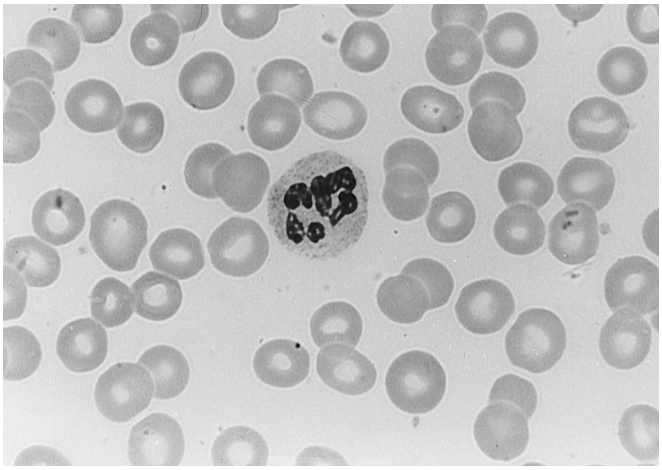


FIGURE 37.6 Hypersegmented polymorphonuclear leukocyte as seen in vitamin B_{12} deficiency or folate deficiency.

vitamin B_{12} deficiency or folate. The precursors of methylmalonic acid (MMA) and homocysteine must also be evaluated since normal vitamin B_{12} levels can still be associated with vitamin B_{12} deficiency. Elevated MMA despite normal B_{12} levels is diagnostic of B_{12} deficiency. RBC folate and not serum folate should be evaluated to accurately assess folate levels.

Nutritional vitamin B_{12} deficiency may occur in breast-feeding infants of mothers on strict vegetarian diets that exclude milk and egg products.

Congenital pernicious anemia is a rare syndrome associated with vitamin B_{12} malabsorption that is caused by gastric intrinsic factor deficiency. Children who have had resection of the terminal ileum, the site of absorption of vitamin B_{12}, may develop megaloblastic anemia. Vitamin B_{12} malabsorption may occur with inflammatory disease involving the terminal ileum such as Crohn disease or ulcerative colitis. Rare congenital disorders that affect vitamin B_{12} transport, absorption, or metabolism can also occur.

Unlike body stores of vitamin B_{12}, which may provide several years' reserve, folate stores are limited to several weeks' supply. Folate is ubiquitous in food sources; hence, nutritional deficiency is unusual. Infants fed unsupplemented goat's milk may develop profound folate deficiency. Malabsorption of folate can occur in children who have limited small bowel absorptive capacity as a result of surgical resection or inflammatory disease.

Anemia caused by increased red blood cell destruction. The hemolytic disorders (Figs. 37.1 and 37.4) are characterized by shortened RBC survival and compensatory reticulocytosis. Normal RBCs survive approximately 120 days in the circulation. New RBCs are manufactured at a rate equivalent to the destruction of senescent RBCs so that under normal circumstances an appropriate hemoglobin level is maintained. Intrinsic or extrinsic RBC factors can lead to accelerated RBC destruction. Several clinical and laboratory hallmarks are associated with hemolysis (Table 37.12). It is imperative that a technically adequate peripheral blood smear be examined whenever hemolysis is suspected. Although normal RBC structure does not exclude a diagnosis of hemolytic anemia, most hemolytic diseases are associated with morphologic abnormalities (Table 37.13). Depending on the cause of the hemolysis, RBCs may be removed from the circulation by reticuloendothelial cells (extravascular hemolysis) or may lyse within the circulation (intravascular hemolysis). With intravascular hemolysis, hemoglobin is released into the plasma and bound by the serum protein haptoglobin. In states of brisk intravascular hemolysis, haptoglobin may be depleted and free hemoglobin may be filtered by the kidney resulting in a pink appearance of the urine. A urinary dipstick test result is positive for blood, but the microscopic examination of the urinary sediment does not demonstrate intact RBCs.

Disturbances of any of the 3 key components of the RBC—the membrane, enzymes, and hemoglobin—may lead to ongoing or intermittent hemolysis.

Membrane defects. The prototypic intrinsic membrane defect is **hereditary spherocytosis**, which is an inherited disorder that can be inherited as autosomal dominant or autosomal recessive, or be a new mutation. This disorder occurs in approximately 1/5000 live births. It is seen most typically in individuals of Northern European descent, but may be identified in any population. The basic defect is an abnormality of a membrane protein (spectrin, protein 3, or ankyrin) that allows the RBC membrane to lose its redundancy and the usual biconcave disk shape resulting in a small, dense cell of spheroid configuration (Fig. 37.2*D*). Hemolysis occurs because the spheroid RBCs are far less distensible and are unable to successfully traverse the microcirculation of the spleen. Characteristic clinical findings include anemia, reticulocytosis, and the presence of abundant microspherocytes on peripheral smear. Associated nonspecific findings of chronic hemolysis are often

TABLE 37.12 Clinical and Laboratory Features Suggestive of Hemolytic Anemia

Pallor
Icterus
Splenomegaly
Gallstones
History of neonatal icterus
Positive family history of anemia, splenectomy, cholecystectomy
↑ Reticulocyte count
↑ RDW (due to ↑ reticulocyte count)
Abnormal RBC morphology
↑ Indirect bilirubin (normal direct bilirubin)
↓ Serum haptoglobin level
↑ Urinary urobilinogen level
Hemoglobinuria (+ dipstick test result for blood; no RBCs in urine)
↑ LDH level

LDH, lactate dehydrogenase; RBC, red blood cell; RDW, red blood cell distribution width.

TABLE 37.13 Hemolytic Anemia: Diagnostic Clues Based on Red Blood Cell Structure

Sickle cells: sickle cell disease
Target cells: hemoglobinopathies (HbC, HbS, thalassemia), liver disease
Schistocytes/burr cells/helmet cells/RBC fragments: microangiopathic hemolytic anemia—DIC, HUS, TTP
Spherocytes: hereditary spherocytosis, autoimmune hemolytic anemia
Cigar-shaped cells: hereditary elliptocytosis
"Bite" cells: G6PD deficiency
Poikilocytosis, microcytosis, fragmented erythrocytes, elliptocytes: hereditary pyropoikilocytosis

DIC, disseminated intravascular coagulation; G6PD, glucose-6-phosphate dehydrogenase; Hb, hemoglobin; HUS, hemolytic uremic syndrome; RBC, red blood cell; TTP, thrombotic thrombocytopenic purpura.

present including pallor, icterus, and splenomegaly. The family history is often positive for anemia, splenectomy, or cholecystectomy.

Newborns with hereditary spherocytosis frequently develop jaundice within the first 24 hours after birth necessitating phototherapy and occasionally exchange transfusion. Diagnosis may be confirmed by an osmotic fragility test reflecting the limited capacity of the RBC to expand when incubated in a hypotonic solution. The clinical spectrum of disease is broad. Some patients have mild, well-compensated hemolysis and their condition is detected during their adult years after a diagnosis in 1 of their children. Other patients may have brisk hemolysis during infancy necessitating intermittent transfusion support. Most patients have a disease course characterized by mild to moderate anemia, reticulocytosis, and splenomegaly. Patients are susceptible to exacerbations of anemia as a result of virus-induced hyperhemolysis or transient RBC hypoplasia. Parvovirus B19 may cause superimposed transient RBC hypoplasia of about 1 week's duration, resulting in moderate to severe anemia that requires transfusion.

Hereditary elliptocytosis represents a heterogeneous group of inherited disorders characterized by variable chronic hemolysis and abundant elliptical RBCs on peripheral smear. The clinical and laboratory findings are similar to those seen in hereditary spherocytosis. Splenectomy is appropriate in patients with moderate to severe hemolytic disease.

Hereditary pyropoikilocytosis is an autosomal recessive membrane disorder that manifests in the newborn period and is characterized by marked jaundice and anemia, reticulocytosis, and striking aberrations of RBC structure (Table 37.13). Hemolysis lessens with advancing age.

Enzyme defects. The most common RBC enzyme defect is G6PD deficiency. An X-linked disorder, G6PD deficiency occurs most commonly in individuals of African and Mediterranean descent and should always be considered in the differential diagnosis of acute hemolytic anemia in boys. Deficiency of G6PD activity renders hemoglobin susceptible to oxidant insult leading to precipitation of hemoglobin, membrane damage, and ultimately RBC destruction. Oxidant injury may occur because of intercurrent infection or ingestion of various substances, including medications (i.e., classically sulfa drugs), toxins, and foods such as fava beans (Table 37.14).

The common African variant of G6PD, termed *G6PD deficient variant A–*, is not necessarily associated with chronic hemolysis but usually manifests as mild acute hemolytic anemia related to specific precipitating factors. Rarely is hemolysis sufficiently severe to warrant transfusion therapy. Patients are often incidentally found to be anemic with evidence of an appropriate reticulocyte response. A peripheral blood smear may demonstrate "bite" cells as portions of the RBC (precipitates of hemoglobin) are removed by reticuloendothelial cells (Fig. 37.7). G6PD enzyme assay is necessary for the establishment of a diagnosis, but the test must be performed on a sample that has been depleted of reticulocytes because newly released RBCs have large amounts of G6PD. The Mediterranean variety of G6PD deficiency tends to be more severe and may be associated with chronic hemolysis as well as with superimposed acute events caused by infection or medication leading to symptomatic anemia and the occasional need for transfusion therapy.

Although rare, **pyruvate kinase deficiency (PKD)** is the second most common enzyme deficiency after G6PD deficiency. Inheritance of PKD is autosomal recessive. PKD is characterized by absence of or significantly reduced levels of the intracellular RBC enzyme, pyruvate kinase. Lack of this enzyme leads to decreased levels of ATP and subsequent brisk hemolysis. The clinical spectrum of PKD is variable but can result in severe chronic hemolytic anemia that is present in utero and postnatally. In its most severe form, hemolysis is extremely brisk, and it is not uncommon for patients with PKD to maintain reticulocyte counts of 40% or higher. Peripheral blood smear may demonstrate spiculated RBCs. Specific enzyme assay can be performed by specialized laboratories to aid in the diagnosis. Patients with PKD usually require lifelong RBC transfusions that often result in transfusional iron overload. Splenomegaly is often present and splenectomy can ameliorate the condition and decrease the number of required transfusions. Patients with PKD are also extremely susceptible to transient RBC hypoplasia caused by parvovirus B19 infection.

Hemoglobinopathies. Hemoglobinopathies usually occur as a result of a single amino acid substitution in α- or β-globin chains.

TABLE 37.14 Factors Known to Promote Hemolysis in Patients with G6PD Deficiency

Viral or bacterial infection
Fava beans
Vitamin C (large doses)
Mothballs (naphthalene)
Benzene and other volatiles
Medications
Sulfonamides*
Antimalarial drugs†
Nitrofurantoin
Nalidixic acid
Chloramphenicol
Vitamin K analogs
Methylene blue
High-dose aspirin
Stibophen
Niridazole
Probenecid
Dimercaprol (BAL)
Toluidine blue
Phenylhydrazine

*Sulfanilamide, sulfapyridine, sulfadimidine, sulfacetamide, sulfafurazole, salicylazosulfapyridine (Azulfidine), dapsone, sulfoxone, septrin.
†Primaquine, pamaquine, chloroquine (use with caution).
G6PD, glucose-6-phosphate dehydrogenase.

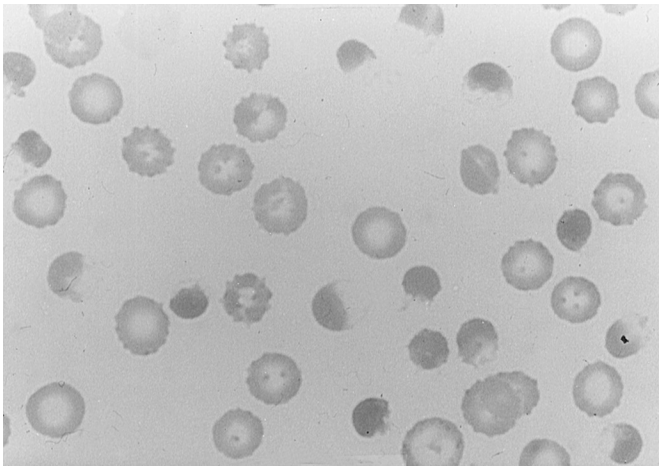


FIGURE 37.7 "Bite" cells and burr cells as seen in G6PD deficiency hemolysis. G6PD, glucose-6-phosphate dehydrogenase.

Hemoglobinopathies are among the most common causes of chronic hemolytic disease. α- and β-Thalassemia syndromes were previously discussed. Sickle cell syndromes are the most frequently encountered hemoglobinopathies.

The sickle hemoglobinopathy syndromes are a group of genetically inherited disorders encountered most frequently in individuals of African descent. Thus, a form of **sickle cell disease** should be considered in the differential diagnosis of anemia in any African-American child. These disorders occur less frequently in individuals of Mediterranean or Arabic background.

Sickle hemoglobin is characterized by a single amino acid substitution of the β-globin chain, namely valine for glutamic acid in the number 6 position. Sickle hemoglobin has a tendency to form insoluble fibers and polymerization within the RBC when deoxygenated. This ultimately leads to the formation of the characteristic crescent-shaped sickled erythrocytes (Fig. 37.8). When sickle hemoglobin trait is inherited from both parents in an autosomal recessive fashion the child has homozygous Hemoglobin SS disease. This is the most severe form of sickle cell disease. Sickle hemoglobin may also be co-inherited with other β-globin gene defects such as hemoglobin C or β-thalassemia and give rise to other heterozygous forms of sickle cell disease that can be less severe than Hemoglobin SS disease. Approximately 1/400 African-Americans has sickle cell disease.

Approximately 8% of African-Americans are carriers of the hemoglobin S gene, which is also termed **sickle cell trait**. Sickle cell trait is rarely associated with clinical disease except under states of unusually severe arterial hypoxemia. Spontaneous hematuria may occasionally occur in sickle trait as a result of the induction of sickling in the extremely hypertonic environment of the renal medulla. Patients with sickle cell trait are distinctly not anemic and have a normal peripheral blood smear.

The diagnosis of sickle cell disease is usually straightforward. Children are variably anemic with reticulocytosis. The peripheral blood smear demonstrates characteristic sickled erythrocytes (Fig. 37.8). The definitive diagnosis must be established by hemoglobin identification methods (Table 37.15). The hemoglobin solubility test (sickle preparation, Sickledex) should not be used to make the diagnosis as false-negative tests can occur. Diagnosis in newborns is routinely and accurately performed in most locations within the United States as a component of state-mandated universal neonatal screening programs.

Sickle cell disease is a multiorgan system disease. The clinical manifestations are extremely broad but generally include (1) chronic hemolytic anemia, (2) vasoocclusion resulting in ischemic injury to tissue, and (3) susceptibility to infection (Table 37.16). Infants younger than 4-6 months usually show no clinical manifestations because of naturally high levels of fetal hemoglobin. By 1-2 years of age, most affected patients have had a specific sickle cell–related manifestation.

Patients may appear variably pale and icteric depending on the degree of hemolysis. Splenomegaly can be seen in children between 6 and 36 months of age in patients with hemoglobin SS disease and may persist into adolescence in some patients with milder variants (SC disease, S-β^+-thalassemia). Autoinfarction from microvascular occlusion ultimately leads to fibrosis of splenic tissue by age 3-4 years in most patients with hemoglobin SS disease. Gallstones occur regularly and may lead to symptoms of cholelithiasis, acute cholecystitis, biliary tract obstruction, and/or pancreatitis. Many patients have delayed growth and pubertal development, but ultimately achieve normal adult height. Exacerbation of anemia can occur as a result of infection-induced hyperhemolysis or transient RBC aplasia commonly associated with parvovirus B19 infection. Hyperhemolytic episodes may also occur in male patients with concomitant G6PD deficiency. RBC transfusions are necessary when progressive anemia is accompanied by significant clinical symptoms and definitely in the context of RBC aplasia.

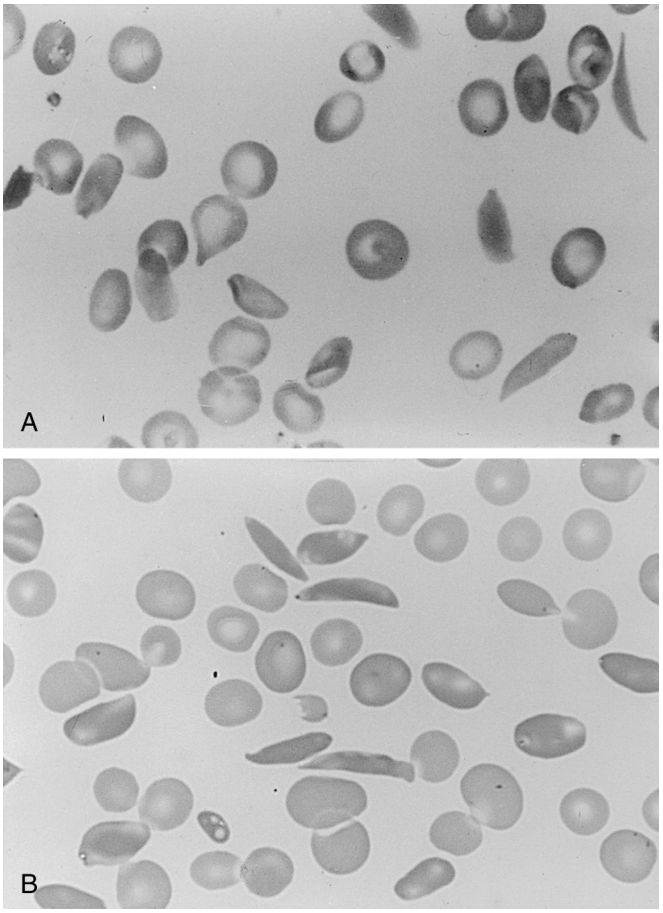


FIGURE 37.8 Sickle cell anemia. *A and B,* Sickled erythrocytes and target cells.

TABLE 37.15 Hemoglobin Electrophoresis Diagnosis of Sickle Hemoglobinopathy

Disease	Hemoglobin Type
Normal	A
SS disease	S (no hemoglobin A)
S trait	A + S (about equal proportions)
SC disease	S + C (about equal proportions)
S-β-thalassemia	S > A (S predominant hemoglobin)

Hemoglobin E is seen with considerable frequency among individuals of Asian descent. Hemoglobin E trait is characterized by mild anemia and mild microcytosis. There are no significant clinical implications. The diagnosis is confirmed by hemoglobin electrophoresis. When hemoglobin E occurs in the double heterozygous state with β-thalassemia, patients often have a moderately severe thalassemic syndrome; hence, genetic counseling is advisable.

Acquired autoimmune hemolytic anemia. This condition may occur as a transient, postviral process or in conjunction with underlying immunologic dysfunction (immunodeficiency, human immunodeficiency virus [HIV] infection, lymphoid malignancy). Hemolysis is usually brisk; thus, most patients are symptomatic and present with pallor, jaundice, fatigue and tachycardia. Splenomegaly is variably

TABLE 37.16 Clinical Manifestations of Sickle Cell Anemia*

Manifestation	Comments
Anemia	Chronic onset, 3–4 mo of age; folate therapy may be required for chronic hemolysis; hematocrit usually 18–26%
Aplastic crisis	Parvovirus infection, reticulocytopenia, acute and reversible
Sequestration crisis	Massive splenomegaly, shock; treat with transfusion
Hemolytic crisis	May be associated with G6PD deficiency
Dactylitis	Hand-foot swelling in early infancy
Painful crisis	Microvascular painful vasoocclusive infarctions of muscle, bone, bone marrow, lung intestines
Cerebral vascular accidents	Large- and small-vessel sickling and thrombosis (stroke); necessitates chronic transfusion
Acute chest syndrome	Infection, infarction, hypoventilation, bone marrow emboli, severe hypoxemia, infiltrate, dyspnea, rales
Chronic lung disease	Pulmonary fibrosis, restrictive lung disease, cor pulmonale
Priapism	Causes eventual impotence; treat with transfusion, oxygen, or corpora cavernosa to spongiosa shunt, local injection of α-adrenergic agents
Ocular	Retinopathy
Gallbladder disease	Bilirubin stones; cholecystitis
Renal	Hematuria, papillary necrosis, renal-concentrating deficit; nephropathy
Cardiomyopathy	Heart failure (fibrosis)
Leg ulceration	Seen in older patients
Infections	Functional asplenia, defects in properdin system; pneumococcal bacteremia, meningitis and arthritis; deafness from meningitis in 35%, *Haemophilus influenzae* sepsis. *Salmonella* and *Staphylococcus aureus* osteomyelitis; severe *Mycoplasma* pneumonia; *Escherichia coli*; urinary tract infection; transfusion-acquired (HIV; hepatitis A, B, C, D and E; EBV; CMV)
Growth failure, delayed puberty	May respond to nutritional supplements
Psychologic problems	Narcotic addiction, dependence unusual, chronic illness

*Clinical manifestations with sickle cell trait are unusual but include renal papillary necrosis (hematuria), sudden death on exertion, intraocular hyphema extension, and sickling in unpressurized airplanes.

CMV, cytomegalovirus; EBV, Epstein–Barr virus; G6PD, glucose-6-phosphate dehydrogenase; HIV, human immunodeficiency virus.

Modified from Scott JP. Hematology. In: Behrman RE, Kliegman RM, eds. *Nelson Essentials of Pediatrics*. 2nd ed. Philadelphia: WB Saunders; 1994:530.

present. The degree of anemia is highly variable, and the reticulocyte count is elevated in most patients; however, a minority of patients present with a low reticulocyte count because of immune destruction of reticulocytes. The peripheral smear demonstrates microspherocytes. The direct Coombs test is positive confirming the diagnosis. Consideration should be given to evaluating immunologic dysfunction, infection, and malignancy (immunoglobulin [Ig] levels, T and B lymphocyte counts, HIV and Epstein–Barr virus studies, chest radiography). The characteristics of the antibody types are noted in Table 37.17. Warm antibodies (usually IgG) may be idiopathic or associated with lymphoma, HIV or Epstein–Barr virus infections, rheumatologic disorders, or most likely a nonspecific infectious phenomenon. Cold antibodies (usually IgM) may also be seen in response to viral infections, *Mycoplasma pneumoniae* and syphilis infections, or in the context of autoimmune disorders.

Aggressive therapy is recommended because life-threatening anemia is known to occur. Corticosteroids (prednisone) should be administered if the patient is found to have warm autoimmune hemolytic anemia. RBC transfusion should be considered based on the degree of the anemia; however, cross-matching blood is likely to be difficult due to the autoantibody. Intravenous immunoglobulin and high-dose steroids (methylprednisolone) should be considered in severe cases. Frequent hemoglobin monitoring and reticulocyte counts should be done to follow the rate of hemolysis. The role of steroids in the treatment of cold autoimmune hemolytic anemia is less clear and is classically reserved for prolonged cases requiring frequent RBC transfusions. Recombinant antibodies directed to B lymphocytes such as rituximab have been effective in refractory cases.

ANEMIA IN THE NEONATE

Neonatal anemia should be viewed in the context of 3 possible pathophysiologic pathways (Table 37.18): (1) acute blood loss, (2) anemia of underproduction, and (3) anemia associated with increased destruction. Familial genetic disorders may manifest in the neonatal period or any time during infancy (Table 37.19).

The full-term infant has a normal hemoglobin value (hemoglobin, 15-21 g/dL; hematocrit, 45-65%) that is substantially higher than that in older infants and young children. This finding represents a functional adaptation to the relatively hypoxic in utero environment. The reticulocyte count is elevated to about 7-8% during the 1st 3 days of life, after which there is an abrupt cessation of erythropoiesis until 2 months of age, when a physiologic hemoglobin nadir of about 9.5-10 g/dL is reached. This physiologic anemia of infancy is exaggerated in preterm infants whose hemoglobin levels may fall to approximately 7 g/dL at about 1-1.5 months of age. This fall in hemoglobin value represents a physiologic response to the oxygen-rich extrauterine environment.

Neonatal Anemia Caused by Blood Loss

Anemia caused by blood loss is often obvious. It occurs in placenta previa, abruptio placentae, or a large cephalohematoma. Other etiologies of hemorrhage may be occult and include intracranial and intrahepatic hematomas. Internal hemorrhage is much more likely to occur in difficult, traumatic deliveries. Twin-twin transfusion may occur leading to anemia in 1 infant and polycythemia in the other. Fetal–maternal hemorrhage is sufficiently severe to cause anemia in only a small percentage of neonates. The Kleihauer–Betke test may detect the presence of fetal RBCs in the maternal circulation, but may yield false-negative results, particularly in mothers with type O blood who have antibodies against infant A, B, or AB blood cells. Fetal–maternal hemorrhage must always be suspected when otherwise unexplained anemia occurs in a newborn.

The time course and extent of blood loss determine the clinical presentation. If blood loss is mild or chronic, infants may appear normal or have mild pallor and tachycardia. In the event of severe acute blood loss, the newborn may present with signs of acute illness

TABLE 37.17 Characteristics of Antibodies in Immune Hemolytic Anemia

	Warm-Antibody	Cold Agglutinin Disease	Paroxysmal Cold Hemoglobinuria	Drug Related Immune, Type 1	Drug Related Immune, Type II
Antibody isotype	IgG(rarely IgA)	IgM	IgG	IgG	IgM, IgG
Optimum temperature of reaction	37°C	0°C	0°C	37°C	37°C
Direct Coombs test	IgG ± C3	C3 only	C3 only	IgG only	C3 only
Agglutination in saline	None (rarely +)	++++	+	0 to +	0 to ++ (with drug)
Lysis by complement in vitro	Rare	Poor	Well	None	Sometimes well
Clinical severity	Mild to very severe	Mild to moderate	Moderate to severe	Mild to moderate	Mild to severe
Response to prednisone	Often	None	Often	If needed	Not needed
Response to splenectomy	Often	Rare	None	Not needed	Not needed

IgA, IgG, and IgM, immunoglobulins A, G, and M; +, strength of agglutination response.
From Rose MG, Berliner N. Disorders of red blood cells. In: Andreoli TE, Carpenter CJ, Bennett JC, et al., eds. *Cecil Essentials of Medicine.* 4th ed. Philadelphia: WB Saunders; 1997:389.

TABLE 37.18 Anemia in the Neonate

Blood Loss (Common)
Placenta previa
Abruptio placentae
Twin-twin transfusion
Fetal–maternal hemorrhage (acute versus chronic)
Neonatal hemorrhage

Decreased RBC Production (Unusual)
Diamond–Blackfan anemia
Congenital leukemia
Transient myeloproliferative syndrome in Down syndrome
Osteopetrosis

Hemolysis
Intrinsic RBC defect (uncommon)
- Membrane (hereditary spherocytosis or elliptocytosis)
- Enzyme (G6PD, PK)
- Hemoglobin (α or γ chain abnormality)

Extrinsic RBC defect
- Immune (ABO, Rh, minor group incompatibilities) (common)
- Infection (intrauterine infection, bacterial, viral, protozoal)
- DIC
- Kasabach–Merritt syndrome
- Galactosemia

DIC, disseminated intravascular coagulation; G6PD, glucose-6-phosphate dehydrogenase; PK, pyruvate kinase; RBC, red blood cell.

including lethargy, tachycardia, hypotension, and respiratory distress. The hemoglobin value is a poor index of the severity of acute blood loss because equilibration of fluid compartments may take 24-36 hours. Blood loss as a cause of anemia should always be suspected in cases of obstetric complications, multiple births, or difficult and traumatic deliveries. In cases of severe blood loss, emergency transfusion therapy is appropriate. In the neonate who is hemodynamically stable but has experienced significant blood loss, a more conservative approach is recommended.

Neonatal Anemia Caused by Decreased Red Blood Cell Production

Anemia caused by decreased RBC production in the newborn is unusual. Infants with congenital hypoplastic anemia (Diamond–Blackfan anemia) are usually only mildly anemic during the newborn period. Congenital leukemia is a rare disorder characterized by infiltration of the bone marrow leading to anemia, thrombocytopenia, and leukocytosis in association with hepatosplenomegaly and occasionally cutaneous leukemic infiltrates manifesting as blue papular lesions ("blueberry muffin" spots). Infants with Down syndrome may present with a clinical and hematologic picture identical to that of congenital leukemia, which is a transient myeloproliferative process that spontaneously remits over several months. Infantile osteopetrosis (marble bone disease), a disorder characterized by a limited ability to degrade bone, usually does not cause pancytopenia until a few months after birth.

Neonatal Anemia Caused by Increased Red Blood Cell Destruction

Anemia caused by increased RBC destruction (hemolytic anemia) places the neonate at risk for indirect hyperbilirubinemia as a result of the limited hepatic bilirubin-conjugating ability during the 1st weeks of life. Even relatively small increases in the rate of RBC destruction can lead to marked increases in serum bilirubin level. All infants who have elevations of indirect bilirubin levels above the normal range during the 1st 3 days of life should be evaluated for possible hemolysis, with a CBC, reticulocyte count, peripheral blood smear, maternal and infant blood type assessments, and direct Coombs test.

Intrinsic disorders of the erythrocyte may manifest in the neonate. Infants with hereditary spherocytosis, pyropoikilocytosis, or elliptocytosis may develop anemia and extreme hyperbilirubinemia that necessitates phototherapy and, rarely, exchange transfusion. A peripheral blood smear and family history may be helpful in identifying an intrinsic RBC membrane defect.

G6PD deficiency can occur in newborn boys (rarely girls) of African or Mediterranean descent. Because of the increased susceptibility of neonatal RBCs to oxidant injury, anemia, reticulocytosis, and hyperbilirubinemia may occur without an obvious precipitating oxidant insult. Hemoglobinopathies rarely manifest during the neonatal period. β-globin chain defects such as sickle cell disease and thalassemia are not clinically apparent until about 4-6 months of age because of the predominance of fetal hemoglobin in the perinatal period.

Severe α-thalassemia, including α-thalassemia major or hemoglobin Bart's disease, can affect the fetus. Such infants develop severe in utero anemia with resultant hydrops fetalis because of the limited ability of hemoglobin Bart's to release oxygen to tissues.

Isoimmune hemolytic anemia is the most common cause of hemolytic anemia in the newborn. It is caused by incompatibility

TABLE 37.19 Genetic Disorders Associated with Anemia in the Neonate

Syndrome	Genetic Characteristics	Hematologic Phenotype
Diamond–Blackfan syndrome	Autosomal recessive (AR); sporadic mutations and autosomal dominant (AD) inheritance have been described	Steroid-responsive hypoplastic anemia after 5 mo of age
Fanconi anemia	AR, probably abnormalities in multiple genes (at least 5 genetic subtypes have been identified)	Steroid-responsive hypoplastic, macrocytic anemia DNA is hypersensitive to injury
Aase syndrome	AR, possible AD	Steroid-responsive hypoplastic anemia; macrocytic; improves with age
Pearson syndrome	Mitochondrial DNA abnormalities, X-linked or AR	Hypoplastic sideroblastic anemia unresponsive to pyridoxine
Lethal osteopetrosis	AR, caused by defective resorption of immature bone	Hypoplastic anemia due to marrow encroachment
Congenital dyserythropoietic anemia (CDA)	AR	Type I: megaloblastoid erythroid and nuclear chromatin bridges between cells Type II: hereditary erythroblastic multinuclearity and positive acidified serum test results (HEMPAS) Type III: erythroblastic multinuclearity and macrocytosis
Peutz–Jeghers syndrome	AD	Iron deficiency, anemia from chronic blood loss
Dyskeratosis congenita	X-linked recessive, locus on Xq28; some cases with AD inheritance	Hypoplastic anemia; usually present between 5 and 15 yr of age
X-linked α-thalassemia/mental retardation (ATR-X and ATR-16) syndromes	ATR-X: X-linked recessive, mapped to Xq13.3; ATR-16: mapped to 16p13.3; deletions of α-globin locus	ATR-X: hypochromic, microcytic anemia, mild form of hemoglobin H disease; ATR-16: more significant hemoglobin H disease and anemia are present
Thrombocytopenia with absent radius (TAR) syndrome	AR	Hemorrhagic anemia, possibly hypoplastic anemia as well
Osler hemorrhagic telangiectasia syndrome	AD, mapped to 9q33-34	Hemorrhagic anemia

From Ohls RK. Evaluation and treatment of anemia in the neonate. In: Christensen RD, ed. *Hematologic Problems of the Neonate*. Philadelphia: Saunders; 2000:153.

between maternal and fetal blood groups, including Rh, ABO, or minor blood group antigens. In Rh incompatibility, the mother is Rh negative and the infant is Rh positive (inherited from the father). If the mother has been exposed to Rh-positive blood cells through prior pregnancy, miscarriage, therapeutic abortion, or mismatched blood transfusion, IgG antibodies may develop that traverse the placenta and cause immune destruction of fetal Rh-positive cells. In such instances hemolysis occurs in utero and in the neonatal period. In severe circumstances the fetus may be extremely anemic, which results in heart failure, hydrops fetalis, and death. In less serious instances infants may be born quite anemic and develop brisk hyperbilirubinemia, which can lead to kernicterus. The severity of Rh immune hemolytic disease increases with successive pregnancies. This disorder is uncommon because of the routine practice of administering Rh immunoglobulin to Rh-negative mothers who are 28-30 weeks pregnant and within 72 hours of delivery or after spontaneous or therapeutic abortion. Prenatal management of the affected fetus may include spectrophotometric assessment of amniotic fluid as an assessment of fetal bilirubin level and in high-risk situations serial fetal hemoglobin levels obtained by ultrasonographically guided aspiration of umbilical cord blood (cordocentesis). When the fetus demonstrates progressive in utero severe anemia, intrauterine intravascular blood transfusion therapy has been shown to decrease the risk for fetal demise. Management of the neonate relates largely to the severity of the hemolysis. Hyperbilirubinemia must be treated aggressively with phototherapy and if severe, exchange transfusion. RBC transfusions are appropriate for symptomatic anemia. On occasion, anemia is detected several weeks after Rh hemolysis and may be associated with a profoundly depressed reticulocyte count. This late anemia is of uncertain origin, but inappropriately low erythropoietin levels have been noted. Symptomatic infants may require transfusion therapy. Affected infants have been successfully treated with human recombinant erythropoietin.

Immune incompatibility in the ABO system is common and usually occurs when mothers with type O blood have newborns whose blood type is A or B. The degree of hemolysis is usually much less severe than in Rh disease. Fetal hydrops is extremely rare. Most babies with ABO incompatibility manifest jaundice from indirect hyperbilirubinemia during the 1st 1-2 days after birth. Hemoglobin levels are often within the normal to mildly anemic range, but moderate anemia occasionally occurs. The reticulocyte count is usually mildly elevated, and the peripheral blood smear may show microspherocytes. Results of the Coombs test are usually weakly or moderately positive, but false-negative results do occur. Treatment is generally directed toward hyperbilirubinemia and may require phototherapy. Intravenous immunoglobulin therapy has been helpful in some selected patients. Exchange transfusion is rarely necessary. Anemia occasionally necessitates blood transfusion. Immune incompatibility may also occur on the basis of minor blood groups antigens such as the Duffy or Kell antigen systems. Clinical and laboratory findings are similar to those in ABO hemolytic disease except that the direct Coombs test result is usually strongly positive.

Other causes of hemolytic anemia in the newborn include bacterial sepsis and intrauterine infection (cytomegalovirus, toxoplasmosis, herpes, rubella, and syphilis). Intrauterine infectious syndromes can cause mild to moderate hemolytic anemia of several months' duration.

Such infants may demonstrate physical stigmata including small size for gestational age, microcephaly, chorioretinitis, hepatosplenomegaly, intracranial calcifications, and "celery stalking" of the long bones on radiographic study.

Microangiopathic hemolytic anemia can occur in the newborn as a result of disseminated intravascular coagulation (DIC). In the neonate, DIC is usually caused by serious infection, hypoxemia resulting from respiratory distress syndrome in the preterm infant, or ischemic tissue injury related to birth asphyxia. Newborns with hemolysis resulting from infection or DIC are often extremely ill and require RBC transfusion support.

Microangiopathic hemolytic anemia and consumptive thrombocytopenia can occur in the Kasabach–Merritt syndrome, which is associated with cavernous hemangiomas and localized intravascular coagulation. Some infants have obvious expansive cutaneous and subcutaneous lesions, but occult visceral hemangiomas, particularly in the liver, can occur. The peripheral blood smear demonstrates evidence of RBC fragments and burr cells. Kasabach–Merritt syndrome may necessitate treatment with plasma and platelet transfusions if consumptive coagulopathy is severe. Corticosteroids and interferon therapy have been helpful in some affected infants.

The diagnostic approach to anemia in the neonate requires a careful assessment of maternal, prenatal, and perinatal history as well as the clinical status of the neonate (Fig. 37.9). CBC, reticulocyte count, peripheral blood smear, maternal and infant blood types, and direct Coombs tests are virtually always necessary laboratory studies. Other studies must be dictated by the clinical and initial laboratory findings.

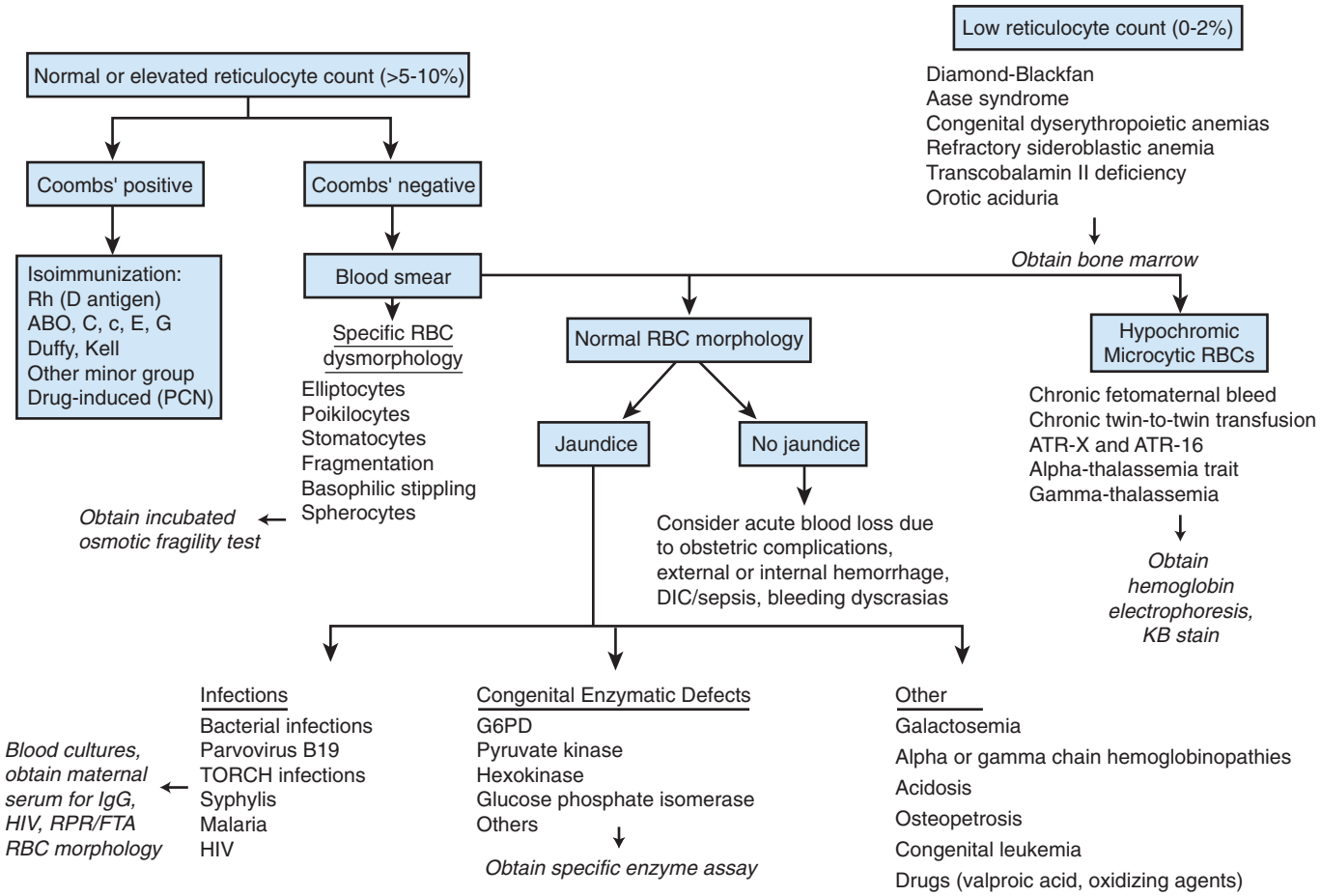


FIGURE 37.9 Differential diagnosis of neonatal anemia. The physician first seeks information from the family, maternal, and labor and delivery histories and then obtains initial laboratory tests: hemoglobin, reticulocyte count, blood type, direct Coombs test, peripheral smear, red blood cell (RBC) indices, and bilirubin concentration. Results are used to navigate the diagnostic flow chart. ATR-16, α-thalassemia retardation syndrome, chromosome 16–linked; ATR-X, α-thalassemia retardation syndrome, X-linked; DIC, disseminated intravascular coagulation; FTA, fluorescent treponemal antibody test; G6PD, glucose-6-phosphate dehydrogenase; HIV, human immunodeficiency virus; KB, Kleihauer–Betke; PCN, penicillin; RPR, rapid plasma reagin test; TORCH, toxoplasmosis, other infections, rubella, cytomegalovirus, and herpes simplex. (From Ohls RK. Evaluation and treatment of anemia in the neonate. In: Christensen RD, ed. *Hematologic Problems of the Neonate*. Philadelphia: Saunders; 2000:162.)

SUMMARY AND RED FLAGS

Anemia is a common finding in children. A complete and thorough evaluation of clinical findings by a detailed history and physical examination is the most important element in the establishment of a diagnosis and in defining appropriate therapy.

Anemia may be a primary event reflecting intrinsic hematologic disease or it may be a manifestation of a wide variety of systemic disorders involving virtually any organ system. Anemia must always be fully evaluated in view of the potential diagnostic and therapeutic implications. Patients who appear acutely ill should have a more thorough and prompt evaluation because acute blood loss must be treated quickly. If acute blood loss is not suspected, acute hemolysis or splenic sequestration of RBCs must be considered.

Anemia is often a sign of underlying acute or chronic disease. In such cases, anemia is not usually an isolated finding. Therefore, symptoms such as shortness of breath, extreme pallor, weight loss, fevers, lethargy, and fatigue should prompt a thorough evaluation of the patient.

On physical examination, the findings of abnormal vital signs, failure to thrive, bleeding or bruising, adenopathy, or organomegaly should lead the examiner to suspect that a potentially serious underlying disorder is present (Table 37.20). When a CBC is obtained, a low hemoglobin value accompanied by any abnormality of MCV, WBC, or platelet count should be taken seriously and should be more thoroughly investigated. The work-up should be directed accordingly based on these abnormal findings.

TABLE 37.20 Red Flags

Anemia Accompanied by
Abnormal vital signs (tachycardia, hypotension, hypertension)
Neutropenia and/or thrombocytopenia
High MCV with normal RDW
Blasts on the peripheral smear
Firm adenopathy
Bruising or bleeding
Weight loss, failure to thrive
Shortness of breath, fatigue
Fever
Hypoxia
Organomegaly
Edema
Oliguria-anuria
Bloody diarrhea
Red urine (hemoglobinuria)
Family history of anemia

MCV, mean corpuscular volume; RDW, red blood cell distribution width.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Work-up of Anemia

Bessman JD, Jilmer PR, Gardner FH. Classification of red cell disorders by MCV and RDW. *Am J Clin Pathol*. 1983;80:322.

Hermiston ML, Mentzer WC. A practical approach to the evaluation of the anemic child. *Pediatr Clin North Am*. 2002;49:877.

Hoffman R, Benz EJ, Shattil SJ, et al. *Hematology: Basic Principles and Practice*. 3rd ed. New York: Churchill Livingstone; 2000.

Kline NE. A practical approach to the child with anemia. *J Pediatr Health Care*. 1996;10:99.

Kohli-Kumar M. Screening for anemia in children: AAP recommendations—a critique. *Pediatrics*. 2001;108:E56.

Nathan DG, Orkin SH, Ginsburg D, et al. *Nathan and Oski's Hematology of Infancy and Childhood*. 6th ed. Philadelphia: Saunders; 2003.

Novak RW. Red blood cell distribution within pediatric microcytic anemias. *Pediatrics*. 1987;80:251.

Segel GB, Hirsh MG, Feig SA. Managing anemia in a pediatric office practice: part 1. *Pediatr Rev*. 2002;23:75.

Segel GB, Hirsh MG, Feig SA. Managing anemia in a pediatric office practice: part 2. *Pediatr Rev*. 2002;23:111.

Walters MC, Abelson HT. Interpretation of the complete blood count. *Pediatr Clin North Am*. 1996;43:599.

Anemia with Acute and Chronic Disease

Abshire TC. The anemia of inflammation: a common cause of childhood anemia. *Pediatr Clin North Am*. 1996;43:623.

Cowin HL, Krantz SB. Anemia of the critically ill: "acute" anemia of chronic disease. *Crit Care Med*. 2000;28:3098.

Fitzsimons EJ, Brock JH. The anaemia of chronic disease. *BMJ*. 2001;322: 811.

Ganz T. Hepcidic, a key regulator of iron metabolism and mediator of anemia of inflammation. *Blood*. 2003;102:783-788.

Means RT Jr. Advances in the anemia of chronic disease. *Int J Hematol*. 1999;70:7.

Hemolytic Anemia

Beutler E. Glucose-6-phosphate dehydrogenase deficiency. *N Engl J Med*. 1991;324:169.

Davidson RN, Wall RA. Prevention and management of infections in patients without a spleen. *Clin Microbiol Infect*. 2001;7:657.

Grace RF, Zanella A, Neufeld EJ, et al. Erythrocyte pyruvate kinase deficiency: 2015 status report. *Am J Hematol*. 2015;90:825-830.

Lynch AM, Kapila R. Overwhelming postsplenectomy infection. *Infect Dis Clin North Am*. 1996;10:693.

Prchal JT, Gregg XT. Red cell enzymes. *Hematology Am Soc Hematol Educ Program*. 2005;19-23.

Sackey K. Hemolytic anemia: part 1. *Pediatr Rev*. 1999;20:152.

Sackey K. Hemolytic anemia: part 2. *Pediatr Rev*. 1999;20:204.

Trivedi DH, Bussel JB. Immunohematologic disorders. *J Allergy Clin Immunol*. 2003;S669.

Hypoplastic Anemia

Cherrick I, Karayalcin G, Lanzkowsky P. Transient erythroblastopenia of childhood. Prospective study of fifty patients. *Am J Pediatr Hematol Oncol*. 1994;16:320.

DaCosta L, Thiebant-Noel W, Fixler J, et al. Diamond-Blackfan anemia. *Curr Opin Pediatr*. 2001;13:10.

Farhi DC, Luebbers EL, Rosenthal NS. Bone marrow biopsy findings in childhood anemia: prevalence of transient erythroblastopenia of childhood. *Arch Pathol Lab Med*. 1998;122:638.

Krijanovski OI, Sieff CA. Diamond-Blackfan anemia. *Hematol Oncol Clin North Am*. 1997;11:1061.

van den Akker M, Dror Y, Odame I. Transient erythroblastopenia of childhood is an underdiagnosed and self-limiting disease. *Acta Paediatr*. 2014;103:e288-e294.

Iron Deficiency

Abelson HT. Complexities in recognizing and treating iron deficiency anemia. *Arch Pediatr Adolesc Med*. 2001;155:332.

Alter BP. Bone marrow failure syndromes in children. *Pediatr Clin North Am*. 2002;49:973.

American Academy of Pediatrics Committee on Nutrition. iron fortification of infant formulas. *Pediatrics*. 1999;104:119.

Bogen DL, Duggan AK, Dover GJ, et al. Screening for iron deficiency anemia by dietary history in a high-risk population. *Pediatrics*. 2000;105:1254.

Cheng TL. Iron deficiency anemia. *Pediatr Rev*. 1998;19:321.

Greer FR. How much iron is needed for breastfeeding infants? *Curr Pediatr Rev*. 2015;11(4):298-304.

Kwiatkowski JL, West TB, Heidary N, et al. Severe iron deficiency anemia in young children. *J Pediatr*. 1999;135:514.

Lozoff B, Wolf AW, Jimenez E. Iron-deficiency anemia and infant development: effects of extended oral iron therapy. *J Pediatr*. 1996;129:382.

Nuesslein TG, Teig N, Rieger CH. Pulmonary haemosiderosis in infants and children. *Paediatr Respir Rev*. 2006;7:45-48.

Tsai SF, Chen SJ, Yen HJ, et al. Iron deficiency anemia in predominantly breastfed young children. *Pediatr Neonatol*. 2014;55:466-469.

Walters T, Pino P, Pizarro F, et al. Prevention of iron deficiency anemia: comparison of high and low iron formulas in healthy infants after six months of life. *J Pediatr*. 1998;132:635.

Wang W, Bourgeois T, Klima J, et al. Iron deficiency and fatigue in adolescent females with heavy menstrual bleeding. *Haemophilia*. 2013;19:225-230.

Wharton BA. Iron deficiency in children: detection and prevention. *Br J Haematol*. 1999;106:270.

Macrocytic Anemia

Cancio MI, Helton KJ, Schreiber JE, et al. Silent cerebral infarcts in very young children with sickle cell anaemia are associated with a higher risk of stroke. *Br J Haematol*. 2015;171(1):120-129.

DeBaun MR, Gordon M, McKinstry RC, et al. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. *N Engl J Med*. 2014;37:699-710.

Dobrozsi S, Flood VH, Panepinto J, et al. Vitamin B12 deficiency: the great masquerader. *Pediatr Blood Cancer*. 2014;61:753-755.

Fixler J, Styles L. Sickle cell disease. *Pediatr Clin North Am*. 2002;49: 1193.

Kapadia CR. Vitamin B12 in health and disease: part I–inherited disorders of function, absorption, and transport. *Gastroenterologist*. 1995;3(4):329-344.

Kassim AA, Galadanci NA, Pruthi S, et al. How I treat and manage strokes in sickle cell disease. *Blood*. 2015;125:3401-3410.

Kinney TR, Sleeper LA, Wang WC, et al. Silent cerebral infarcts in sickle cell anemia: a risk factor analysis. The Co-operative study of sickle cell disease. *Pediatrics*. 1999;103:640.

Quinn CT, Buchanan GR. The acute chest syndrome of sickle cell disease. *J Pediatr*. 1999;135:416.

Rucknagel DL. Progress and prospects for the acute chest syndrome of sickle cell anemia. *J Pediatr*. 2001;138:160.

Schatz J, Brown RT, Pascual JM, et al. Poor school and cognitive functioning with silent cerebral infarcts and sickle cell disease. *Neurology*. 2001;56:1109.

Section on Hematology/Oncology Committee on Genetics, American Academy of Pediatrics. Health supervision for children with sickle cell disease. *Pediatrics*. 2002;109:526.

Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National acute chest syndrome study group. *N Engl J Med*. 2000;342:1855.

Walters MC, Storb R, Patience M, et al. Impact of bone marrow transplantation for symptomatic sickle cell disease: an interim report. Multicenter investigation of bone marrow transplantation for sickle cell disease. *Blood*. 2000;95:1998.

Wang W, Enos L, Gallagher D, et al. Neuropsychologic performance in school-aged children with sickle cell disease: a report from the cooperative study of sickle cell disease. *J Pediatr*. 2001;139:391.

Wethers DL. Sickle cell disease in childhood: part II. Diagnosis and treatment of major complications and recent advances in treatment. *Am Fam Physician*. 2000;62:1309.

Woodard P, Lubin B, Walters CM. New approaches to hematopoietic cell transplantation for hematological diseases in children. *Pediatr Clin North Am*. 2002;4:989.

Yaster M, Kost-Byerly S, Maxwell LG. The management of pain in sickle cell disease. *Pediatr Clin North Am*. 2000;47:699.

38

Bleeding and Thrombosis

Veronica H. Flood and J. Paul Scott

Hemostasis is a process that maintains normal blood flow through healthy vessels but, when a vessel is damaged, rapidly generates a clot at the site of vascular injury. The major components of the hemostatic mechanism are the platelets, the anticoagulant proteins, the procoagulant proteins, and the various components of the vascular wall. Normal hemostasis is an interactive process in which each element cooperates closely to generate a rapid, cohesive, focused reaction. An abnormality of 1 element destabilizes the system, but significant clinical symptoms often manifest only when 2 components are affected. Typical examples include the patient with hemophilia who bleeds after sustaining trauma and the antithrombin (AT) 3–deficient woman in whom thrombosis develops during pregnancy. The astute clinician is aware of situations that may exacerbate preexisting conditions. Pretreatment of known predisposing conditions can prevent complications, as exemplified by infusion of factor 8 concentrate before and after surgery to a patient with hemophilia A to prevent excessive bleeding. Table 38.1 shows common bleeding symptoms and the most common disorders that trigger these symptoms.

COAGULATION CASCADE

Two opposing systems generate local clots but limit the clot to the area of vascular damage. Fig. 38.1 shows the sequence of activation of coagulation. The cascade is capable of rapid response because generation of a small number of activated factors at the "top" of the cascade leads to thousands of molecules of thrombin. Deficiencies of proteins at or below factors 11 or 7 in the coagulation cascade sequence result in clinical bleeding symptoms, whereas deficiencies of factor 12, prekallikrein, and high–molecular-weight kininogen do not. The coagulation mechanism is continuously generating a small amount of thrombin. If there is trauma, tissue factor and factor 7 combine to activate factor 10 to factor 10a both directly and indirectly via factor 9. Factor 10a then forms a complex on a membrane surface (provided by the activated platelet) with factor 5 and calcium, which results in more thrombin generation. Platelets stick to areas of vessel injury, thus restricting thrombin generation and clot formation to the area of damage.

Thrombin exerts positive feedback on the system by acting on factor 11 to trigger the intrinsic system, cleaving factors 5 and 8 to activate them, further accelerating thrombin generation, aggregating platelets, and activating factor 13. In this model, coagulation is always "turned on" and therefore, reacts faster than if it were static and suddenly had to initiate a series of reactions to trigger clot formation. This dynamic concept underscores the impact of deficiencies in anticoagulant protein as the system is continuously generating thrombin. A deficiency of an inhibitory enzyme or a cofactor removes part of the "brakes" on the system and causes increased thrombin generation.

COAGULATION INHIBITORS

Four key systems interact to inhibit the coagulation mechanism:

- AT
- Protein C/S system
- Fibrinolytic system
- Tissue factor pathway inhibitor (TFPI)

Antithrombin

AT is a member of the serine protease inhibitor family (serpins) that inhibits thrombin, factor 10a, and, less efficiently, factors 9a and 11a. When AT is bound to heparin, this reaction is accelerated 1000-fold. AT is the active anticoagulant operative during heparin therapy; if AT is deficient, heparin therapy may fail. Heparin-like molecules are synthesized by endothelial cells and interact with AT on the vessel wall to inhibit coagulation. Both congenital and acquired AT deficiencies are associated with a predisposition toward thrombosis. AT is consumed during clotting.

Protein C/Protein S System

The protein C/protein S system is complex and limits clot extension by inactivating the rate-limiting coenzymes of the coagulation cascade, factors 5 and 8. To prevent extension of the clot, the anticoagulant mechanism must limit thrombin formation to areas of vascular damage. As a 1st step, thrombin binds to the protein thrombomodulin on intact endothelial cells. Thrombomodulin-bound thrombin then converts protein C into its activated form, activated protein C (APC). APC then combines with protein S to inactivate factors 5 and 8. In addition, APC may promote fibrinolysis. Thrombin itself is inactivated when bound to thrombomodulin and simultaneously augments the anticoagulant response by generating APC. APC limits the amount of thrombin that can be generated subsequently.

AT3, protein C, and protein S are important inhibitors of clotting because deficiencies of each of these proteins, either inherited or acquired, are associated with an increased risk for thrombosis. A mutation in factor 5 (factor 5 Leiden) that makes it less susceptible to proteolysis by APC (resistance to APC) is the most common hereditary predisposition to thrombosis. TFPI is an inhibitor of factor 7a (Fig. 38.2).

Fibrinolytic System

The fibrinolytic system dissolves and removes clots from the vascular system so that normal flow through vessels can be restored. Endothelial cells synthesize 2 activators of plasminogen: tissue-type plasminogen activator (TPA) and urokinase, both of which convert plasminogen to plasmin, the enzyme that degrades fibrin. Normally, plasminogen activator and its inhibitor, plasminogen activator inhibitor, are synthesized in equimolar amounts and are released from endothelial cells in

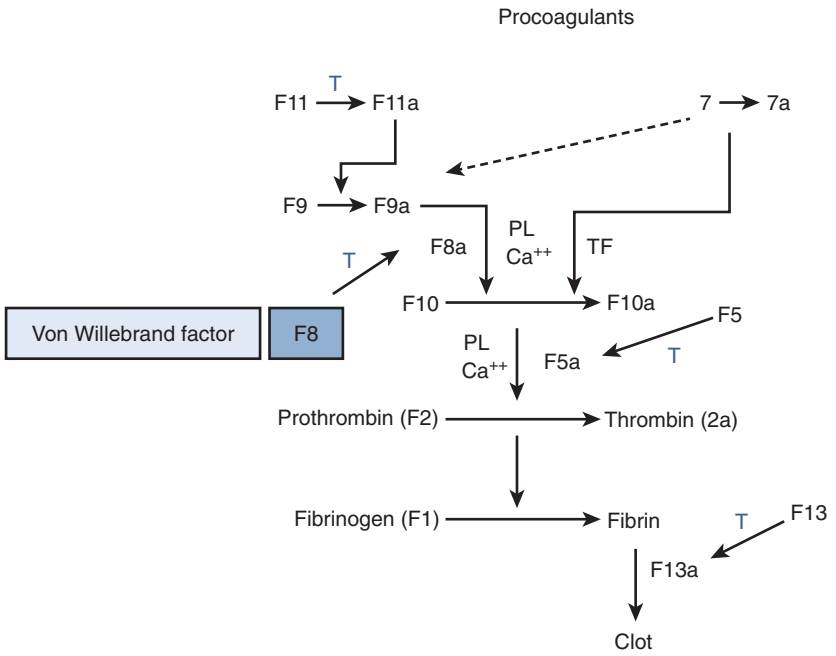


FIGURE 38.1 The coagulation cascade and the critical positive feedback role of factor IIa (thrombin) (T) on multiple aspects of the coagulation cascade. In addition, thrombin aggregates platelets and thereby contributes to platelet plug formation. The *dotted line* connecting factor 7a with factor 9 depicts the physiologic pathway of factor 9 activation *in vivo*. Factor 8 circulates bound to von Willebrand factor. After activation by thrombin, factor 8a can participate with factor 9a in the activation of factor 10. Factor 13a cross-links fibrin and stabilizes the fibrin clot. Ca^{2+}, calcium; PL, platelet phospholipid surface; TF, tissue factor. (Modified from Montgomery RR, Scott JP. Hemorrhage and thrombotic diseases. In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics*. 16th ed. Orlando, FL: WB Saunders; 1999:1505.)

TABLE 38.1 Common Causes of Clinical Bleeding Symptoms

Mucocutaneous Bleeding
Immune thrombocytopenic purpura
Child abuse
Trauma
Poisoning with anticoagulants (rat poison)
Chronic/insidious
von Willebrand disease
Platelet function defect
Marrow infiltration/aplasia

Deep/Surgical Bleeding
Hemophilia
Vitamin K deficiency
von Willebrand disease

Generalized Bleeding
Disseminated intravascular coagulation
Vitamin K deficiency
Liver disease
Uremia

parallel, leading to minimal amounts of active fibrinolysis. Increased activation or damage to the vascular system can alter this balance and result in increased TPA release, thus generating plasmin and lysing local clots. Plasminogen activator has been synthesized in a recombinant form (rTPA) and is an effective pharmacologic fibrinolytic agent in vivo.

PLATELET-ENDOTHELIAL CELLS AXIS

Clotting is initiated when platelets adhere to damaged endothelium (Fig. 38.3). In areas of vascular damage, the adhesive protein, von Willebrand factor (VWF), binds to the exposed subendothelial collagen matrix and undergoes a conformational change. VWF then binds to its platelet receptor, glycoprotein Ib, and activates platelets. Activated platelets secrete adenosine diphosphate (ADP), which induces nearby circulating platelets to aggregate. Platelet-to-platelet cohesion is mediated by the binding of fibrinogen to its platelet receptor, glycoprotein IIb/IIIa. Therefore, both VWF and fibrinogen play essential roles in normal platelet function *in vivo*. Simultaneously with the platelet adhesion-aggregation response, coagulation is being activated. The platelet membrane brings the reactants of the cascade into close proximity, promoting rapid, effective factor catalysis and accelerating the reactions 1000-fold faster than would occur in the absence of the appropriate surface.

Normally, endothelial cells provide an antithrombotic surface through which blood flows without interruption. The endothelial cell is capable of a rapid change in function and character so that it can augment coagulation after stimulation with a variety of modulating agents, including lymphokines and cytokines, as well as noxious agents such as endotoxin and infectious viruses (Fig. 38.4). Widespread

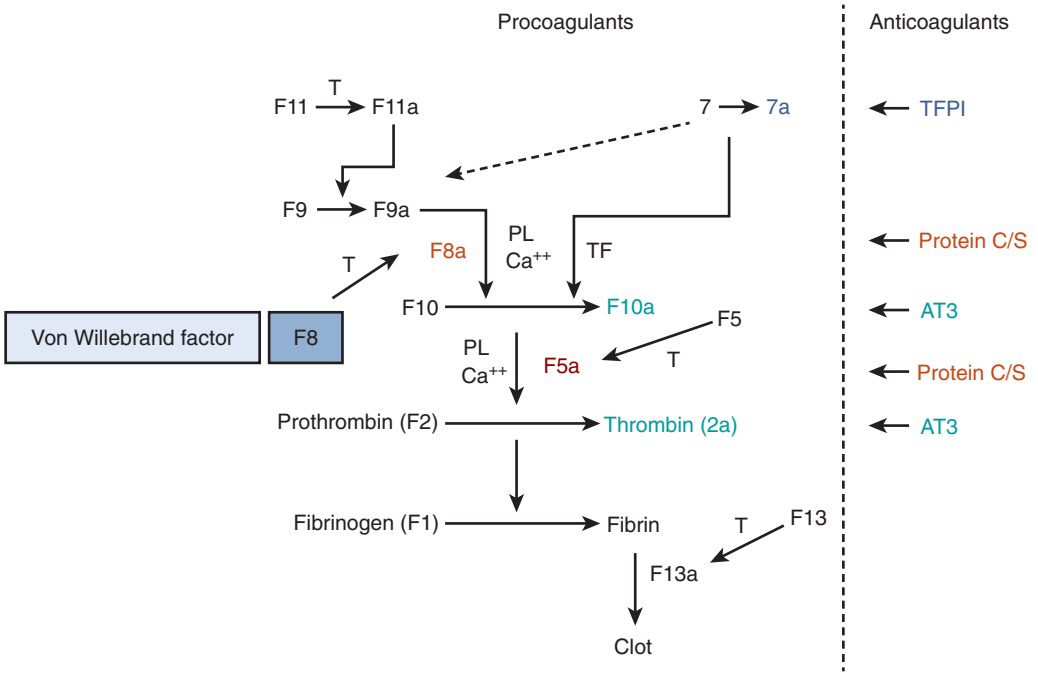


FIGURE 38.2 The major sites of action of the physiologic anticoagulants. Antithrombin (AT) irreversibly binds and inactivates factor 10a and thrombin. Thrombin binds to endothelial thrombomodulin and activates protein C. The activated protein C/protein S complex (P-C/S) proteolyses and inactivates factors 5a and 8a. The tissue factor pathway inhibitor (TFPI) binds to the complexes of factor 7a–tissue factor–factor 10a and inactivates factor 7a. Ca^{2+}, calcium; PL, platelet phospholipid surface; TF, tissue factor. (Modified from Montgomery RR, Scott JP. Hemorrhage and thrombotic diseases. In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics*. 16th ed. Orlando, FL: WB Saunders; 1999:1505.)

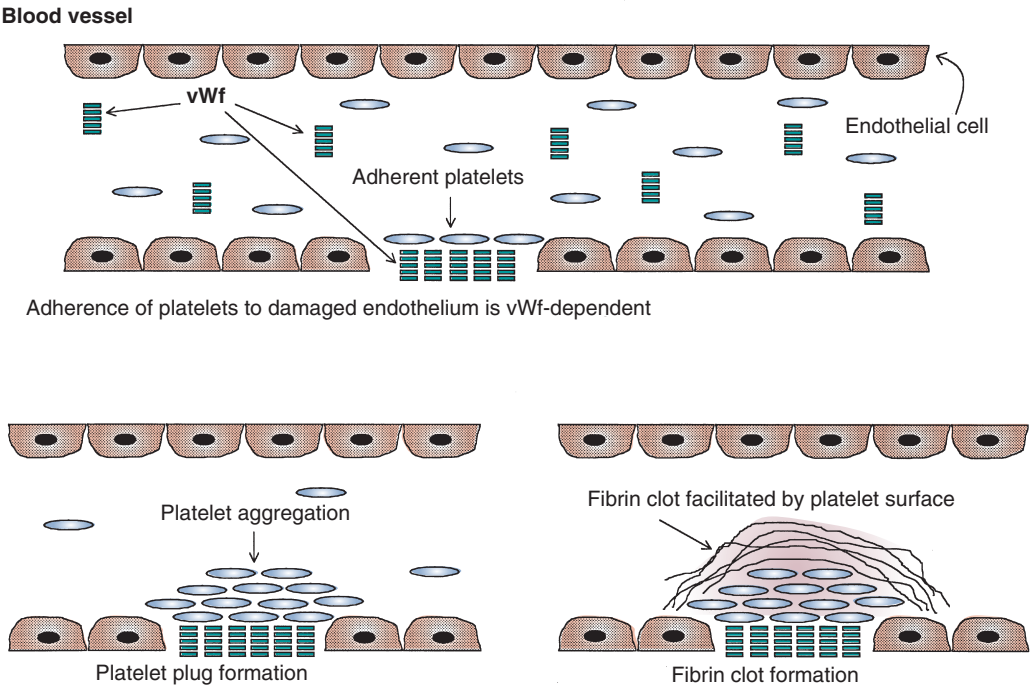


FIGURE 38.3 The endothelial cell–platelet–von Willebrand factor (VWF) interaction that results in initiation of the normal platelet plug by the adhesion of platelets to damaged endothelium, mediated by VWF with subsequent formation of the platelet plug and fibrin clot. (Courtesy R.R. Montgomery.)

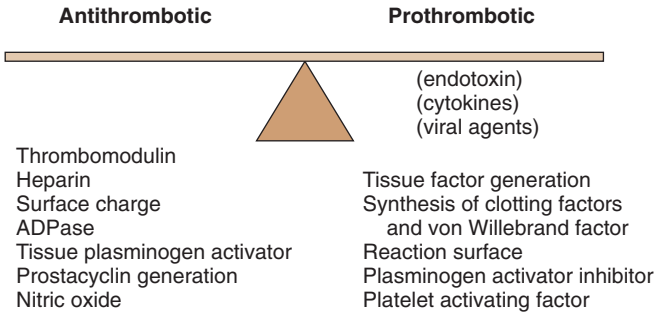


FIGURE 38.4 Endothelial balance. The pivotal role of the endothelium in maintaining a balance between antithrombotic and prothrombotic activities, as influenced by endotoxins, viruses, and immunomodulatory cytokines. ADPase, adenosine diphosphatase.

alteration of endothelial cell function can shift and dysregulate the hemostatic response and promote activation of clotting, which is the probable mechanism by which sepsis induces the clinical syndrome of disseminated intravascular coagulation (DIC).

DEVELOPMENTAL HEMOSTASIS

Hemostatic disorders in newborns are more common than at any other pediatric age. The neonate is relatively deficient in most procoagulant and anticoagulant proteins. Platelet function may also be impaired. Blood flow characteristics in the newborn are unique because of the high hematocrit, small-caliber vessels, low blood pressure, and special areas of vascular fragility. Table 38.2 presents the normal values for coagulation screening tests and procoagulant proteins in preterm and full-term infants, as well as in older children. Table 38.3 presents age-specific values for the anticoagulant and fibrinolytic proteins.

Levels of factors 5 and 8, fibrinogen, VWF, and platelets become normal by 28 weeks of gestation. Protein S levels are also normal at birth, but levels of other anticoagulant proteins, especially protein C, AT3, and plasminogen, are low in full-term infants and are even lower in premature neonates. The levels of most procoagulant and anticoagulant proteins increase throughout gestation; therefore, the most immature infant has the lowest levels of these proteins and is at the highest risk for either bleeding or thrombotic complications.

Vitamin K deficiency is a particular problem of the newborn. Vitamin K is a fat-soluble vitamin that induces the post-translational γ-carboxylation of the vitamin K-dependent substances (factors 2, 7, 9, and 10; protein C; and protein S). This carboxylation step occurs after the protein is synthesized in the liver and must occur for the vitamin K-dependent coagulation factor to bind calcium, the bridge to the membrane surface on which these proteins form complexes with other members of the clotting cascade and catalyze subsequent reactions. Vitamin K deficiency effectively renders these proteins unable to bind to a surface. Most of the vitamin K in adults originates from the diet and from bacterial production in the intestine. The breast-fed neonate is at high risk for vitamin K deficiency because human milk is relatively deficient in vitamin K, the neonatal liver itself is immature, and the newborn's gut requires several days to develop normal bacterial flora.

Severe vitamin K deficiency in neonates, **hemorrhagic disease of the newborn** (HDN), occurs in breast-fed infants who have not received intramuscular vitamin K prophylaxis. Such infants may experience diffuse bleeding and even central nervous system hemorrhage at 3-5 days of life. HDN is an extraordinarily rare event in the United States because of nearly universal neonatal administration of vitamin K. In the evaluation of bleeding in a newborn, the clinician should confirm that vitamin K has been administered. Patients with disorders of the gastrointestinal tract, those taking broad-spectrum antibiotics, those born of mothers who received phenobarbital or phenytoin during pregnancy (very–early-onset HDN), and those with cholestasis and malabsorption (late-onset HDN) are at higher risk for vitamin K deficiency.

CLUES FROM HISTORY AND PHYSICAL EXAMINATION

◆ History

Table 38.4 is an outline of historical questions that are important for the diagnosis of bleeding disorders as it is critical to obtain quantifiable, precise information. Easy bruising and nosebleeds are common in children, although the presence of large (>2 inches in diameter) bruises at multiple sites, prolonged nosebleeds (>15-30 minutes), and hematoma formation are seen in up to 20-40% of children with a bleeding disorder. Bleeding post-circumcision should raise the suspicion of hemophilia, while bleeding from the umbilical cord stump is associated with factor 13 deficiency. Some helpful questions include "What was the biggest bruise you ever had, and what caused it?" and "Have you ever noted little red dots [petechiae] on your skin?"

A personal or family history of gynecologic bleeding is often valuable. Menorrhagia causing iron deficiency anemia, bleeding after childbirth, or need for transfusion or early hysterectomy because of bleeding is often inappropriately assumed to have anatomic causes ("dysfunctional uterine bleeding"). The clinician must ascertain the number of pads used per day, in addition to the length and the frequency of each menstrual cycle. If the majority of women in a family have an underlying bleeding disorder, then that family's "normal menstrual periods" may be quite abnormal. Many adolescent girls with menorrhagia caused by an underlying bleeding disorder respond to oral contraceptive agents; *therefore, improvement in bleeding symptoms after starting oral contraceptive agents does not rule out a bleeding disorder.*

Historical information is equally important in deciding who requires evaluation for a predisposition to thrombosis. Virtually all pediatric patients in whom a blood clot develops in the absence of major vascular instrumentation, catheter placement, underlying infection, or other inflammatory state merit careful laboratory screening for a prothrombotic state (a hereditary or acquired disorder that predisposes to clotting). Even in the situation of a provoked thrombosis, a detailed family history should be documented for early-onset stroke; early myocardial infarction; and blood clots in the veins, arteries, or lungs.

◆ Physical Examination

The most important determination is whether the patient appears acutely or chronically ill, including vital signs and growth parameters. The nose should be examined for ulcers or anatomic bleeding sites, and the heart should be examined for the presence of murmurs (as occur in anemia and endocarditis). Joints should be examined for chronic arthropathy (as occurs in hemophilia) or joint laxity (as occurs in Ehlers–Danlos syndrome), and the extremities are examined for thumb or radial anomalies (thrombocytopenia–absent radius syndrome, or Fanconi anemia). The abdomen and lymph nodes should be examined for the presence of hepatosplenomegaly and adenopathy.

The examination of the skin should include a search for pallor, hematomas, petechiae, ecchymoses, telangiectasias, poor wound healing (large or abnormal scars), lax (loose) skin, and varicose veins (possible deep venous thrombosis). Petechiae are pinpoint, flat, dark red lesions caused by capillary bleeding into the skin. Ecchymoses

TABLE 38.2 Reference Values for Coagulation Tests in Healthy Children*

Test	19–27 Wk Gestation†	28–31 Wk Gestation†	30–36 Wk Gestation	Full Term	1–5 Yr	6–10 Yr	11–18 Yr	Adult
PT (sec)	—	15.4 (14.6–16.9)	13.0 (10.6–16.2)	13.0 (10.1–15.9)	11 (10.6–11.4)	11.1 (10.1–12.0)	11.2 (10.2–12.0)	12 (11.0–14.0)
INR	—	—	1.0 (0.61–1.7)	1.00 (0.53–1.62)‡	1.0 (0.96–1.04)	1.01 (0.91–1.11)	1.02 (0.93–1.10)	1.10 (1.0–1.3)
APTT (sec)	—	108 (80–168)	53.6 (27.5–79.4)‡§	42.9 (31.3–54.3)‡	30 (24–36)	31 (26–36)	32 (26–37)	33 (27–40)
Fibrinogen	1.00 (±0.43)	2.56 (1.60–5.50)	2.43 (1.50–3.73)‡§	2.83 (1.67–3.99)	2.76 (1.70–4.05)	2.79 (1.57–4.0)	3.0 (1.54–4.48)	2.78 (1.56–4.0)
Bleeding	—	—	—	—	6 (2.5–10)‡	7 (2.5–13)‡	5 (3.8)‡	4 (1–7) time (min)
Factor 2	0.12 (±0.02)	0.31 (0.19–0.54)	0.45 (0.20–0.77)‡	0.48 (0.26–0.70)‡	0.94 (0.71–1.16)‡	0.88 (0.67–1.07)‡	0.83 (0.61–1.04)‡	1.08 (0.70–1.46)
Factor 5	0.41 (±0.10)	0.65 (0.43–0.80)	0.88 (0.41–1.44)§	0.72 (0.34–1.08)‡	1.03 (0.79–1.27)	0.90 (0.63–1.16)‡	0.77 (0.55–0.99)‡	1.06 (0.62–1.50)
Factor 7	0.28 (±0.04)	0.37 (0.24–0.76)	0.67 (0.21–1.13)‡	0.66 (0.28–1.04)‡	0.82 (0.55–1.16)‡	0.86 (0.52–1.20)‡	0.83 (0.58–1.15)‡	1.05 (0.67–1.43)
Factor 8 procoagulant	0.39 (±0.14)	0.79 (0.37–1.26)	1.11 (0.5–2.13)	1.00 (0.50–1.78)	0.90 (0.59–1.42)	0.95 (0.58–1.32)	0.92 (0.53–1.31)	0.99 (0.50–1.49)
VWF	0.64 (±0.13)	1.41 (0.83–2.23)	1.36 (0.78–2.10)	1.53 (0.50–2.87)	0.82 (0.60–1.20)	0.95 (0.44–1.44)	1.00 (0.46–1.53)	0.92 (0.50–1.58)
Factor 9	0.10 (±0.01)	0.18 (0.17–0.20)	0.35 (0.19–0.65)‡§	0.53 (0.15–0.91)†‡	0.73 (0.47–1.04)‡	0.75 (0.63–0.89)‡	0.82 (0.59–1.22)‡	1.09 (0.55–1.63)
Factor 10	0.21 (±0.03)	0.36 (0.25–0.64)	0.41 (0.11–0.71)‡	0.40 (0.12–0.68)‡	0.88 (0.58–1.16)‡	0.75 (0.55–1.01)‡	0.79 (0.50–1.17)	1.06 (0.70–1.52)
Factor 11	—	0.23 (0.11–0.33)	0.30 (0.08–5.2)‡§	0.38 (0.40–0.66)‡	0.97 (0.52–1.50)‡§	0.86 (0.52–1.20)	0.74 (0.50–0.97)‡	0.97 (0.67–1.27)
Factor 12	0.22 (±0.03)	0.25 (0.05–0.35)	0.38 (0.10–0.66)‡§	0.53 (0.13–0.93)‡	0.93 (0.64–1.29)	0.92 (0.60–1.40)	0.81 (0.34–1.37)‡	1.08 (0.52–1.64)
PK	—	0.26 (0.15–0.32)	0.33 (0.09–0.89)‡	0.37 (0.18–0.69)‡	0.95 (0.65–1.30)	0.99 (0.66–1.31)	0.99 (0.53–1.45)	1.12 (0.62–1.62)
HMWK	—	0.32 (0.19–0.52)	0.49 (0.09–0.89)‡	0.54 (0.06–1.02)‡	0.98 (0.64–1.32)	0.93 (0.60–1.30)	0.91 (0.63–1.19)	0.92 (0.50–1.36)
Factor 13a	—	—	0.70 (0.32–1.08)‡	0.79 (0.27–1.31)‡	1.08 (0.72–1.43)	1.09 (0.65–1.51)	0.99 (0.57–1.40)	1.05 (0.55–1.55)
Factor 13b	—	—	0.81 (0.35–1.27)‡	0.76 (0.30–1.22)‡	1.13 (0.69–1.56)‡	1.16 (0.77–1.54)‡	1.02 (0.60–1.43)	0.98 (0.57–1.37)

*All factors except fibrinogen are presented as U/mL (fibrinogen in mg/mL), where pooled normal plasma contains 1 U/mL. All data are expressed as the mean followed by the upper and lower boundaries encompassing 95% of the normal population.

†Levels for 19–27 wk and 28–31 wk are from multiple sources and cannot be analyzed statistically.

‡Values are significantly different from those of adults.

§Values are significantly different from those of full-term infants.

APTT, activated partial thromboplastin time; HMWK, high-molecular-weight kininogen; INR, international normalized ratio; PK, prekallikrein; PT, prothrombin time; VWF, von Willebrand factor.

Data from Andrew M, Paes B, Johnston M. Development of the hemostatic system in the neonate and young infant. *Am J Pediatr Hematol Oncol*. 1990;12:95-104; and Andrew M, Vegh P, Johnston M, et al. Maturation of the hemostatic system during childhood. *Blood*. 1992;80:1998-2005.

TABLE 38.3 Reference Values for the Inhibitors of Coagulation in Healthy Children in Comparison with Adults*

Inhibitor	19–27 Wk Gestation†	28–31 Wk Gestation†	30–36 Wk Gestation	Full Term	1–5 Yr	6–10 Yr	11–18 Yr	Adult
AT3	0.24 (±0.03)‡	0.28 (0.20–0.38)‡	0.38 (0.14–0.62)‡§	0.63 (0.39–0.87)‡	1.11 (0.82–1.39)	1.11 (0.90–1.31)	1.06 (0.77–1.32)	1.0 (0.74–1.26)
Protein C	0.11 (±0.03)‡	—	0.28 (0.12–0.44)‡§	0.35 (0.17–0.53)‡	0.66 (0.40–0.92)‡	0.69 (0.45–0.93)‡	0.83 (0.55–1.11)‡	0.96 (0.64–1.28)
Protein S	—	—	—	—	—	—	—	—
Total (U/mL)	—	—	0.26 (0.14–0.38)‡§	0.36 (0.12–0.60)‡	0.86 (0.54–1.18)	0.78 (0.41–1.14)	0.72 (0.52–0.92)	0.81 (0.61–1.13)
Free (U/mL)	—	—	—	—	0.45 (0.21–0.69)	0.42 (0.22–0.62)	0.38 (0.26–0.55)	0.45 (0.27–0.61)
Plasminogen (U/mL)	—	—	1.70 (1.12–2.48)‡	1.95 (1.25–2.65)‡	0.98 (0.78–1.18)	0.92 (0.75–1.08)	0.86 (0.68–1.03)	0.99 (0.77–1.22)
TPA (ng/mL)	—	—	8.48 (3.00–16.70)	9.6 (5.0–18.9)	2.15 (1.0–4.5)‡	2.42 (1.0–5.0)‡	2.16 (1.0–4.0)‡	1.02 (0.68–1.36)
α_2AP (U/mL)	—	—	0.78 (0.40–1.16)	0.85 (0.55–1.15)	1.05 (0.93–1.17)	0.99 (0.89–1.10)	0.98 (0.78–1.18)	1.02 (0.68–1.36)
PAI–1	—	—	5.4 (0.0–12.2)‡	5.42 (1.0–10.0)	5.42 (1.0–10.0)	6.79 (2.0–12.0)‡	6.07 (2.0–10.0)‡	3.60 (0–11.0)

*All values are expressed in U/mL, where pooled plasma contains 1 U/mL, with the exception of free protein S, which contains a mean of 0.4 U/mL. All values presented as the mean by the upper and lower boundaries encompassing 95% of the population.
†Levels for 19–27 wk and 28–31 wk are from multiple sources and cannot be analyzed statistically.
‡Values are significantly different from those of adults.
§Values are significantly different from those of full-term infants.
α_2AP, α_2-antiplasmin; AT3, antithrombin 3; PAI-1, plasminogen activator inhibitor type 1; TPA, tissue plasminogen activator.
Data from Andrew M, Paes B, Johnston M. Development of the hemostatic system in the neonate and young infant. *Am J Pediatr Hematol Oncol*. 1990;12:95-104; and Andrew M, Vegh P, Johnston M, et al. Maturation of the hemostatic system during childhood. *Blood*. 1992;80:1998-2005.

are larger lesions (bruises) that are flat and usually not palpable. Hematomas are accumulations of blood in the skin or deeper tissues; in the skin, hematomas are raised and palpable. Bruises should be described in detail, including whether hematomas are associated with bruises and whether petechiae are present. Petechiae and ecchymoses are usually painless. Purpura refers to any group of disorders characterized by the presence of dark-red, purplish, or brown lesions of the skin and mucous membranes. The discoloration is caused by the leakage of red blood cells from affected vessels. Purpuric lesions can be caused by abnormalities of the platelets, of coagulation proteins, or of vessel walls.

Coagulation Screening Tests

After obtaining a history and performing a physical examination, the clinician must determine the need for a hemostatic evaluation. The history is likely to be the most sensitive screening tool for a significant bleeding disorder, although its use in a very young child, especially before toddler age, is limited and attention must shift to the perinatal and family history. For patients with clinical clues of a coagulation disorder, the initial screening studies should assess the clotting factors and platelet function. No set of screening tests is complete and capable of detecting the panorama of hemorrhagic disorders, but the screen should include:

- Complete blood count (CBC) to evaluate hemoglobin and platelet count
- Prothrombin time (PT)
- Partial thromboplastin time (PTT)
- Functional fibrinogen level or thrombin time
- VWF testing

If there is high suspicion for an underlying bleeding disorder, screening for von Willebrand disease and platelet function defects should be considered. There are no satisfactory tests to screen for a thrombotic tendency.

Prothrombin Time and Partial Thromboplastin Time

The PT and PTT (Fig. 38.5) are measures of all the coagulation factors except factor 13. Fibrinogen function should be measured as fibrinogen activity or thrombin time. The PTT is the screening test that checks for deficiency of all clotting factors except factors 7 and 13. The PTT can be prolonged either by a deficiency of a clotting factor or by the presence of an agent in the plasma that delays the clotting time (an inhibitor). The PT is especially sensitive to deficiencies of factor 7.

To test for an inhibitor, 1 part of the patient's plasma is mixed with 1 part of pooled normal plasma obtained from 20-50 healthy adults. Pooled normal plasma provides a 100% level of each clotting factor. If mixed 1:1 with plasma that is deficient in 1 or several factors, the mixture should possess at least a 50% level of each factor and the PTT should correct to the normal range. If an inhibitor is present, the PTT usually does not correct to normal. The most common types of inhibitors include anticoagulants, such as heparin, and autoantibodies directed against either specific clotting factors (factor 8 inhibitors) or the phospholipid substances used in the PTT (lupus-type anticoagulants).

TABLE 38.4 History of a Bleeding Disorder

I. History of Disorder
- A. Onset of symptoms
  1. Age
  2. Acute versus lifelong
  3. Triggering event
  4. Timing of bleeding after injury: immediate vs delayed
- B. Sites of bleeding
  1. Mucocutaneous*
     - a. Epistaxis (1) Duration, frequency, seasonal tendency (2) Associated trauma (nose picking, allergy, infection) (3) **Resultant anemia, emergency department evaluation, cautery**
     - b. Oral (gingiva, frenulum, tongue lacerations, bleeding after tooth brushing, after dental extractions requiring sutures/packing)
     - c. Bruising (number, sites, size, **raised** [other than extremities], spontaneous versus trauma, knots within center, skin scarring)
     - d. Gastrointestinal bleeding
  2. Deep
     - a. Musculoskeletal (1) Hemarthroses, unexplained arthropathy (2) Intramuscular hematomas
     - b. Central nervous system hemorrhage
     - c. Genitourinary tract
  3. Surgical
     - a. Minor (sutures, lacerations, poor or delayed wound healing)
     - b. Major (1) Tonsillectomy and adenoidectomy (2) Abdominal surgery
- C. Perinatal history
     - a. Superficial (bruising, petechiae)
     - b. Deep (1) Circumcision (2) Central nervous system bleeding (3) Gastrointestinal bleeding (4) Cephalohematoma (5) Unexplained anemia or hyperbilirubinemia (6) Delayed cord separation, bleeding after cord separation
     - c. Vitamin K administration
     - d. Maternal drugs
- D. Obstetric/gynecologic bleeding
  1. Menorrhagia
     - a. Onset, duration, amount (number of pads), frequency, persistence after childbirth
     - b. Resultant anemia, iron deficiency
  2. Bleeding at childbirth (onset, duration, **transfusion requirement**, history of traumatic delivery, recurrences with subsequent pregnancies, spontaneous abortions)
- E. Medications
     - a. Aspirin and nonsteroidal antiinflammatory drugs
     - b. Anticoagulants
     - c. Antibiotics
     - d. Anticonvulsants
- F. Diet
     - a. Vitamin K
     - b. Vitamin C

II. Family History

Draw family tree. The items just listed should be applied to immediate family members, especially a history of easy bruising, epistaxis, excessive bleeding after surgery, menorrhagia, excessive bleeding after childbirth, or a family history of others with diagnosed or suspect bleeding disorders. Attempt to deduce inheritance pattern.

*Significant historical information is presented in boldface type.

The PTT is especially sensitive to deficiencies of factors 8, 9, and 11 (hemophilia A, B, and C, respectively). A prolonged PTT in an asymptomatic child is most commonly caused by factor 12 deficiency or by a lupus-type anticoagulant. The PTT can also yield a false result:

1. When poor venipuncture technique, by adding tissue factor to the blood, activates clotting and artifactually shortens the PTT.
2. When insensitive laboratory reagents fail to detect clinically significant deficiencies (most common in mild factor 9 deficiency).
3. When the citrate concentration is not corrected for blood with a high hematocrit (in neonates and in patients with cyanotic congenital heart disease), leading to a prolonged PTT.

Bleeding Time

The bleeding time is an indirect measure of platelet number and a more direct measure of platelet function, vascular integrity, and platelet interaction with the vascular subendothelium. As such, the bleeding time should be abnormal in patients with thrombocytopenia, platelet function abnormalities, abnormal collagen (Ehlers–Danlos syndrome), and von Willebrand disease. Unfortunately, because of its insensitivity and high level of variability, the bleeding time is a relatively poor tool for detecting the milder forms of these hemostatic disorders and cannot be used to rule out von Willebrand disease and mild or moderate platelet function deficits.

Platelet Function Analysis

Platelet function analysis was originally recommended as a screening test for von Willebrand disease and platelet function defects. Its sensitivity and specificity are insufficient for diagnosis, but it may have utility as a screen for severe platelet function defects in very small infants where rapid results are needed and size prohibits collection of large volumes of blood needed for platelet aggregation testing.

Figs. 38.6 and 38.7 provide an approach to evaluate the patient with an isolated prolongation of the PT or PTT.

Thrombin Time and Reptilase Time

The thrombin time and reptilase time are tests that measure the conversion of fibrinogen to fibrin. The thrombin time is sensitive to heparin effect, whereas the snake venom reptilase time remains normal in the presence of heparin. Both the thrombin time and the reptilase time are prolonged by uremia, by dysfibrinogenemia, and by low fibrinogen levels (<75 mg/dL).

MUCOCUTANEOUS BLEEDING

Mucocutaneous bleeding occurs within the skin or mucous membranes. Common complaints include prolonged, frequent nosebleeds; gum bleeding; prolonged bleeding after tooth extraction; menorrhagia; and easy bruising with or without petechiae formation. Mucocutaneous bleeding is usually associated with abnormalities of platelet number or function, of platelet cofactors, or of the vessel wall. The well-appearing child who presents with the acute onset of petechiae and purpura, often in association with nosebleeds or bleeding gums, and otherwise normal examination findings typically has **acute immune thrombocytopenic purpura (ITP)**. The majority of affected children have an antecedent viral illness. After exposure to the viral infection, an antibody that binds to the platelet membrane develops, leading to the premature destruction of the antibody-coated platelets in the spleen.

The peak ages for the presentation of ITP are 1-4 years of age and adolescence, but ITP occurs throughout childhood and adolescence. Girls are more commonly affected in adolescence but not in childhood. The work-up of a child with thrombocytopenia should include a

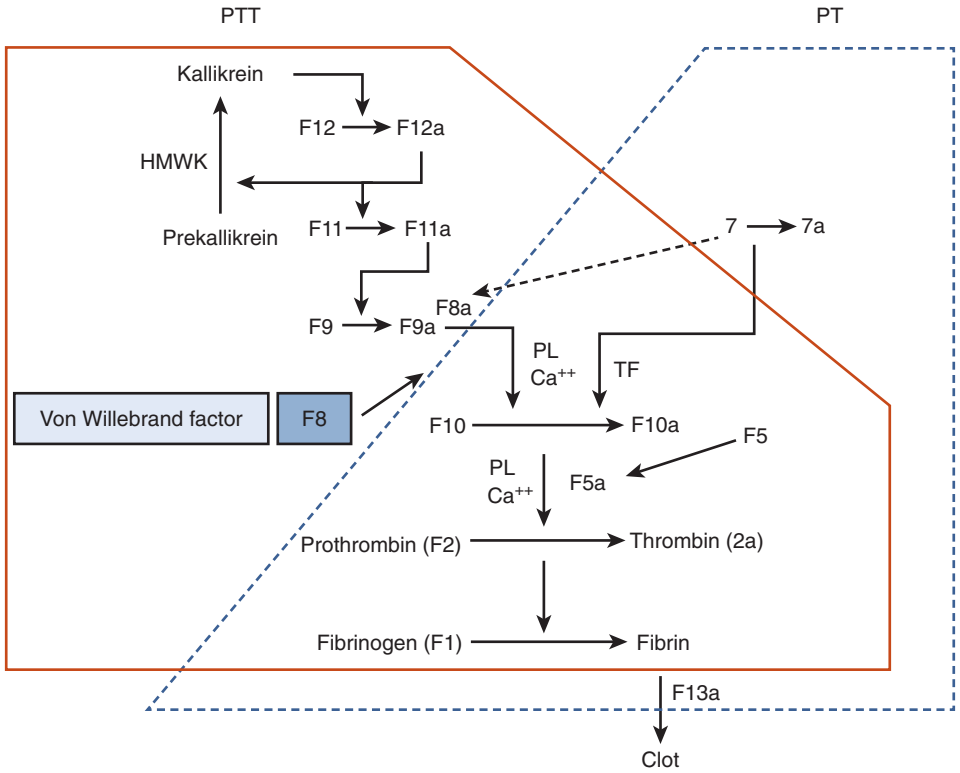


FIGURE 38.5 Elements of the coagulation cascade measured by the prothrombin time (PT) and the partial thromboplastin time (PTT). Note that prekallikrein (PK), high-molecular-weight kininogen (HMWK), and factor 12 are shown in this figure and not in the depiction of the coagulation cascade in Fig. 38.1, because a deficiency of PK, HMWK, or factor 12 can cause a prolongation of the PTT. However, a deficiency of any of these proteins alone is not associated with a clinical bleeding disorder. Ca^{2+}, calcium; PL, platelet phospholipid surface; TF, tissue factor. (Modified from Montgomery RR, Scott JP: Hemorrhage and thrombotic diseases. In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics*. 16th ed. Orlando, FL: WB Saunders; 1999:1505).

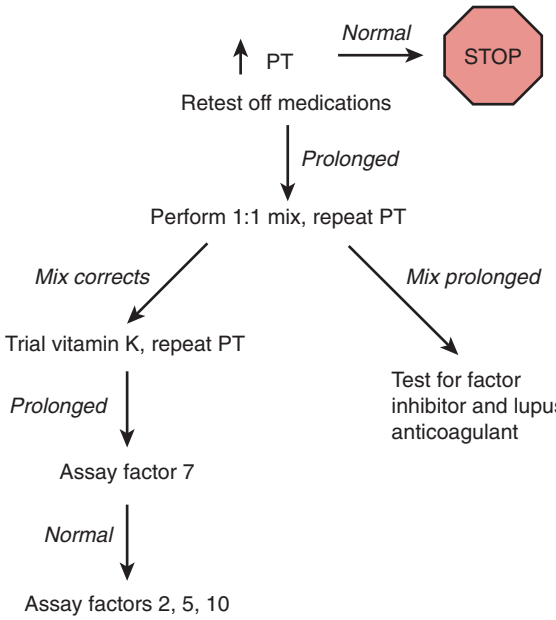


FIGURE 38.6 Flow diagram for the evaluation of a patient with an isolated prolongation of the prothrombin time (PT).

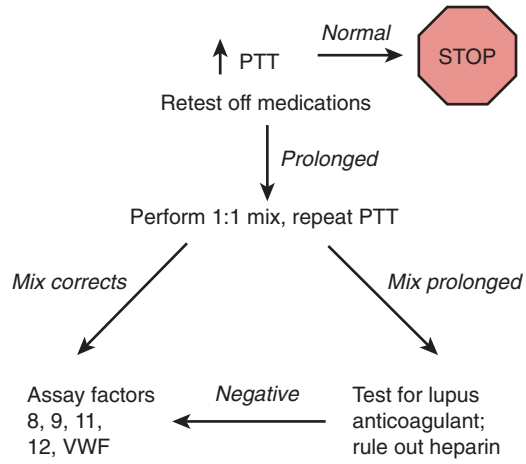


FIGURE 38.7 Flow diagram for the evaluation of a patient with an isolated prolongation of the partial thromboplastin time (PTT). To rule out heparin effect, the thrombin time is compared with the reptilase time. If the thrombin time is significantly longer than the reptilase time, heparin is present in the sample. VWF, von Willebrand factor.

careful history aimed at detecting symptoms (e.g., weight loss, fever, bone pain, anorexia) of other preexisting illnesses (e.g., leukemia, systemic lupus erythematosus [SLE], endocarditis, human immunodeficiency virus [HIV]), exposures to drugs or toxins, and a personal or family history of thrombocytopenia. The physical examination must be detailed and include a search for signs of malignancy (e.g., lymphadenopathy, hepatosplenomegaly), chronic illness, and congenital malformations. When evaluating the CBC, the clinician should ensure that the hemoglobin, white blood cell count, differential, indices, and smear are normal, which would make the diagnosis of a hematologic malignancy or other marrow failure syndrome unlikely. The presence of large platelets on the smear or measured as a high mean platelet volume suggests accelerated thrombopoiesis and increased platelet destruction. The differential diagnosis of thrombocytopenia is noted in Table 38.5.

After the presumptive diagnosis of ITP, a Coombs test may be considered to rule out a simultaneous autoimmune hemolytic anemia. The role of studies for platelet antibodies is unclear; there are no data indicating that these studies are either diagnostic or prognostic in children. If the child is male, is young, and has a history of eczema or recurrent infection, immunoglobulin levels to rule out **Wiskott–Aldrich syndrome** are indicated. Similarly, in older children, especially girls as they approach adolescence, an antinuclear antibody test to rule out **SLE** manifesting as thrombocytopenia may be considered, although it is more likely to yield positive results in children with chronic ITP. **HIV** infection occasionally manifests as ITP. The diagnostic yield of bone marrow examination in a child with normal findings on a careful physical examination (no lymphadenopathy or hepatosplenomegaly) and a completely normal CBC including a manual white blood cell differential, other than isolated thrombocytopenia, is negligible.

Once a diagnosis of ITP is made, several therapeutic options are available, including simple observation and education. The family should be advised that the child must avoid activities that increase the risk of head injury. Treatment should be reserved for children at high risk for clinical bleeding (platelet count <20,000/mm^3 and children with petechiae and mucosal hemorrhages). Some authorities argue that patients with mucous membrane purpura are at higher risk and definitely require treatment. Treatment is not recommended for patients without bleeding symptoms. The major cause of mortality in ITP is related to intracranial hemorrhage, which has been observed in fewer than 0.5-1% of patients. Table 38.6 provides a perspective on treatment alternatives for ITP. Options for initial therapy for patients

TABLE 38.5 Differential Diagnosis of Thrombocytopenia in Children

I. Destructive Thrombocytopenias	
Primary platelet consumption syndromes	Idiopathic thrombocytopenia purpura Drug–induced thrombocytopenia Infection-induced thrombocytopenia (human immunodeficiency virus)
Immunologic	Posttransfusion purpura Autoimmune or lymphoproliferative disorders Neonatal immune thrombocytopenias Allergy and anaphylaxis Posttransplantation thrombocytopenia Chronic microangiopathic hemolytic anemia and thrombocytopenia Hemolytic uremic syndrome
Nonimmunologic	Thrombotic thrombocytopenic purpura Catheters, prostheses, or cardiopulmonary bypass Congenital or acquired heart disease
Combined platelet and fibrinogen consumption syndromes	Disseminated intravascular coagulation Kasabach–Merritt syndrome Other causes of local consumption coagulopathy
Miscellaneous causes	Phototherapy Perinatal aspiration syndromes Persistent pulmonary hypertension Rhesus alloimmunization
Specific to the neonate	Status post exchange transfusion Polycythemia Metabolic inborn errors of metabolism Maternal HELLP syndrome Glomerular disease Preeclampsia
II. Impaired or Ineffective Production	
Congenital and hereditary disorders	TAR syndrome Other congenital thrombocytopenias with megakaryocytic hypoplasia Fanconi aplastic anemia Bernard–Soulier syndrome*
Primary hematologic processes	May–Hegglin anomaly* Wiskott–Aldrich syndrome* Miscellaneous hereditary thrombocytopenias (X-linked or autosomal)* Mediterranean thrombocytopenia Associated with trisomy 13 or 18
Metabolic inborn errors	Holocarboxylase synthetase deficiency Isovaleric acidemia Some mitochondrial disorders Methylmalonic acidemia Ketotic glycinemia
Acquired disorders	Aplastic anemia Marrow infiltrative processes Drug or radiation induced Nutritional deficiency states (iron, folate, or vitamin B_{12})
III. Sequestration	Hypersplenism Hypothermia

*These hereditary thrombocytopenias can be associated with normal or increased bone marrow megakaryocytes.
HELLP, hypertension, elevated liver enzymes, low platelets; TAR, thrombocytopenia–absent radius.
Modified from Schultz Beardsley D. Platelet abnormalities in infancy and childhood. In: Nathan DG, Oski FA, eds. *Hematology of Infancy and Childhood*. 4th ed. Philadelphia: WB Saunders; 1993;2:1566.

TABLE 38.6 Common Treatment Alternatives for Childhood Acute Immune Thrombocytopenic Purpura (ITP)

Drug	Route of Administration	Pros	Cons	Cost (Assuming Typical 15 kg Toddler)
IVIG	IV	Rapid onset of action Does not rely on patient/family giving medication at home Effective in 75–80% of patients	IV required Either inpatient or prolonged (4–6 hr) visit to clinic Does not alter long-term outcome	$3000 for 1 mg/kg dose
Prednisone	Oral (can also be given IV)	Outpatient administration Rapid onset of action Effective in 75–80% of patients Does not require placement of an IV Short course likely minimal side effects	Steroid side effects (GI, mood swings, growth issues with long-term use) May need multiple courses No effect on long-term outcome	2-wk course of 2 mg/kg/day: $15
Rituximab	IV	Durable remission in 40–60%	IV administration May cause reactivation of hepatitis	4 doses of 375 mg/m^2, approximately $5000–15,000
Splenectomy	Surgery	Curative in 80% of patients	Expensive Invasive Impairs host defense against encapsulated organisms Reserved for chronic ITP and/or serious bleeding complications	$10,000–$20,000
Thrombopoietin agonists	Oral (options also come as IV, SQ)	Noninvasive Outpatient treatment	Associated with elevation in liver enzymes Require frequent monitoring Not curative, most patients require ongoing administration	1-mo course of 25 mg/day, $3000

GI, gastrointestinal; IV, intravenous; IVIG, intravenous immunoglobulin; SQ, subcutaneous.

in need of treatment include intravenous immunoglobulin (IVIG) and prednisone. Transfusion of platelets should be reserved for life-threatening bleeding, because transfused platelets are rapidly destroyed. Thrombopoietin receptor agonists have been approved for use in adults.

Ten to 20% of children with ITP have persistence of thrombocytopenia for more than 6 months **(chronic ITP)**. These patients are more likely to be older (adolescent) girls or to have had an insidious onset of symptoms. The clinician must look carefully for predisposing causes, including SLE, HIV infection, autoimmune lymphoproliferative syndrome (ALPS), or medications. The treatment of chronic ITP is evolving and includes repeated doses of IVIG, prolonged steroid use, and consideration of rituximab, thrombopoietin receptor agonists, or splenectomy. Because of improved medical therapy, splenectomy is limited to patients with severe, refractory chronic ITP.

Neonatal Thrombocytopenia

Thrombocytopenia is common, especially in sick newborns. The differential diagnosis of neonatal thrombocytopenia includes most of the causes seen in older children and a few additional specific to the newborn (Fig. 38.8, in the shaded areas; see also Table 38.5). When evaluating the thrombocytopenic newborn, the physician must know the perinatal history including the mother's health during this and previous pregnancies, history of current or previous low platelets, or of children dying of hemorrhage. A maternal history of fever, viral infection (cytomegalovirus, rubella), sexually transmitted infections (syphilis, HIV), medications, toxemia, or collagen vascular disease (SLE) is informative. The family history should be evaluated for bleeding disorders, recurrent infections, or malignancies, especially in siblings, both as neonates or any age.

During examination of the newborn, the most important element to determine is the child's general well-being. The examiner should look especially for signs of systemic illness, as well as lymphadenopathy, hepatosplenomegaly, mass lesions, hemangiomas, bruits, and congenital anomalies, especially of the radial bones. The examiner should carefully evaluate the hemoglobin, the white blood cell count, and the differential for the presence of abnormal cells (blasts). Red blood cell structure should be examined for signs of microangiopathy. Small platelets (low mean platelet volume) suggest abnormal thrombopoiesis, whereas large platelets are found with accelerated platelet destruction. *Thrombocytopenia can be caused by synthetic failure, sequestration, or destructive processes.* The destructive processes are most common and are either immune or nonimmune in origin. Nonimmune causes of platelet consumption—for example, DIC, sepsis, congenital infections, or thrombotic events—are usually associated with obvious clinical findings. When evaluating the ill-appearing neonate or child for thrombocytopenia, the examiner should perform coagulation studies to detect fibrinogen consumption (fibrinogen level, D-dimer). Neonates with immune-mediated platelet destruction usually appear healthy.

After the clinician obtains a thorough history, performs a careful physical examination, and evaluates the CBC, the initial step in management of the child with thrombocytopenia depends on the cause and severity of the thrombocytopenia. In the neonate with severe thrombocytopenia (platelet count <40,000/mm^3) delivered vaginally, an ultrasound study of the head should be done to rule out intracranial bleeding. Platelet transfusion for thrombocytopenia can serve both as a therapeutic tool for stopping the bleeding and as a diagnostic maneuver. In patients with decreased platelet synthesis, survival of transfused platelets should be normal, whereas in thrombocytopenic states caused

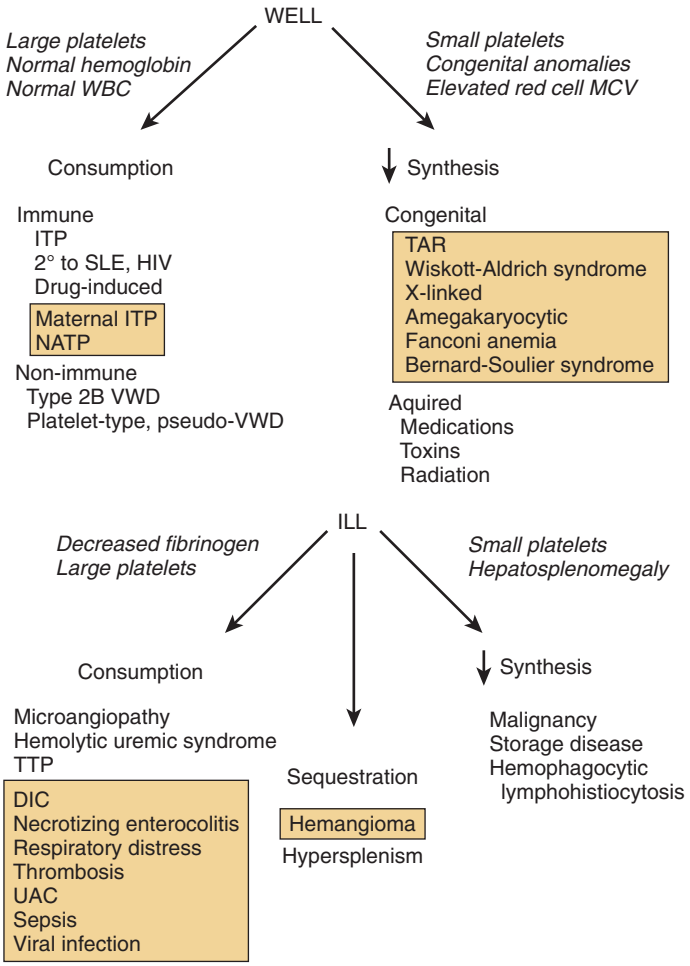


FIGURE 38.8 Differential diagnosis of childhood thrombocytopenic syndromes. The syndromes are initially separated by their clinical appearance. Clues leading to the diagnosis are presented in italics. The mechanisms and common disorders leading to these findings are shown in the lower part of the figure. Disorders that commonly affect neonates are listed in the shaded boxes. DIC, disseminated intravascular coagulation; HIV, human immunodeficiency virus; ITP, idiopathic immune thrombocytopenic purpura; MCV, mean corpuscular volume; NATP, neonatal alloimmune thrombocytopenic purpura; SLE, systemic lupus erythematosus; TAR, thrombocytopenia–absent radius (syndrome); TTP, thrombotic thrombocytopenic purpura; UAC, umbilical artery catheter; VWD, von Willebrand disease; WBC, white blood cell; 2°, secondary.

by platelet destruction, transfused platelets should be cleared rapidly. For this reason, platelet transfusions are usually contraindicated in thrombocytopenic states caused by accelerated platelet destruction, as in ITP and hemolytic uremic syndrome (except in the event of life-threatening bleeding such as intracranial hemorrhage). The yield and survival of the transfused platelets should be monitored with serial platelet counts after transfusion.

Antibody-mediated thrombocytopenia in the neonate is caused by transfer of maternal IgG antibodies that react with the neonate's platelets. A mother with active ITP or a history of previous ITP is at risk for delivering a thrombocytopenic baby. There is no definitive, noninvasive method to determine the newborn's risk of thrombocytopenia, although the actual risk for severe bleeding during delivery appears low. In contrast, children born to mothers who are sensitized to paternal alloantigens present on the fetal platelets have a higher risk for perinatal hemorrhage and symptomatic thrombocytopenia. **Neonatal alloimmune thrombocytopenic purpura (NATP)**, the platelet equivalent of maternal Rh isoimmunization, differs from Rh disease in that first-born children are commonly affected. The importance of this diagnosis is that it is commonly associated with prenatal intracranial hemorrhage with a resultant high rate of morbidity and mortality (15%). Therefore, recognition of the diagnosis in the 1st pregnancy can have a major impact on the management of subsequent pregnancies. Transfusion of washed maternal platelets that lack the paternal alloantigen toward which the maternal antibody is directed will correct the platelet count and prevent further bleeding. Random donor platelets are rapidly destroyed. Newborns with NATP can be easily differentiated from thrombocytopenic newborns of mothers with ITP on the basis of the mother's platelet count. Mothers with ITP are thrombocytopenic unless they have had a splenectomy. Mothers of infants with NATP have normal platelet counts.

Although the initial diagnosis of NATP is usually made by studying the reaction of maternal sera against paternal platelets, prenatal diagnosis is performed with molecular biologic techniques to detect the allelic differences between the mother and the fetus by analysis of various fetal DNA sources. After prenatal diagnosis, treatment of the mother with IVIG has been shown to raise the fetal platelet count and prevent fetal bleeding. In addition, postnatal treatment of the neonate with IVIG and corticosteroids may be helpful after restoration of a normal platelet count by transfusion of washed maternal platelets. *All blood products administered to the neonate with thrombocytopenia should be radiated to prevent graft-versus-host disease, because some patients may have a congenital immunodeficiency syndrome manifested by thrombocytopenia.*

Child Abuse

The most common cause of remarkable bruising and bleeding with normal hemostatic screening studies in infancy is child abuse.

Chronic/Insidious Onset of Mucocutaneous Bleeding

When symptoms of skin and mucous membrane bleeding are lifelong, the most common cause is von Willebrand disease (VWD). Congenital platelet function defects are almost as common, while congenital thrombocytopenic syndromes, and abnormalities of the vessel wall are less common. Von Willebrand disease, the deficiency of VWF, is the most common hereditary bleeding disorder, with a prevalence of approximately 1/1000 in the milder forms. The inheritance of von Willebrand disease is usually autosomal dominant. VWF is a large, multimeric protein that functions as the bridge between platelets and damaged vessel walls; therefore, deficient or dysfunctional VWF causes delayed formation of the platelet plug (see Fig. 38.3). In addition, VWF serves as a carrier protein for factor 8. A profound deficiency of VWF is associated with low levels of factor 8, so that the patient with severe von Willebrand disease has the clinical manifestations of both von Willebrand disease and hemophilia.

The presentation of von Willebrand disease is highly variable. Mucocutaneous bleeding or no symptoms are the most common findings. Because neonatal VWF levels are often elevated after vaginal delivery, the onset of clinical symptoms for mild and moderate von Willebrand disease is usually during the toddler stage or later. The only presenting complaint may be abnormal preoperative coagulation studies. The laboratory diagnosis of the disease is particularly challenging because there is no single test that optimally measures VWF function.

The PTT and bleeding time are only abnormal in about half of patients with von Willebrand disease. A von Willebrand screen, including VWF antigen (to measure total protein) and activity (to measure

protein function) is recommended to fully assess for von Willebrand disease. The need for additional work-up is defined by the clinical clues, including the patient's personal history of bleeding, the family history, and the potential for surgery.

The diagnosis of von Willebrand disease is further complicated by the observation that VWF is a labile protein and levels can be increased by stress, medication, trauma, pregnancy, and difficult venipuncture. VWF levels are also elevated following vaginal delivery in infants with type 1 VWD. This can be helpful in terms of ability to perform circumcision in males with potential type 1 VWD, but problematic in terms of making an immediate diagnosis. It remains unclear whether there is a physiologically different hemostatic level of VWF for different blood groups. Age has been shown to influence VWF levels in adults, but this has not been adequately investigated in children. Furthermore, there are multiple variants of von Willebrand disease; the clinician should perform repeated studies if there is a high index of suspicion or abnormal positive screening tests.

Von Willebrand disease can be classified as type 1 (classic disease with mild or moderate deficiency), type 2 (a dysproteinemia), or type 3 (severe disease: virtual absence of VWF and low levels of factor 8). The treatment of the disease is dependent on the type and the response to 1-deamino(8-D-arginine) vasopressin (DDAVP). DDAVP is a synthetic vasopressin analog that induces the release of VWF and factor 8. Levels of these factors rise threefold to fourfold after a dose of 0.3 μg/kg. For most cases of von Willebrand disease, DDAVP is the treatment of choice. A therapeutic trial with measurements of VWF before and both 1 hour and 4 hours after DDAVP administration should be performed to document the efficacy of DDAVP before surgery. The late timepoint is useful to identify clearance defects that may have an initial response but lack the sustained response critical for clinical use of DDAVP. Patients with rare variant forms of von Willebrand disease (type 2A, type 2B, and platelet type) may have no response or an adverse response to DDAVP; therefore, full studies to identify the subtype are needed before a trial of DDAVP. These studies correlate functional levels of VWF with the amount of protein measured antigenically (the VWF antigen), the multimeric size of the protein (VWF multimers), and the aggregation response of the patient's platelet-rich plasma to high and low concentrations of ristocetin.

Most patients with mild and moderate type 1 von Willebrand disease have a satisfactory response to DDAVP; hemostasis for most surgical procedures can be provided with daily doses of DDAVP on consecutive days. For severely affected patients or those with variant forms of the disease noted previously (type 2A, type 2B, platelet type), treatment should be individualized. Some patients with type 2A respond to DDAVP. Severely affected patients with von Willebrand disease and those with the 2B variant should receive a clotting factor concentrate containing a full complement of normal VWF multimers (Humate-P or Wilate are the currently approved products) in doses similar to those outlined for factor 8 in Table 38.7.

TABLE 38.7 Characteristics of Factors 8 and 9 and Respective Modes of Treatment for Bleeding Episodes Caused by Hemophilia A or B

	Factor 8	Factor 9
Yield	1.5–2%/U/kg infused	0.7–1%/U/kg infused
Half-life	8–12 hr	18–24 hr
Goal therapeutic level: Life and limb-threatening, acute hemarthrosis treatment	80–100%	80–100%
Minor bleeds (gingival bleeding, epistaxis)	40–50%	30–50%
Dose computation*	Level desired × weight (kg) × 0.5	Level desired × weight (kg) × 1.3
Therapeutic alternatives	Desmopressin† Plasma-derived factor 8 concentrate	Plasma-derived factor 9 concentrate Prothrombin complex concentrate‡

*Assumes use of a recombinant factor replacement product.
†After adequate response has been demonstrated.
‡Repeat doses have been associated with increased risk for thrombosis.

Platelet Function Defects

For patients with mucocutaneous bleeding but a normal platelet count and normal VWF studies, platelet aggregation studies should be performed to evaluate for a primary or secondary platelet function defect. A large number of medications alter platelet function and may induce an acquired abnormality of platelet function. A careful history to elicit exposure to medications and to determine whether clinical symptoms correlate with exposure to specific drugs is critical. Common medications that alter platelet functions are aspirin, nonsteroidal antiinflammatory drugs, alcohol, penicillin in high doses, and valproic acid.

Most primary platelet function defects cause relatively mild mucocutaneous bleeding symptoms. In these disorders, there is most commonly an abnormality of the storage granules or release mechanism within the platelet, causing delayed or diminished response to agonists that induce platelet aggregation, such as collagen. Platelet function defects, like most other hemostatic defects, are accentuated by medications that impair platelet function. In rare instances, a patient demonstrates impressive petechiae and hematomas at birth because of an absence of 1 of the essential platelet membrane receptors for the adhesive proteins VWF or fibrinogen. These disorders, Glanzmann thrombasthenia (deficiency of glycoprotein αIIbβ3, the fibrinogen receptor) and Bernard–Soulier syndrome (deficiency of glycoprotein Ib, the von Willebrand receptor), represent the most severe types of platelet function defects. The platelet count is normal in Glanzmann thrombasthenia thrombocytopenia, but patients with Bernard–Soulier syndrome usually have thrombocytopenia with remarkably large platelets.

Milder thrombocytopenia syndromes have been well characterized due to advances in genetics; a defect in the myosin heavy chain 9 gene *(MYH9)* causes congenital macrothrombocytopenia, associated in some cases with deafness, ocular abnormalities, or nephritis. Congenital amegakaryocytic thrombocytopenia is caused by a defect in the thrombopoietin receptor c-Mpl, while X-linked thrombocytopenia is caused by a defect in *GATA-1*. Patients with mild or moderate platelet function defects often respond to DDAVP, but more severe bleeding may necessitate platelet transfusions.

Chronic Thrombocytopenic Syndromes

Patients with long-standing thrombocytopenia usually present with mucocutaneous bleeding. Mechanisms of the thrombocytopenia include impaired marrow synthesis, sequestration, and increased destruction (see Fig. 38.8). These can be acquired or congenital. The **congenital thrombocytopenic syndromes** usually manifest at the time of birth or early in infancy. These syndromes may be associated with congenital anomalies (thrombocytopenia–absent radius syndrome and Fanconi anemia) or as part of a complex hereditary syndrome

(Wiskott–Aldrich syndrome with small platelets, eczema, and immunodeficiency) in addition to thrombocytopenia. Small platelets are a frequent finding in many of the syndromes associated with decreased platelet production. During the physical examination of patients with suspected congenital thrombocytopenia, the clinician must search not only for the signs of bleeding but also for subtle congenital anomalies, including abnormal growth parameters, the presence of skin hyperpigmentation or café-au-lait spots, and anomalies of the limbs, axial skeleton, and urinary tract.

The **acquired causes of thrombocytopenia** resulting from decreased production usually have an insidious onset of symptoms and are often associated with other abnormalities in the blood count. The aplastic syndromes (congenital aplastic anemia and acquired aplastic anemia) are associated with the gradual onset of thrombocytopenia, usually in association with a falling granulocyte count and anemia. Platelets are small, and the mean corpuscular volume is usually elevated.

Infiltration of the marrow by malignant cells or storage cells interferes with normal thrombopoiesis and commonly results in thrombocytopenia. Common malignancies associated with thrombocytopenia include acute lymphoblastic leukemia, lymphomas, Langerhans cell histiocytosis, and metastatic solid tumors (neuroblastoma). Abnormalities of other blood elements, as well as findings of adenopathy, hepatosplenomegaly, or masses, are clues to the presence of an infiltrative disorder.

Disorders of the vessel walls may present either acutely or chronically. Vasculitic disorders often manifest with lesions of the skin and mucous membranes that appear hemorrhagic and are associated with clinical symptoms related to involvement of other organ systems (gastrointestinal, renal, central nervous system). Paradoxically, patients with these disorders usually have normal coagulation studies and normal platelet counts. Henoch–Schönlein purpura is an example; it manifests with a purpuric rash, including both petechiae and larger palpable purpuric lesions of the lower extremities and buttocks, often found in association with arthritis, cramping abdominal pain, and focal glomerulonephritis.

Petechiae and ecchymoses are also common symptoms of disorders of the collagen matrix. Patients with Ehlers–Danlos syndrome have lax joints, hyperelastic skin, and abnormal wound healing. These patients frequently present with ecchymoses and rarely with petechiae. Bleeding time is usually prolonged and the diagnosis is made on the basis of clinical findings.

DEEP BLEEDING

Bleeding into the tissues of the muscles or joints is characteristic of hemophilia. The presentation of the patient with hemophilia varies with severity, age, and exposure to trauma. Only 30% of boys with hemophilia bleed excessively at circumcision, while neonatal intracranial bleeding is rare despite the trauma of a vaginal delivery. After the neonatal period, children with hemophilia usually present as toddlers with either intramuscular hematomas or hemarthroses. In the toddler stage, the most commonly affected joints are the ankles and elbows; the knees, hips, and shoulders are affected later. The affected children, who are usually boys, bruise easily and hematomas frequently develop over areas of common trauma (the forehead, arms, and legs, especially pretibial). Other common bleeding sites include the frenulum and sites of venipuncture. Sites of life-threatening bleeding include the central nervous system (the most common cause of death from hemorrhage); the mouth and throat, resulting in airway obstruction; and the retroperitoneal area or gastrointestinal tract, leading to exsanguination.

Red flags for the diagnosis of hemophilia are:

- Persistent bleeding after circumcision
- Hemarthrosis/intramuscular hematoma
- Bleeding frenulum

The deficiency of factor 8 (hemophilia A) or factor 9 (hemophilia B) causes bleeding because delayed thrombin formation results in a large, friable clot. Often there is an initial hemostatic plug that breaks down hours after the injury (secondary bleeding). Because factors 8 and 9 are necessary for normal wound healing, patients with inadequate replacement or untreated hemophilia frequently have poorly healed wounds.

Hemophilia A occurs in 1/10,000 live births and hemophilia B in about 1/40,000. The PTT is prolonged and should correct on 1:1 mix with normal plasma. Specific assays for factors 8 and 9 should be performed to identify the deficient factor. Severity is determined by the level of the deficient clotting factor. Severe hemophilia is defined as less than 1% factor activity, moderate as 1-5% activity, and mild as greater than 5% activity. These factor levels correlate approximately with clinical symptoms: Patients with severe deficiency bleed spontaneously; patients with moderate deficiency bleed with minor trauma; and patients with mild deficiency bleed only after significant trauma, and their condition may go undiagnosed for many years. Because hemophilias A and B are transmitted as X-linked traits, the family history may be informative if there is a history of male maternal relatives with a bleeding disorder. Approximately 33% of affected patients have new mutations and therefore have a negative family history. Bleeding complications have occurred in female carriers, especially at surgery; thus, all carriers should have factor levels measured.

Treatment of hemophilia requires prompt replacement or correction of the deficient factor with the safest available material. Table 38.7 provides dosing information and therapeutic alternatives for factors 8 and 9 deficiency. Treatment of bleeding episodes should be continued until the wound has healed. Recombinant factor 8 or 9 concentrate appears to be the current optimal treatment product, with purified plasma-derived factor as a 2nd choice. Long-acting factor products are being developed and may improve quality of life by reducing the frequency of infusions. For patients with mild hemophilia A who respond to DDAVP with adequate levels, DDAVP is the treatment of choice. Prophylaxis with factor concentrates has revolutionized the care of children with hemophilia by preventing chronic arthropathy and muscular atrophy. Patients with hemophilia should be monitored at comprehensive treatment centers that are experienced in the medical, social, physical, and financial impact of hemophilia care.

The common complications of hemophilia treatment can be divided into those of immunologic origin and those caused by infectious organisms. In 15-25% of patients with hemophilia A and a smaller percentage of patients with hemophilia B, inhibitors to clotting factor replacement material develop. These inhibitors, usually IgG antibodies, lead to rapid inactivation and clearance of infused replacement material. The presence of an inhibitor should be suspected and tested for in any patient with hemophilia who does not respond appropriately to factor replacement. The treatment of patients with inhibitors is problematic and should be relegated to experts in hemophilia care. The management of acute bleeding episodes may require administration of an activated clotting factor concentrate to "bypass" the inhibitor.

Infectious complications of hemophilia therapy were once exceedingly common but, fortunately, have been curtailed by donor screening, sophisticated viral inactivation processes, and chemical purification techniques used in the preparation of plasma-derived replacement material. Recombinant factor concentrates represent the culmination of these efforts. Older patients treated before 1983 with concentrates were exposed to HIV, hepatitis C, and sometimes to hepatitis B. Most

patients exposed to HIV became infected and manifested the spectrum of signs and symptoms of HIV infection. Viral inactivation techniques in conjunction with intense donor screening for hepatitis C antibody have greatly decreased the risk for hepatitis C exposure. Nevertheless, chronic non-A, non-B hepatitis is a common finding in older patients with hemophilia who were treated with concentrates.

The need for intravenous access to provide factor infusions creates another complication with the use of indwelling central venous catheters to facilitate factor delivery to young children with poor venous access. While some patients can be treated with less frequent dosing through peripheral veins, some patients undergo surgery for placement of a central venous catheter. Although these catheters undoubtedly increase adherence to prophylactic treatment, they can serve as a nidus for infection, thrombosis, or lead to complications due to surgery required for insertion or removal.

Surgical Bleeding

Aside from technical causes, most surgical bleeding results from a failure to recognize a preexisting coagulopathy. Von Willebrand disease and primary or secondary platelet dysfunction are the most common causes of bleeding after ear, nose, and throat surgery. Significant hemorrhaging after general surgery is often a manifestation of previously undiagnosed mild or moderate hemophilia or vitamin K deficiency.

When elective surgery is planned, the decision to perform preoperative hemostatic screening is influenced by the patient's age (and therefore previous exposure to trauma), personal and family histories of bleeding, and type of surgery. Certain surgeries, such as tonsillectomy, scoliosis repair, and central nervous system surgery, provide major challenges to hemostasis, having a high frequency of bleeding complications. In contrast, most general surgical procedures, such as hernia repair, rarely involve clinical bleeding. The diagnostic yield of preoperative studies before tonsillectomy and adenoidectomy remains controversial.

GENERALIZED BLEEDING

Generalized bleeding is a manifestation of a major disorder of hemostasis, usually caused by a deficiency of multiple factors in association with deficient or dysfunctional platelets. Generalized bleeding occurs most commonly in the context of DIC in seriously ill patients.

Disseminated Intravascular Coagulation

DIC is a generalized consumption of clotting factors, anticoagulant proteins, and platelets triggered by a life-threatening illness and usually accompanied by ischemia, hypoxia, and shock (Table 38.8). DIC may be either a hemorrhagic or a thrombotic disorder, or both, inasmuch

TABLE 38.8 Causes of Disseminated Intravascular Coagulation Infection

Infection
Meningococcemia (purpura fulminans)
Other gram-negative bacteria (*Haemophilus* species, *Salmonella* species, *Escherichia coli*)
Gram-positive bacteria (group B streptococci, staphylococci)
Rickettsiae (Rocky Mountain spotted fever)
Virus (cytomegalovirus, herpes, hemorrhagic fevers)
Malaria
Fungus

Tissue Injury
Central nervous system trauma (massive head injury)
Multiple fractures with fat emboli
Crush injury
Profound shock or asphyxia
Hypothermia or hyperthermia
Massive burns

Malignancy
Acute promyelocytic leukemia
Acute monoblastic or myelocytic leukemia
Widespread malignancies (neuroblastoma)

Venom or Toxin
Snake bites
Insect bites

Microangiopathic Disorders
"Severe" thrombotic thrombocytopenic purpura or hemolytic uremic syndrome
Giant hemangioma (Kasabach–Merritt syndrome)

Gastrointestinal Disorders
Fulminant hepatitis
Severe inflammatory bowel disease
Reye syndrome

Hereditary Thrombotic Disorders
Antithrombin deficiency
Homozygous protein C deficiency

Neonatal Disorders
Maternal toxemia
Group B streptococcal infections
Abruptio placentae
Severe respiratory distress syndrome
Necrotizing enterocolitis
Congenital viral disease (cytomegalovirus, herpes)
Erythroblastosis fetalis

Miscellaneous Disorders
Severe acute graft rejection
Acute hemolytic transfusion reaction
Severe collagen vascular disease
Kawasaki disease
Heparin-induced thrombosis
Infusion of "activated" prothrombin complex concentrates
Hyperpyrexia/encephalopathy, hemorrhagic shock syndrome

Modified from Montgomery RR, Scott JP. Hemostasis: disease of the fluid phase. In: Nathan DG, Oski FA, eds. *Hematology of Infancy and Childhood*. 4th ed. Philadelphia: WB Saunders; 1993;2:1639.

as the clinical manifestations of this generalized coagulopathy are highly variable. Laboratory studies usually demonstrate a prolonged PT, decreased fibrinogen level, and decreased platelet level (these are the most reliable indicators of DIC), in addition to elevated D-dimer levels and a prolonged PTT.

Several mechanisms can trigger acute DIC, including widespread endothelial damage induced directly or indirectly by infectious organisms and release of procoagulant material after trauma. Virtually any life-threatening illness can trigger DIC. In acute DIC, activation of the clotting mechanism leads to consumption of clotting factors (1, 2, 5, 8), anticoagulant proteins (C, S, AT, plasminogen), and platelets. In the syndrome known as purpura fulminans, microvascular thromboses develop in the skin, causing painful purpuric lesions that progress to localized necrotic lesions. Table 38.9 presents laboratory findings in DIC in comparison with those in other acquired coagulopathies that potentially could be confused with DIC. Because DIC is virtually always seen in a child with a life-threatening illness, the clinical diagnosis is usually made on the basis of the child's clinical appearance in association with laboratory abnormalities. Clotting factor and anticoagulant protein levels are confirmatory but seldom necessary to reach a diagnosis of DIC. The only diagnosis difficult to differentiate from DIC in the laboratory is that of severe hepatic disease with impending liver failure. The patient with severe liver disease is markedly jaundiced and the thrombocytopenia is relatively mild.

The treatment of DIC focuses on the cause of the DIC, on the altered homeostasis that sustains the coagulopathy, and on the bleeding or thrombotic complications that ensue. Shock itself plays a critical role in DIC because shock reduces the reticuloendothelial clearance of activated clotting factors and complexes. Reduced hepatic blood flow causes decreased synthesis of depleted clotting and anticoagulant proteins.

To summarize the treatment of DIC:

1. Treat the initiating and propagating events.
2. Optimize cardiorespiratory status by improving perfusion and correcting acidosis.
3. Replace deficient platelets, clotting factors, and anticoagulant proteins (Table 38.10) if needed. Specific indications for replacement are variable and depend on the patient's clinical condition and severity of bleeding.

The following are rough guidelines for treatment:

- Fresh-frozen plasma, 10-15 mL/kg every 6-12 hours, to provide clotting factors
- Platelets, ½-1 single donor apheresis unit for platelet count less than 50,000/mm^3
- Cryoprecipitate, 1 bag/5 kg for fibrinogen level less than 100 mg/dL
- Anticoagulant therapy for major vessel thrombosis

The efficacy of anticoagulant therapy in DIC has not been proved in controlled prospective studies. Heparin has been used for the

TABLE 38.9 Differential Diagnosis of Coagulopathies That Can Be Confused with Disseminated Intravascular Coagulation

	Prothrombin Time	Partial Thromboplastin Time	Fibrinogen	Platelets	Clinical Keys
DIC	Increased	Increased	Decreased	Decreased	Shock
Liver failure	Increased	Increased	Decreased	Normal or decreased	Jaundice
Vitamin K deficiency	Increased	Increased	Normal	Normal	Malabsorption, GI or liver disease
Sepsis without shock	Increased	Increased	Normal	Normal	Fever

DIC, disseminated intravascular coagulation; GI, gastrointestinal.

TABLE 38.10 Commonly Used Hemostatic Agents*

Component	Contents	Usual Dose	Comments/Disadvantages
FFP (unit)	1 U/mL of each clotting factor	10–15 mL/kg	Large volume Infectious risk
Cryoprecipitate (1 bag)	100 units factor 8/bag 150 mg fibrinogen/bag Factor 13, fibronectin	0.2 bag/kg	Infectious risk
Platelets (unit)	5.0–7.0 × 10^{10} platelets in 30–60 mL of plasma	½ – 1 single donor apheresis unit	Infectious risk
Factor concentrates (unit)	Units as labeled	Factor 8, 20–50 U/kg Factor 9, 30–130 U/kg	Recombinant
Desmopressin	4 μg/mL	0.3 μg/kg/dose	Increases factor 8 and VWF Improve platelet function Also used in uremia, liver disease Risk for hyponatremia (rare if fluid restriction observed)
AT concentrate	Units as labeled	(Desired AT – baseline AT) × weight (kg)/1.4	Plasma derived or recombinant available

*Key points to transfusion: (1) Determine deficiency state. (2) Use appropriate dose and material. (3) Measure response 1–2 hr and 24 hr after transfusion.

AT, antithrombin; FFP, fresh-frozen plasma; DDAVP, 1-deamino(8-D-arginine) desmopressin; VWF, von Willebrand factor.

TABLE 38.11 Comparison of Antithrombotic Agents

	Fibrinolytic Therapy	Standard Heparin	Low-Molecular-Weight Heparin	Warfarin
Indication	Recent onset of life- or limb-threatening thrombus	Thrombus of indeterminate age	Thrombus of indeterminate age	Long-term oral anticoagulation
Dose	rTPA, 0.1–0.2 mg/kg/hr IV	50 U/kg bolus, then 20–25 U/kg/hr continuous IV infusion	1 mg/kg SQ every 12 hr (1.5 mg/kg if <2 mo of age)	0.1–0.2 mg/kg/day PO
Adjustment	Increase dose for lack of clinical effect	Adjust dose by 5–10% every 6 hr until desired level or PTT achieved	Check level after 2nd or 3rd dose No further monitoring required once in goal range	Daily until stable INR
Course	1–72 hr	5–14 days	5 days–mo	Weeks to months
Monitor by:	"Lytic state" with D-dimer	PTT, 2–2.5× control value	Low-molecular-weight heparin level, 0.5–1.0	INR, 2.0–3.0
Mechanism	Activation of plasminogen to plasmin	Accelerates AT-dependent inactivation of factors 2a (thrombin) and 10	Accelerates AT-dependent inactivation of factor 10	Impairs vitamin K-dependent carboxylation of factors 2, 7, 9, 10
Risk for bleeding	Medium/high	Low	Low	Low

AT, antithrombin; INR, international normalized ratio; IV, intravenously; PO, per os (orally); PTT, partial thromboplastin time; rTPA, recombinant tissue-type plasminogen activator; SQ, subcutaneous; UK, urokinase.

treatment of purpura fulminans, acute promyelocytic leukemia, and thromboses that develop in conjunction with DIC. Most patients with DIC have a coagulopathy that consumes procoagulant proteins and causes clinical oozing or bleeding; in a small percentage of patients, however, thrombosis develops. In these patients, anticoagulant therapy may decrease morbidity and should be administered in a manner similar to that for those patients who have major vascular thrombosis (Table 38.11). Deficient clotting factors and platelets should be transfused to prevent further development of thrombosis or bleeding during anticoagulation.

Neonatal Purpura Fulminans

The differential diagnosis of a neonate who presents with multiple purpuric lesions over the buttocks, trunk, extremities, and face (nose, ears) that change from dark red to purple and black over a few minutes in association with abnormal neurologic findings or an abdominal mass includes sepsis with DIC and a generalized viral infection. A key finding in such a neonate for a homozygous protein C deficiency is the presence of painful petechiae and purpura (purpura fulminans). After viral and bacterial cultures, diagnostic studies should include a CBC and coagulation screening for DIC, as well as measurements of protein C, protein S, AT3, and plasminogen.

To confirm this diagnosis, the clinician must differentiate DIC from congenital protein C deficiency. DIC is characterized by the consumption of clotting factors, anticoagulant proteins, and platelets. Although protein C levels fall in DIC, patients with congenital protein C deficiency have strikingly low levels of protein C. Anticoagulant proteins are routinely consumed in situations of widespread activation of the clotting mechanism. Therefore, mildly depressed levels of protein S, AT3, and plasminogen would be expected when there is generalized intravascular coagulation. In congenital protein C deficiency, the protein C level is strikingly lower than that of the other anticoagulant proteins, which increases the likelihood that the deficiency of protein C represents the primary cause of the coagulopathy. To determine whether the deficiency is hereditary, the next step is to obtain blood samples from the parents to measure levels of the deficient protein or proteins. In homozygous deficiencies, the levels of both parents should be reduced. Deficiency of protein C, protein S, or AT usually manifests as venous thromboembolic disease in adulthood and is inherited as a co-dominant trait. Congenital severe, symptomatic protein C deficiency is usually inherited in an autosomal recessive manner from asymptomatic parents.

Therapy must be instituted promptly to replace the deficient anticoagulant protein with fresh-frozen plasma. Fresh-frozen plasma contains all of the clotting factors in an unconcentrated form. Protein C has a short half-life and may need to be infused every 6-12 hours to maintain measurable levels. This, unfortunately, leads to problems with fluid and protein overload if repeated doses of plasma are necessary. *Protein C concentrate* is now available as specific therapy for patients with protein C deficiency. The patient should also undergo anticoagulation with heparin to limit further thromboses. A striking improvement after administration of protein C, either as plasma or as concentrate, is strong evidence of the diagnosis. Warfarin therapy has been effective in managing such patients on a chronic basis.

Other Causes of Generalized Bleeding

A coagulopathy is a common complication of severe liver disease, resulting from deficient production of multiple clotting factors and anticoagulant proteins in association with increased D-dimer formed as a result of hyperfibrinolysis. This may contribute to inhibition of platelet function.

Uremia results in a diffuse bleeding diathesis, with mucosal bleeding (epistaxis, gastrointestinal bleeding) as a major manifestation. The major underlying mechanism in uremic bleeding appears to be increased nitric oxide generation, leading to abnormal platelet function. Many patients with bleeding caused by uremia or liver disease respond to DDAVP.

Vitamin K deficiency manifests as generalized bleeding into the skin, gastrointestinal tract, and central nervous system. Children at highest risk are breast-fed neonates, malnourished individuals, those receiving broad-spectrum antibiotics, those with cholestatic liver disease and subsequent vitamin K malabsorption, and those who have ingested rat poison (warfarin). The treatment of patients with vitamin K deficiency is parenteral vitamin K. The response is usually rapid, but in emergency situations, transfusion of fresh-frozen plasma corrects the coagulopathy faster. Differentiation of some of these syndromes from DIC is presented in Table 38.9.

THROMBOSIS

Thromboembolic disease in pediatrics has a bimodal age distribution. Venous and arterial thrombi are common in newborns, especially in premature neonates, because of the combination of low levels of anticoagulant proteins, decreased blood flow, elevated blood viscosity because of high hematocrit, and, in particular, because of the placement of intravascular catheters for monitoring and nutrition. The second peak of thromboembolic disease, usually venous in character, is in adolescence, when patients with primary deficiencies of anticoagulant proteins typically present and when secondary disorders (e.g., vasculitis, pregnancy, malignancy, surgery, major trauma, inflammatory bowel disease, and infection) induce a higher frequency of venous thrombosis.

Venous Thromboembolic Disease

Diagnostic Approach

Venous thromboembolic disease classically manifests with a warm, swollen, tender extremity or affected organ. The differential diagnosis in such cases includes trauma, infection, stasis without thrombosis, lymphedema, edema, and neoplasm. In children and adolescents, thrombi may develop within major internal organs with distinctive clinical manifestations, including sagittal sinus thrombosis with resultant increased intracranial pressure; hepatic vein thrombosis with the **Budd-Chiari syndrome**; portal vein thrombosis associated with splenomegaly and varices; and **renal vein thrombosis** with a resultant abdominal mass, hematuria, and proteinuria. Long-term central venous access is associated with a significant risk for asymptomatic venous thrombosis. **Pulmonary emboli** may manifest as "atypical" pneumonia resulting in shortness of breath and hypoxemia in the absence of fever. The hypoxemia may occur in the presence of minimal findings on routine chest radiographs.

The clinician should obtain a careful history for antecedent trauma, infection, or other predisposing causes of thromboembolic disease (Table 38.12). The abdomen and extremities should be carefully examined for mass lesions leading to venous stasis. The presence of a bruit or hemihypertrophy of the affected limb is a clue to an arteriovenous malformation. In addition, masses within the bone, abdominal tumors, and lymphatic obstruction should be considered. Initial laboratory studies should include a CBC, platelet count, and evaluation for DIC, as well as cultures of the blood if the patient is febrile. During the process of a localized thrombosis, there may be consumption of clotting factors, but rarely is the consumption significant enough in older children and adults to induce abnormal results on routine coagulation screening tests (platelets, PT, PTT, fibrinogen). Tests for fibrin breakdown (D-dimer) may be positive. Unfortunately, these tests are nonspecific and not necessarily diagnostic of vascular thrombosis. Studies in adults have indicated that a negative assay for D-dimer has a strong negative predictive value for pulmonary embolus, especially when combined with an algorithm for risk assignment. The diagnostic approach to a patient with suspected venous thrombosis is presented in Fig. 38.9.

Specific Diagnostic Studies

Compression ultrasonography is generally used to assess for the presence of a lower extremity thrombosis and many episodes of upper extremity thrombosis. While ultrasound with Doppler flow studies to look at flow of red blood cells through arteries or veins may be sufficient for diagnosis of renal or hepatic thrombosis as well, consideration should be given to other modalities, including computed tomography (CT) scan, echocardiogram, and venography. Magnetic resonance imaging and magnetic resonance venography can be useful in diagnosis of venous dural sinus thrombosis.

TABLE 38.12 Hypercoagulable States

Primary Disorders (Congenital)

Factor V Leiden (activated protein C resistance)
Prothrombin 20210 mutation
Protein C deficiency
Protein S deficiency
Antithrombin deficiency
Plasminogen deficiencies
Homocystinuria
Dysfibrinogenemia

Secondary Disorders (Acquired)

Coagulopathies

Lupus anticoagulant (antiphospholipid syndrome)
Nephrotic syndrome
Oral contraceptives
Malignancy
Therapy with activated prothrombin complex concentrates
Pregnancy
Autoimmune disorders

Platelet Disorders

Diabetes mellitus
Myeloproliferative disorders
Thrombocythemia
Paroxysmal nocturnal hemoglobinuria

Flow and Vessel Disorders

Polycythemia-hyperviscosity
Marfan syndrome
Vasculitis
Vessel grafts
Vascular stasis
Trauma
Indwelling catheters
Surgery
Immobilization

Modified from Schafer A. The hypercoagulable states. *Ann Intern Med.* 1985;102:814; and from Behrman RE, Kliegman RM, eds. *Nelson Essentials of Pediatrics.* 2nd ed. Philadelphia: WB Saunders; 1994:56.

If pulmonary embolism is suspected, a spiral CT scan is the diagnostic study of choice. CT scan is indicated in any patient with a venous thrombosis, cardiac and/or respiratory symptoms, including tachycardia, tachypnea, and hypoxia. Pulmonary embolism may be present without significant respiratory distress, and should be considered in patients with chest pain or hemoptysis, particularly following surgery and immobilization.

Thrombophilia Testing

In children, the diagnosis of venous thrombosis in the setting of risk factors, such as surgery, immobilization, or catheter placement, does not generally warrant any additional work-up. Adult guidelines specifically recommend against thrombophilia testing in thrombosis in the setting of major transient risk factors. *An unprovoked thrombosis merits work-up for a congenital or acquired thrombophilic condition.*

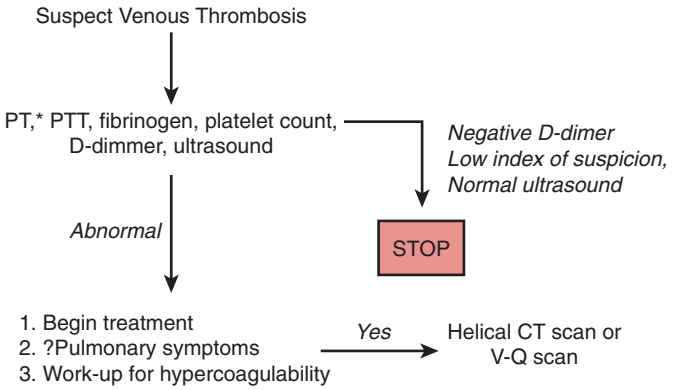


FIGURE 38.9 Flow diagram for the approach to a patient with venous thromboembolic disease. *See Table 38.12. The INR corrects the PT for institutional differences in reagents and instruments. When a patient is taking a stable warfarin dosage, the INR is calculated by a ratio of the patient's PT to the control PT raised to a correction factor (the International Sensitivity Index) that allows for comparison of different PT reagents and machines in different laboratories. For all patients receiving chronic warfarin therapy, their anticoagulant therapy should be measured as the INR. The INR level should be maintained between 2.0 and 3.0 for effective, safe anticoagulant therapy. An INR exceeding 3.0 has been associated with increased risk for bleeding without improved therapeutic effects for patients with venous thromboembolic disease. CT, computed tomography; PT, prothrombin time; PTT, partial thromboplastin time; V-Q, ventilation-perfusion.

The most severe inherited thrombophilias are deficiencies of anticoagulant proteins C, S, and AT. Although rare, these are associated with a higher relative risk for thrombosis than the more common thrombophilias. Levels of protein C, AT3, and plasminogen may be depleted after development of deep vein thrombosis, pulmonary emboli, or both; low levels do not necessarily imply a congenital deficiency. If low levels are found, studies should be performed on the parents to establish the inheritance of the deficiency because all these are inherited as autosomal co-dominant traits. The patient's levels should be re-evaluated several months after the acute event; the clinician should remember that warfarin reduces functional levels of all the vitamin K-dependent proteins, including proteins C and S.

Less severe, but more common, thrombophilias include **factor 5 Leiden and the prothrombin gene mutation**. These occur in up to 5% of the US population and have a lower relative risk for thrombosis. Testing of asymptomatic family members is not generally required, although affected females should be counseled to avoid estrogen-containing oral contraceptives due to a higher risk for thrombosis.

The **lupus anticoagulant** causes a prolonged PTT that fails to correct on mixing with normal plasma because of the presence of an antibody that reacts with the phospholipid reagent in the PTT. The lupus anticoagulant does not bind in vivo to the platelet membrane; thus, the whole blood clotting time is normal. Paradoxically, the lupus anticoagulant is associated with venous and arterial thromboembolic disease and spontaneous abortions but is usually not a cause of clinical bleeding. If these study findings are negative, the thrombin time should be measured or a comparison of functional and antigenic levels of fibrinogen should be done to detect a dysfibrinogenemia.

Arterial Thrombosis

Arterial thrombi are rare in older children and adolescents and are frequently a manifestation of a systemic disorder resulting in vascular damage or embolic disease such as sickle cell anemia, Kawasaki disease, bacterial endocarditis, periarteritis nodosa, homocystinuria, or cocaine ingestion. The presence of an intraarterial catheter is an obvious nidus for thrombosis. Neck trauma that is often mild can cause carotid or vertebral artery dissection or aneurysms. These dissections or aneurysms can result in emboli to the brain. A history of neck trauma should be sought in older children who present with arterial stroke.

Anticoagulant Therapy

Heparin

Heparin is the most commonly used agent for the initial treatment of venous or arterial thrombosis. Heparin functions as an anticoagulant by binding to AT3 and accelerating the AT3-dependent inactivation of thrombin and factor 10a, as well as of factors 9a and 11a. Although most studies of heparin pharmacokinetics have been performed in adults, there are important differences in the pharmacologic features of heparin in children and especially neonates. Thirty-nine percent of children achieve a prolongation of the PTT within the target range after a bolus dose of 50 U/kg. Children younger than 1 year require an average of 28 U/kg/hr to maintain a therapeutic level of the PTT. In contrast, most children older than 1 year are satisfactorily maintained on 20 U/kg/hr of heparin. One protocol recommends an initial bolus of 50 U/kg of heparin, with 20-25 U/kg/hr for a minimum of 5 days to maintain a PTT of approximately 2-2.5 times the control value. The heparin dose should be adjusted every 4-6 hours until a satisfactory level is attained. Reports in adults suggest that the heparin level is superior for monitoring heparin therapy. Studies have documented an increased risk for recurrent thrombi in patients who failed to achieve adequate anticoagulant levels promptly. Heparin levels are especially useful in premature and full-term newborns who may have a "normal" prolonged PTT. A therapeutic range of 0.3-0.6 U/dL appears to be effective.

Low-molecular-weight (LMW) heparin provides an alternative to standard heparin therapy. Pediatric experience with LMW heparin given subcutaneously is similar to that in adults. LMW heparin given to infants and children with thromboses appears to be as effective as standard heparin, with a similar or reduced risk for bleeding. LMW heparin requires much less laboratory monitoring. The therapeutic dose of the LMW heparin enoxaparin in pediatrics is 1.5 mg/kg for neonates and 1.0 mg/kg every 12 hours for older children.

For long-term anticoagulant therapy, warfarin can be started after the institution of heparin therapy. Total length of therapy for provoked clots should not exceed 3 months, while therapy for unprovoked clots may extend to 6-12 months or indefinitely, depending on the presence of other prothrombotic conditions.

Fibrinolytic Therapy

Fibrinolytic therapy is indicated for serious and potentially life-threatening thrombosis because it provides a more rapid lysis of clots than standard anticoagulant treatment with heparin and is clinically effective in both arterial and venous clots. Because bleeding complications are many times higher than those with heparin in older individuals, the clinical severity of the clot must justify the use of lytic therapy. For smaller thrombi or those in nonvital locations, heparin is safe and effective. Lytic therapy is best used early in the evolution of the thrombus. If the clot has been long-standing, it is unlikely that fibrinolytic therapy will be efficacious.

The presence of any intracranial process, recent major surgery, or recent significant bleeding is an absolute contraindication to fibrinolytic therapy and a relative contraindication to heparin treatment. In patients with a normal cranial sonogram (or CT) and complete occlusion of the aorta or evidence of compromise of major organ function, fibrinolytic therapy has been safely and successfully administered with very careful monitoring. Table 38.11 outlines dose and monitoring studies for 2 commonly used fibrinolytic agents: recombinant TPA and

urokinase. Fibrinolytic therapy appears to result in a more rapid return of pulmonary artery flow after pulmonary emboli and may decrease the likelihood of postphlebitic syndrome after deep vein thrombosis.

Warfarin

Warfarin remains the anticoagulant of choice for long-term oral therapy. Newer oral agents available are less well studied in children. Warfarin acts by blocking the vitamin K–dependent post-translational modification of factors 2, 7, 9, and 10 and of protein C and protein S. The usual dose is 0.1-0.2 mg/kg/day. Younger children appear to require higher doses to achieve a therapeutic level of the international normalized ratio (INR). If warfarin therapy is started early in the course of heparin therapy for thrombotic disease, effective oral anticoagulant effect is often achieved by day 5, at which time levels of all the vitamin K–dependent factors should be depressed by warfarin. Early in the course of treatment with warfarin, the PT is affected first because factor 7 has the shortest half-life of the vitamin K–dependent procoagulants and factor 7 levels fall briskly after warfarin treatment. The aim of warfarin therapy for venous thromboembolic disease is to achieve a stable INR of 2.0-3.0.

For prevention of embolization from prosthetic valves, a higher INR may be preferable. Patients with protein C or protein S deficiency are at risk for warfarin-induced skin necrosis when warfarin therapy is initiated, particularly if high doses are used. These individuals should be given heparin before warfarin is started, and they should not receive a loading/high dose of warfarin.

Warfarin may be reversed by administration of either intravenously (IV) or oral vitamin K. Although IV vitamin K may work slightly faster, response rates at 24 hours are identical and IV vitamin K carries the associated risk for over-correction and prolonged subtherapeutic INRs. Therefore oral administration is preferable for non–life-threatening bleeding.

SUMMARY AND RED FLAGS

Bleeding and thrombotic problems are often familial but may be acquired. A family history and personal history that quantitate bleeding episodes are of utmost help in planning an evaluation. Red flags include anemia; signs of end-organ bleeding or vascular occlusion, particularly the central nervous system; signs of a systemic disorder (pancytopenia, hypotension, rash, weight loss, chronic fever, liver-renal-pulmonary system involvement); and signs of hemorrhagic shock.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

General

Andrew M. The relevance of developmental hemostasis to hemorrhagic disorders of newborns. *Semin Perinatol*. 1997;21:70-85.

Burk CD, Miller L, Handler SD, et al. Preoperative history and coagulation screening in children undergoing tonsillectomy. *Pediatrics*. 1992;89:691-695.

Mann KG, Brummel-Ziedens K. Blood coagulation. In: Orkin SH, Nathan DG, Ginsburg D, eds. *Nathan and Oski's Hematology of Infancy and Childhood*. 7th ed. Philadelphia: Saunders; 2009.

Rydz N, James PD. Why is my patient bleeding or bruising? *Hematol Oncol Clin North Am*. 2012;26:321-344.

Scott JP. Hemorrhagic and thrombotic diseases. In: Kliegman RM, Stanton BF, St Geme JW, et al., eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Saunders; 2016.

Coagulopathy

Kaufman RJ, Powell JS. Molecular approaches for improved clotting factors for hemophilia. *Blood*. 2013;122:3568-3574.

Leissinger C, Gringeri A, Antmen B, et al. Anti-inhibitor coagulant complex prophylaxis in hemophilia with inhibitors. *N Engl J Med*. 2011;365:1684-1692.

Malfait F, De Paepe A. Bleeding in the heritable connective tissue disorders: mechanisms, diagnosis, and treatment. *Blood Rev*. 2009;23:191-197.

Montgomery RR, Gill JC, Di Paola J. Hemophilia and von Willebrand disease. In: Orkin SH, Nathan DG, Ginsburg D, eds. *Nathan and Oski's Hematology of Infancy and Childhood*. 7th ed. Philadelphia: Saunders; 2009.

Pipe SW, Goldenberg NA. Acquired disorders of hemostasis. In: Orkin SH, Nathan DG, Ginsburg D, eds. *Nathan and Oski's Hematology of Infancy and Childhood*. 7th ed. Philadelphia: Saunders; 2009.

Robertson J, Lillicrap D, James PD. Von Willebrand disease. *Pediatr Clin North Am*. 2008;55:377-392.

Sharathkumar AA, Carcao M. Clinical advances in hemophilia management. *Pediatr Blood Cancer*. 2011;57:910-920.

Wada H, Thachil J, Di Nisio M, et al. Guidance for diagnosis and treatment of disseminated intravascular coagulation from harmonization of the recommendations from three guidelines. *J Thromb Haemost*. 2013;11:761-767.

Platelets

Israels SJ, Kahr WAH, Blanchette VS, et al. Platelet disorders in children: a diagnostic approach. *Pediatr Blood Cancer*. 2011;56:975-998.

Kuter DJ. The biology of thrombopoietin and thrombopoietin receptor agonists. *Int J Hematol*. 2013;98:10-23.

Lambert MP, Poncz M. Inherited platelet disorders. In: Orkin SH, Nathan DG, Ginsburg D, eds. *Nathan and Oski's Hematology of Infancy and Childhood*. 7th ed. Philadelphia: Saunders; 2009.

Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*. 2011;117:4190-4207.

Peterson JA, McFarland JG, Curtis BR, et al. Neonatal alloimmune thrombocytopenia: Pathogenesis, diagnosis, and management. *Br J Haematol*. 2013;161:3-14.

Thrombosis

Agnelli G, Becattini C. Acute pulmonary embolism. *N Engl J Med*. 2010;363:266-274.

Giannakopoulos B, Krilis SA. The pathogenesis of the antiphospholipid syndrome. *N Engl J Med*. 2013;368:1033-1044.

Goldenberg NA, Bernard TJ. Venous thrombosis in children. *Hematol Oncol Clin North Am*. 2010;24:151-166.

Holzhauer S, Goldenberg NA, Junker R, et al. Inherited thrombophilia in children with venous thromboembolism and the familial risk of thromboembolism: an observational study. *Blood*. 2012;120:1510-1515.

Klaaasen ILM, van Ommen CH, Middeldorp S. Manifestations and clinical impact of pediatric thrombophilia. *Blood*. 2015;125:1073-1077.

Leys D, Lucas C, Gobert M, et al. Cervical artery dissections. *Eur Neurol*. 1997;37:3-12.

Raffini L, Trimarchi T, Beliveau J, et al. Thromboprophylaxis in a pediatric hospital: a patient-safety and quality-improvement initiative. *Pediatrics*. 2011;127:e1326-e1332.

Yang JYK, Chan AKC. Pediatric thrombophilia. *Pediatr Clin N Am*. 2013;60:1443-1462.

Therapy

Goel R, Vedantham S, Goldenberg NA. Antithrombotic therapies: anticoagulation and thrombolysis. *Pediatr Clin N Am*. 2013;60:1463-1474.

Monagle P, Chan AKC, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis. 9th ed. American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141:e737S-e801S.

Roach ES, Golomb MR, Adams R, et al. Management of stroke in infants and children: a scientific statement from a special writing group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young. *Stroke*. 2008;39:2644-2691.

van Es N, Coppens M, Schulman S, et al. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. *Blood*. 2014;124:1968-1975.

39

Fever

Patricia S. Lye and Emily M. Densmore

Two-thirds of all children visit a physician for fever before they reach the age of 2 years. Fever in the pediatric population is usually grouped into 4 categories:

- Fever in the neonate
- Fever with localizing signs
- Fever without source (FWS)
- Fever of unknown origin (FUO)

PATHOPHYSIOLOGY OF FEVER

Temperature is controlled by the thermoregulatory center, located in the preoptic area of the anterior hypothalamus. The thermoregulatory center receives input from peripheral receptors and the temperature of the blood bathing the hypothalamus and acts on autonomic, endocrine, and behavioral mechanisms to maintain the body temperature at a particular set point. The hypothalamic set point normally maintains body temperature around 37°C, but there can be significant variation among individuals. Normal temperatures range from 36-37.8°C, depending on the time of day, with the peak in the afternoon (5-7 P.M.) and the trough in the early morning (2-6 A.M.). Although the circadian rhythm is not well established in infancy, it becomes more reliable by the 2nd year of life.

The febrile response not only produces an elevation in body temperature but also causes physiologic changes that enhance the individual's ability to eliminate infection. Production of acute-phase reactants and alterations in metabolism and endocrine function are examples of these changes. **Acute-phase reactants**—proteins that are produced in response to infection or injury—include ceruloplasmin, C-reactive protein, haptoglobin, amyloid A, complement, and fibrinogen. Hormones and cytokines, some of which are endogenous pyrogens, regulate the production of acute-phase proteins. Exogenous pyrogens, such as bacteria or endotoxins, generate the production of endogenous pyrogens, which play a vital role in prostaglandin-related set point elevation and regulation of acute-phase responses.

Fever results when the thermoregulatory set point is elevated above the normal set point; the hypothalamus then generates physiologic changes involving endocrine, metabolic, autonomic, and behavioral processes. Diversion of blood from peripheral vessels to central vessels causes coolness of the extremities but helps increase core temperature. Shivering increases metabolic activity and heat production. The affected patient may feel cold and seek a warmer environment or add clothing to feel warmer and prevent heat loss. Once these processes have resulted in increasing the core temperature to match the elevated set point, the thermoregulatory center works to maintain the temperature as it does during normothermia. The thermoregulatory point returns to normal once the infection is resolved. The hypothalamus then produces physiologic changes to decrease the core temperature; these include sweating, dilation of cutaneous blood vessels, and the sensation of feeling hot, which may lead to behaviors such as removing clothing or seeking a cooler environment.

Fever has both positive and negative effects. High body temperatures may impair the reproduction and survival of some invading microorganisms by decreasing required nutrients, such as free iron, or by increasing immunologic responses such as phagocytosis. However, at extremely high temperatures, immunologic responses may be impaired. Fever increases the basal metabolic rate by 10-12% for each degree Celsius elevation of temperature. This increases oxygen consumption, carbon dioxide production, and fluid and caloric needs. Fluid requirements increase 100 mL/m^2/day for each 1°C rise in temperature above 37.8°C.

Heat illness must be distinguished from fever as a cause for elevated body temperature. In heat illness, there is an unregulated rise in body temperature, despite the fact that the hypothalamic set point is normal. It can result from excessive heat production or inadequate heat dissipation. Temperatures may reach extreme heights and can result in multiorgan dysfunction and death. Restoration of normal body temperature in heat illness is mandatory (Table 39.1).

FEVER WITHOUT SOURCE

A child with fever of recent onset with no obvious historical or physical explanation for the fever is said to have fever without source (FWS). Bacterial pathogens account for a small but clinically significant number of cases. The risk of bacterial infection decreases with increasing age and is highest for infants less than 3 months of age, compared to infants and toddlers 3-36 months of age, and even lower for children over the age of 36 months. Most of the patients in all age groups have a self-limited viral illness. The challenge is to identify which children have fever caused by bacterial pathogens, or other pathogens requiring treatment, in order to avoid the morbidity and mortality associated with delayed treatment, balanced against the risks of testing or treatment when neither is needed. Bacterial infection must be considered in immunocompromised patients or those with central lines or shunts. Studies in adults suggest that patients with high fever (>105°F) and rigors have a higher risk of bacterial infection; exceptions to this include influenza and adenoviral infections.

TABLE 39.1 Causes of Hyperthermia

Excessive Heat Production
Exertion
Heat stroke (exertion)
Malignant hyperthermia (anesthesia induced)
Neuroleptic malignant syndrome
Catatonia
Tetanus
Status epilepticus
Delirium
Endocrine disorders (hyperthyroidism, pheochromocytoma)
Drugs (cocaine, amphetamines, ephedrine, phencyclidine, tricyclic antidepressants, LSD, lithium, thyroid hormone, salicylates)

Diminished Heat Dissipation
Heat stroke
Occlusive dressings
Dehydration
Extensive burns (including severe sunburn)
Anhidrotic ectodermal dysplasias
Anticholinergic-like drugs (atropine, antihistamines, phenothiazines, tricyclic antidepressants)
Autonomic neuropathy
Spinal cord level paralysis (spinal crisis)
Possible overbundling (especially in a warm environment)
Therapeutic hyperthermia

Hypothalamic Dysfunction*
Stroke
Encephalitis
Granulomatous processes (sarcoid, tuberculosis, eosinophilic)
Trauma
Central: idiopathic
Phenothiazines
Hemorrhage

*Usually associated with hypothermia.
LSD, lysergic acid diethylamide.

◆ History

A detailed history may reveal a potential source for infection. A complete history addresses several important issues: (1) onset and duration of fever; (2) degree of temperature; (3) by what method and in which anatomic site the temperature was taken; (4) medications given, including antipyretics, antibiotics, or home remedies; (5) environmental exposures; (6) associated symptoms; (7) ill contacts; (8) recent immunizations, and (9) recent travel. Inquiry into the child's medical history may reveal important information such as recurrent febrile illnesses, primary or acquired immunodeficiency, or medications such as chemotherapy that alter host defenses.

Fever: Temperature Measurement

Rectal temperature measurement is considered to be the gold standard for children 3 years of age or younger. The most widely accepted definition of fever is rectal temperature of 38°C (100.4°F) or higher. It is important to consider that infants, especially those younger than 2 months of age, may have a blunted febrile (or hypothermic) response to infection. Hence, lack of fever should not be used as a criterion for ruling out infection in infants. Although rectal temperature measurement is the gold standard, it should be avoided in neutropenic immunocompromised patients, in whom rectal manipulation may seed the blood with bacteria.

Oral thermometry can be considered for cooperative patients who are older than 4-5 years of age. **Axillary temperatures** are commonly done and tympanic membrane and temporal artery temperatures are newer modalities with some studies examining their reliability. Axillary temperatures are less precise than rectal temperatures. There is a correlation between axillary and rectal temperature measurements; the axillary temperature is usually 0.5-0.85°C *lower*. **Tympanic membrane thermometers** are often inaccurate in children. **Temporal artery temperature** measurement correlates well with rectal temperature in some studies, but has been shown to be inferior when patients are febrile. It can be considered in settings when children are not likely to be febrile and are over 3 months of age. *When detection of fever is critical for diagnosis and management, rectal temperatures should be used in the child 3 years of age and younger.*

◆ Physical Examination

Many children will have a source for fever identified on their history and/or physical examination. If no focus of infection is found on the physical examination, the clinician must rely on history and observation to determine the appropriate next steps. The child may appear ill or well. Ill-appearing children are typically lethargic or irritable. They may show signs of shock, including weak peripheral pulses, tachycardia, poor perfusion, respiratory distress, mottling, cyanosis, or decreased mental status (Table 39.2). After thorough clinical and laboratory evaluation, ill-appearing children should be admitted to the hospital, and will likely need empiric antibiotic treatment.

Observational Scales

Infants and children with fever without source who do not appear ill create important decision processes in terms of evaluation and management. The physician's ability to make a hypothesis about the child's degree of illness, on the basis of observation, is critical in the evaluation. An objective scoring measure may be used in an effort to assess serious illness in young febrile children. The Acute Illness Observation Scale (AIOS) (Table 39.3), also known as the Yale Observation Score, is a 6-item predictive model graded on a scale of 1-5. Use of the AIOS in conjunction with the history and physical examination has a higher sensitivity for identifying serious illness than history and physical examination alone. The AIOS is most useful in patients younger than 24-36 months; *it has not been shown to provide sufficient data to identify serious illness in 4- to 8-week-old infants, and has not been evaluated in infants less than 4 weeks old.*

◆ Differential Diagnosis

Most children who present with fever without source (FWS) are subsequently determined to have a self-limited benign viral infection. In 1 study in 2-36 month old children who presented with FWS, 76% had 1 or more known pathogenic viruses found; 57% had adenovirus, human herpesvirus 6 (HHV-6: roseola), enterovirus, or parechovirus detected. Other identifiable viruses include respiratory syncytial virus, parainfluenza viruses, influenza viruses, varicella (chickenpox), human metapneumovirus and parvovirus (fifth disease/erythema infectiosum). Measles, mumps, and rubella are uncommon in developed countries but have been reported in epidemics following imported cases or in underimmunized communities. Although rapid testing for viral pathogens is often readily available, a detailed investigation to identify a viral pathogen is not necessary unless the confirmation of a viral infection will change the acute diagnostic plan; treatment with antivirals is an option (HSV, influenza) if the fever is prolonged and evolves into FUO or if there is end-organ involvement, as in hepatitis, myocarditis, encephalitis, or meningitis.

Most viral infections do not have simultaneous co-infection with a bacterial pathogen. Exceptions include croup due to parainfluenza

TABLE 39.2 International Consensus Definitions for Pediatric Sepsis

Infection	Suspected or Proven Infection or a Clinical Syndrome Associated with High Probability of Infection
SIRS	Two of 4 criteria, 1 of which must be abnormal temperature or abnormal leukocyte count: 1. Core temperature >38.5°C (101.3°F) or <36°C (96.8°F) (rectal, bladder, oral, or central catheter) 2. Tachycardia: Mean heart rate >2 SD above normal for age in absence of external stimuli, chronic drugs or painful stimuli or Unexplained persistent elevation over 0.5–4 hr or In children <1 yr old, persistent bradycardia over 0.5 hr (mean heart rate <10th percentile for age in absence of vagal stimuli, β-blocker drugs, or congenital heart disease) 3. Respiratory rate >2 SD above normal for age or acute need for mechanical ventilation not related to neuromuscular disease or general anesthesia 4. Leukocyte count elevated or depressed for age (not secondary to chemotherapy) or >10% immature neutrophils
Sepsis	**SIRS Plus a Suspected or Proven Infection**
Severe sepsis	Sepsis plus 1 of the following: 1. Cardiovascular organ dysfunction, defined as: Despite >40 mL/kg of isotonic intravenous fluid in 1 hr: • Hypotension <5th percentile for age or systolic blood pressure <2 SD below normal for age *or* • Need for vasoactive drug to maintain blood pressure or • 2 of the following: • Unexplained metabolic acidosis: base deficit >5 mEq/L • Increased arterial lactate: >2 times upper limit of normal • Oliguria: urine output <0.5 mL/kg/hr • Prolonged capillary refill: >5 sec • Core to peripheral temperature gap >3°C (5.4°F) 2. ARDS as defined by the presence of a Pa_{O_2}/Fi_{O_2} ratio ≤300 mm Hg, bilateral infiltrates on chest radiograph, and no evidence of left heart failure *or* Sepsis plus 2 or more organ dysfunctions (respiratory, renal, neurologic, hematologic, or hepatic)
Septic shock	Sepsis plus cardiovascular organ dysfunction as defined above
MODS	Presence of altered organ function such that homeostasis cannot be maintained without medical intervention

ARDS, acute respiratory distress syndrome; Fi_{O_2}, fraction of inspired oxygen; MODS, multiple organ dysfunction syndrome; Pa_{O_2}, partial pressure arterial oxygen; SIRS, systemic inflammatory response syndrome.

From Turner DA, Cheifetz IM. Shock. In: Kliegman RM, Stanton BF, St Geme JW III, et al, eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:522, Table 70.7.

virus, which may predispose to bacterial tracheitis and influenza, which may predispose to bacterial pneumonia. The sequence may be biphasic with viral symptoms followed by improvement, followed by worsening symptoms of the bacterial superinfection, or both phases may not be apparent as the child demonstrates no improvement or deterioration. Respiratory syncytial virus (RSV) may predispose patients to otitis media.

Noninfectious conditions manifesting with FWS are extremely rare. Historical clues (recurrences, chronicity) or systemic signs usually indicate malignancy or rheumatic disorders. If the history and physical examination are not suggestive, these diagnoses need not be pursued. Heat-related illness or drug ingestion may be considered if supported by the history. Fever caused by immunizations may not be accompanied by other signs or symptoms, but the history should suggest immunization as the cause.

Urinary Tract Infections (UTIs)

UTIs are the most common serious bacterial infection in children less than 36 months of age who present with FWS. UTIs are almost always occult in children younger than 24 months because the symptoms, except for fever, are nonspecific or nonexistent. UTI occurs in 7% of febrile children younger than 2 years. The prevalence of UTI varies by height of the fever, duration of the fever, age, gender, race, and circumcision status. Children with fever greater than 39°C are at a higher risk of UTIs. Boys with fever for more than 2 days and girls with fever for more than 1 day are more likely to have a UTI. Higher rates of UTIs are found in girls, especially those younger than 12 months of age. For febrile boys younger than 3 months of age, 20.1% of those who are uncircumcised have a UTI; for circumcised boys the rate is 2.4%. UTI rates are higher among white infants than among black infants and among children with abnormal genitourinary tract anatomy or neurogenic bladder.

Urine specimens should be obtained from the following children with FWS: those with a history of UTI, those with a history of urinary tract anomalies or vesicoureteral reflux, all infants younger than 2 months, girls younger than 12-24 months, uncircumcised boys younger than 12 months, and circumcised boys younger than 6 months. There is an age-associated risk of bacteremia with UTIs, particularly in infants. The incidence of bacteremia in patients younger than 2 months with UTI is 10%. The incidence of bacteremia in patients younger than 2 months with UTI ranges from 4-15% depending on the setting. Opinions regarding when to obtain blood cultures in infants with UTI differ, but a reasonable approach would be to obtain blood cultures in children younger than 2-6 months with suspected UTI, and in older infants with UTI if they are ill-appearing (urosepsis).

Bacteremia

Occult bacteremia is defined by the presence of a positive blood culture for pathogenic bacteria in a febrile patient who does not appear extremely ill and who has no focus of infection, excluding otitis media. Following the introduction of the 7-valent pneumococcal vaccine in 2007, invasive pneumococcal disease decreased dramatically. Pneumococcal bacteremia decreased from 80% of the cases of bacteremia to 30%. *Most cases of bacteremia in children were not occult.* Bacteremic children were either ill or had a focus of infection, such as a UTI. In 1 study, the rate of occult bacteremia after 2007 was 0.25%. After the 13-valent pneumococcal vaccine was introduced in 2010, the incidence of invasive pneumococcal disease in children less than 5 years old decreased again with 1 state-based population study showing incidence rates dropping from 46/100,000 to 23/100,000 with the age group most involved being children 2-23 months of age. *Escherichia coli* is the most common cause of bacteremia in children aged less than 12 months, all due to UTIs. Other less common causes of bacteremia in young

TABLE 39.3 Acute Illness Observation Scale

Observation Item	1 Normal	3 Moderate Impairment	5 Severe Impairment
Quality of cry	Strong with normal tone *or* Content and not crying	Whimpering *or* Sobbing	Weak *or* Moaning *or* High-pitched
Reaction to parent stimulation	Cries briefly, then stops *or* Content and not crying	Cries off and on	Continual cry *or* Hardly responds
State variation	If awake → stays awake *or* If asleep and stimulated → wakes up quickly	Eyes close briefly → awakens *or* Awakes with prolonged stimulation	Falls asleep *or* Will not rouse
Color	Pink	Pale extremities *or* Acrocyanosis	Pale *or* Cyanotic *or* Mottled *or* Ashen
Hydration	Skin normal, eyes normal *and* Mucous membranes moist	Skin, eyes normal *and* Mouth slightly dry	Skin doughy *or* Skin tented *and* Dry mucous membranes *and/or* Sunken eyes
Response (talk, smile) to social overtures	Smiles *or* Alert (≤2 mo)	Brief smile *or* Alert briefly (≤2 mo)	No smile; face anxious, dull, expressionless *or* No alertness (≤2 mo)

From McCarthy PL, Sharpe MR, Spiesel SZ, et al. Observation scales to identify serious illness in febrile children. *Pediatrics*. 1982;70:802.

children are *N. meningitidis*, nontyphoidal *Salmonella*, *Staphylococcus aureus*, and group A streptococcus. *Neisseria meningitidis* bacteremia is frequently associated with serious sequelae. Children with *N. meningitidis* bacteremia are much more likely to progress to meningitis than are those with *S. pneumoniae* bacteremia. Nontyphoidal *Salmonella* bacteremia is often accompanied or preceded by enteritis. In some instances, particularly in young infants, the diarrhea is mild or even absent. The prevalence of *Salmonella* bacteremia among patients with *Salmonella enteritis* has been reported to be between 2% and 45%; fever is not always present. *Salmonella* infection seldom causes serious complications in patients with normal host defenses and resolves spontaneously. *Infants younger than 3 months, malnourished, and immunocompromised individuals are exceptions.*

◆ Role of Diagnostic Testing in Patients with Fever Without Source

Evaluation is usually divided into 4 different age ranges: younger than 1 month, 1-3 months, 3-36 months, and older than 36 months. Testing for each individual age group is based on risks for diseases and prevalence of pathogens.

Complete Blood Count and Other Markers of Inflammation

The white blood cell (WBC) count is the most commonly used test in young children with FWS. Complete blood count (CBC) is less useful as a marker for invasive disease caused by *E. coli* than by *S. pneumoniae*, thus its utility has declined with the reduction of the incidence of invasive pneumococcal disease. Similarly, band counts are less commonly used, except in the 29-60 day old infant as part of identifying a low-risk cohort. A WBC count of 5,000-15,000 is generally considered normal for children over 1 month of age. A WBC count less than 15,000/mm^3 or even leukopenia may be found in children with *N. meningitidis* bacteremia. A minority of children with occult nontyphoidal *Salmonella* bacteremia have been found to have a WBC count exceeding 15,000/mm^3. C-reactive protein (CRP) and procalcitonin combined with a urine dipstick (the lab score) can be used to screen for bacterial infection. This combination of tests has been validated for children 7 days to 36 months of age.

Polymerase Chain Reaction (PCR)

PCR is useful in identifying the cause of fever for common viruses such as respiratory syncytial virus, influenza viruses, parainfluenza viruses, enteroviruses, parechovirus, adenoviruses, or herpes simplex virus.

Additional methods available or in development that may be helpful to identify serious bacterial infections and distinguish bacterial from viral infections utilize molecular microbiology methods. **Gene expression profiles** of the patient's peripheral blood leukocytes demonstrate different biosignatures of RNA production that may differentiate bacterial from viral infections. This method does not identify the

specific pathogen. **Rapid multiplex PCR** combined with standard blood culture methods may identify a specific pathogen much sooner (~20 hours) than standard blood culture techniques. Specific bacteria may be identified using **16S ribosomal RNA** bacterial gene detection. This method does not require bacterial growth. 16S rRNA detection may be helpful when antibiotics were administered before the sample was obtained, and in patients with ventilator-associated pneumonia or bacteria that grow poorly or are present in effusions or tissues (heart valves).

Blood Cultures

Blood cultures are the gold standard for determination of bacteremia. Although blood cultures do not provide immediate results, methods allow for continuous and more rapid detection of bacterial growth. Blood cultures are easy to perform and provide essential information in the diagnosis and management of patients with possible bacteremia. Preliminary blood culture results are typically available within 24 hours, with positive identification of most organisms within 48 hours.

False-negative blood culture results may be due to prior treatment with antibiotics, missing an episode of bacteremia if it is intermittent, and inoculation of too little blood into the culture media. Alternatively, too much blood inoculated into the blood culture bottle may yield a false-negative result because of ongoing killing of bacteria by neutrophils. Three to 5 mL of blood should be added to each blood culture bottle. False-positive results may be due to inadequate skin preparation, leading to contamination with skin flora.

Urinalysis and Urine Culture

A positive urine culture was once considered the gold standard; current recommendations include a urinalysis that has pyuria (defined as >5 WBCs/high-power field [hpf] on the microscopic examination or a positive leukocyte esterase on dipstick) and a positive urine culture for a uropathogen in an appropriately collected specimen. Fifty to 100,000 colonies of a single organism is considered positive (see Chapter 18). Children should have a catheterized urine specimen obtained, unless they are toilet-trained and can supply a clean voided specimen. Suprapubic aspiration is acceptable but requires technical expertise, and parents often perceive it as unsuitably invasive; it may be the only alternative for boys with severe phimosis. The use of plastic receptacles attached to the perineum should be discouraged because contamination from skin and fecal flora commonly occurs.

Lumbar Puncture

Lumbar puncture is indicated if the patient is younger than 28 days or if a diagnosis of sepsis, meningitis, or encephalitis is considered, regardless of the child's age. Normal cerebrospinal fluid (CSF) findings, including chemistry, cell count with differential, Gram stain, PCR, and culture, help exclude the diagnosis of meningitis. Less than 1% of children with normal preliminary CSF results have a positive culture; in most of these, the pathogen is *N. meningitidis*. Thus, even in the presence of normal preliminary CSF results, close follow-up is essential.

Chest Radiographs

Chest radiographs are usually normal in children who have FWS. Respiratory signs or symptoms, such as tachypnea, retractions, crackles, wheezing, rhonchi, nasal flaring, grunting, cough, or hypoxia, may predict chest radiograph findings consistent with pneumonia. In practice, pneumonia can often be diagnosed solely on the basis of the clinical findings of fever, tachypnea, and crackles; chest radiographs are not always necessary. However, chest radiographs may be useful in evaluating for the presence of pleural effusion or other complications of pneumonia.

Stool Cultures

Most acute diarrhea and fever is caused by viral pathogens in developed countries. Obtaining a stool culture is indicated if bacterial enteritis is indicated by the presence of risk factors in the history, such as blood in the stool or certain exposures (petting zoos) (see Chapter 11).

◆ Evaluation and Management

Children Younger Than 3 Months

Febrile infants younger than 3 months have a higher incidence of serious bacterial infections than older infants. The relatively high incidence of bacterial disease probably results from a combination of factors unique to this age group: decreased opsonin activity; decreased macrophage function; decreased neutrophil function; poor immunoglobulin G antibody response to encapsulated bacteria; and susceptibility to bacterial pathogens such as group B streptococci (GBS), gram-negative enteric organisms, and *Listeria monocytogenes*. The incidence of early-onset group B streptococcal infections has decreased with routine screening and the intrapartum treatment of GBS-positive pregnant women; the incidence of late-onset GBS (>1 week) has not decreased. *E. coli* is the most common organism causing bacterial infections in neonates and young infants.

In very young infants, clinical evaluation alone is inadequate for excluding serious bacterial infections. Management of febrile infants **younger than 28 days** includes a sepsis evaluation and hospitalization for parenteral antimicrobial therapy pending culture results. The reasoning for this conservative approach lies in the difficulty in evaluating the behavioral state of neonates, the rapid clinical deterioration of infants with bacterial infections, the immature neonatal immune system, and the possibility of life-threatening viral infections caused by herpes simplex viruses (HSV) or enteroviruses. Sepsis evaluation should include culture of the CSF, blood, and urine; a complete blood cell count with differential; examination of the CSF for cells, protein, and glucose; and urinalysis. A chest radiograph should be considered if the patient has signs or symptoms of a respiratory infection. Testing (blood and CSF PCR for HSV) and treatment for possible HSV infection should be considered in ill-appearing infants, those with a seizure prior to presentation, and those with a vesicular rash consistent with HSV.

A combination of clinical evaluation and laboratory studies can be used to define a specific population of infants **aged 29-60 days** who do not appear ill and are at low risk for bacterial infections. Infants at low risk for bacterial infections are those who are previously healthy with no focus of bacterial infection on physical examination and who have negative laboratory screening results. A number of prospective studies have contributed to the development of specific low-risk screening criteria (Table 39.4). The age groups included vary by study, ranging from 0-90 days to 29-56 days. Because there are differences in study criteria used to define infants at low risk for bacterial infections the most conservative values have been used in the guidelines presented in this chapter. Negative laboratory screening results consist of a WBC count of 5000-15,000/mm^3; fewer than 1500 bands/mm^3 or a band-to-neutrophil ratio of less than 0.2; fewer than 10 WBCs/hpf and no organisms on urinalysis; and fewer than 8 WBCs/hpf and no organisms on CSF Gram stain. Some experts also include a negative chest radiograph and, when diarrhea is present, a stool examination with fewer than 5 WBCs/hpf.

Most experts suggest that febrile infants 29-60 days old who meet the low-risk criteria and have access to close follow-up can be managed as outpatients. Blood, urine, and CSF cultures should be obtained before empirical antibiotic treatment so that viral and bacterial causes

may be distinguished. An alternative strategy is to manage such infants as outpatients, without empirical antibiotic therapy, after blood, CSF, and urine cultures are obtained. Although most of the original studies on outpatient management of febrile infants included infants aged 2-3 months, many experts agree that infants aged 2-3 months can be managed safely according to the guidelines for infants and children aged 3-36 months (Table 39.4).

Regardless of whether the clinician chooses to treat the patient with empiric antibiotics, all low-risk infants should be re-evaluated within 24 hours. Those who appear ill or who have positive culture results should be admitted for parenteral antibiotics. If a child appears well and all culture results are negative, close follow-up should be continued and a 2nd return visit made in 24 hours.

Children Aged 3 to 36 Months

The risk of bacteremia for children with FWS in this age group has decreased with the routine use of pneumococcal vaccines. The most common occult bacterial infection in this age group is UTI. For children in this age group who appear ill, a full sepsis evaluation should be undertaken (Table 39.5).

TABLE 39.4 Low-Risk Criteria in a Child 1–3 Mo Old with Fever

Boston Criteria

Infants are at low risk if they appear well, have a normal physical examination, and have a caretaker reachable by telephone, and if laboratory tests are as follows:

- CBC: <20,000 WBC/μL
- Urine: negative leukocyte esterase
- CSF: leukocyte count less than 10×10^6/L

Philadelphia Protocol

Infants are at low risk if they appear well and have a normal physical examination, and if laboratory tests are as follows:

- CBC: <15,000 WBC/μL; band: total neutrophil ratio <0.2
- Urine: <10 WBC/hpf; no bacteria on Gram stain
- CSF: <8 WBC/μL; no bacteria on Gram stain
- Chest radiograph: no infiltrate
- Stool: no RBC; few to no WBC

Pittsburgh Guidelines

Infants are at low risk if they appear well and have a normal physical examination, and if laboratory tests are as follows:

- CBC: 5,000–15,000 WBC/μL; peripheral absolute band count <1,500/μL
- Urine (enhanced urinalysis): 9 WBC/μL and no bacteria on Gram stain
- CSF: 5 WBC/μL and negative Gram stain; if bloody tap, then WBC:RBC ≤1 : 500
- Chest radiograph: no infiltrate
- Stool: 5 WBC/hpf with diarrhea

Rochester Criteria

Infants are at low risk if they appear well and have a normal physical examination, and if laboratory findings are as follows:

- CBC: 5,000–15,000 WBC/μL; absolute band count ≤1,500/μL
- Urine: <10 WBC/hpf at ×40
- Stool: <5 WBC/hpf if diarrhea

CBC, complete blood count; CSF, cerebrospinal fluid; hpf, high-powered field; RBC, red blood cell; WBC, white blood cell.
From Nield LS, Kamat D. Fever without a focus. In: Kliegman RM, Stanton BF, St Geme JW III, et al, eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:1281, Table 177.2.

Screening urinalysis (UA) for UTI should be considered in children with a history of UTI, children with a history of urinary tract anomalies or vesicoureteral reflux, girls younger than 12-24 months, especially when the temperature is greater than 39.0°C, uncircumcised boys younger than 12 months, and circumcised boys younger than 6 months. Blood cultures are recommended for children with probable UTIs who are less than 6 months of age. A febrile child with moderate leukocyte esterase on urine dipstick testing or pyuria on an appropriately collected specimen should be treated presumptively for a UTI. Urine cultures should be obtained for any patient with a suspected UTI. The choice of antibiotics should be guided by knowledge of the common pathogens that cause UTIs and by patterns of antibiotic sensitivity in the community. Hospitalization should be considered for the child who is vomiting, is dehydrated, or appears ill; for those in whom compliance is likely to be poor; and for any patient with underlying renal or urologic anomalies.

Examination and culture of the CSF are the only tests to exclude the diagnosis of meningitis and encephalitis. They should be considered in any child in whom the diagnosis of sepsis, meningitis or encephalitis is suspected on the basis of the history, observation, and physical examination findings. Outpatient management of children with FWS is acceptable for those with a low probability of meningitis, good follow-up, and reliable caregivers. Blood cultures should be obtained for all children in whom sepsis or meningitis is suspected. Empiric treatment with antibiotics should be considered in those suspected of sepsis or meningitis after appropriate cultures are obtained.

In summary, management of children aged 3-36 months with fever is based on clinical experience and numerous study results:

- Child who appears ill on initial evaluation or on follow-up: Admit to the hospital for parenteral antibiotics after appropriate laboratory evaluation.
- Well-appearing children with FWS should be screened for UTIs, based on their number of risk factors. Risk factors for girls are: age <12 months, white race, temperature greater than 39°C, and fever for 2 or more days. Girls 2-24 months of age with 1 or more of these risk factors have a greater than 1% probability of having a UTI, and should be screened for a UTI.

  For boys, the risk factors are uncircumcised status, nonblack race, temperature greater than 39°C, and fever for over 24 hours. All uncircumcised boys less than 12 months old, even if they don't have other risk factors, should be screened for a UTI. For boys who are circumcised, 2 or more of the other risk factors increases the risk to over 1% and they should be screened.
- Child with positive blood culture: Reevaluation should occur in any child whose blood culture is presumptively positive. If the blood is found to contain *N. meningitidis* or *Haemophilus influenzae* (which has been rare since the advent of *H. influenzae b* immunization), a CSF sample and a repeat blood culture should be obtained, and the child should be admitted to the hospital for parenteral antibiotics, pending the results of the cultures. The child with occult pneumococcal bacteremia who appears well and is afebrile when returning for a follow-up may be managed as an outpatient with parenteral ceftriaxone followed by oral antibiotics according to the sensitivity of the organism. Because of the concern of pneumococcal resistance to penicillin, a 2nd dose of intramuscular ceftriaxone may be given until sensitivity results are available. If the culture is positive for nontyphoidal *Salmonella* organisms and the child is younger than 3 months, full sepsis evaluation and intravenous antibiotics are recommended. Oral antibiotics and close follow-up are recommended for older children with *Salmonella* bacteremia.
- Child with positive urine culture: If the child is afebrile and appears well, treatment with oral antibiotics is recommended, according to the sensitivity of the organism.

TABLE 39.5 Management of Fever Without Source

Group	Management
Any toxic-appearing child 0–36 mo and temperature ≥38°C (100.4°F)	Hospitalize, broad cultures plus other tests,* parenteral antibiotics
Child <1 mo and temperature ≥38°C (100.4°F)	Hospitalize, broad cultures plus other tests,* parenteral antibiotics
Child 1–3 mo and temperature ≥38°C (100.4°F)	**Two-Step Process** 1. Determine risk based on history, physical examination, and laboratory studies. Low risk: • Uncomplicated medical history • Normal physical examination • Normal laboratory studies • Urine: negative leukocyte esterase, nitrite and <10 WBC/hpf • Peripheral blood: 5,000–15,000 WBC/mm^3; <1,500 bands or band: total neutrophil ratio <0.2 • Stool studies if diarrhea (no RBC and <5 WBC/hpf) • CSF cell count (<8 WBC/μL) and negative Gram stain • Chest radiograph without infiltrate 2. If child fulfills all low-risk criteria, administer no antibiotics, ensure follow-up in 24 hr and access to emergency care if child deteriorates. Daily follow-up should occur until blood, urine, and CSF cultures are final. If any cultures are positive, child returns for further evaluation and treatment. If child does not fulfill all low-risk criteria, hospitalize and administer parenteral antibiotics until all cultures are final and definitive diagnosis determined and treated
Child 3–36 mo and temperature 38–39°C (100.4–102.2°F)	Reassurance that diagnosis is likely self-limited viral infection, but advise return with persistence of fever, temperatures >39°C (102.2°F), and/or new signs and symptoms
Child 3–36 mo and temperature >39°C (102.2°F)	**Two-Step Process** 1. Determine immunization status 2. If received conjugate pneumococcal and *Haemophilus influenzae* type b vaccines, obtain urine studies (urine WBC, leukocyte esterase, nitrite, and culture) for all girls, all boys <6 mo old, all uncircumcised boys <2 yr, all children with recurrent urinary tract infections If did not receive conjugate pneumococcal and *H. influenzae* type b vaccines, manage according to the 1993 Guidelines (see Baraff et al. *Ann Emerg Med.* 1993;22:1198-1210.)

*Other tests may include chest radiograph, stool studies, herpes simplex virus polymerase chain reaction.
CSF, cerebrospinal fluid; hpf, high-powered field; RBC, red blood cell; WBC, white blood cell.
From Nield LS, Kamat D. Fever without a focus. In: Kliegman RM, Stanton BF, St Geme JW III, et al, eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016: Table 177.3.)

Children Older Than 36 Months

Evaluation and management of ill-appearing children older than 36 months with fever without source are similar to those of younger children. For children in this age group who do not appear ill, no screening diagnostic tests are indicated. Close attention should be paid to environmental exposures and ill contacts because of the high likelihood of increased contacts in this school-aged cohort.

CENTRAL NERVOUS SYSTEM INFECTIONS

Bacterial Meningitis

Bacterial meningitis is usually a disease of infants and young children. The attack rate is highest between the ages of 3 and 8 months; 66% of cases occur in children younger than 5 years of age. Bacterial meningitis is seen during all seasons; however, there may be a seasonal correlation between the presence of preceding respiratory pathogens in the upper respiratory tract and the subsequent development of bacterial meningitis. Bacterial meningitis usually occurs sporadically. Clusters of cases have been noted in day care centers, colleges, and other closed communities. Bacterial meningitis occurs more frequently in children with traumatic fractures of the cribriform plate or paranasal sinuses or with a cochlear implant (pneumococci); in children who have undergone neurosurgical procedures such as ventricular shunts (*S. aureus*, *S. epidermidis*, *Corynebacterium* species); in children with congenital or acquired immunodeficiencies (pneumococci, *L. monocytogenes*, meningococci); in children with anatomic or functional asplenia (pneumococci, meningococci); and in children with sickle hemoglobinopathies (pneumococci). There may be a genetic predisposition in some groups to the development of meningitis, inasmuch as there is an increased incidence of *H. influenzae* type b meningitis in Navahos and Eskimos.

Bacterial meningitis manifests in 2 patterns. In the 1st, the symptoms develop slowly over several days, the initial symptoms being those of a nonspecific illness. The signs and symptoms of meningitis develop subsequently. In the 2nd pattern, the disease develops suddenly and quickly, the 1st indications of illness being the signs and symptoms of meningitis and/or sepsis.

The manifestations of meningitis depend on the child's age. In infants, the findings are usually nonspecific and may be subtle; they include vomiting, diarrhea, irritability, lethargy, poor appetite, respiratory distress, seizures, hypothermia, and jaundice. Only 50% of affected infants have fever; some present only with fever. It is uncommon for affected young infants to have a stiff neck; only 30% have a bulging fontanel.

Older children present with more specific meningeal signs. They complain of a headache that is described as being severe, generalized, deep-seated, and constant. They complain about neck stiffness, caused by inflammation of the cervical dura and reflex spasm of the extensor muscles of the neck. There is pain and limitation of motion on flexion

of the neck, but lateral movement of the neck may be normal and pain-free. They also complain of nausea, vomiting, anorexia, and photophobia.

On examination, they demonstrate irritability, mental confusion or altered consciousness, nuchal rigidity, and, occasionally, hyperesthesia and ataxia. The clinician demonstrates nuchal rigidity by feeling resistance and observing a painful response while flexing the patient's neck. The stiffness may not be recognized until the end of flexion. The neck usually can be rotated without symptoms. In the child who is crying and tensing the muscles, nuchal rigidity may be demonstrated if the examiner places 1 hand under the occiput of the supine patient and lifts the child. If the neck does not flex, it is stiff. Alternatively, a sitting child may be observed following an object as it falls to the floor. The child who flexes the neck to look at the object does not have nuchal rigidity. In the presence of meningitis, flexion of the neck causes spontaneous flexion of the legs at the hips and knees, the **Brudzinski sign** (Fig. 39.1). The **Kernig sign** is elicited when the patient lies supine and, with the knee flexed, the leg is flexed at the hip. The knee is then extended. A positive sign is present if this movement is limited by contraction of the hamstrings and causes pain. Absence of nuchal rigidity is found in 1.5% of older children with meningitis; it may be absent in children who have overwhelming infections, are deeply comatose, or who have focal or global neurologic impairment.

As many as 15% of children with bacterial meningitis initially present in a **comatose** or semicomatose state (see Chapter 31). Because

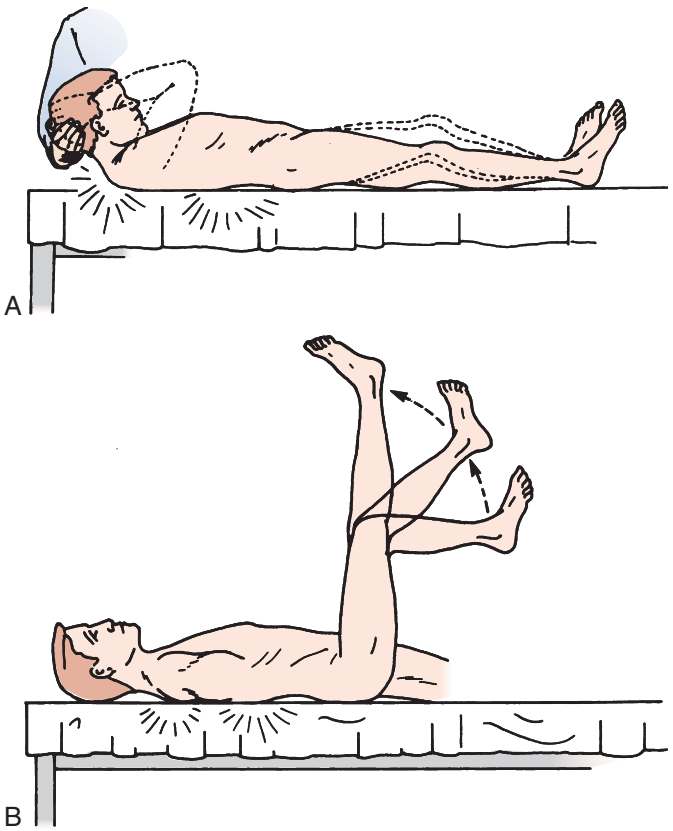


FIGURE 39.1 *A,* Brudzinski sign. The patient lies supine, and the head is passively elevated from the table by the examiner. The patient complains of neck and low back discomfort and attempts to relieve the meningeal irritation by involuntary flexion of the knees and hips. *B,* Kernig sign. The patient lies supine, with the hips and knees flexed. The knees are then gradually extended. Complaints of pain in the lower back, neck, and/or head are suggestive of meningeal irritation. (From Reilly BM. *Practical Strategies in Outpatient Medicine.* 2nd ed. Philadelphia: WB Saunders; 1991:95.)

of the short duration and inconsistent development of increased intracranial pressure, **papilledema** is usually not seen at presentation. When it is present, venous sinus thrombosis, subdural effusion, or an intracranial abscess must be considered. **Seizures** occur before hospital admission in up to 20% of affected patients.

Children with meningitis may also present with cutaneous findings. Although commonly associated with meningococcal disease, purpura, petechiae, or a diffuse nonspecific maculopapular rash may be present in meningitis caused by any of the common bacterial pathogens (see Chapter 40).

Septic arthritis may be seen simultaneously with bacterial meningitis. This has been assumed to be caused by simultaneous localizing infection after a primary bacteremia. Reactive arthritis caused by immune complex deposition is also seen with bacterial meningitis. This arthritis affects 1 large joint and appears 5-7 days after treatment for meningitis has started. In general, arthritis occurring acutely with meningitis should be assumed to be infectious (see Chapter 33).

Various eye disorders have also been described with acute bacterial meningitis, including transient cataracts, paralysis of the extraocular muscles, pupillary dysfunction, dendritic ulcers, endophthalmitis, cortical blindness, and conjunctivitis.

Recurrent episodes of bacterial meningitis rarely occur. Potential etiologies include congenital CSF fistulas (inner ear, dermal sinus, neuroenteric cysts, lumbosacral sinus tracts), traumatic or surgical CSF fistula (skull fracture, postoperative nasal surgery, cochlear implant), immunodeficiency states and parameningeal infections (mastoiditis, sinusitis, craniofacial osteomyelitis).

◆ Diagnostic Studies

Lumbar Puncture and Cerebrospinal Fluid Analysis

The definitive diagnosis of meningitis is based on examination of the cerebrospinal fluid (CSF). The CSF is usually obtained via a lumbar puncture (spinal tap). The lumbar puncture is performed by introducing a small-bore, short-beveled, spinal needle with a stylet into the subarachnoid space at the L3-L4 or L4-L5 level (Figs. 39.2 to 39.4). A needle with a stylet is used to minimize the risk of introducing a nest of epidermal cells into the subarachnoid space that may later grow into a cord-compressing epidermoid tumor. Approximately 3 mL of fluid is removed for analysis.

There are a few **contraindications** for the performance of a lumbar puncture. The 1st is cardiorespiratory compromise. Performance of the lumbar puncture requires that the child be held in flexion to open the intervertebral spaces. In seriously ill children or children with significant underlying cardiac or pulmonary disease, this positioning may be enough to cause respiratory compromise. The lumbar puncture may need to be postponed, be performed cautiously with continuous oxygen saturation monitoring, or performed with the patient in the sitting position.

Second, children with **increased intracranial pressure** from a focal central nervous system (CNS) lesion, such as brain abscess or tumor, or from illnesses associated with cerebral edema have a high risk of cerebral herniation after a lumbar puncture. If signs or symptoms of increased intracranial pressure are present, the lumbar puncture should be postponed until the increased pressure is lowered with appropriate treatment. *If a lumbar puncture is delayed, appropriate antibiotic therapy should be initiated without further delay.* Third, a lumbar puncture should not be done if the spinal needle must pass through an area of infection on its way to the subarachnoid space. To do so might introduce pathogens into the CNS that could cause meningitis.

Epidural hematomas causing lower limb paralysis may be a complication of lumbar punctures in children with bleeding disorders. Therefore, in children with hemophilia, disseminated intravascular

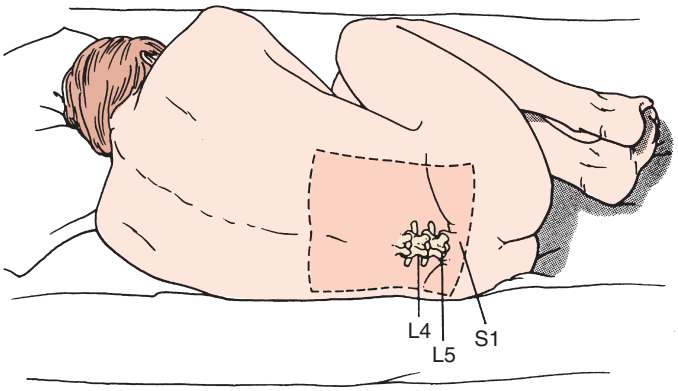


FIGURE 39.2 Lateral decubitus position for a lumbar puncture. L4-L5 position is determined by a vertical line drawn between the superior iliac crests. (From Davidson RI. Lumbar puncture. In: Vander Salm TJ, Cutler BS, Wheeler HB, eds. *Atlas of Bedside Procedures*. 2nd ed. Boston: Little, Brown; 1992:443.)

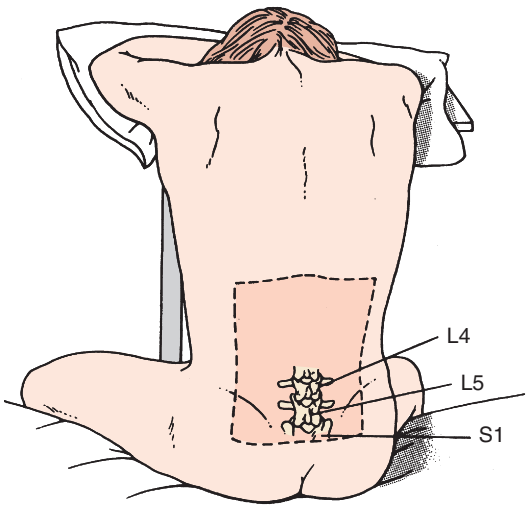


FIGURE 39.3 Sitting position for a lumbar puncture. (From Davidson RI. Lumbar puncture. In: Vander Salm TJ, Cutler BS, Wheeler HB, eds. *Atlas of Bedside Procedures*. 2nd ed. Boston: Little, Brown; 1992:443.)

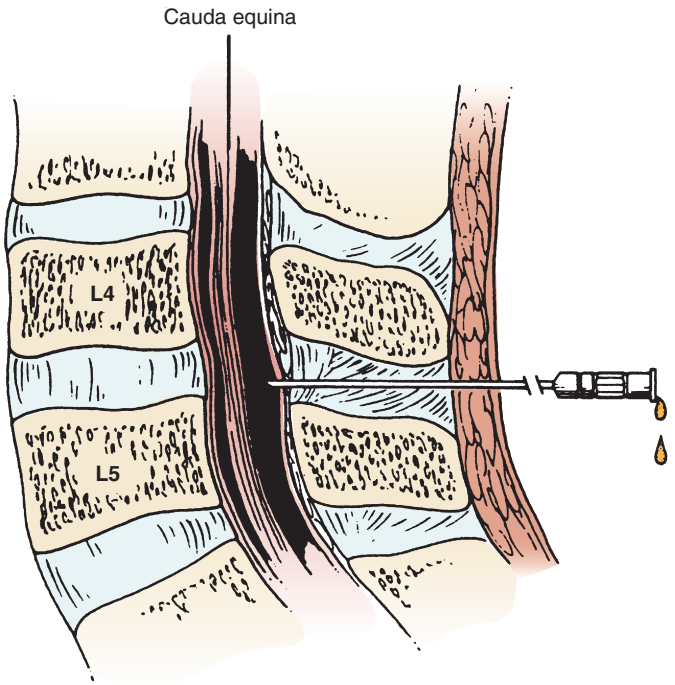


FIGURE 39.4 The needle and stylet are advanced into the subarachnoid space. On penetration into the space, the examiner often feels a give or pop after moving through the dura. After the needle enters into the subarachnoid space, the clinician removes the stylet and collects the cerebrospinal fluid. (From Davidson RI. Lumbar puncture. In: Vander Salm TJ, Cutler BS, Wheeler HB, eds. *Atlas of Bedside Procedures*. Boston: Little, Brown; 1992:447.)

coagulopathy, or thrombocytopenia, lumbar puncture should be postponed until the bleeding disorder is corrected, and extra care should be taken to avoid a traumatic lumbar puncture. Such children should be monitored after the procedure for the development of neurologic deficits. *Empirical therapy may be started while the coagulopathy is corrected.*

Other, rarer complications of lumbar puncture include cortical blindness from compression of the posterior cerebral artery against the tentorium cerebelli, causing ischemic infarction of the occipital lobes. Cervical spinal cord infarction, with respiratory arrest and flaccid tetraplegia, may occur if intracranial hypertension causes herniation of the cerebellar tonsils through the foramen magnum with resulting compression of the anterior spinal artery or its penetrating branches. Post–lumbar puncture headache may occur in up to 10% of older children and adults; it is presumably caused by persistent CSF leakage at the lumbar puncture site.

The CSF is examined for red blood cells (RBCs), white blood cells (WBCs) and differential, glucose, protein, and the presence (by culture, by Gram stain or other stain, or by antigen or DNA-PCR testing for specific agents) of pathogenic organisms. Opening pressure measurements are obtained with the head of the bed flat and with the child relaxed and in the lateral decubitus position with the back no longer tightly flexed. The upper limit of normal value in children 1-18 years of age is less than 25 cm of water. Opening pressure is less than 5 cm H_2O in premature infants and less than 10 cm H_2O in normal newborns. Opening pressure measurements are elevated if the lumbar puncture is performed with the patient in the sitting position and if the patient is combative or performing the Valsalva maneuver. Obstructive hydrocephalus, hyperventilation, or removal of fluid can all lead to lowering of the measurement. Children with bacterial meningitis usually have a mean opening pressure of 18 ± 7 cm H_2O.

Normal CSF is clear and colorless (Table 39.6). Blood in the CSF indicates a traumatic lumbar puncture or a CNS hemorrhage. Obtaining a RBC count on tubes 1 and 3 may differentiate the 2 conditions because the count is unchanged in CNS hemorrhage but may decline in traumatic taps. Centrifugation of the CSF sample may also help differentiate between a traumatic tap and a CNS hemorrhage. When blood has been present in the CSF for several hours, the CSF is xanthochromic after centrifugation. However, if the blood was recently mixed with CSF, as in the case of a traumatic tap, the supernatant is clear. Xanthochromic CSF can also be caused by icterus or an elevated CSF protein concentration.

The normal values for WBCs in the CSF are shown in Table 39.6. Most children with bacterial meningitis have a WBC count of at least $1000/mm^3$ in their CSF, but, in general, more than $6/mm^3$ in children after the neonatal period is considered abnormal. Normal values for neonates are 0-18 (mean: 6) WBCs in the CSF.

An absolute neutrophil count exceeding $3/mm^3$ (neutrophils may be as high as 35%) is also considered abnormal and evidence of a

TABLE 39.6 Cerebrospinal Fluid Findings in Central Nervous System Disorders

Condition	Pressure (mm H_2O)	Leukocytes (mm^3)	Protein (mg/dL)	Glucose (mg/dL)	Comments
Normal	50–80	<5, ≥75% Lymphocytes	20–45	>50 (or 75% serum glucose)	
Common Forms of Meningitis					
Acute bacterial meningitis	May be elevated (100–300)	100–10,000 or more; usually 300–2,000; PMNs predominate	Usually 100–500	Decreased, usually <40 (or <50% serum glucose)	Organisms usually seen on Gram stain and recovered by culture
Partially treated bacterial meningitis	Normal or elevated	5–10,000; PMNs usual but mononuclear cells may predominate if pretreated for extended period of time	Usually 100–500	Normal or decreased	Organisms may be seen on Gram stain. Pretreatment may render CSF sterile. Organism detected by antigen or PCR tests
Viral meningitis or meningoencephalitis	Normal or slightly elevated (80–150)	Rarely >1,000 cells. Eastern equine encephalitis and lymphocytic choriomeningitis may have cell counts of several thousand. PMNs early but mononuclear cells predominate through most of the course	Usually 50–200	Generally normal; may be decreased to <40 in some viral diseases, particularly mumps (15–20% of cases)	HSV encephalitis is suggested by focal seizures or by focal findings on CT or MRI scans or EEG. HSV and enteroviruses may be detected by PCR of CSF
Uncommon Forms of Meningitis					
Tuberculous meningitis	Usually elevated	10–500; PMNs early, but lymphocytes predominate through most of the course	100–3,000; may be higher in presence of CSF block	<50 in most cases; decreases with time if treatment is not provided	Acid-fast organisms almost never seen on smear. Organisms may be recovered in culture of large volumes of CSF. *Mycobacterium tuberculosis* may be detected by PCR of CSF; elevated ADA and gamma interferon
Fungal meningitis	Usually elevated	5–500; PMNs early but mononuclear cells predominate through most of the course. Cryptococcal meningitis may have no cellular inflammatory response	25–500	<50; decreases with time if treatment is not provided	Budding yeast may be seen. Organisms may be recovered in culture. Cryptococcal antigen (CSF and serum) may be positive in cryptococcal infection
Syphilis (acute) and leptospirosis	Usually elevated	50–500; lymphocytes predominate	50–200	Usually normal	Positive CSF serology. Spirochetes not demonstrable by usual techniques of smear or culture; dark-field examination may be positive
Amebic (*Naegleria*) meningoencephalitis	Elevated	1,000–10,000 or more; PMNs predominate	50–500	Normal or slightly decreased	Mobile amebas may be seen by hanging-drop examination of CSF at room temperature

TABLE 39.6 Cerebrospinal Fluid Findings in Central Nervous System Disorders—cont'd

Condition	Pressure (mm H_2O)	Leukocytes (mm^3)	Protein (mg/dL)	Glucose (mg/dL)	Comments
Brain Abscesses and Parameningeal Focus					
Brain abscess	Usually elevated	5–200; CSF rarely acellular; lymphocytes predominate; if abscess ruptures into ventricle, PMNs predominate and cell count may reach >100,000	75–500	Normal unless abscess ruptures into ventricular system	No organisms on smear or culture unless abscess ruptures into ventricular system
Subdural empyema	Usually elevated	100–5,000; PMNs predominate	100–500	Normal	No organisms on smear or culture of CSF unless meningitis also present; organisms found on tap of subdural fluid
Cerebral epidural abscess	Normal to slightly elevated	10–500; lymphocytes predominate	50–200	Normal	No organisms on smear or culture of CSF
Spinal epidural abscess	Usually low, with CSF block	10–100; lymphocytes predominate	50–400	Normal	No organisms on smear or culture of CSF
Chemical (drugs, dermoid cysts, myelography dye)	Usually elevated	100–1,000 or more; PMNs predominate	50–100	Normal or slightly decreased	Epithelial cells may be seen within CSF by use of polarized light in some children with dermoids
Noninfectious Causes					
Sarcoidosis	Normal or elevated slightly	0–100; mononuclear	40–100	Normal	No specific findings
Systemic lupus erythematosus with CNS involvement	Slightly elevated	0–500; PMNs usually predominate; lymphocytes may be present	100	Normal or slightly decreased	No organisms on smear or culture. Positive neuronal and ribosomal P protein antibodies in CSF
Tumor, leukemia	Slightly elevated to very high	0–100 or more; mononuclear or blast cells	50–1,000	Normal to decreased (20–40)	Cytology may be positive
Acute disseminated encephalomyelitis	Normal or elevated	~100 lymphocytes	Normal to elevated	Normal	MRI adds to diagnosis
Autoimmune encephalitis	Normal	~100 lymphocytes	Normal to elevated	Normal	Anti-NMDAR antibody positive

CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogram; HSV, herpes simplex virus; MRI, magnetic resonance imaging; NMDAR, *N*-methyl-D-aspartate receptor; PCR, polymerase chain reaction; PMN, polymorphonuclear neutrophils; ADA, adenosine deaminase.
From Prober CG, Srinivas NS, Mathew R. CNS infections. In: Kliegman RM, Stanton BF, St Geme JW III, et al, eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016, Table 603.1.

bacterial infection. Although there are case reports of children with proven, usually rapidly fulminant meningococcal bacterial meningitis who do not have CSF pleocytosis, the CSF of 98% of children with meningitis has pleocytosis and more than 50% neutrophils. It takes 200-400 WBCs/mm^3 to turn CSF turbid.

On occasion, the spinal needle is advanced too far and passes through the subarachnoid space and penetrates the richly vascularized ventral epidural space. Blood is thereby introduced into the subarachnoid space, and the CSF appears bloody. This occurrence is often called a traumatic tap. It is then difficult to know whether the WBCs seen on examination of the CSF are caused by CSF pleocytosis or are peripheral blood WBCs contaminating the CSF. To aid in this determination, the ratio of WBCs to RBCs in the CSF is compared with the ratio of WBCs to RBCs in the patient's peripheral blood. A higher ratio in the CSF indicates the presence of CSF pleocytosis. When the CSF ratio is at least 10 times higher than the blood ratio, bacterial meningitis is indicated, with a sensitivity of 88% and a specificity of 90%. Conversely, the negative predictive value for the presence of bacterial meningitis of a less than 10-fold difference between the ratios is 99%. Traumatic taps usually do not alter the CSF glucose, Gram stain, or culture findings, which are often abnormal with bacterial meningitis. When there is doubt about the validity of the cell count after a bloody tap, the lumbar puncture should be repeated after several hours by introducing the spinal needle 1 intervertebral space above the original tap site.

In normal CSF, the glucose concentration is two-thirds that of serum glucose concentration. The CSF glucose concentration is low in most infected infants and younger children and in 45% of school-aged children with bacterial meningitis. In children older than 2 months of age, a CSF/serum glucose ratio of less than 0.4 is 80% sensitive and 98% specific for the presence of bacterial meningitis. The presence of RBCs in a CSF sample that is promptly analyzed does not affect the glucose concentration.

The normal CSF protein concentration is less than 45 mg/dL in children older than 2 months. The mean CSF protein concentration is 90 (range, 20-170) in full-term infants and 115 (range, 65-150) in preterm infants.

The CSF protein concentration is elevated in more than 90% of younger children with bacterial meningitis but in only 60% of infected school-aged children. Every 1000 RBCs in the CSF (from a traumatic tap) increases the protein concentration by approximately 1 mg/dL.

The presence of bacterial pathogens in the CSF should be investigated. Microscopic examination of a Gram-stained sample of the fluid is performed first. The sensitivity of this test is directly related to the number of organisms in the CSF and is inversely related to the age of the patient. The Gram stain identification of certain organisms, such as *H. influenzae*, may be problematic. A decision whether to treat a child for bacterial meningitis should not be based on the Gram stain alone; the definitive diagnosis is based on the CSF culture. Rapid diagnostic tests for bacterial antigens in CSF, including countercurrent immunoelectrophoresis and latex particle agglutination, suffer from variations in sensitivity and specificity that limit their value in clinical practice.

Some patients will have been treated with antibiotics before the lumbar puncture is performed. When the CSF from such a child is examined, organisms may not be seen on Gram stain or recovered on culture. However, abnormalities of CSF cell count (including elevated leukocytes), protein concentration, and glucose concentration usually continue to suggest the diagnosis of bacterial meningitis. In this setting, presumptive treatment for bacterial meningitis is initiated. If an organism is identified by culture or antigen detection, definitive antibiotic treatment is administered. If no organism is identified, the decision to continue treatment depends on the clinical suspicion of bacterial meningitis and the exclusion of other causes of aseptic meningitis (Tables 39.7 and 39.8). Newer laboratory techniques that utilize PCR to detect bacterial pathogens are being developed and may be useful in the diagnosis of bacterial meningitis in patients who have been treated with antibiotics before lumbar puncture.

Computed Tomography

Routine computed tomography (CT) of the head is not indicated in children with suspected meningitis. Even though children with bacterial meningitis have increased intracranial pressure, most CT scans are normal. In addition, most lumbar punctures do not result in cerebral herniation in patients with meningitis. CT should be reserved for children who show clinical signs of herniation or cerebral edema and for those who may have an intracranial mass causing signs and symptoms similar to meningitis.

Other Laboratory Tests

Usually, the peripheral blood WBC and platelet counts are elevated with bacterial meningitis. A low WBC count and thrombocytopenia may also be seen; these are associated with overwhelming infection and a poor outcome. The sensitivity (70%), specificity (54%), and negative predictive value (81%) of the differential WBC count are too low to render the differential WBC examination useful in making the diagnosis of bacterial meningitis.

Blood cultures may be useful in identifying the bacterial pathogen of meningitis. However, a negative blood culture may be found in up to 33% of children with meningococcal meningitis, 20% of children with pneumococcal cases, and 10% of patients with *H. influenzae* type b meningitis. These numbers increase with prior antibiotic therapy. In addition, there is a negative correlation between the length of illness before diagnosis and the rate of positive blood cultures. A bacterial meningitis score has been developed to attempt to distinguish between bacterial and aseptic (nonbacterial) meningitis in patients with CSF pleocytosis. The risk of bacterial meningitis is low if *none* of the following criteria are present: history of a seizure with the illness, blood neutrophil count $\geq 10 \times 10^9$ cells/L, positive CSF Gram stain, CSF protein ≥80 mg/dL, or CSF neutrophil count $\geq 1 \times 10^9$ cells/L. This diagnostic tool is 99% sensitive and 62% specific for bacterial meningitis. It should only be applied to non–ill-appearing children older than 2 months without petechiae, purpura, or other concerning findings on examination who have not been pretreated with antibiotics.

Aseptic Meningitis

Aseptic meningitis is an inflammatory process of the meninges, most often characterized by acute signs and symptoms of meningeal irritation; CSF pleocytosis, usually with a predominance of mononuclear cells; a normal or, less frequently, elevated CSF protein concentration; normal or, less often, low CSF glucose concentration; and no organisms demonstrable by Gram stain or bacterial cultures. There are many causes of aseptic meningitis (see Table 39.7). The most common cause is viral infection; up to 90% of cases are caused by enteroviruses and arbovirus. The definitive diagnosis is made by identifying the organism in the CSF. However, this is not always possible, and other causes must be excluded by history, presence or absence of associated symptoms, and appropriate laboratory tests (Tables 39.7 and 39.8).

Viral Meningitis

Enteroviral meningitis occurs most often during the summer and early fall months. Transmission is via the fecal-oral route, and young children exhibit increased transmission of the viruses and more severe disease in comparison with other age groups. Initially, patients may have a respiratory tract infection, a nonspecific febrile illness, or vomiting and diarrhea. Viral infection of the meninges occurs 7-10 days after initial exposure. The clinical course may be biphasic. Virus from the oropharynx can be cultured only during the 1st 5-7 days of the illness but may be excreted in stool for 6-8 weeks.

Children with viral meningitis present with fever, nuchal rigidity, irritability, headache, and vomiting. Less common symptoms are anorexia, drowsiness, photophobia, myalgia, and malaise. As in bacterial meningitis, affected young infants often lack meningeal signs. In addition, children may have an altered sensorium, but focal neurologic signs are rare. Seizures are more common in infants.

The number of WBCs in the CSF varies from zero to several thousand (Table 39.6). Up to 75% of *initial (early in the illness)* CSF specimens contain a predominance of polymorphonuclear cells. Mononuclear cells predominate by 2 days after the onset of symptoms. Of children with enteroviral meningitis, 18% may have decreased CSF glucose concentrations, whereas 12% may have elevated CSF protein. Treatment of enteroviral meningitis is supportive. Admission to the hospital may be required while bacterial meningitis is being ruled out and for intravenous hydration. Analgesics and antipyretics may also be indicated. The lumbar puncture performed to diagnose viral meningitis is often helpful in ameliorating the acute symptoms. The mechanism for this is not clear.

The outcome is quite good for patients in whom common viral pathogens cause aseptic meningitis. Sequelae in older children are rare. Adverse outcomes are more common (but unusual) in children who have viral meningitis during the 1st year of life. Speech and language development may be affected. Treatment and outcome for the other types of aseptic meningitis depend on the underlying cause.

Tuberculous Meningitis

Tuberculous meningitis is an important treatable cause of aseptic meningitis. During the primary pulmonary tuberculous infection and

TABLE 39.7 Clinical Conditions and Infectious Agents Associated with Aseptic Meningitis

Viruses
Enteroviruses (coxsackievirus, echovirus, poliovirus, enterovirus)
Parechovirus
Arboviruses: Eastern equine, Western equine, Venezuelan equine, St. Louis encephalitis, Powassan and California encephalitis, West Nile virus, Colorado tick fever
Herpes simplex (types 1, 2)
Human herpesvirus (types 6, 7)
Varicella–zoster virus
Epstein–Barr virus
Parvovirus B19
Cytomegalovirus
Adenovirus
Variola (smallpox)
Measles
Mumps
Rubella
Influenza A and B
Parainfluenza
Rhinovirus
Rabies
Lymphocytic choriomeningitis
Rotaviruses
Coronaviruses
Human immunodeficiency virus type 1

Bacteria
Mycobacterium tuberculosis
Leptospira species (leptospirosis)
Treponema pallidum (syphilis)
Borrelia species (relapsing fever)
Borrelia burgdorferi (Lyme disease)
Nocardia species (nocardiosis)
Brucella species
Bartonella species (cat-scratch disease)
Rickettsia rickettsiae (Rocky Mountain spotted fever)
R. prowazekii (typhus)
Ehrlichia canis
Coxiella burnetii
Mycoplasma pneumoniae
M. hominis
Chlamydia trachomatis
C. psittaci
C. pneumoniae
Partially treated bacterial meningitis

Bacterial Parameningeal Focus
Sinusitis
Mastoiditis
Brain abscess
Subdural–epidural empyema
Cranial osteomyelitis

Fungi
Coccidioides immitis (coccidioidomycosis)
Blastomyces dermatitidis (blastomycosis)
Cryptococcus neoformans (cryptococcosis)
Histoplasma capsulatum (histoplasmosis)
Candida species
Other fungi (*Alternaria*, *Aspergillus*, *Cephalosporium*, *Cladosporium*, *Dreschlera hawaiiensis*, *Paracoccidioides brasiliensis*, *Petriellidium boydii*, *Sporotrichum schenckii*, *Ustilago* species, Zygomycetes)

Parasites (Eosinophilic)
Angiostrongylus cantonensis
Gnathostoma spinigerum
Baylisascaris procyonis
Strongyloides stercoralis
Trichinella spiralis
Toxocara canis
Taenia solium (cysticercosis)
Paragonimus westermani
Schistosoma species
Fasciola species

Parasites (Noneosinophilic)
Toxoplasma gondii (toxoplasmosis)
Acanthamoeba species
Naegleria fowleri
Malaria

Postinfectious
Vaccines: rabies, influenza, measles, poliovirus
Demyelinating or allergic encephalitis

Systemic or Immunologically Mediated
Bacterial endocarditis
Autoimmune encephalitis
Kawasaki disease
Systemic lupus erythematosus
Vasculitis, including polyarteritis nodosa
Sjögren syndrome
Mixed connective tissue disease
Rheumatoid arthritis
Behçet syndrome
Polyangiitis with granulomatosis
Lymphomatoid granulomatosis
Granulomatous arteritis
Sarcoidosis
Familial Mediterranean fever
Vogt–Koyanagi–Harada syndrome

Malignancy
Leukemia
Lymphoma
Metastatic carcinoma
Central nervous system tumor (e.g., craniopharyngioma, glioma, ependymoma, astrocytoma, medulloblastoma, teratoma)

Continued

TABLE 39.7 Clinical Conditions and Infectious Agents Associated with Aseptic Meningitis—cont'd

Drugs	Miscellaneous
Intrathecal injections (contrast media, serum, antibiotics, antineoplastic agents)	Heavy metal poisoning (lead, arsenic)
Nonsteroidal antiinflammatory agents	Foreign bodies (shunt, reservoir)
OKT3 monoclonal antibodies	Subarachnoid hemorrhage
Carbamazepine	Postictal state
Azathioprine	Postmigraine state
Intravenous immune globulins	Mollaret syndrome (recurrent)
Antibiotics (trimethoprim-sulfamethoxazole, sulfasalazine, ciprofloxacin, isoniazid)	Intraventricular hemorrhage (neonate)
	Familial hemophagocytic syndrome
	Post neurosurgery
	Dermoid–epidermoid cyst

Data from Cherry JD. Aseptic meningitis and viral meningitis. In: Feigin RD, Cherry JD, eds. *Textbook of Pediatric Infectious Diseases*. 4th ed. Philadelphia: WB Saunders; 1998:450; and from Davis LE. Aseptic and viral meningitis. In: Long SS, Pickering LK, Prober CG, eds. *Principles and Practice of Pediatric Infectious Disease*. New York: Churchill Livingstone; 1997:329.

subsequent lymphohematogenous spread to extrapulmonary sites, tubercle bacilli produce local microscopic granulomas in the CNS and meninges. If this primary CNS infection is not contained by host defense mechanisms (T lymphocytes, monocytes), or if host defense mechanisms fail at a later period, tuberculous meningitis may result. Meningitis occurs weeks to months after the primary pulmonary process.

The symptoms of tuberculous meningitis are insidious and subacute (weeks to months). Stage 1 is a prodrome with nonspecific manifestations (apathy, poor school function, irritability, weight loss, fever, night sweats, nausea); stage 2 is heralded by the onset of neurologic signs (headache, cranial neuropathy, nuchal rigidity, signs of increased intracranial pressure); and stage 3 manifests with altered levels of consciousness (lethargy, stupor, coma). Meningismus is not present in all patients.

The diagnosis is supported by a history of contacts with adults with known active tuberculosis, a chronic cough, or human immunodeficiency virus (HIV) disease or by a history of immigration, poverty, or homelessness. In addition, the patient's chest radiograph is consistent with active or, more often, quiescent tuberculosis (parenchymal-hilar node calcifications, infiltrates, hilar adenopathy, and, in rare cases, endobronchial or cavitary lesions), and the patient's tuberculin skin test yields a positive result (see Chapter 2). Cranial CT or magnetic resonance imaging (MRI) may show the most intense meningeal inflammation around the base of the brain or inflammatory mass lesions (tuberculomas). The CSF results (Table 39.6) include profound hypoglycorrhachia, a high CSF protein, lymphocyte- or monocyte-predominant cells (usually 500 cells/mm^3), increased opening pressure, and, on occasion, tubercle organisms on acid-fast staining. PCR amplification of *Mycobacterium tuberculosis* DNA aids in making a more rapid diagnosis than does culture of CSF, sputum, or gastric aspirates, which traditionally requires 2-6 weeks. The differential diagnosis depends on the stage of the illness.

Encephalitis

Encephalitis is inflammation of the brain parenchyma, whereas meningoencephalitis is inflammation of the brain accompanied by inflammation of the meninges. Meningoencephalitis is distinguished from aseptic meningitis by evidence of brain parenchymal involvement, including behavior or personality changes; altered level of consciousness (including agitation or coma); generalized seizures; focal neurologic signs, including focal seizures and focal motor defects (hemiparesis or ataxia); or movement disorders.

Enteroviruses and arboviruses cause most cases of infectious encephalitis in children. Enterovirus encephalitis, uncommon without meningeal involvement, is suggested by epidemic occurrence and presence of typical prodrome or associated findings (Table 39.8); prompt diagnosis is by PCR for enterovirus in CSF, blood, throat, or stool specimens. A CSF or blood specimen is preferred because PCR may identify enterovirus in throat and especially stool for weeks after the primary infection has resolved. Arbovirus encephalitis is suggested by mosquito or tick exposure and epidemic occurrence and is diagnosed by findings of arbovirus immunoglobulin M in CSF or blood or by paired serologic findings for immunoglobulin G.

Infections with herpes simplex virus (HSV) occur throughout the year. In neonates, HSV encephalitis usually occurs between 7 and 21 days of age; may produce focal or generalized CNS disease; and may occur with or without conjunctivitis, oral mucosal involvement, vesicles on skin, or disseminated disease (hepatitis, pneumonia, septic appearance). After the neonatal period, HSV encephalitis is usually isolated to the CNS and classically produces necrotizing encephalitis with a focus in the temporal lobe. Symptoms in persons with HSV encephalitis range broadly from those suggesting mild aseptic meningitis to the presence of status epilepticus and coma and then death. In addition to neutrophils and monocytes, CSF examination may show increased numbers of erythrocytes and elevated protein. CT, MRI, and an electroencephalogram (EEG) may suggest a temporal lobe focus. Specific diagnosis is by PCR of CSF for herpes simplex DNA. CSF culture is usually negative. In the appropriate clinical setting, presumptive therapy with intravenous acyclovir, 60 mg/kg/day given every 8 hours, is indicated while the results of PCR of CSF for HSV are awaited.

Autoimmune encephalitis. Anti-D-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a novel and relatively common form of encephalitis. Data from the California Encephalitis Project showed that anti-NMDAR encephalitis was the most common identifiable cause of encephalitis in their cohort, which included patients from 6 months to 30 years. Most of the cases occurred in children and adolescents. Patients present with similar features as viral encephalitis, but seizures, language dysfunction, psychosis, autonomic dysfunction, movement disorders, and EEG abnormalities are more common in these patients.

FEVER OF UNKNOWN ORIGIN

In adults, FUO is defined as an illness lasting more than 3 weeks, a fever higher than 38.3°C (101°F) on several occasions, and uncertainty

TABLE 39.8 Characteristics of the Most Common Causes of Aseptic Meningitis Syndrome

Organism	Age Group Serology	Season	Prodrome	Clinical Characteristics	Epidemiologic Characteristics	Agent Identification	Serologic Diagnosis
Common							
Enteroviruses	Infants, young children	Summer, fall	None, or mild GI or pharyngitis syndrome for 1–3 days	Exanthem, myopericarditis, conjunctivitis, pleurodynia, hand–foot–mouth disease, herpangina, myositis, hepatitis	Epidemic	Culture or PCR of CSF, blood, throat, stool	Enterovirus serologic study
Arboviruses	Children, elderly	Summer, early fall	Fever, rash, malaise for 1–5 days	Encephalitis or aseptic meningitis	Geographic area, contact with insect vector, encephalitis in community or animals	PCR of CSF	IgM, paired IgG
Herpes simplex type 2	Young adults	Year round	Genital vesicles for 1–7 days	Associated primary herpes lesions	Sexual exposure	Culture of genital lesions; PCR of CSF	IgM, paired IgG
Borrelia burgdorferi (Lyme disease)	Children, adults	Spring–late fall	Erythema migrans; secondary symptoms weeks to months later	Facial palsy or other cranial nerve palsy; radiculitis; heart block	Endemic area, deer tick exposure (often unrecognized)	PCR of CSF	IgG, IgM: EIA with Western blot confirmation
Less Common							
Mumps	5- to 9-year-olds	Late winter–spring	Parotitis, orchitis: 2–10 days	Parotitis, orchitis, oophoritis, pancreatitis	Exposure to mumps or vaccination	PCR of CSF, throat	IgM, paired IgG
HIV	Young adults	Year round	Fever, arthralgias, maculopapular rash, pharyngitis, adenopathy	Same as prodrome; meningitis may occur 1–5 days into the illness	2–6 wk after sexual or blood exposure	Blood PCR for HIV, RNA, or DNA	IgG (EIA) negative at this stage
Lymphocytic choriomeningitis virus	Older children, young adults	Fall, early winter	Fever and flulike syndrome, 5–21 days	Orchitis, alopecia	Exposure to mice, hamsters	PCR of CSF, blood	IgG
Mycobacterium tuberculosis	Infants (primary infection), young adults (reactivation)	Year round	Fever	Pneumonia, basilar inflammation with cranial nerve palsy and intracranial hypertension	History of tuberculosis or exposure, HIV risk factors	Culture, PCR of CSF for mycobacteria	None
Leptospira	Young adults	Late summer, early fall	Hepatitis and hematuria, 1–7 days	Conjunctivitis, splenomegaly, jaundice, nephritis, rash	Exposure to animals, water contaminated with animal urine	Culture of blood, CSF, urine	Paired IgG
Fungal	Premature infant, young adult	Year round	Fever	Basilar inflammation on CT or MRI, cranial nerve findings	Endemic area (blastomycosis, histoplasmosis) Immunodeficiency (cryptococcosis) Prematurity (candidal disease)	Culture of CSF for fungus, meningeal biopsy	Specific IgG
Mycoplasma organisms	Children, young adults	Fall, winter	Fever, malaise, sore throat, cough	Cough, rash, hemolytic anemia	Family or community epidemic	PCR of CSF, nasopharyngeal secretions	IgM

CSF, cerebral spinal fluid; CT, computed tomography; EIA, enzyme immunoassay; GI, gastrointestinal; HIV, human immunodeficiency virus; IgG and IgM, immunoglobulins G and M; MRI, magnetic resonance imaging; PCR, polymerase chain reaction.

Modified from Connolly KJ, Hammer SM. The acute aseptic meningitis syndrome. *Infect Dis Clin North Am.* 1990;4:599-622; and from Davis LE. Aseptic and viral meningitis. In: Long SS, Pickering LK, Prober CG, eds. *Principles and Practice of Pediatric Infectious Disease*. New York: Churchill Livingstone; 1997:331.

TABLE 39.9 Summary of Definitions and Major Features of the Four Subtypes of Fever of Unknown Origin

	Classic FUO	Health Care–Associated FUO	Immune-Deficient FUO	HIV-Related FUO
Definition	>38.0°C, >3 wk, >2 visits or 3 days in hospital	>38.0°C, >3 days, not present or incubating on admission	>38.0°C, >3 days, negative cultures after 48 hr	38.0°C, >3 wk for outpatients, >3 days for inpatients, HIV infection confirmed
Patient location	Community, clinic, or hospital	Acute care hospital	Hospital or clinic	Community, clinic, or hospital
Leading causes	Infections, cancer, inflammatory conditions, undiagnosed, habitual hyperthermia	Health care–associated infections, postoperative complications, drug fever	Majority due to infections, but cause documented in only 40–60%	HIV (primary infection), typical and atypical mycobacteria, CMV, lymphomas, toxoplasmosis, cryptococcosis, immune reconstitution inflammatory syndrome (IRIS)
History emphasis	Travel, contacts, animal and insect exposure, medications, immunizations, family history, cardiac valve disorder	Operations and procedures, devices, anatomic considerations, drug treatment	Stage of chemotherapy, degree and duration of neutropenia; drugs administered, underlying immunosuppressive disorder	Drugs, exposures, risk factors, travel, contacts, stage of HIV infection
Examination emphasis	Fundi, oropharynx, temporal artery, abdomen, lymph nodes, spleen, joints, skin, nails, genitalia, rectum, lower limb deep veins	Wounds, drains, devices, sinuses, lungs, venous thrombosis urine	Skin folds, IV sites, lungs, sinuses, perianal area	Mouth, sinuses, skin, lymph nodes, eyes, lungs, perianal area
Investigation emphasis	Imaging, biopsies, sedimentation rate, skin tests	Imaging, bacterial cultures	CXR, CT scan bacterial cultures	Blood and lymphocyte count; serologic tests; CXR; stool examination; biopsies of lung, bone marrow, and liver for cultures and cytologic tests; brain imaging
Management	Observation, outpatient temperature chart, investigations, avoidance of empirical drug treatments	Depends on situation	Antimicrobial treatment protocols	Antiviral and antimicrobial protocols, vaccines, revision of treatment regimens, good nutrition
Time course of disease	Months	Weeks	Days	Weeks to months
Tempo of investigation	Weeks	Days	Hours	Days to weeks

FUO, fever of unknown origin; CMV, cytomegalovirus; CXR, chest radiograph; HIV, human immunodeficiency virus; IV, intravenous.
Modified from Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practices of Infectious Diseases*. 7th ed. Philadelphia: Churchill Livingstone; 2010:780, Table 51.1.

of diagnosis after a 1-week study in the hospital (Table 39.9). In pediatrics, the defined duration of fever is variable, from 8 days to 3 weeks (average, 2 weeks). This may be dependent on the age of the patient, with shorter periods of fever in young infants and more traditional adult standards in adolescent patients. FUO is defined as a temperature higher than 38°C (100.4°F) daily for at least 8-14 days and no diagnosis after an initial evaluation. The initial evaluation recommended varies but always includes a noncontributory history and physical examination, and nondiagnostic initial laboratory and radiologic tests. In accordance with this definition, the differential diagnosis for FUO in children is large (Table 39.10).

Most children with FUO have an infectious disease; in a systematic review of studies of children with FUO, 51% of children had an infectious cause, 9% had a collagen vascular cause and 6% had a malignancy. There were 11% identified as otherwise miscellaneous which included Kawasaki disease and inflammatory bowel disease; 23% were without a formal diagnosis. Infections identified included urinary tract infections (UTI) and tuberculosis in all children; and osteomyelitis and bartonellosis in developed countries and brucellosis and typhoid in developing countries. Often patients with an FUO have atypical manifestations of common childhood bacterial or viral diseases rather than unusual or uncommon disorders.

◆ Evaluation

The evaluation of a child with FUO centers on a detailed history and physical examination. Taking the history should be repeated because parents often remember important details after the initial interview. The physical examination findings may also change during the course of the investigation revealing important clues (Fig. 39.5, Table 39.11).

◆ History

The history should include the time of day of the fever, who measured the temperature, and the instrument that was used to measure the temperature. Increased temperatures after exercise and in the afternoon often represent normal variations. The appearance of the

TABLE 39.10 Diagnostic Considerations of Fever of Unknown Origin in Children

Abscesses
Abdominal
Brain
Dental
Hepatic
Pelvic
Perinephric
Rectal
Subphrenic
Psoas

Bacterial Diseases
Actinomycosis
Bartonella henselae (cat-scratch disease)
Brucellosis
Campylobacter
Francisella tularensis (tularemia)
Listeria monocytogenes (listeriosis)
Meningococcemia (chronic)
Mycoplasma pneumoniae
Rat bite fever (*Streptobacillus moniliformis*; streptobacillary form of rat bite fever)
Salmonella
Tuberculosis
Whipple disease
Yersiniosis
Chlamydia
Lymphogranuloma venereum
Psittacosis

Localized Infections
Cholangitis
Infective endocarditis
Mastoiditis
Osteomyelitis
Diskitis
Pneumonia
Pyelonephritis
Sinusitis

Spirochetes
Borrelia burgdorferi (Lyme disease)
Relapsing fever *(Borrelia recurrentis)*
Leptospirosis
Rat bite fever (*Spirillum minus*; spirillary form of rat bite fever)
Syphilis

Fungal Diseases
Blastomycosis (extrapulmonary)
Coccidioidomycosis (disseminated)
Histoplasmosis (disseminated)

Rickettsiae-like organisms
Q fever
Rocky Mountain spotted fever
Tick-borne typhus
Anaplasmosis
Ehrlichosis

Viruses
Cytomegalovirus
Hantavirus
Hepatitis viruses
Human immunodeficiency virus
Epstein–Barr virus

Parasitic Diseases
Amebiasis
Babesiosis
Giardiasis
Malaria
Toxoplasmosis
Trichinosis
Trypanosomiasis
Visceral larva migrans *(Toxocara)*

Rheumatologic Diseases
Behçet syndrome
Juvenile dermatomyositis
Juvenile idiopathic arthritis
Rheumatic fever
Systemic lupus erythematosus
Vasculitis

Hypersensitivity Diseases
Drug fever
Hypersensitivity pneumonitis
Serum sickness
Weber–Christian disease

Neoplasms
Atrial myxoma
Cholesterol granuloma
Hodgkin disease
Inflammatory pseudotumor
Leukemia
Lymphoma
Pheochromocytoma
Neuroblastoma
Wilms tumor

Granulomatous Diseases
Crohn disease
Granulomatous hepatitis
Sarcoidosis
Polyangiitis with granulomatosis

Familial and Hereditary Diseases
Anhidrotic ectodermal dysplasia
Autonomic neuropathies
Fabry disease
Familial dysautonomia
Familial Hibernian fever
Familial Mediterranean fever and the many other autoinflammatory diseases (see Chapter 41)
Hypertriglyceridemia
Ichthyosis
Sickle cell crisis
Spinal cord/brain injury

Continued

TABLE 39.10 Diagnostic Considerations of Fever of Unknown Origin in Children—cont'd

Miscellaneous	
Addison disease	Infantile cortical hyperostosis
Allergic Alveolitis	Inflammatory bowel disease
Castleman disease	Kawasaki disease
Chronic active hepatitis	Kikuchi–Fujimoto disease
Cyclic neutropenia	Metal fume fever
Diabetes insipidus (nonnephrogenic and nephrogenic)	Pancreatitis
Factitious fever	Periodic fever syndromes
Hemophagocytic syndromes	Poisoning
Hypereosinophilia syndromes	Pulmonary embolism
Hypothalamic-central fever	Thrombophlebitis
	Thyrotoxicosis, thyroiditis

TABLE 39.11 Examples of Subtle Physical Findings Having Special Significance in Patients with Fever of Unknown Origin

Body Site	Physical Finding	Diagnosis
Head	Sinus tenderness	Sinusitis
Temporal artery	Nodules, reduced pulsations	Temporal arteritis, vasculitis
Oropharynx	Ulceration Tender tooth	Disseminated histoplasmosis, SLE, Behçet syndrome, IBD Periapical abscess
Fundi or conjunctivae	Choroid tubercle Petechiae, Roth spot	Disseminated granulomatosis* Endocarditis
Thyroid	Enlargement, tenderness	Thyroiditis
Heart	Murmur	Infective endocarditis, rheumatic fever
Abdomen	Enlarged iliac crest lymph nodes, splenomegaly	Lymphoma, endocarditis, disseminated granulomatosis*
Rectum	Perirectal fluctuance, tenderness Perianal skin tags, fistula	Abscess IBD
Genitalia	Testicular nodule Epididymal nodule	Periarteritis nodosa, tumor Disseminated granulomatosis*
Lower extremities	Deep venous tenderness	Thrombosis or thrombophlebitis; malignancy, autoimmune disease
Skin and nails	Petechiae, splinter hemorrhages, subcutaneous nodules, clubbing	Vasculitis, endocarditis, bronchiectasis

*Includes tuberculosis, histoplasmosis, coccidioidomycosis, sarcoidosis, and syphilis.
SLE, systemic lupus erythematosus; IBD, inflammatory bowel disease.
Modified from Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practices of Infectious Diseases.* 7th ed. Philadelphia: Churchill Livingstone; 2010:785, Table 51.8.

child while febrile is also important. Increased temperature without sweating might be seen in a child with ectodermal dysplasia or factitious fever.

The pattern of fever should be noted (Fig. 39.6). Sustained fever, intermittent fever, and relapsing fever have been associated with different disease states. Sustained or remittent fever remains elevated with little variation during the day and has been associated with enteric (typhoid) fever, tularemia, and rickettsial diseases such as typhus and Rocky Mountain spotted fever. Intermittent fever normalizes at least once a day and is associated with tuberculosis, abscesses, lymphomas, juvenile idiopathic arthritis (JIA), and some forms of malaria. Children with relapsing fever have afebrile days between febrile episodes. Relapsing fever has been associated with rat bite fever, *Borrelia* species infection, malaria, brucellosis, subacute bacterial endocarditis, African trypanosomiasis, lymphomas, and Lyme disease. Saddle-back or double-hump fever lasts a few days, is followed by an afebrile day or 2, and then returns. It has been associated with some viruses and dengue fever. Double quotidian fever (2 fever spikes each day) occurs in kala-azar, malaria, and gonococcal endocarditis. Periodic fevers occur as acute febrile episodes separated by prolonged afebrile, healthy periods. Diseases to consider include cyclic neutropenia, familial Mediterranean fever, and the syndrome of periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA). Periodic fever syndromes have different prevalence patterns in different ethnic groups and different inheritance patterns. A detailed family history is particularly important when these diagnoses are considered (see Chapter 41).

Unfortunately, neither the fever pattern nor the duration is specific for a particular cause. Fevers lasting for more than 1 year are not usually infectious; factitious fever, rheumatic or granulomatous disorders, familial diseases, or malignancies need to be considered in these patients.

A history of rash is important for diagnosing Lyme disease, JIA, and acute rheumatic fever (see Chapter 40). A history of pica is associated with visceral larva migrans and toxoplasmosis. Exposure to domestic and wild animals should be identified to exclude zoonoses (see Chapter 40). The food history should be detailed and should include water sources, use of game meats, cooking practices, and consumption of unpasteurized, raw milk, or soft cheese.

Travel history is critically important in the establishment of a differential diagnosis. Areas visited, accommodations, activities,

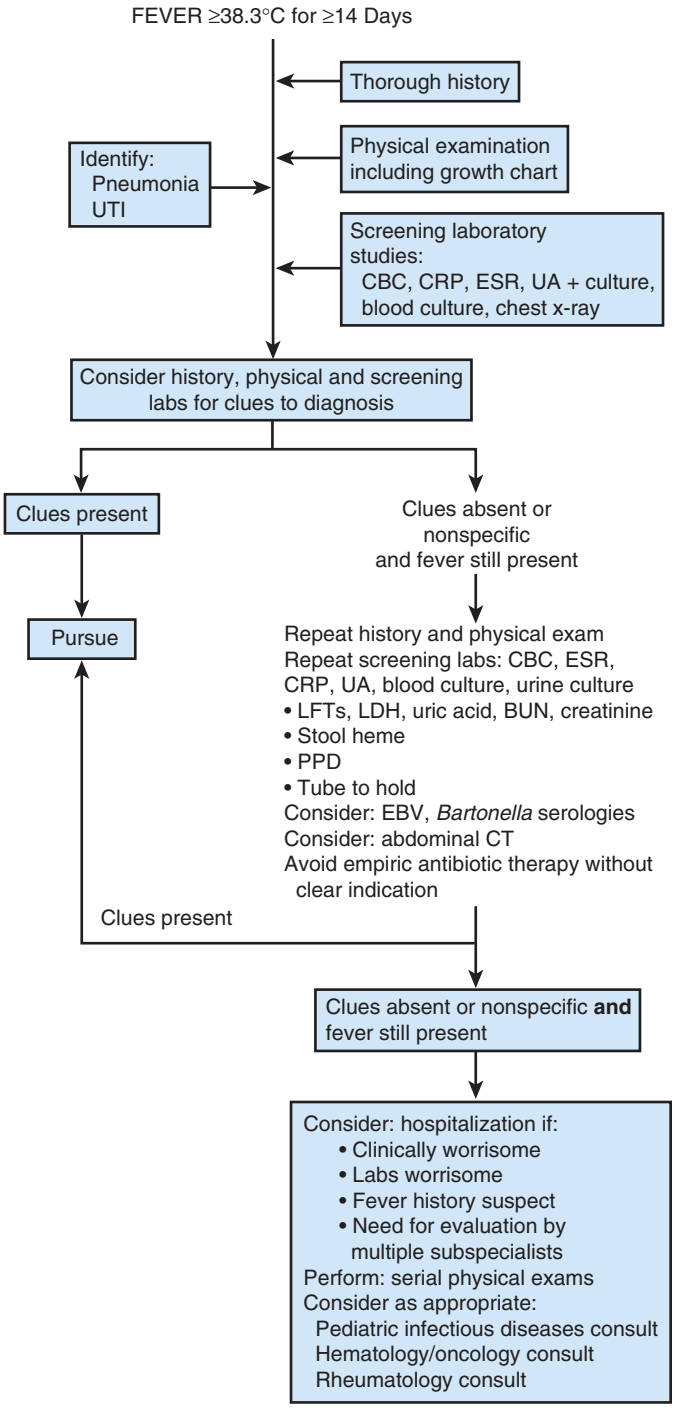


FIGURE 39.5 Approach to the evaluation of fever of unknown origin (FUO). BUN, blood urea nitrogen; CBC, complete blood count; CT, computed tomography; CRP, C-reactive protein; EBV, Epstein–Barr virus; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; LFT, liver function test; PPD, purified protein derivative; UA, urinalysis; UTI, urinary tract infection.

prophylactic treatments, animal and insect exposures, and water and food sources should be reviewed. Coccidioidomycosis, histoplasmosis, malaria, Lyme disease, and Rocky Mountain spotted fever have regional distributions. Children who have traveled to or have emigrated from developing countries are at increased risk for endemic diseases and *M. tuberculosis* (Table 39.12).

Previous medical records should be reviewed. Weight loss is important for diagnosing many chronic diseases such as lymphoma, tuberculosis, and inflammatory bowel disease. Poor weight gain and growth, with or without gastrointestinal symptoms, may be the only historical clue to inflammatory bowel disease (see Chapter 11). HIV risk factors in the parents and child should be reviewed. Past and current medications should also be reviewed. The review of systems may reveal heat intolerance, palpitations, tremors, and declining quality of schoolwork in a child with hyperthyroidism. A history of severe head trauma may be associated with hypothalamic dysfunction and central fevers.

◆ Physical Examination

Whenever possible, the patient should be examined during a febrile episode. A high fever in the absence of an increased pulse may be present in a patient with factitious fever. To verify this diagnosis, the temperature of freshly voided urine may be recorded. Tremor, tachycardia, palpitations, exophthalmos, lid lag, eyelid retraction, and smooth, flushed skin with diaphoresis are suggestive of hyperthyroidism.

Eyes

The ophthalmologic examination should include assessment of visual acuity, extraocular motion, visual field integrity, and gaze, as well as inspection of external structures and ophthalmoscopic examination (see Chapter 32). Conjunctivitis, iritis-uveitis-scleritis, or both may be seen in a variety of infectious conditions, including Epstein–Barr virus (EBV) infection, leptospirosis, rickettsial infection, and cat-scratch disease. Conjunctivitis, uveitis, or both occur with Kawasaki disease, systemic lupus erythematosus (SLE), polyarteritis nodosa, and JIA. Sarcoidosis may be associated with conjunctival and uveal tract nodules. A thorough ophthalmoscopic evaluation (and, if needed, slit-lamp examination) should be performed. Sarcoidosis may be accompanied by vascular occlusions, hemorrhages, vascular sheathing, and preretinal inflammatory exudates. Cytomegalovirus (CMV) produces chorioretinitis associated with white infiltrates near vessels and confluent depigmented areas. Histoplasmosis causes small atrophic spots and, in rare cases, focal granulomas of the retina and choroid. *Toxoplasma gondii* is a common cause of recurrent retinochoroiditis. Retinal changes also occur with bacterial endocarditis. Tuberculosis can cause formation of choroidal tubercles and also ulcerative palpebral conjunctival lesions. Slit-lamp examination may also reveal iridocyclitis in JIA, Behçet syndrome, and inflammatory bowel disease.

Ears, Nose, and Throat

The frontal and maxillary sinuses should be palpated for tenderness. The nares should be inspected for inflamed mucosa and purulent discharge. Tympanic membranes should be viewed and insufflated (see Chapter 4). The mouth should be checked for lesions, inflammation, and tooth tenderness. Behçet syndrome may manifest with oral aphthous lesions. Inspection of teeth and gums may reveal a dental abscess. Exudative and nonexudative pharyngitis is associated with EBV infection, tularemia, leptospirosis, and CMV. PFAPA syndrome is characterized by periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy. *Candida* infection in the mouths of children older than 2 years may result from immunodeficiency such as HIV or from the use of inhaled steroids.

Neck

The neck should be examined for adenopathy or thyroid enlargement (see Chapter 36). The rest of the lymphatic system should be carefully examined. A single tender node may be seen with cat-scratch disease. Generalized adenopathy can be seen in CMV infection, EBV infection, and systemic JIA (see Chapter 33).

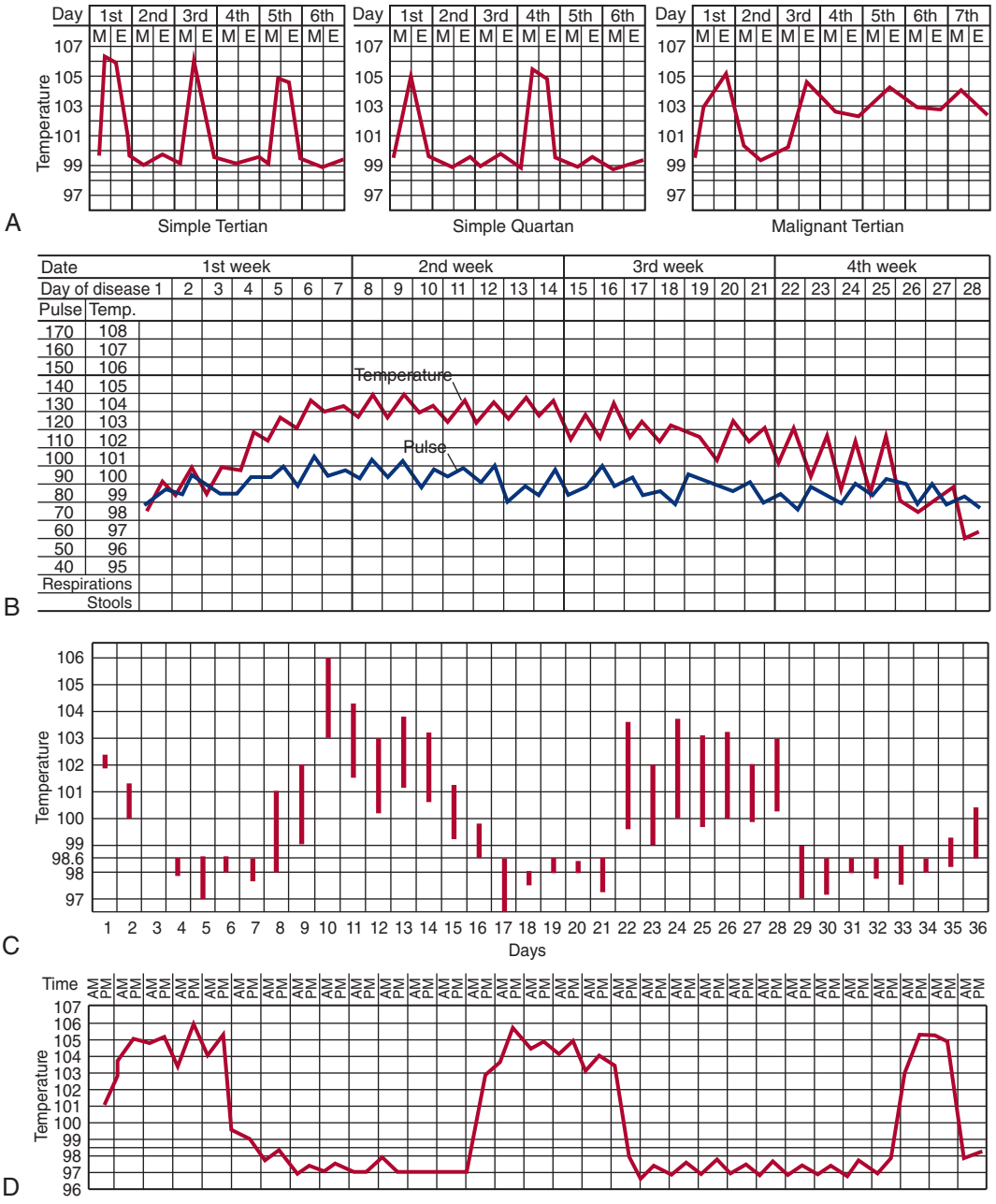


FIGURE 39.6 Distinctive Fever Patterns. *A,* Malaria. *B,* Typhoid fever (demonstrating relative bradycardia). *C,* Hodgkin disease (Perl-Ebstein pattern). *D,* Borreliosis (relapsing fever pattern). (Data from Woodward TE. The fever pattern as a clinical diagnostic aid. In: Mackowiak PA, ed. *Fever: Basic Mechanisms and Management*. 2nd ed. Philadelphia: Lippencott-Raven; 1997:215-236.)

Heart, Lungs, and Abdomen

Careful auscultation of the heart and lungs is essential. A mitral or aortic regurgitant murmur may be the initial finding of endocarditis or of carditis in children with acute rheumatic fever. A pericardial friction rub may also suggest JIA, SLE, rheumatic fever, malignancy, or viral pericarditis. The abdomen must be carefully palpated for evidence of masses or hepatosplenomegaly (see Chapters 14 and 17). Abdominal tenderness may be present with abdominal abscesses, hepatosplenomegaly, and inflammatory bowel disease. A rectal examination should be performed, and stool should be tested for occult blood. Sexually active girls should have a pelvic examination. Pain on movement of the uterus during the pelvic examination may indicate pelvic inflammatory disease.

Musculoskeletal Evaluation

The musculoskeletal examination should include assessments of strength and of active and passive range of motion and evaluation for warmth, tenderness, or swelling of joints. Irritability and pain on palpation over a bone or disuse pseudoparalysis may be the 1st clue to osteomyelitis. Bone pain may also result from neoplastic infiltration of the bone marrow or sickle cell anemia. Unexplained fever, arthralgias, and arthritis may be present with acute rheumatic fever, JIA, Lyme disease, Kawasaki disease, SLE, polyarteritis nodosa, and Behçet syndrome (see Chapter 33). Myalgias occur commonly with viral diseases such as influenza, and may be present with rickettsial diseases, polyarteritis nodosa, Takayasu arteritis, and dermatomyositis.

TABLE 39.12 Causes of Fever in the Returned Traveler

Diagnosis	%
Malaria	30–40
Hepatitis	3–6
Respiratory infection*	2–11
Urinary tract infection/pyelonephritis	2–4
Dysentery	4–5
Dengue fever	2–6
Enteric fever	1–2
Tuberculosis	1–2
Rickettsial infection	~1
Acute HIV infection	<1
Amebic liver abscess	<1
Other miscellaneous infections	4–9
Miscellaneous noninfectious causes	1–6
Undiagnosed	~25

*Includes upper respiratory tract infection, pneumonia, and bronchitis.
HIV, human immunodeficiency virus.
Modified from Suh KN, Kozavsky PE, Keystone JS. Evaluation of fever in the returned traveler. *Travel Med.* 1999;83:997-1017.

Skin

The skin must be inspected for evidence of rashes and other lesions (see Chapter 40). JIA may manifest with an evanescent, salmon-colored macular rash over the trunk and joints that may appear and disappear rapidly and be evident only during febrile periods. Dermatomyositis is characterized by a heliotropic rash of the upper eyelids and an erythematous eruption (vasculitis) over the extensor surfaces (Gottron sign). SLE may manifest with a butterfly rash over the nose and malar regions, signs of photosensitivity in sun-exposed areas, or vasculitis. The rash of Kawasaki disease is erythematous and may manifest in many forms; it is most commonly a diffuse maculopapular rash. In Rocky Mountain spotted fever, there are macular erythematous spots on the wrists, ankles, or forearms that may become maculopapular and expand centripetally to the proximal extremities and torso; palms and soles may be involved and petechiae may develop later in the course of the illness. Endocarditis may be associated with splinter hemorrhages or Janeway lesions (painless, small, erythematous or hemorrhagic lesions on the palms and soles). Lyme disease usually manifests with erythema migrans. This rash begins at the site of the tick bite and is erythematous with a pale center. The rash radiates out from the bite in a circular manner and persists for weeks; satellite secondary lesions may also appear.

Tularemia, salmonellosis, listeriosis, and EBV infections may feature generalized maculopapular rashes.

◆ Diagnostic Studies

Laboratory evaluation should proceed in a stepwise, focused manner with emphasis on identifying serious illnesses with defined interventions (see Fig. 39.5). Initial studies should include a complete blood cell count with differential, erythrocyte sedimentation rate (ESR) measurement, CRP, blood cultures, urinalysis, urine culture, tuberculin skin tests with controls (anergy panel) or gamma interferon release assay, and chest radiograph. Because EBV infection is common in childhood, viral-specific antibody titers may also be obtained at the initial evaluation (see Chapter 36). Further studies should be directed by information obtained from detailed histories and physical examinations.

Specific serologic studies aid in the diagnosis of CMV, toxoplasmosis, brucellosis, tularemia, hepatitis A, B, and C, and leptospirosis. Biopsies of lymph nodes, the skin, the liver, or bone marrow may be indicated. Radiologic studies that may be of benefit if directed by the history, physical examination findings, and initial laboratory study results include sinus CT, abdominal imaging, or total body MRI (to evaluate for occult osteomyelitis, malignancy, histiocytic disorders).

The complete blood cell count with differential is neither specific nor diagnostic, except in rare circumstances, such as seeing lymphoblasts on the blood smear. Approximately 30% of patients have abnormal white blood cell counts; 46% may have a left shift, lymphocytosis, atypical lymphocytes, or blasts. An elevated ESR or CRP indicates inflammation. The ESR is usually (70-90% of the time) high in children with FUO caused by infectious pathogens, malignancies, and rheumatic diseases. Of patients with an ESR less than 10 mm/hr, 90% have a self-limited viral disease.

Urinalysis and urine culture identify occult infections, particularly in young girls. The urinalysis may also be abnormal in patients with endocarditis and rheumatic and other inflammatory disorders.

Unexpected consolidations, calcifications, interstitial changes, perihilar adenopathy, or cardiomegaly (heart failure, pericarditis) may be found on chest radiographs. Chest films are abnormal in 10-15% of patients with FUO. CT of the chest may reveal abnormalities not detected by a chest x-ray.

Specialized radiologic studies performed without specific diagnostic clues from the history, physical examination findings, or initial laboratory evaluation results have a low yield. Whole body MRI is another technique that may be useful in children with FUO. It is helpful in identifying abnormal areas in bones, such as with occult osteomyelitis.

Cause

Infections

A wide variety of infections have been identified in children with FUO including subacute bacterial endocarditis, urinary tract infections (UTI), sinusitis, abscesses, osteomyelitis, and rheumatic fever.

Bacterial endocarditis. Bacterial endocarditis is rare in children; incidence increases with advancing age and history of preexisting heart disease (see Chapter 8). A new murmur or a change in the characteristic of an existing murmur may not be initially evident. Vegetations also may not be visible initially by transthoracic echocardiography; a transesophageal approach is much more sensitive. Serial blood cultures with anaerobic and aerobic media are necessary for definitive diagnosis.

Urinary tract infection. Both upper and lower urinary tract infections may be asymptomatic, and leukocytes may not always be present in urine (see Chapter 18). Sterile pyuria may be present with tuberculosis, nongonococcal urethritis, viral cystitis, Kawasaki disease, reactive arthritis, interstitial nephritis, and other rheumatic diseases. Renal ultrasonography may show areas of decreased echogenicity, enlarged echogenic kidneys, and renal or perinephric abscesses. Kidneys may be enlarged with acute pyelonephritis. A CT scan with contrast may show infected parenchyma as a nonenhancing lucency. Nuclear medicine renal scans also identify active areas of infection and old scars.

Sinusitis. Factors that decrease the size and patency of the ostium, or impair the mucociliary transport system predispose a child to sinusitis. Ethmoid and maxillary sinuses are present at birth. The frontal sinuses usually appear near 5 or 6 years of age but may be asymmetric or absent. Sphenoid sinuses may be seen radiographically by 9 years of age. Prolonged nasal congestion, headache, purulent nasal discharge, sore throat, daytime cough, tender teeth, and halitosis may be present

in children with sinusitis. CT studies may be helpful. Rhinoscopy may show purulent material at the ostium of an infected sinus. Infectious complications of sinusitis include dural space empyema or brain abscesses.

Abscesses. Hepatic, renal, perinephric, pelvic, and subphrenic abscesses may present with FUO. Internal jugular thrombophlebitis may manifest with prolonged fever and severe neck pain. Liver abscess may manifest with right upper quadrant tenderness and hepatomegaly. Blood cultures and liver function study results are often normal. The diagnosis may be made with MRI, CT with contrast, or ultrasonography. The diagnosis of perinephric abscesses is made with CT with contrast or ultrasonography. CT or ultrasound guidance may be used to direct percutaneous drainage of many abscesses. Pelvic abscesses should be suspected in children with FUO who have abdominal, rectal, or pelvic tenderness.

Osteomyelitis. Osteomyelitis usually follows bacteremia, but it sometimes follows penetrating injury. Tenderness to palpation over the infected site is common. Abnormalities in plain films appear late (2 weeks). MRI is the imaging modality of choice. The blood or bone culture is often positive, and the ESR is often elevated. Suppurative myositis may mimic osteomyelitis and manifest as an FUO.

Rheumatic fever. Acute rheumatic fever may cause FUO; the diagnosis is made by fulfillment of the Jones criteria, updated in 2015 (see Chapter 8). Initially, a child may present with polyarthralgia and an increased ESR. Elbows, wrists, knees, and ankles are frequently involved. The later migratory nature of the true arthritis differentiates rheumatic fever from JIA.

Bacterial Syndromes

Bacterial syndromes that cause FUO in children include agents of the following:

- Lyme disease
- Cat-scratch disease
- Q fever
- Rat bite fever
- Tularemia
- Brucellosis
- Leptospirosis

Lyme disease. Lyme disease is caused by the spirochete *Borrelia burgdorferi* and is transmitted by the *Ixodes dammini* and *I. pacificus* ticks. The usual manifestation of early Lyme disease is with erythema migrans, an erythematous, annular, expanding rash with central clearing. The rash resolves 1-30 days (usually 2 weeks) after exposure. Patients may exhibit fever, chills, fatigue, headaches, malaise, myalgias, arthralgias, and lymphadenopathy. Early disseminated Lyme disease follows 2-8 weeks after exposure; facial nerve palsy, peripheral neuropathy, cardiac conduction defects, myocarditis, and aseptic meningitis may occur. Diagnosis is made clinically in early localized Lyme disease because serology lacks sensitivity and specificity during early infection and because erythema migrans is so specific for Lyme disease. Diagnosis of early disseminated Lyme disease requires a typical clinical illness, exposure to ticks known to carry *B. burgdorferi* and serologic evidence of infection with a 2-tier testing strategy. The initial test is an enzyme-linked immunosorbent assay (ELISA) or immunofluorescent (IFA) test. If this result is equivocal or positive, a Western immunoblot is performed. Western blot should not be performed if the ELISA is negative or has not been performed because it lacks specificity in this setting.

Cat-scratch disease. Cat-scratch disease is a febrile illness associated with cats (usually kittens) and, more rarely, dogs. *Bartonella henselae*, which may be transmitted by the cat flea and by cat saliva, is the etiologic agent. After a scratch or bite, a papule forms and may persist from days to months. Regional lymphadenopathy with 1 or more nodes occurs proximal to the skin site 1-9 weeks after inoculation. The node or nodes become enlarged and tender and may have overlying erythema. The lymphadenopathy usually resolves after 2 months but may last up to 3 years. Affected children may have adenopathy with fever, headache, malaise, anorexia, sore throat, and conjunctivitis (see Chapter 36).

Q fever. Q fever is caused by *Coxiella burnetii*, formerly classified as a rickettsia. It manifests with headache, fever, chills, malaise, and, on occasion, respiratory symptoms. Hepatic, cardiac, and CNS involvement may occur. Rash is usually not seen. Domestic farm animals, cats, rodents, and marsupials may be infected. Pasteurization destroys the organism in milk. Diagnosis is made by serologic testing.

Rat bite fever. Rat bite fever is a relapsing fever caused by *Streptobacillus moniliformis* or *Spirillum minus*. *S. moniliformis* is a pleomorphic gram-negative bacillus transmitted by rat bite or by contaminated food or water. In 1-10 days after exposure, patients may exhibit fever, chills, malaise, and muscle aches. A rash may form on the extremities; arthralgias and arthritis may occur. Complications include abscesses, pneumonia, endocarditis, myocarditis, and meningitis. Diagnosis is made by blood culture or culture of other infected fluid, such as abscess aspiration.

Tularemia. *Francisella tularensis* is the causative agent of tularemia. The disease is spread by contact with wild animals, such as rabbits and squirrels, and by insects that bite these animals, such as mosquitoes, ticks, and deer flies, as well as by contaminated water. A maculopapular nodule forms at the portal of entry and later becomes ulcerated. The child may present with fever, chills, and headache. Lymphadenopathy, pharyngitis, conjunctivitis, hepatosplenomegaly, and pneumonia may also occur. Diagnosis is made by serologic study.

Brucellosis. Brucellosis is caused by gram-negative coccobacilli: *Brucella abortus*, *B. melitensis*, *B. suis*, or *B. canis*. The microorganisms are found in sheep, goats, cattle, swine, and dogs. Infection may occur by airborne spread or by ingestion of meat or milk. The child may present with fever, chills, malaise, headache, arthralgias, or myalgias. Pneumonia, cardiac involvement, and CNS involvement occur in rare cases. Diagnosis is made by special culture techniques and serologic study.

Leptospirosis. Leptospirosis is caused by members of the spirochete genus *Leptospira*. Infection is spread by contact with the urine of wild or domestic animals. In 1-2 weeks after exposure, patients experience the abrupt onset of fever, chills, nausea, vomiting, headache, and occasionally conjunctival suffusion and rash. Liver, renal, and CNS involvement may also occur. Diagnosis is made by special culture techniques and serologic testing.

Fungal Infections

Fungal causes of FUO include:

- Blastomycosis
- Histoplasmosis
- Coccidioidomycosis
- Cryptococcoses

Blastomyces dermatitidis is a saprophytic fungus with both yeast and mycelial forms; it is found in the soil all over the world but is common in the Americas. It is endemic in the Southeast and Midwest regions of North America. Infections with this fungus may be disseminated or pulmonary. The diagnosis is made by visualization of single-budding yeast in clinical material, culture on Sabouraud agar, or serologic tests.

Histoplasma capsulatum is a yeast found in soil in the Ohio River valley and other locations in the United States that causes pulmonary and disseminated disease. Diagnosis is made by the demonstration of the microorganism in biopsy specimens or by complement-fixing antibody.

Coccidioides immitis is found in soil in the southwestern United States. Infections in humans are associated with a febrile pulmonary disease characterized by cough, rash, and chest pain. Diagnosis is usually made serologically.

Cryptococcus neoformans is often found in pigeon droppings and can cause a variety of diseases. The diagnosis is made by culture or by identification of encapsulated yeast in collected specimens.

Chlamydial Infection

Psittacosis and lymphogranuloma venereum are chlamydial causes of FUO. *Chlamydia psittaci* may be transmitted by infected birds and produces respiratory illness with fever. Cardiac, liver, CNS, and thyroid involvement are rare. Diagnosis is made serologically. *C. trachomatis* is a sexually transmitted organism that causes urogenital infections, perihepatitis, invasive lymphadenopathy (lymphogranuloma venereum), neonatal conjunctivitis, and neonatal pneumonia. Diagnosis is by cell culture and rapid antigen tests.

Rickettsial Infections

Rocky mountain spotted fever. Rocky Mountain spotted fever manifests with fever, headache, intense myalgias, and abdominal symptoms. A characteristic rash is usually present by the 6th day of illness. The rash covers the palms, wrists, soles, and ankles and progresses from macular to petechial. The disease can last up to 3 weeks. Many end organs, including the heart, kidneys, and CNS, can be involved. Transmission of the causative agent, *Rickettsia rickettsii*, occurs by tick bite. Diagnosis is made by PCR testing of blood.

Ehrlichiosis and Anaplasmosis. These infections are caused by *Ehrlichia chaffeensis*, *Anaplasma phagocytophilia*, and *E. ewingii* and are transmitted by the Lone Star tick. Anaplasmosis is caused by Anaplasma phagocytophilia and is transmitted by the black legged deer tick. These illnesses are usually seen in the southeastern and upper Midwestern United States, respectively, and have manifestations similar to that of Rocky Mountain spotted fever. The patient presents with headache, myalgias, fever, chills, nausea, vomiting, weight loss, thrombocytopenia, and leukopenia. Rash is inconsistent but may be seen after 1 week. Pulmonary and renal complications can occur. Mental status changes are less frequent. Diagnosis is confirmed by PCR.

Viral Infections

Cytomegalovirus infection. CMV may cause a mononucleosis-like syndrome in children. Generalized or cervical adenopathy may be seen along with fatigue, malaise, fever, hepatosplenomegaly, and abdominal pain (see Chapter 36). A morbilliform rash may also be present. Retinitis, hepatitis, colitis, and pneumonia may occur in children with impaired immune systems. The virus is transmitted by contact with secretions. Infection is diagnosed by culture (nasopharyngeal, blood, urine) or by the detection of specific immunoglobulin G and immunoglobulin M antibodies.

Infectious mononucleosis. Infectious mononucleosis is typically caused by EBV and may manifest with fever, exudative pharyngitis, malaise, and fatigue (see Chapter 36). The appearance of rash is sometimes preceded by amoxicillin therapy, but rash may occur without antibiotic administration. Tender lymphadenopathy and hepatosplenomegaly may occur. The diagnosis may be made by nonspecific tests (heterophile antibody or Monospot) in older patients, but these studies are unreliable for young children. Specific antibody tests against viral capsid antigen, early antigen, and nuclear antigen are recommended in younger children. Treatment is supportive.

Human immunodeficiency virus infection. Infection with HIV or associated opportunistic infections or associated malignancies is another cause of FUO in children.

Parasites

FUO in children may be caused by parasitic infections, including (1) babesiosis, (2) toxoplasmosis, and (3) toxocariasis.

Babesiosis is caused by *Babesia microtia* and is a parasite of rodents transmitted to humans by tick bite. Infection may result in fever, chills, nausea, vomiting, night sweats, myalgias, and arthralgias. Identification of the organism in a thick smear of red blood cells is diagnostic.

T. gondii is a protozoan parasite. Children become infected from eating contaminated, undercooked meat or from exposure to the feces of domestic cats. Most infections acquired postnatally are asymptomatic but children may develop a mononucleosis-like illness (see Chapter 36).

Toxocariasis (previously visceral larva migrans) results from ingestion of larvae of *Toxocara canis* or from *T. cati* shed in dog and cat feces, respectively. Infection results in fever, intense eosinophilia, hepatomegaly, and hypergammaglobulinemia. Lung, heart, and CNS involvement is rare. The eye may become infected. Diagnosis is presumed with increased eosinophils and hypergammaglobulinemia, and elevated titers of isohemagglutinin to A and B blood group antigens.

Infections in Children Who Live in or Have Traveled to Developing Countries

In a child who has traveled to or lives in a developing country, consideration must be given to the area, water sources, and activities. Some causes of FUO to consider include malaria, hepatitis, typhoid fever, tuberculosis, and amebic liver abscess (Table 39.12).

Malaria

Malaria is transmitted by the bite of an infected mosquito carrying 1 of the 5 species of the *Plasmodium* genus that cause disease in humans. The patient experiences chills, rigors, high fever, diaphoresis, and headaches. The incubation period varies among species, from 1 week to several months. Demonstration of the parasite on thick peripheral blood smear is diagnostic. Risk for malaria can be checked for areas of the world on www.cdc.gov/malaria.

Hepatitis

Hepatitis A may be contracted by ingestion of contaminated food or water. Hepatitis B and C viruses are transmitted through blood products or sexual contact. Diagnosis is by serologic testing. Symptoms can include fever, malaise, jaundice, hepatomegaly, nausea, and anorexia. Hepatitis B and C can become chronic (see Chapter 15).

Typhoid Fever (Enteric Fever)

Enteric fever is caused by infection with 3 serovars of *S. enterica*, which includes *S. typhi*. After ingestion of contaminated water or food, incubation lasts from 1-6 weeks. Persistent fever, headache, malaise, anorexia, and rose spots are clinical hallmarks of enteric fever. Diagnosis is by blood culture.

Tuberculosis

Tuberculosis may manifest as FUO in children (see Chapters 2 and 36). Affected children may have pulmonary or extrapulmonary disease. The signs and symptoms of pulmonary disease may vary greatly from weight loss, tuberculin skin test conversion, and low-grade fever to mass effect from mediastinal lymphadenopathy and fulminant disseminated pulmonary involvement with miliary infiltrates or, in rare cases, cavitation. Nonpulmonary tuberculosis more commonly manifests as FUO, inasmuch as positive chest radiograph findings and pulmonary signs may initiate an early work-up for tuberculosis. Hematogenous spread may cause liver, heart, or renal involvement. Ingested bacilli may result in gastrointestinal tuberculosis. The diagnosis requires demonstration of

acid-fast bacilli from sputum, gastric aspirate, or the affected organ. Skin testing may yield negative results even with positive controls.

Amebiasis

Intestinal infection with *Entamoeba histolytica* may produce invasion of the mucosal lining and spread to other organs such as the liver. Amebic liver abscess may manifest with fever, weight loss, right upper quadrant pain, and anorexia. The patient may have painful hepatomegaly without splenomegaly. The abscess may be localized with abdominal ultrasonography or CT. Diagnosis is by serologic study.

Rheumatic Causes of Fever of Unknown Origin

Rheumatic diseases as a cause of FUO are the 2nd most common identified cause of FUO after infections. In a systematic review, the most common causes were JIA and SLE (see Chapter 33).

Juvenile Idiopathic Arthritis

JIA is a diagnosis that requires time to identify all of its manifestations and to exclude other entities. JIA is defined by arthritis of unknown origin that begins in a child younger than 16 years and persists for a minimum of 6 weeks. JIA is divided into 3 subtypes: systemic, polyarticular, and oligoarticular. The systemic form often manifests with prolonged high fever. Affected children often have a daily fever and may have a fine macular rash, arthralgias, arthritis, hepatosplenomegaly, or pericardial involvement. Polyarticular JIA may manifest with arthritis, low-grade fever, morning stiffness, anorexia, and weight loss.

Polyarteritis

Polyarteritis is a necrotizing vasculitis that may manifest with myalgia, arthralgia, fever, vasculitic skin lesions, and abdominal pain. Cardiac, CNS, and renal involvement may also occur. The ESR usually is markedly elevated. Biopsy and the presence of antibodies to proteinase 3 and myeloperoxidase (antineutrophil cytoplasmic antibodies) are helpful.

Systemic Lupus Erythematosus

SLE may manifest with fever, photosensitivity, mouth sores, weight loss, rash, myalgias, malaise, and hepatosplenomegaly. Patients may also have serositis and renal involvement. Laboratory tests that are helpful include lupus erythematosus cell preparation and those for antinuclear antibody, anti-Smith antibody, anti-ribonuclear protein antibody, anti-Ro (Sjögren syndrome type A) antibody, and anti-La (Sjögren syndrome type B) antibody.

Behçet Syndrome

Behçet syndrome is very rare in children but may manifest with FUO. Patients may have aphthous stomatitis, arthritis, genital ulcers, uveitis, and erythema nodosum.

Neoplasms

Hodgkin disease, lymphoma, neuroblastoma, and leukemia may all manifest as FUO. In young children, leukemia, neuroblastoma, and lymphoma should be suspected, whereas in adolescents, Hodgkin disease and Ewing sarcoma are more common as causes of FUO.

Hodgkin Disease

Hodgkin disease may manifest with firm, nontender adenopathy, fever, night sweats, and weight loss. Diagnosis is made through biopsy.

Lymphoma

Non-Hodgkin lymphoma may manifest as painless adenopathy, cough or dyspnea from a mediastinal mass, abdominal mass, nerve compression, bone pain, fever, and weight loss. Diagnosis is by biopsy.

Neuroblastoma

Neuroblastoma may manifest as abdominal, thoracic, or pelvic masses; spinal cord compression; bone pain; hypertension; hepatomegaly; diarrhea; and fever (see Chapter 17). Diagnosis is aided by radiologic studies and urinary catecholamine measurements and is confirmed by biopsy.

Leukemia

Both acute lymphocytic leukemia and acute nonlymphocytic leukemia may manifest with lethargy, pallor, bleeding, fever, bone pain, lymphadenopathy, and arthralgias. Diagnosis is made by blood smear and bone marrow biopsy.

Pheochromocytoma

Pheochromocytomas are rare catecholamine-secreting tumors; 10% occur in children. These tumors manifest with paroxysmal or sustained hypertension, headache, excessive sweating, fever, hyperglycemia, and palpitations. The tumors are usually in the adrenal medulla, but 35% of those occurring in children are multiple or extraadrenal. Diagnosis is made by measuring urinary or plasma metanephrine or catecholamine levels. Localization of tumor is by CT, MRI, or iodine 131-metaiodobenzylguanidine scanning.

Miscellaneous Causes of Fever of Unknown Origin

Genetic Diseases (See Chapter 41)

Familial Mediterranean fever is an autosomal recessive trait seen in Sephardic Jews and people of Middle Eastern descent. The fever may be accompanied by joint, abdominal, and chest pain. Anhidrotic ectodermal dysplasia is an X-linked recessive disorder associated with decreased ability to sweat, dental abnormalities, and sparse hair. Eyebrows and eyelashes may be absent. Fever may result from the inability of the body to cool itself. Diagnosis is made by skin biopsy that shows an absence of eccrine glands.

Drug Fever

Drug fever is a diagnosis of exclusion. Some drugs are more likely than others to cause drug fever (α-methyldopa, quinidine, penicillins). There is no characteristic fever pattern. There is a highly variable lag time between the initiation of the drug and the onset of fever, and there is an infrequent association with rash or eosinophilia. Some drugs may cause fever by virtue of physiologic side effects. Anticholinergic drugs may decrease sweating and diminish the body's ability to cool itself. Chronic salicylate intoxication can cause increased heat production by uncoupling oxidative phosphorylation.

Kawasaki Disease

Kawasaki disease may manifest with a variety of signs, including rash; lymphadenopathy; conjunctival hyperemia; strawberry tongue; erythematous lips; swelling of hands and feet; arthralgia; arthritis; myocarditis; late desquamation of hands, feet, and perineal area; and sterile pyuria. Fever may be high and spiking. Diagnosis is by fulfillment of clinical criteria (see Chapter 40).

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD; ulcerative colitis, Crohn disease) may manifest with FUO. Ulcerative colitis may manifest with bloody diarrhea, fever, fecal urgency, and straining (see Chapter 11). Pyoderma gangrenosum, arthritis, and erythema nodosum can also be seen. Crohn disease (regional enteritis) may manifest with abdominal pain, fever, anorexia, and growth failure. Diarrhea may develop later. Arthritis, erythema nodosum, and finger clubbing may also occur. Diagnosis of IBD is by endoscopy and histology.

Thyrotoxicosis

Hyperthyroid states may manifest with FUO. Children usually have multiple symptoms, such as irritability, tremor, eyelid lag, and exophthalmos. Diagnosis is made from thyroid function studies.

Factitious Disorders

Factitious fever may be a form of factitious disorder imposed on self (formerly Munchausen syndrome) or medical child abuse (formerly Munchausen syndrome by proxy) (see Chapter 26). A variety of techniques have been used to falsely elevate a recorded temperature. A mercury thermometer may be rubbed between hands or placed near a light bulb. Hot liquids may be placed in the mouth before an oral temperature is taken. Hot rectal douches have also been reported to raise a rectally taken temperature. Even with pathologic fevers, there is some circadian rhythm to the temperature curve; with factitious fever there is no rhythm. In addition, there is usually no vasoconstriction, sweating, tachypnea, or tachycardia. If factitious fever is suspected, the temperature should be obtained while the patient is observed. The temperature of freshly voided urine can also be recorded.

Other patients may produce actual diseases that cause true fevers, such as by injecting infected pyogenic material subcutaneously or intravenously or by taking toxic levels of thyroid hormone. Once the diagnosis is documented, psychiatric care is indicated.

Patients in Whom No Diagnosis Is Made

If no diagnosis is made, most patients are clinically well and asymptomatic on follow-up. Some may be determined to be healthy from the start; most are in good health at follow-up, whereas few have symptoms at the end of evaluation. Some may have relapses of fever for a few months. JIA, inflammatory bowel disease, and PFAPA syndrome may not be immediately diagnosed but usually manifest typical symptoms and signs within 2 years of the onset of the FUO.

SUMMARY AND RED FLAGS

Many children with fever will have a source identified on their initial history and physical examination. Red flags include patients with symptoms or signs of sepsis (tachycardia, hypotension) or meningitis or encephalitis (fever, headache, irritability, altered mental status and for the older child, meningismus). Affected infants with meningitis are more likely than older children to have subtle and nonspecific symptoms.

A child with fever of recent onset with no adequate historical or physical explanation for the fever is said to have fever without source (FWS). Because of the high volume of children with FWS, it is important to have a reliable system for individual patient evaluation and management. Although the majority of patients with FWS have a self-limited viral illness, 5-10% have an invasive bacterial infection, with young infants at highest risk. Because of the potential for morbidity and mortality from the organisms that cause invasive disease, identification of patients at high risk is essential. Although there is no single, timely series of tests that correctly categorizes all patients, the combination of careful clinical evaluation and appropriate laboratory screening criteria can help identify a level of risk in children of different ages. The reduction of bacteremia due to vaccine-serotype pneumococcus has led to a careful reduction in diagnostic testing, especially in the 3-36 month old child with FWS. Red flags include a history of immunodeficiency or other chronic medical illness, no prior immunizations, toxic appearance, signs of shock, petechiae or purpura, poor responsiveness, and other signs of altered mental status.

Some children, who are initially thought to have FWS, develop into patients with FUO. Definitions of FUO in children vary. A practical definition balancing different recommendations is FUO is a temperature higher than 38°C (100.4°F) daily for at least 8-14 days and no diagnosis after an initial evaluation. Work-up of the patient with FUO should proceed in a stepwise manner. It should be kept in mind that many patients with FUO have unusual, atypical, or complicated manifestations of common childhood illness, mainly infections. Red flags include weight loss, night sweats, signs of organ system dysfunction or failure, or unstable vital signs suggestive of sepsis. Only in this last category should a rapid diagnostic approach be performed and empirical antibiotic therapy initiated.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

General

Bahorski J, Repasky T, Ranner D, et al. Temperature measurement in pediatrics: a comparison of the rectal method versus the temporal artery method. *J Pediatr Nurs*. 2012;27:243-247.

Banerjee R, Teng CB, Cunningham SA, et al. Randomized trial of rapid multiplex polymerase chain reaction – based blood culture identification and susceptibility testing. *Clin Infect Dis*. 2015;61:1071-1080.

Carr EA, Wilmoth ML, Eliades AB. Comparison of temporal artery to rectal temperature measurements in children up to 24 months. *J Pediatr Nurs*. 2011;26:179-185.

Cheng TL, Partridge JC. Effect of bundling and high environmental temperature on neonatal body temperature. *Pediatrics*. 1993;92: 238-240.

Cimpello LB, Goldman DL, Khine H. Fever pathophysiology. *Clin Pediatr Emerg Med*. 2000;1:84-93.

Goldstein B, Giroir B, Randolph A, et al. International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6(1):2-8.

Grover F, Berkowitz CD, Lewis RJ, et al. The effects of bundling on infant temperature. *Pediatrics*. 1994;94:669-673.

Mahajan P, Ramilo O, Kupperman N. The future possibilities of diagnostic testing for the evaluation of febrile infants. *JAMA Pediatr*. 2013;167(10):888-898.

Stine CA, Flook DM, Vincze DL. Rectal versus axillary temperatures: is there a significant difference in infants less than 1 year of age? *J Pediatr Nurs*. 2012;27:265-270.

Sullivan JE, Farrar HC. Fever and antipyretic use in children. *Pediatrics*. 2011;127(3):580-587.

Vincent JL, Brealey D, Libert N, et al. Rapid diagnosis of infection in the critically ill: a multicenter study of molecular detection in bloodstream infections, pneumonia, and sterile site infections. *Crit Care Med*. 2015;43(11):2283-2291.

Wolfe M, Bachur R. Serious bacterial infection in recently immunized young febrile infants. *Acad Emerg Med*. 2009;16(12):1284-1289.

Fever Without Source

American Academy of Pediatrics. Clinical practice guideline for the diagnosis and management of the initial urinary tract infection in febrile infants and young children 2-24 months of age. *Pediatrics*. 2011;128(3):595-609.

Andreola B, Bressan S, Callegaro S, et al. Procalcitonin and C-reactive protein as diagnostic markers of severe bacterial infections in febrile infants and children in the emergency department. *Pediatr Infect Dis J*. 2007;26(8):672-677.

Arora R, Mahajan P. Evaluation of child with fever without source: review of literature and update. *Pediatr Clin North Am*. 2013;60(5):1049-1062.

Biondi E, Evans R, Mischler M, et al. Epidemiology of bacteremia in febrile infants in the United States. *Pediatrics*. 2013;132(6):990-996.

Colvin JM, Muenzer JT, Jaffe DM, et al. Detection of viruses in young children with fever without an apparent source. *Pediatrics*. 2012;130(6):e1455-e1462.

Coulthard MG, Kalra M, Lambert HJ, et al. Redefining urinary tract infections by bacterial counts. *Pediatrics*. 2010;125(2):335-341.

Greenhow TL, Hung Y, Herz AM. Changing epidemiology of bacteremia in infants aged 1 week to 3 months. *Pediatrics*. 2012;129(3):e590.

Herz AM, Greenhow TL, Alcantara J, et al. Changing epidemiology of outpatient bacteremia in 3 to 36 month old children after the introduction of the heptavalent-conjugated pneumococcal vaccine. *Pediatr Infect Dis J*. 2006;25(4):293-300.

Huppler AR, Eickhoff JC, Wald ER. Performance of low-risk criteria in the evaluation of young infants with fever: review of the literature. *Pediatrics*. 2010;125(2):228-233.

Olarte L, Barson WJ, Barson RM, et al. Impact of the 13-valent pneumococcal conjugate vaccine on pneumococcal meningitis in US children. *Clin Infect Dis*. 2015;61(5):767-775.

Pantell RH, Newman TB, Bernzwig J, et al. Management and outcomes of care of fever in early infancy. *JAMA*. 2004;291(10):1203-1212.

Rudinsky SL, Carstairs KL, Reardon JM, et al. Serious bacterial infections in febrile infants in the post-pneumococcal conjugate vaccine era. *Acad Emerg Med*. 2009;16(7):585-590.

Sanders S, Barnett A, Correa-Velez I, et al. Systematic review of the diagnostic accuracy of C-reactive protein to detect bacterial infection in nonhospitalized infants and children with fever. *J Pediatr*. 2008;153:570-574.

Schroeder AR, Chang PW, Shen MW, et al. Diagnostic accuracy of the urinalysis for urinary tract infection in infants < 3 months of age. *Pediatrics*. 2015;135(6):965-971.

Shaikh N, Morone NE, Bost JE, et al. Prevalence of urinary tract infection in childhood—a meta-analysis. *Pediatr Infect Dis J*. 2008;27:302-308.

Tam PI, Madoff LC, Coombes B, et al. Invasive pneumococcal disease after implementation of 13-valent conjugate vaccine. *Pediatrics*. 2014;134(2):210-217.

Van den Bruel A, Haj-Hassan T, Thompson M, et al. Diagnostic value of clinical features at presentation to identify serious infection in children in developed countries: a systematic review. *Lancet*. 2010;375:834-845.

Whitney C, Farley M, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med*. 2003;348:1737-1746.

Yo CH, Hsieh PS, Lee SH, et al. Comparison of the test characteristics of procalcitonin to C-reactive protein and leukocytosis for the detection of serious bacterial infections in children presenting with fever without source: a systematic review and meta-analysis. *Ann Emerg Med*. 2012;60(5):591-600.

Central Nervous System Infection

Avery RA, Licht DJ, Shah SS, et al. CSF opening pressure in children with optic nerve head edema. *Neurology*. 2011;76:1658-1661.

Avery RA, Shah SS, Licht DJ, et al. Reference range for cerebrospinal fluid opening pressure in children. *N Engl J Med*. 2010;363(9):891-892.

Byington CL, Kendrick J, Sheng X. Normative cerebrospinal fluid profiles in febrile infants. *J Pediatr*. 2011;158(1):33-37.

Curtis S, Stobart K, Vandermeer B, et al. Clinical features suggestive of meningitis in children: a systematic review of prospective data. *Pediatrics*. 2010;126(5):952-960.

Feigin RD, McCracken GH, Klein JO. Diagnosis and management of meningitis. *Pediatr Infect Dis J*. 1992;11:785.

Freedman SB, Marrocco A, Pirie J, et al. Predictors of bacterial meningitis in the era after *Haemophilus influenzae*. *Arch Pediatr Adolesc Med*. 2001;155:1301.

Gable MS, Sheriff H, Dalmau J, et al. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California encephalitis project. *Clin Infect Dis*. 2012;54:899-904.

Kanegaye JT, Soliemanzadeh P, Bradley JS. Lumbar puncture in pediatric bacterial meningitis: defining the time interval for recovery of cerebrospinal fluid pathogens after parenteral antibiotic pretreatment. *Pediatrics*. 2001;108:1169.

Kim KS. Acute bacterial meningitis in infants and children. *Lancet Infect Dis*. 2010;10(1):32-42.

Kimberlin DW, Lin CY, Jacobs RF, et al. Natural history of neonatal herpes simplex virus infections in the acyclovir era. *Pediatrics*. 2001;108:223.

Kimberlin DW, Lin CY, Jacobs RF, et al. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. *Pediatrics*. 2001;108:230.

Kulik DM, Uleryk EM, Maguire JL. Does this child have bacterial meningitis? a systematic review of clinical prediction rules for children with suspected bacterial meningitis. *J Emerg Med*. 2013;45(4):508-519.

Lee MW, Vedanarayanan VV. Cerebrospinal fluid opening pressure in children: experience in a controlled setting. *Pediatr Neurol*. 2011;45:238-240.

Newton RW. Tuberculous meningitis. *Arch Dis Child*. 1994;70:364.

Nigrovic LE, Malley R, Kuppermann N. Meta-analysis of bacterial meningitis score validation studies. *Arch Dis Child*. 2012;97(9):799-805.

Waecker NJ, Connor JD. Central nervous system tuberculosis in children: a review of 30 cases. *Pediatr Infect Dis J*. 1990;9:539.

Wong M, Schlaggar BL, Buller RS, et al. Cerebrospinal fluid protein concentration in pediatric patients. *Arch Pediatr Adolesc Med*. 2000;154:827.

Fever of Unknown Origin

American Academy of Pediatrics. *Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015.

Centers for Disease Control and Prevention. *Malaria*. [Updated 8-17-2015; cited 8-25-2017]. Available from: <http://www.cdc.gov/malaria>.

Chovel-Sella A, Ben Tov A, Lahav E, et al. Incidence of rash after amoxicillin treatment in children with infectious mononucleosis. *Pediatrics*. 2013;131:e1424.

Chow A, Robinson JL. Fever of unknown origin in children: a systematic review. *World J Pediatr*. 2011;7(1):5-10.

Hocqueloux L, Guinard J, Buret J, et al. Do penicillins really increase the frequency of a rash when given during Epstein-Barr virus primary infection? *Clin Infect Dis*. 2013;57:1661-1662.

Lohr JA, Hendley JO. Prolonged fever of unknown origin. *Clin Pediatr (Phila)*. 1977;16:768-773.

McClung MC. Prolonged fever of unknown origin in children. *Am J Dis Child*. 1972;124:544-550.

Palazzi DL, McClain DL, Kaplan SL. Hemophagocytic syndrome in children: an important diagnostic consideration in fever of unknown origin. *Clin Infect Dis*. 2003;36(3):306-312.

Pizzo PA, Lovejoy FH, Smith DH. Prolonged fever in children: review of 100 cases. *Pediatrics*. 1975;55:468-473.

Steele RW, Jones SM, Lowe BA, et al. Usefulness of scanning procedures for diagnosis of fever of unknown origin in children. *J Pediatr*. 1991;119:526-530.

Talano JAM, Katz BZ. Long-term follow-up of children with fever of unknown origin. *Clin Pediatr (Phila)*. 2000;39:715-717.

Woods CR. Rocky Mountain spotted fever in children. *Pediatr Clin North Am*. 2013;60(2):455-470.

40

Fever and Rash

Emily M. Densmore and Patricia S. Lye

The coexistence of fever and rash suggests a relatively wide spectrum of pathologic entities for diagnostic consideration. This spectrum includes local or systemic infection with a wide range of microbial pathogens; toxin-mediated disorders, including those associated with bacterial superantigen production; inflammatory conditions, including vasculitides and rheumatologic diseases; and hypersensitivity disorders. While most conditions causing fever and rash are benign and self-limited, a thorough clinical evaluation is crucial to identify those caused by life-threatening diseases or those requiring specific treatment. The essential elements for accurate diagnosis include a detailed history and a thorough physical examination including a careful systematic observation of the patient for evidence of toxicity. Because this approach lacks perfect sensitivity, the laboratory may play an important role in the diagnostic process.

FEVER AND RASH

◆ History

Information about the features of the rash includes when it occurred in relation to the fever, its evolution or progression, its anatomic distribution, and whether it is pruritic or painful (Table 40.1). Degree of illness should be evaluated, especially in the infant and toddler, by assessing oral intake, activity level, and urine output. A description of the fever pattern can be useful (see Chapter 39) and immunization status will help prioritize the differential diagnosis. Essential information from the epidemiologic and social history should include season of the year; geographic location of the patient's residence; exposure to known ill contacts; recent travel or exposure to individuals from different geographic areas; exposure to pets, wildlife, or insects; recent immunizations; a detailed list of medications; previous blood transfusion; and for the adolescent patient, intravenous drug use and sexual activity.

The medical and family history should be used to assess the overall health of the patient over time, as well as that of family members, to determine the possibility of underlying primary or acquired immunodeficiency or diseases associated with autoimmunity or chronic inflammation. A history of increased susceptibility to infection, as manifested by chronic or recurrent infectious illnesses after infancy, such as pneumonia, sinusitis, bronchitis, otitis media, diarrhea, and bacteremia, is an important indicator of underlying immunodeficiency disease (see Chapter 41). In addition, the occurrence of an unusually severe infection or an infection with a pathogen of low virulence (e.g., *Pneumocystis jiroveci*) should raise a suspicion of an immunodeficiency state. A history of hemolytic anemia, leukopenia, thrombocytopenia, or arthritis suggests an autoimmune disorder or malignancy, which may also be associated with impairment in immune function (see Chapter 33).

In a thorough systems review, the clinician should assess the probability of a subacute or chronic underlying infectious, inflammatory, or malignant disease by inquiring about anorexia, nausea, vomiting, weight loss or failure to thrive, night sweats, fatigue, cough, and exercise intolerance. The clinician should seek symptoms suggesting multisystem disease, such as myalgias, arthralgias, headache, precordial pain or pain with inspiration, abdominal pain, jaundice, skin photosensitivity, peripheral edema, alopecia, Raynaud phenomenon, and hematuria. In patients with symptoms that indicate the presence of multisystem disease, a thorough survey of the functional status of the central, peripheral, and autonomic nervous systems is clinically relevant. Specific inquiries into visual disturbances, photophobia, disordered mentation, neck stiffness, paresthesia, weakness, or seizure activity are essential and may reveal potentially life-threatening infection within the central nervous system or a systemic vasculitis involving the nervous system, such as systemic lupus erythematosus (SLE) or polyarteritis nodosa.

◆ Examination

The physical examination is used to refine the probability of underlying serious illness, to identify rashes typical of a specific diagnosis, to look for noncutaneous disease manifestations, and to identify if further testing or treatment is indicated (Table 40.2; also see Chapters 39 and 48).

A critical 1st step is an assessment of the patient's vital signs and degree of toxicity. Lethargy, irritability, altered mental status, decreased activity, poor perfusion, pallor, or cyanosis indicate serious illness; resuscitation and treatment directed at the most likely diagnoses should be initiated without delay. The importance of the height of fever in predicting the risk of serious illness is unclear. Underlying chronic illness and degree of toxicity are more useful for risk assessment than fever height. The presence of tachycardia and tachypnea in any patient with fever and rash suggests the possibility of sepsis. Tachycardia may also be seen in endocarditis or in myocarditis secondary to certain viruses, Kawasaki disease (KD), or acute rheumatic fever. Evidence of alteration in mental status suggests either sepsis associated with decreased organ perfusion or primary meningoencephalitis. The presence of hypotension usually indicates septic shock, but other disorders such as toxic shock syndrome (TSS), dengue hemorrhagic shock syndrome, hemorrhagic fever with renal syndrome caused by Hantavirus, and the hemorrhagic shock and encephalopathy syndrome must also be considered in this context. Hypertension may be noted in association with vasculitic disorders involving small- to medium-sized arteries, such as polyarteritis and SLE.

The clinical characteristics of the rash are often helpful in establishing an etiologic diagnosis. A morphologic nomenclature of cutaneous manifestations helps the clinician with differential diagnosis,

TABLE 40.1 Essential Elements of the History in the Clinical Assessment of Fever and Rash

Demographic Data
Age
Sex
Ethnicity
Season
Geographic area
Exposures
Ill contacts (home, daycare, school, workplace)
Sexual contacts
Travel outside area of residence
Pets, wildlife, insects (especially ticks)
Medications and drugs
Transfusions
Immunizations
Occupational
Features of Rash
Temporal associations (onset relative to fever)
Progression and evolution
Location and distribution
Pain or pruritus
Timing and pattern of desquamation
Associated Symptoms
Focal (suggesting organ-specific illness)
Systemic (suggesting generalized or multisystem illness)
Prior Health Status
Medical and surgical history
Growth and development
Recurrent infectious illnesses
Family History

TABLE 40.2 Essential Elements of the Physical Examination in the Clinical Assessment of Fever and Rash

Degree of Toxicity
Vital Signs
Fever pattern
Tachycardia or bradycardia
Tachypnea
Hypotension or hypertension
Characteristics of Rash
Macular
Papular
Maculopapular
Petechiae or purpura
Diffuse erythroderma
Accentuation in flexural creases
Desquamation with stroking (Nikolsky sign) or spontaneous
Localized erythroderma
Expansile
Painful
Urticaria
Vesicles, pustules, bullae
Nodules
Ulcers
Distribution and Localization of Rash
Generalized or localized
Symmetric or asymmetric
Centripetal or centrifugal
Associated Enanthem
Buccal mucosa
Palate
Pharynx and tonsils
Genitals
Associated Findings (Isolated or in Clusters)
Ocular
Cardiac
Pulmonary
Gastrointestinal
Musculoskeletal
Neurologic
Lymphadenopathy
Hepatosplenomegaly
Arthritis

documentation, and communication (see Chapter 48). An **exanthem** is defined as a skin eruption occurring as a sign of a generalized disease. An **enanthem** is an eruption on the mucous membranes that occurs in the context of generalized disease. Exanthems and enanthems may be macular, maculopapular, vesicular, urticarial, petechial, or diffusely erythematous. Rashes are usually classified according to their most typical lesion morphology. However, morphology may vary as rashes evolve; the rash of Rocky Mountain spotted fever is classically described as petechial, but it may initially be maculopapular. Because a wide variety of infectious agents, including viruses, bacteria, and the rickettsiae, as well as drugs and inflammatory conditions can cause exanthems and enanthems, few of these eruptions are pathognomonic (Tables 40.3, 40.4, and 40.5).

Specific Skin Lesions

Maculopapular Eruptions

Macules are flat, nonpalpable circumscribed lesions, while **papules** are <1 cm, circumscribed palpable lesions. Maculopapular lesions may coalesce into a more confluent morbilliform (measles-like) eruption. A rash with multiple small papules that feels like sandpaper is described as **scarlatiniform**. Maculopapular rashes are usually seen in viral illnesses, drug eruptions, and immune complex-mediated disorders. The classic childhood exanthems such as measles, rubella, erythema infectiosum (fifth disease, caused by parvovirus B19), and roseola (exanthem subitum, caused by human herpesvirus types 6 and 7) produce a maculopapular rash and are usually clinically recognizable (Figs. 40.1 and 40.2; see Table 40.5). Other organisms that commonly cause a maculopapular rash include enteroviruses, Epstein–Barr virus

Text continued on p. 734

TABLE 40.3 Differential Diagnosis of Fever and Rash

Lesion	Pathogen or Associated Factor
Maculopapular or Macular Rash	***Viruses***
	Measles (confluent), rubella (discrete), roseola (human herpesvirus 6),* fifth disease (parvovirus),* EBV,* enteroviruses,* hepatitis B virus (papular acrodermatitis or Gianotti–Crosti syndrome), HIV, dengue virus, adenovirus
	Bacteria
	Rheumatic fever (group A streptococcus), scarlet fever, erysipelas, *Arcanobacterium haemolyticum*, secondary syphilis, leptospirosis, *Pseudomonas*, meningococcal infection (early), *Salmonella* (typhoid rose spots), Lyme disease, *Mycoplasma pneumoniae*,* *Listeria monocytogenes*, *Brucella melitensis*
	Rickettsiae
	Early Rocky Mountain spotted fever, typhus (scrub, endemic), ehrlichiosis (monocytic)
	Other
	Kawasaki disease,* *Coccidioides immitis*, drug reactions, SJIA, hereditary fever syndromes, HLH
Diffuse Erythroderma	***Bacteria***
	Scarlet fever (group A streptococcus),* other streptococci, toxic shock syndrome (*Staphylococcus aureus* and group A streptococcus),* staphylococcal scarlet fever, ehrlichiosis *(Ehrlichia chaffeensis)*
	Fungi
	Candida albicans
Urticarial Rash	***Viruses***
	EBV, hepatitis B, HIV, enteroviruses
	Bacteria
	M. pneumoniae, group A streptococci, *Shigella*, meningococcus, *Yersinia*
	Other
	Various parasites, insect bites, food-drug allergens (usually afebrile)
Vesicular, Bullous, Pustular	***Viruses***
	Herpes simplex,* varicella-zoster,* coxsackieviruses,* echoviruses, vaccinia, variola
	Bacteria
	Staphylococcal scalded skin syndrome, staphylococcal bullous impetigo, group A streptococcal crusted impetigo, gonococcemia*
	Other
	Toxic epidermal necrolysis, Stevens–Johnson syndrome,* rickettsialpox

Lesion	Pathogen or Associated Factor
Petechial-Purpuric	***Viruses***
	Atypical measles, congenital rubella, cytomegalovirus, enterovirus, HIV, hemorrhagic fever viruses, hemorrhagic varicella, EBV, hepatitis B, adenovirus, yellow fever
	Bacteria
	Sepsis (meningococcal,* gonococcal, pneumococcal,* *S. aureus*,*), endocarditis, rat-bite fever (*Spirillum minus* or *Streptobacillus moniliformis*), *Pseudomonas aeruginosa*, group A streptococcus rickettsiae, *Capnocytophaga canimorsus*
	Rickettsiae
	Rocky Mountain spotted fever,* epidemic typhus, ehrlichiosis
	Other
	Vasculitis, thrombocytopenia, Henoch–Schönlein purpura,* malaria
Erythema Nodosum	***Viruses***
	EBV, hepatitis B, C, HSV, HIV
	Bacteria
	Group A streptococcus, tuberculosis, *Yersinia*, cat-scratch disease, brucellosis, Q fever, *M. pneumoniae*, tularemia, syphilis
	Fungi
	Coccidioidomycosis, histoplasmosis, blastomycosis, sporotrichosis, cryptococcosis
	Other
	Sarcoidosis, inflammatory bowel disease, estrogen-containing oral contraceptives, systemic lupus erythematosus, Behçet disease, lymphoma
Distinctive Rashes	
Ecthyma gangrenosum	*P. aeruginosa*, *Vibrio vulnificus*
Erythema migrans	Lyme disease
Necrotic eschar	Aspergillosis, mucormycosis
Erysipelas	Group A streptococcus
Koplik spots	Measles
Erythema Marginatum	Acute rheumatic fever (group A streptococcus)
Erythema Multiforme	Herpes simplex virus or *M. pneumoniae*
Rose spots	*Salmonella*

*Common.

EBV, Epstein–Barr virus; SJIA, systemic juvenile idiopathic arthritis; HLH, hemophagocytic lymphohistiocytosis; HSV, herpes simplex virus; HIV, human immunodeficiency virus

Modified from Prince A. Infectious diseases. In: Behrman RE, Kliegman RM, eds. *Nelson Essentials of Pediatrics*. 2nd ed. Philadelphia: WB Saunders; 1994:299.

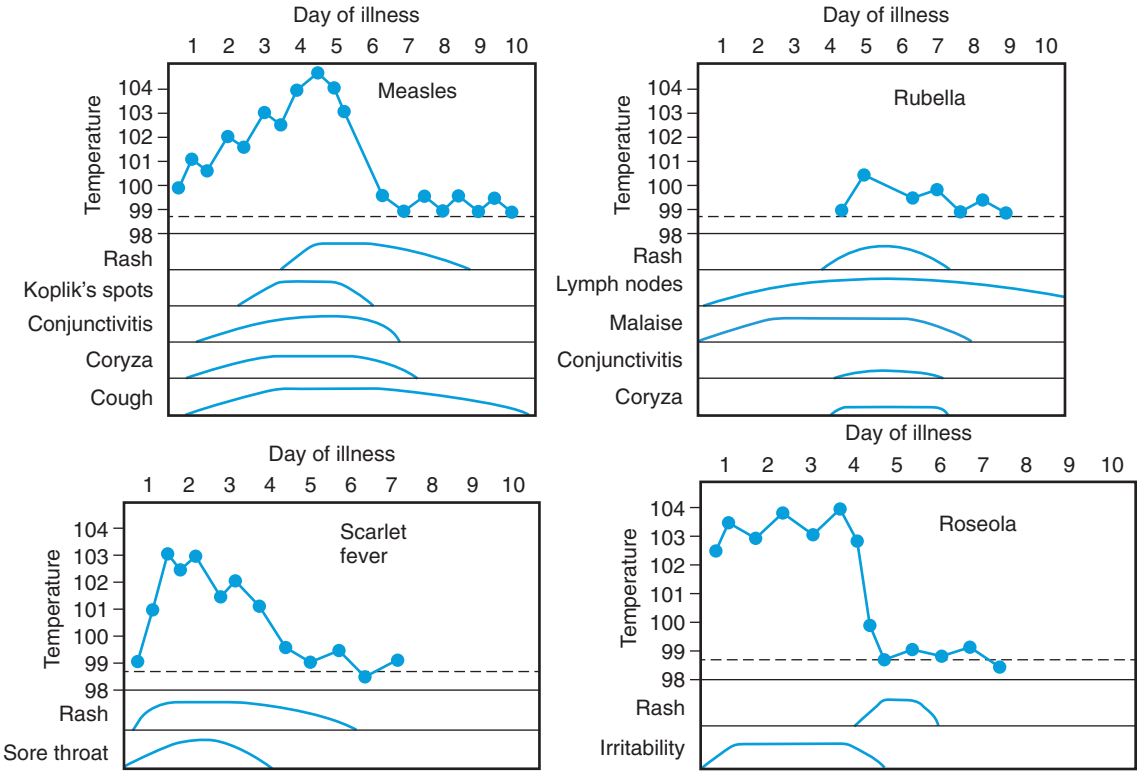


FIGURE 40.1 Schematic diagrams illustrating differences among 4 acute exanthems characterized by maculopapular eruptions. (Modified from Gershon AA, Hotez PJ, Katz SL, eds. *Krugman's Infectious Diseases of Children*. 11th ed. Philadelphia: Mosby; 2004:927, Fig. 45.1.)

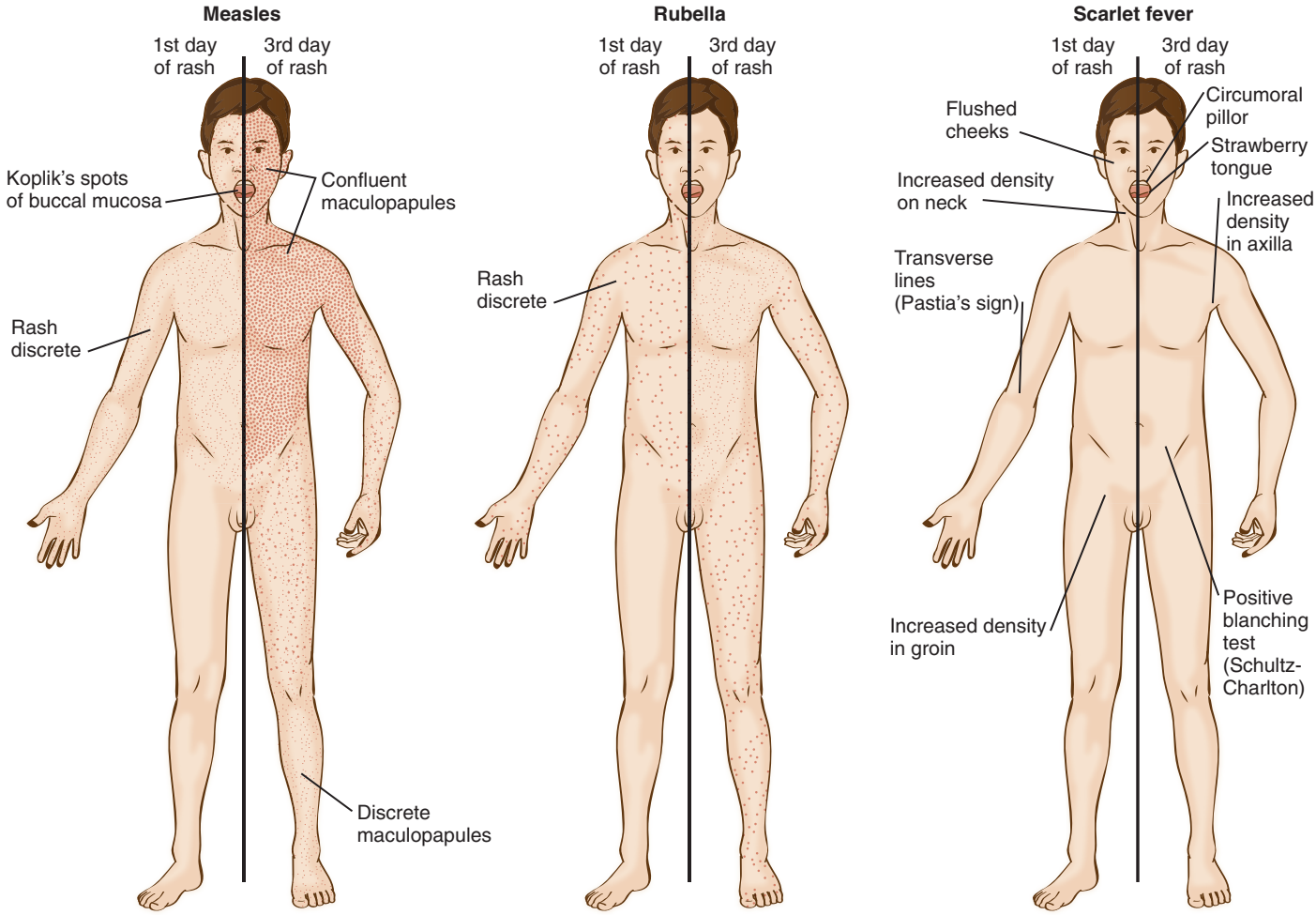


FIGURE 40.2 Schematic drawings illustrating difference in appearance, distribution, and progression of rashes of measles, rubella, and scarlet fever. (From Gershon AA, Hotez PJ, Katz SL, eds. *Krugman's Infectious Diseases of Children*. 11th ed. Philadelphia: Mosby; 2004:928.)

TABLE 40.4 Common Bacterial Exanthems

Disease	Cause	Age	Season	Transmission	Incubation (Days)	Prodrome
Scarlet fever	Group A streptococcus	School age	Fall, winter, spring	Direct contact, droplets	1–4	Sore throat, headache, abdominal pain, cervical lymphadenopathy, fever, 0–2 days, acute onset
Staphylococcal scalded skin syndrome (SSSS)	*Staphylococcus aureus* producing exfoliative toxin	Neonates and infants	Any	Colonization, contact	Unknown	None
Toxic shock syndrome (TSS)	*S. aureus* producing toxic shock syndrome toxin-1 (TSST-1) and staphylococcal enterotoxins (SEs) Group A streptococcus producing *Streptococcus pyogenes* exotoxins (SPEs)	Adolescent girls if menstrual; others variable	Any	Colonization, contact	Variable, often 1–5	Myalgias, fevers, and gastrointestinal symptoms May be secondary to wound infection, trivial mucosal or respiratory infection, or necrotizing fasciitis or myositis
Meningococcemia	*Neisseria meningitidis*	Any (<5 yr and adolescents)	Winter, spring, follows influenza epidemics	Close, prolonged contact	5–15	Fever, malaise, myalgia, 1–10 days
Rocky Mountain spotted fever (RMSF)	*Rickettsia rickettsii*	Any (>5 yr), male > female	Summer	Carrier ticks	3–12	Fever, myalgia, headache, malaise, ill appearance, 2–4 days
Rickettsialpox	*R. akari*	Any	Any	Mouse mite	7–14	Fever, chills, headache, malaise, 4–7 days

Common Bacterial Exanthems, cont.

Features and Rash Structure	Enanthem	Complications	Prevention/Treatment	Comments
Diffuse erythema with "sandpaper" feel: accentuation of erythema in flexural creases (Pastia lines); circumoral pallor, lasts 2–7 days; may exfoliate	Palatal petechiae, strawberry tongue	Peritonsillar abscess, rheumatic fever, glomerulonephritis	Prevent rheumatic fever with penicillin within 10 days of onset of pharyngitis, treat with penicillin	Similar syndrome may be noted with *Arcanobacterium haemolyticum* in adolescents; group A streptococci may also produce toxic shock or true bacteremic shock syndromes in addition to cellulitis, lymphangitis, and erysipelas; *S. aureus* may produce a scarlatiniform rash
Sudden onset, tender erythroderma progressing to diffuse flaccid bullae; significant perioral, perinasal peeling; eventual diffuse exfoliation (positive Nikolsky sign), possibly conjunctivitis, purulent rhinorrhea	Unusual	Shock	Treat with intravenous antibacterial active against *S. aureus*	—
Diffuse sunburn-like erythroderma; hypotension, diarrhea, emesis, mental status changes; late desquamation	Conjunctivitis	Shock, multisystem organ dysfunction/failure	Treat with intravenous antibacterial active against *S. aureus*; penicillin if group A streptococcus suspected; clindamycin; possible intravenous immune globulin; prevent menstrual-associated TSS by frequent changes of tampon	—
Erythematous, nonconfluent, discrete papules (early); petechiae, purpura present on trunk, extremities, palms, soles	Petechiae	Shock, meningitis, pericarditis, arthritis, endophthalmitis, gangrene, disseminated intravascular coagulation	Contacts: rifampin; general: vaccine; treat with ceftriaxone, cefotaxime, penicillin (if sensitive)	*Neisseria gonorrhoeae*, pneumococcus, *Haemophilus influenza* type b, group A streptococcus may produce similar clinical manifestations
Early maculopapular, then petechial or, rarely, purpuric; present on extremities, then trunk, palms, and soles	Petechiae variable	Shock, myocarditis, encephalitis, pneumonia	Remove ticks as soon as possible; use tick repellants; treat with doxycycline	*Ehrlichia chaffeensis* and other rickettsiae may produce similar illnesses with or without a rash
At primary bite site, eschar; secondary papulovesicles in same stage throughout illness; fewer vesicles than in chickenpox (5–30); present on trunk and proximal extremities	Unknown	Usually none	Treat with doxycycline	Often confused with chickenpox; may be more common than expected, especially in crowded urban settings with poor housing

TABLE 40.5 Common Viral Exanthems

Disease	Cause	Age	Season	Transmission	Incubation (Days)	Prodrome
Measles (rubeola)	Measles virus	Infants, adolescents	Winter, spring	Respiratory droplet	10–12	High fever, cough, coryza, conjunctivitis, 2–4 days
Rubella (German measles)	Rubella virus	Infants, young adults	Winter, spring	Respiratory droplet	14–21	Malaise, fever <101°F, posterior auricular, cervical, occipital adenopathy, 0–4 days
Roseola (exanthem subitum)	Human herpesvirus type 6 (HHV-6), Human herpesvirus type 7 (HHV-7)	Infants (6 mo–2 yr) for HHV-6, can be older children for HHV-7	Any	Unknown; saliva of asymptomatic carrier?	9–10 (HHV-6); unknown (HHV-7)	Irritability, high fever 3–7 days, cervical, occipital adenopathy;
Fifth disease (erythema infectiosum)	Parvovirus B19	Prepubertal children, schoolteachers	Winter, spring	Respiratory droplets; blood transfusion, placenta	5–15	Headache, malaise, myalgia; often afebrile
Chickenpox (varicella)	Varicella-zoster virus	1–14 yr	Late fall, winter, early spring	Respiratory droplet	12–21	Fever
Enteroviruses	Coxsackievirus, echovirus, and others	Infants, young children	Summer, fall	Fecal-oral	4–6	Variable: irritable, fever, sore throat, myalgias, headache
Mononucleosis	Epstein–Barr virus	Children, adolescents	Any	Close contact, saliva, blood transfusion	28–49	Fever, adenopathy, eyelid edema, sore throat, hepatosplenomegaly, malaise; atypical lymphocytosis
Gianotti–Crosti syndrome (papular acrodermatitis of childhood)	Hepatitis B virus, Epstein–Barr virus, coxsackieviruses, others	1–6 yr	Any	Variable; fecal, sexual, blood products for hepatitis B	Unknown; 50–180 days for hepatitis B	Usually none except for specific viral disease; arthritis-arthralgia for hepatitis B

CNS, central nervous system; HBIG, hepatitis B virus immune globulin; VZIG, varicella-zoster immune globulin.

Common Viral Exanthems, cont.

Features and Rash Structure	Enanthem	Complications	Prevention/ Treatment	Comments
Maculopapular (confluent), begins on face, spreads to trunk; lasts 3–6 days Brown color develops; fine desquamation; toxic, uncomfortable appearance, photophobia; rash may be absent in human immunodeficiency virus infection	Koplik spots on buccal mucosa before rash	Febrile seizures, otitis, pneumonia, encephalitis, laryngotracheitis, thrombocytopenia; delayed subacute sclerosing panencephalitis	General: measles vaccine at 12–15 mo and again at 4–6 yr Exposure: measles vaccine if within 72 hr; immune globulin if within 6 days of exposure (must then wait 5–6 mo to vaccinate) The World Health Organization recommends treatment with vitamin A in all patients with measles	Reportable to public health department; epidemics reported, contagious 3 days before symptoms and to 4 days after rash Increasing incidence as vaccination rates are decreasing
Discrete, nonconfluent, rose-colored macules and papules, begins on face and spreads downward; lasts 1–3 days	Variable erythematous macules on soft palate	Arthritis, thrombocytopenia, encephalopathy; fetal embryopathy	General: rubella vaccine at 12–15 mo and again at 4–6 yr; exposure: possibly immune serum globulin	Reportable to public health department; epidemics reported, contagious 2 days before symptoms and 5–7 days after rash
Discrete macules on trunk, neck; sudden-onset rash with defervescence; lasts 0.5–2 days; some patients have no rash	Variable erythematous macules on soft palate	Single or recurrent febrile seizures; encephalopathy; dissemination (e.g., liver, CNS, lung) in immunosuppressed patients	None	No epidemics
Local erythema of cheeks (slapped cheek appearance); lacy pink red erythema of trunk and extremities, ± pruritus; rash may lag prodrome by 3–7 days; lasts 2–4 days, may recur 2–3 wk later	None	Arthritis, aplastic crisis in patients with chronic hemolytic anemia (e.g., sickle cell), fetal anemic hydrops, vasculitis, Wegner granulomatosis	Isolation of patients with aplastic crisis but not normal host with fifth disease	Epidemics reported; once rash is present, the normal host is not contagious; patients with aplastic crisis often have no rash
Pruritic papules, vesicles in various stages, 2–4 crops and then crusts; distributed on trunk and then face, extremities; lasts 7–10 days; recurs years later in dermatomal distribution (zoster, shingles)	Oral mucosa, tongue	Staphylococcal or streptococcal skin infection, arthritis, cerebellar ataxia, encephalitis, thrombocytopenia, Reye syndrome (with aspirin), myocarditis, nephritis, hepatitis, pneumonia; dissemination in immunocompromised	VZIG for exposed immunosuppressed patients, susceptible pregnant women, preterm neonates, and infants at birth whose mother developed varicella 5 days before and 2 days after birth; active immunization with live attenuated vaccine at 12 mo	Acyclovir therapy for immunosuppressed and possibly normal patients (controversial); contagious 1–2 days after rash (usually no longer contagious when all lesions are crusted and no new lesions appear)
Hand–foot–mouth: vesicles in those locations; others: nonspecific, usually fine nonconfluent, macular or maculopapular rash, rarely petechial, urticarial, or vesicular; lasts 3–7 days	Yes	Aseptic meningitis, hepatitis, myocarditis, paralysis: usually in younger patients	None	Rash may appear with fever or after defervescence; rash may be present in <50% of enteroviral illnesses; epidemics possible, contagious up to 2 wk
Maculopapular or morbilliform on trunk, extremities; may be confluent; often elicited by simultaneous administration of ampicillin or allopurinol; rash in 15% and in 50% with drug-induced form, lasts 2–7 days	Variable	Anemia, thrombocytopenia, aplastic anemia, hepatitis; rarely hemophagocytic lymphohistiocytosis, lymphoproliferative syndrome	None	Cytomegalovirus and toxoplasmosis also produce mononucleosis-like illness; monospot or heterophile tests negative
Papules, papulovesicles, discrete or confluent; face, arms, extremities, often spares trunk; lasts 4–10 days	Variable	As per specific disease	Hepatitis B: HBIG plus vaccine	—

(EBV), cytomegalovirus, adenovirus, and hepatitis B virus. **Erythema migrans,** the distinctive rash of Lyme disease (caused by the tick-borne spirochete *Borrelia burgdorferi*), begins as a papule at the site of a recent tick bite and slowly expands over days to weeks to form an erythematous, annular lesion, sometimes with partial central clearing (Fig. 40.3). **Erythema marginatum,** a rare but major manifestation of acute rheumatic fever, is also distinctive (Fig. 40.4).

FIGURE 40.3 Erythema Migrans—Erythematous Target-Like Plaque of Lyme Disease. The primary skin lesion of *B. burgdorferi* infection is noted for centrifugal expansion, sometimes leaving a central clearing. (Courtesy James Gathany; Content Providers CDC/James Gathany—this media comes from the Centers for Disease Control and Prevention's Public Health Image Library [PHIL], with identification number #9875. From Borchers AT, Keen CL, Huntley AC, et al. Lyme disease: a rigorous review of diagnostic criteria and treatment. *J Autoimmun.* 2015;57:82-115.)

Morbilliform drug eruptions are often indistinguishable from viral exanthems and present 7-14 days after exposure to a drug (Fig. 40.5). As with most viral exanthems, the rash starts on the trunk and spreads to the extremities. Examples of causative agents include aminopenicillins, cephalosporins, antiepileptics, and sulfonamides. Morbilliform drug eruptions usually resolve spontaneously after discontinuation of the culprit drug, but sometimes they are the 1st sign of the potentially life-threatening syndrome drug rash with eosinophilia and systemic symptoms (**DRESS**, also known as drug-induced hypersensitivity syndrome, formerly anticonvulsant hypersensitivity syndrome).

Inflammatory diseases can present with fever and maculopapular rash. Systemic juvenile idiopathic arthritis (SJIA, Still's disease) presents with an evanescent, salmon-colored macular rash on the trunk and proximal extremities that coincide with fever spikes (see Chapter 33). Many of the hereditary periodic fever syndromes manifest with maculopapular (or urticarial) rash associated with fever (see Chapter 41).

FIGURE 40.4 Polycyclic red borders of erythema marginatum in a febrile child with acute rheumatic fever. (From Schachner LA, Hansen RC, eds. *Pediatric Dermatology*. 3rd ed. Philadelphia: Mosby; 2003:808.)

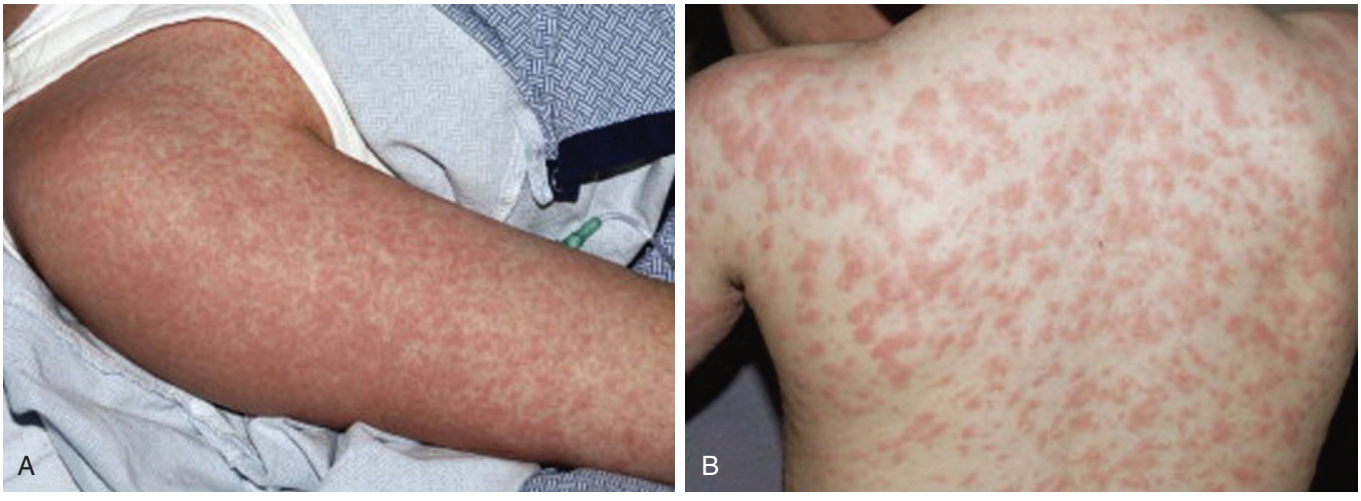


FIGURE 40.5 Morbilliform drug eruptions. *A,* Fine pink macules and thin papules becoming confluent on the posterior upper arm, which is a dependent area in this hospitalized patient. *B,* More edematous ("urticarial") pink papules; unlike true urticaria, these lesions are not transient. (Courtesy Julie V. Schaffer, MD. From Fever and Rash. In: Bolognia JL, ed. *Dermatology Essentials*. Philadelphia: Elsevier; 2014;3:28-38.)

Petechiae and Purpura

Extravasation of red blood cells from the vasculature into the skin produces petechiae and purpura. These lesions do not blanch with applied pressure. **Petechiae** are pinpoint lesions (<3 mm), and **purpura** are larger lesions, and can be either palpable or nonpalpable. While the majority of patients with fever and petechiae have a benign illness, their presence, especially in a child younger than 24 months, is of particular concern. Between 2% and 20% of affected patients have an underlying bacterial infection, and depending on the clinical setting, 0.5-10% have sepsis caused by *Neisseria meningitidis*. Other potentially serious infections signaled by a petechial rash and fever include bacterial endocarditis and Rocky Mountain spotted fever. Group A streptococcal (GAS) pharyngitis is the most common bacterial cause of fever and petechiae, with up to 20% of patients with fever and petechiae being diagnosed with GAS pharyngitis in some studies. Common viral causes include enterovirus and adenovirus. Febrile children may develop petechiae after coughing or vomiting; petechiae in this setting are almost always located in the superior vena cava distribution above the nipple line. Noninfectious causes of fever and petechiae include drug eruptions and acute leukemia. Not all children with fever and petechiae have thrombocytopenia.

Diffuse purpuric lesions may be noted in a wide variety of disorders. These include infectious diseases associated with organisms with a predilection for vascular endothelium, such as *N. meningitidis* and *R. rickettsii*; virus-associated diseases, such as dengue hemorrhagic fever and the hemorrhagic fever with renal syndrome caused by the Hantavirus; uncommon bacterial diseases, such as Brazilian purpuric fever caused by *Haemophilus aegyptius*; and the hemorrhagic shock–encephalopathy syndrome. Purpura is also associated with disseminated intravascular coagulation (DIC) and profound thrombocytopenia, such as in idiopathic thrombocytopenic purpura (see Chapter 38). Purpura followed by subsequent necrosis of skin is referred to as **purpura fulminans**, which has been reported after relatively benign infections such as varicella or with more serious disorders (meningococcemia). Purpura can occur in the noninfectious vasculitides, such as Henoch–Schönlein purpura (HSP). Discrete, raised purpuric lesions (palpable purpura) distributed predominantly over the buttocks and lower extremities are typical for this disorder. While all febrile patients presenting with diffuse or discrete purpuric lesions must be considered to be at risk for bacteremia (Fig. 40.6), patients with HSP are generally well-appearing but may have significant discomfort from arthritis or abdominal pain.

Vesiculobullous Eruptions

Vesicular rashes (sharply demarcated, raised lesions containing clear fluid), **bullae** (vesicles exceeding 1 cm in diameter), or **pustules** (raised lesions containing cloudy fluid composed of serum and inflammatory cells) may be suggestive of focal or disseminated infection with various pathogens or signal a serious drug reaction. **Localized vesicles** may suggest infection with herpes simplex virus (HSV) type 1 or 2 (especially if the vesicles are grouped on an erythematous base), varicella-zoster virus (especially if grouped vesicles are distributed in a dermatomal pattern) (Fig. 40.7), or infection with nonviral pathogens, such as *Rickettsia akari* (the cause of **rickettsialpox**, a mouse mite-borne rickettsiosis found worldwide but common in New York City). Localized pustules and bullae are usually suggestive of pyodermas caused by *Staphylococcus aureus*, but pustular lesions distributed on the palms and soles in the context of fever may represent infective emboli with microabscess formation (Janeway lesions), which are often caused by *S. aureus* endocarditis.

Vesicles distributed in a more **generalized pattern**, especially with a concentration of lesions over the head and trunk, are suggestive of primary varicella-zoster virus infection (**chickenpox**), whereas a more generalized pattern with a concentration over the extremities is suggestive of enteroviral infection, especially with coxsackievirus A16 (**hand–foot–mouth disease**). Orthopoxviruses such as monkeypox, like smallpox, cause a systemic febrile rash illness with lesions that progress from papules to vesicles to pustules concentrated on the face and extremities. **Acute generalized exanthematous pustulosis (AGEP)** is a rare cutaneous hypersensitivity reaction characterized by numerous sterile pustules beginning on the face and spreading to the trunk and limbs. It typically presents within 24 hours after exposure to an offending drug, usually a β-lactam or macrolide antibiotic. The clinician evaluating the sexually active patient presenting with asymmetric generalized pustules or vesicopustular lesions should also consider disseminated infection with *N. gonorrhoeae*. Diffuse vesiculobullae may be noted in Stevens–Johnson syndrome (SJS) or in toxic epidermal necrolysis (TEN), life-threatening mucocutaneous hypersensitivity diseases usually related to drugs.

FIGURE 40.6 Purpuric lesions with sharply marginated borders on the hands of a patient with meningococcemia. (Courtesy Department of Dermatology, Yale University School of Medicine.)

FIGURE 40.7 Skin lesions of chickenpox. Note the varying stages of development (macules, papules, and vesicles) present at the same time. (From Paller AS, Mancini AJ. Hurwitz Clinical Pediatric Dermatology. 5th ed. Philadelphia: Elsevier; 2016.)

Nodules

Nodules (discrete, raised, firm, well-demarcated lesions without fixation to the overlying skin) may be associated with a number of underlying infectious or inflammatory disorders, such as polyarteritis nodosa and Sweet syndrome (acute febrile neutrophilic dermatosis). Red, pink, or plum-colored nodules distributed in a seemingly random manner over the skin surface may represent leukemic infiltrates. The subcutaneous nodules of acute rheumatic fever are usually located over bony extensor surfaces near tendons and are found in <5% of patients with acute rheumatic fever. They may also be found in patients with polyarticular JIA and dermatomyositis.

Erythema nodosum (erythematous and painful nodules usually distributed over the extremities) may be associated with viral infections including hepatitis B and C; bacterial infectious agents, most commonly group A β-hemolytic streptococcus; *Brucella* species; *Yersinia* species; mycobacterial infections; fungal infections with *Candida* species, *Histoplasma capsulatum*, *Blastomyces dermatitidis*; *Cryptococcus neoformans*, or *Coccidioides immitis*; or drug reactions, especially in response to oral contraceptives and sulfonamides. Other noninfectious causes include SLE, sarcoidosis, and inflammatory bowel disease.

Ulcers

Ulcers are depressed lesions in which the epidermis and some or all of the dermis has been destroyed. In immunocompromised hosts, infection with HSV may manifest with shallow erosive or ulcerative lesions. In immunocompetent hosts, cutaneous ulcerations may be noted in noninfectious disorders associated with vasculitis, such as SLE, polyarteritis nodosa, and HSP.

Pyoderma gangrenosum and **ecthyma gangrenosum** are painful cutaneous ulcerative lesions with an erythematous, raised edge. The lesions usually begin as a papule and break down rapidly with central necrosis. It may be seen in immunocompromised patients with systemic infections with bacterial pathogens, such as *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* (ecthyma). In immunocompetent patients, the lesion may manifest in the context of inflammatory bowel disease (pyoderma gangrenosum), PAPA (pyogenic arthritis, pyoderma gangrenosum, acne), or rheumatoid arthritis. Digital ulcerations may be noted in patients with small vessel vasculitis, such as SLE. Oral ulcerations may be noted in those with herpes simplex or coxsackievirus (hand–foot–mouth disease) or as a manifestation of Behçet disease, SLE, PFAPA (periodic fever, aphthous stomatitis, pharyngitis, adenitis), or inflammatory bowel disease.

Erythema

Diffuse erythema (**erythroderma**) is associated with toxin-mediated disorders characterized by superantigen production. Bacterial superantigens cause nonspecific T cell stimulation resulting in several acute rash-fever disorders, such as the staphylococcal scalded skin syndrome (SSSS; Fig. 40.8), streptococcal scarlet fever, staphylococcal or streptococcal toxic shock syndrome, and possibly KD.

FIGURE 40.8 An infant with staphylococcal scalded skin syndrome. (From Kliegman RM, Stanton BF, St Geme JW III, et al, eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016.)

Localized erythema in the context of acute fever is strongly suggestive of cellulitis, erysipelas, or abscess. The presence of warmth, tenderness, and associated lymphangitis is highly indicative. Organisms causing cellulitis or abscess formation are usually inoculated directly into the skin as a result of trauma. However, bacteremic localization is well described among young children with preseptal or facial cellulitis associated with *H. influenzae* type b or *S. pneumoniae*.

Patients with SLE or dermatomyositis may present with an isolated erythematous malar rash (butterfly rash), which is exacerbated by exposure to sunlight. The acute onset of intense "slapped-cheek" erythema of the face suggests erythema infectiosum, a recognizable exanthem caused by parvovirus B19, and should be differentiated easily from the malar rash of SLE, which usually manifests other characteristics, such as chronicity as well as hyperkeratosis and follicular plugging. In addition, patients with erythema infectiosum tend to have a maculopapular, lacelike rash over the arms, which may spread to the buttocks and thighs (Fig. 40.9; see Table 40.5).

Patients with **dermatomyositis** may have localized lilac-colored lesions over the eyelids (heliotrope rash), which may be associated with periorbital edema. Such patients characteristically, but not invariably, have an erythematous, scaly eruption on the face, neck, knees, elbows, and phalanges. When the rash is localized over the knuckles, it resembles dripped wax and has been referred to as Gottron papules.

◆ Other Physical Examination Findings

Joint Manifestations

Pain, swelling, tenderness, and limited range of motion involving 1 joint or multiple joints, or that migrate from joint to joint, or discrete pain at the insertion of tendons, ligaments, or fascia (enthesopathy) indicates a primary infectious illness, a "reactive" (immunologically mediated) disorder, or a systemic inflammatory condition. Primary infectious illnesses associated with this finding include *N. gonorrhoeae*, *B. burgdorferi* (Lyme disease), parvovirus, and rubella, including vaccine-associated strains. Reactive disorders, such as reactive arthritis (arthritis/enthesitis, conjunctivitis, urethritis), may be associated with infection caused by enteric pathogens, such as *Salmonella* and *Shigella*

FIGURE 40.9 Erythema infectiosum. (From Kliegman RM, Stanton BF, St Geme JW III, et al, eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016).

organisms, or genital pathogens, such as *N. gonorrhoeae* or *Chlamydia* species, but may also include diseases of unknown origin, such as inflammatory bowel disease, in which the rash is usually erythema nodosum. A **serum sickness-like reaction** can be seen after treatment with antibiotics. Children with systemic inflammatory conditions including KD, HSP, polyarteritis, SLE, SJIA, acute rheumatic fever, and some of the hereditary periodic fever syndromes may also have joint manifestations (see Chapters 33 and 41).

Cardiac Manifestations

Cardiac manifestations may accompany acute rheumatic fever, bacterial endocarditis, KD, or SJIA (see Chapter 33). The presence of tachycardia out of proportion to the severity of the fever may be indicative of sepsis or the carditis accompanying acute rheumatic fever, KD, or DRESS. A precordial friction rub is suggestive of pericarditis, which is noted frequently in patients with SJIA. The presence of a new murmur or a changing murmur on auscultation is suggestive of bacterial endocarditis, whereas the detection of the apical systolic murmur of mitral regurgitation or the diastolic murmur of aortic insufficiency is suggestive of acute rheumatic fever (see Chapter 8). A gallop rhythm on auscultation indicates underlying myocarditis, which may accompany coxsackievirus infection, rheumatic disease, or KD.

Ocular Manifestations

Isolated ocular manifestations, such as conjunctival injection and frank conjunctivitis, may be suggestive of infection with measles or adenovirus, leptospirosis, KD, SJS, TEN, or reactive arthritis. The skin, eye, mouth form of neonatal HSV can infect the eyes, causing conjunctivitis and keratitis. **Anterior uveitis** (redness with accompanying photophobia or pain or change in vision) may indicate KD, SJIA, sarcoidosis, ulcerative colitis, Behçet syndrome, or uncommonly, an infection such as leptospirosis. Retinal hemorrhages seen on funduscopy may indicate bacterial endocarditis.

Neurologic Manifestations

Neurologic findings accompanying fever and rash may be indicative of specific infectious or immunologically mediated disorders. Mental status findings suggestive of recent-onset psychosis may indicate cerebritis, which can accompany SLE. Significant alteration in mental status accompanied by seizure or focal motor impairment or cerebellar dysfunction may be suggestive of primary infectious encephalitis associated with arbovirus, herpes simplex, measles, varicella-zoster virus, rickettsia, West Nile virus, or *M. pneumoniae* infection. Nuchal rigidity, the Kernig sign, or the Brudzinski sign indicates meningeal irritation, which may accompany infection caused by the enteroviruses; bacteria such as *S. pneumoniae* or *N. meningitidis*; fungi such as *H. capsulatum* and spirochetes such as *B. burgdorferi*; or inflammation caused by underlying SLE, sarcoidosis, or KD. Cranial nerve palsies, ataxia, or peripheral neuropathy may accompany infection with *B. burgdorferi* early in the course of **Lyme disease** (especially Bell's palsy), or it may indicate an underlying vasculitis, such as SLE. Movement abnormalities, particularly chorea, may be suggestive of either SLE or acute rheumatic fever. **Hemophagocytic lymphohistiocytosis (HLH)** is a life-threatening syndrome of excessive immune activation that can have varied neurologic manifestations including seizure, mental status changes, and ataxia. The rash associated with HLH is also variable and can be maculopapular, erythrodermic, petechial, or purpuric. When seen in a patient with SJIA, the syndrome is called macrophage activation syndrome.

Pulmonary Manifestations

The presence of isolated lower respiratory tract findings (decreased breath sounds, rales, expiratory wheezing, respiratory distress, and cyanosis) indicates underlying pulmonary infection with an organism such as measles, respiratory syncytial virus, adenovirus, *Mycoplasma pneumoniae*, or *Legionella pneumophila*. Although sarcoidosis, collagen vascular disease, and systemic vasculitis (granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, HSP) may involve the lower respiratory tract, isolated pulmonary findings are infrequently indicative of these disorders. The acute respiratory distress syndrome can develop in any patient with a serious systemic inflammatory condition such as sepsis, SJS, TEN, HLH, and DRESS.

Clusters of Findings

Clusters of findings on examination that are of diagnostic importance include the following.

The **mucocutaneous–lymph node** cluster (bilateral conjunctival injection, palmar-plantar erythema/indurative edema of the hands and feet, erythema of the oropharyngeal mucosa/"strawberry" tongue, cervical lymphadenopathy) is suggestive of KD, TSS, SJS, streptococcal scarlet fever, Rocky Mountain spotted fever, dengue, and leptospirosis.

The **reticuloendothelial cell hyperplasia cluster** (hepatosplenomegaly with or without generalized adenopathy) is suggestive of (1) disseminated infectious disease caused by bacteria (*Salmonella typhi* or other enteric fever pathogens), virus (cytomegalovirus, human immunodeficiency virus–1 [HIV-1], EBV), rickettsia (*Orientia tsutsugamushi* in "scrub typhus"), protozoa (malaria), or fungus (*H. capsulatum*, *C. immitis*); (2) disseminated malignancy; (3) sarcoidosis; (4) HLH; or (5) rheumatologic disease.

The **mononucleosis-like syndrome cluster** (exudative pharyngitis and regional adenopathy with or without splenomegaly) is suggestive of infection with group A streptococcus, *Arcanobacterium haemolyticum*, *Francisella tularensis*, EBV, toxoplasmosis, cytomegalovirus, or coxsackievirus or DRESS.

◆ Diagnostic Studies

The history and physical examination together determine the prior probability of a specific disease. In the context of a very high or very low prior probability of a specific disease, laboratory testing adds very

little useful information. Thus, ancillary testing is most useful when the prior probability of specific disease is equivocal.

◆ Laboratory Tests

In an ill-appearing child, basic laboratory testing including complete blood count with smear; chemistries; blood, and possibly cerebral spinal fluid cultures should be obtained. Coagulation studies should be completed in patients with petechiae, purpura, bleeding, or concern for DIC.

A Gram stain of any ulcerative, pustular, petechial, or purpuric lesion can be useful. The identification of bacteria suggests pyogenic infection, which may be localized or disseminated. The presence of only polymorphonuclear white blood cells in the fluid of pustular lesions does not exclude bacterial infection from consideration, especially disseminated infection with *N. gonorrhoeae*. Specimens of these lesions or any fluid from a pustule should also be obtained for bacterial culture.

Vesicular and bullous lesions in a febrile child with an uncertain diagnosis can be unroofed, scraped at the base, and submitted for microscopic examination after Tzanck preparation. The presence of multinucleated giant cells or eosinophilic intranuclear inclusions indicates infection with herpesvirus or varicella-zoster virus. The sensitivity of the Tzanck preparation for cutaneous herpes simplex infection is 64% and the specificity is 86%. Because the sensitivity of the procedure is low, a negative result does not exclude the diagnosis of herpes simplex infection. Thus, to identify the virus, a specimen of the lesion should also be obtained for polymerase chain reaction (PCR), which is more sensitive than culture.

Diagnosing a systemic infectious illness may necessitate the use of specific bacterial, viral, or fungal culture techniques; paired acute- and convalescent-phase serologic study; antigen detection systems; or molecular techniques such as PCR or 16S (bacterial) 28S (fungal) ribosomal DNA. Culture techniques are most specific when normally sterile tissue or body fluids are sampled and inoculated directly into liquid or solid media. Interpretation of bacterial cultures obtained from nonsterile sites, such as the tonsils and nasopharynx, are subject to increased rates of false-positive results because of recovery of organisms that colonize these areas.

Serologic techniques are potentially useful in establishing a diagnosis of a specific infection by demonstrating a 4-fold rise in titer between samples obtained during the acute and convalescent phases of illness. Confirmation of infection with the rickettsiae is probably best accomplished through serologic techniques demonstrating a 4-fold increase in titer because culture systems and PCR testing for rickettsiae are not widely available. Detection of a recent infection with group A streptococci may be accomplished by demonstrating antibodies to streptolysin O (ASO titer) or to deoxyribonuclease B (anti-DNAse B). Alternatively, immunoblot or PCR techniques rather than serologic tests best confirm many specific viral pathogens.

Antigen detection systems are useful for rapid diagnosis. A solid-phase detection system, such as enzyme-linked immunosorbent assay (ELISA), has the advantage of being independent of the need for intact cellular material but is affected by antigen or antibody cross-reactivity in the sample (which limits specificity) and by poor antigen-antibody affinity (which limits sensitivity). Nonetheless, ELISA is the preferred technique for the serologic diagnosis of a wide spectrum of infectious agents, including *B. burgdorferi* (Lyme disease pathogen) (as the 1st part in a 2-tier serologic assay, the 2nd being a Western immunoblot; see Chapter 39) and hepatitis B virus.

Latex particle agglutination is an alternative solid-phase antigen detection system that does not require intact cellular material and whose advantages include rapidity of use and ease of interpretation. Latex particle agglutination is used for the rapid identification of patients with group A streptococcal pharyngitis or with invasive disease caused by encapsulated bacteria, such as *S. pneumoniae*, *H. influenzae* type b, *N. meningitidis*, group B streptococci, and *Escherichia coli* BK1. Latex particle agglutination is limited by factors similar to those affecting ELISA. Latex agglutination tests for group A streptococci have specificities of more than 90%, which facilitates their use for clinical confirmation of infection, but their sensitivities are only 60-90%, which limits their use in excluding infection.

The identification of patients with noninfectious systemic illness caused by underlying rheumatologic disease, immune complex disease, or vasculitis is best accomplished through serologic techniques combined with other indirect laboratory evidence of active inflammation or tissue injury (see Chapter 33). Diagnoses of autoinflammatory diseases are based on clinical criteria and can be confirmed with genetic testing (see Chapter 41). Cardiovascular biomarkers such as N-terminal pro-B-type natriuretic peptide (NT-proBNP) are increased in the serum of patients with KD and hold promise in supporting the diagnosis of KD.

Histopathology

Punch biopsy for light and electron microscopy and immunohistologic studies should be considered for diagnostic purposes for patients presenting with fever and bullous lesions that are clearly not typical pyodermas; fever and nodular lesions; or lesions suggestive of vasculitis (palpable purpura, livedo reticularis). A punch biopsy with indirect immunofluorescent antibody staining may also be useful for patients with petechial lesions, especially in an acral distribution, for the early diagnosis (at days 4-8 of illness) of infection with *R. rickettsii*. This procedure has a sensitivity of 53% and a specificity of 100%. The low sensitivity of the test may be related to the rickettsiostatic effect of antimicrobial treatment before presentation, but it indicates clearly that decision making in the acute care setting is limited by the high rate of false-negative classifications expected with this procedure.

Other Diagnostic Studies

Echocardiography and electrocardiography (ECG) are part of the diagnosis of some fever and rash syndromes. The 2015 revision of the Jones criteria for diagnosis of acute rheumatic fever adds echocardiography as a way to diagnose cardiac involvement even when it is not clinically evident. Prolonged P-R interval on ECG remains 1 of the minor Jones criteria. In incomplete KD, echocardiography is used to guide diagnosis when patients do not meet all classic criteria.

◆ Diagnosis and Decision Making

Accurate diagnosis depends on careful synthesis of selected data obtained from the clinical assessment. Because most children with acute episodes of fever and rash have a common, self-limited infectious disease, a specific diagnosis can often be established simply by pattern recognition alone (e.g., visual recognition of the common exanthems of childhood or a specific lesion such as erythema migrans) or with minimal use of adjunctive testing (a rash consistent with scarlet fever accompanied by a positive PCR or latex agglutination test for group A streptococcus). Because the spectrum of infectious pathogens is broad, and the presenting complaints or features of the rash may be atypical, and on occasion, the diagnosis may not yield easily to simple pattern recognition. In these situations, empirical use of the laboratory may prove useful to the clinician.

In a series of febrile children presenting for evaluation of generalized erythematous rashes of various patterns that were not indicative of a specific disorder by history or examination, an infectious cause could be established in 65% after a limited set of laboratory tests. The

tests consisted of a throat culture for streptococci (including non–group A streptococci) and serologic studies to detect rubella, measles, hepatitis A and B viruses, EBV, parvovirus B19, and *M. pneumoniae*. This strategy was based on physician knowledge of the age-specific and/or seasonal incidence of infectious pathogens in the population studied. It may be preferable to "watchful waiting" and serial clinical follow-up when the patient is judged to be at risk for a treatable illness associated with significant subsequent morbidity (e.g., streptococcal infection leading to acute rheumatic fever) or when specific information is necessary to advise parents of the risk of contagion to other children, to immunocompromised contacts, or to pregnant women.

Well-appearing patients with fever and petechial rash present a challenge to the clinician. Such patients with cough or emesis and petechiae only above the nipple line, and a positive streptococcal antigen test, or patients with normal leukocyte, absolute neutrophil, and platelet counts and a normal prothrombin time are exceedingly unlikely to have an invasive bacterial illness such as meningococcemia.

The subset of patients with fever and rash who appear toxic, have unstable vital signs, or altered mental status must have a comprehensive evaluation and a diagnosis confirmed as quickly as possible to detect potentially life-threatening underlying infection. Patients with thrombocytopenia and an abnormal coagulation profile should be admitted for further evaluation and treatment of DIC, which may have an underlying infectious or inflammatory cause. Patients with thrombocytopenia and a normal coagulation profile may have infection with tick-borne rickettsial pathogens, *Ehrlichia chaffeensis*, EBV, an autoimmune disease such as SLE, or a primary hematologic-oncologic disorder, such as idiopathic thrombocytopenic purpura or leukemia associated with an intercurrent infection; such patients should be evaluated for these disorders. Patients with eosinophilia and elevated transaminases may have DRESS.

Several serious diseases present with features that resemble benign processes; it is crucial to distinguish these as early in the clinical course as possible so definitive treatment can be given (Table 40.6).

Clinical Syndromes

In certain instances, the diagnostic approach to disorders manifesting with fever and rash is wholly dependent on an aggregation of nonspecific signs, symptoms, and laboratory results. These disorders either have many underlying causes manifesting with overlapping features or have unknown causes for which no confirmatory tests have yet been devised. These diseases are diagnosed by recognizing patterns and sometimes by excluding other diagnoses; some are based on formalized aggregation, termed *syndromic diagnosis*. Although syndromic diagnosis is based on explicit clinical criteria, some of the clusters of signs, symptoms, and laboratory findings were established originally for epidemiologic purposes (case definition) to facilitate exploration of an underlying cause. As such, although they are usually quite specific, these criteria may be less sensitive when they are applied in the acute care setting for the purposes of clinical diagnosis.

Kawasaki Disease

KD is a medium-vessel vasculitis of childhood with a predilection for the coronary arteries. It is the 2nd most common vasculitis of childhood after HSP, and it is the most common cause of acquired heart disease in children in the United States. Etiology is unknown, but epidemiologic studies support an infectious trigger. A genetic role is suspected given the 10- to 20-fold increased incidence in Japan as compared to the United States and United Kingdom. Genetic linkage studies and genome-wide association studies have demonstrated associations between polymorphisms in the *ITPKC* gene, a T cell regulator, and *FCGR2A*, an immunoglobulin (Ig)G receptor, with increased susceptibility to KD. The majority (75-85%) of affected children are less than 5 years old, and infants aged <6 months and children over 5 years old are at the highest risk for coronary artery aneurysms.

The fever of KD is usually high and unremitting; patients are often irritable and ill-appearing. Rash is seen in more than 80% of patients with KD and is polymorphic. It is often morbilliform, but may also be erythema multiforme-like (fixed erythematous target lesions [see Fig. 40.10]), urticarial, scarlatiniform, or pustular. Erythema and early desquamation (within 48 hours) of the perineum is common. Vesiculobullous lesions and petechiae are unusual.

Diagnosis is made on clinical grounds (Table 40.7 and Figs. 40.10 to 40.15). Fewer than 75% of patients meet the classic complete criteria at presentation; diagnosis of incomplete KD may be made with less than 4 criteria with the addition of laboratory and echocardiographic criteria (Fig. 40.16). Application of this algorithm increases sensitivity for KD to 97%. Early diagnosis is crucial to decrease the risk of coronary artery aneurysms, which decreases to less than 5% in promptly treated patients.

Toxic Shock Syndrome

TSS is a life-threatening illness caused by superantigen-producing strains of group A streptococcus and *S. aureus*. The syndrome is defined by fever, diffuse macular erythroderma with convalescent desquamation, hypotension, mucositis, strawberry tongue, and multiorgan dysfunction. While menstrual staphylococcal TSS classically affects menstruating teenage girls secondary to vaginal colonization with toxic shock syndrome toxin 1 (TSST-1) producing strains of *S. aureus*, streptococcal TSS is usually associated with obvious severe cutaneous infection. Diagnostic criteria are slightly different for each syndrome.

Staphylococcal Toxic Shock Syndrome

Laboratory criteria for diagnosis include negative results on the following tests, if obtained: blood or cerebrospinal fluid cultures (blood culture may be positive for *S. aureus*) and serologies for Rocky Mountain spotted fever, leptospirosis, or measles. A probable case meets the laboratory criteria and 4 of 5 clinical criteria and a confirmed case meets the laboratory and all 5 clinical criteria:

Fever: temperature greater than or equal to 102°F (greater than or equal to 38.9°C)

Rash: diffuse macular erythroderma

Desquamation: 1-2 weeks after onset of rash

Hypotension: systolic blood pressure less than or equal to 90 mm Hg for adults or less than 5th percentile by age for children aged less than 16 years

Multisystem involvement (3 or more of the following organ systems):

1. Gastrointestinal: vomiting or diarrhea at the onset of illness
2. Muscular: severe myalgia or creatine phosphokinase level at least twice the upper limit of normal
3. Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
4. Renal: blood urea nitrogen or creatinine at least twice the upper limit of normal for laboratory or urinary sediment with pyuria (greater than or equal to 5 leukocytes/high-power field) in the absence of urinary tract infection
5. Hepatic: total bilirubin, alanine aminotransferase enzyme, or aspartate aminotransferase enzyme levels at least twice the upper limit of normal for laboratory
6. Hematologic: platelets less than 100,000/mm^3
7. Central nervous system: disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent

TABLE 40.6 Potentially Life-Threatening Conditions with Initial Skin Findings That Can Mimic a More Common Benign Disorder

Potentially Life-Threatening Condition	Benign Disorder That Is Mimicked Early in the Course	Clues to the Diagnosis as the Condition Evolves
DRESS/DIHS*	Morbilliform/urticarial drug eruption > viral exanthem	• Facial swelling • High fever • Prominent lymphadenopathy • Marked peripheral blood eosinophilia, atypical lymphocytes • Elevated transaminases, other signs of internal organ involvement
Stevens–Johnson syndrome/ toxic epidermal necrolysis	Morbilliform/urticarial drug eruption > viral exanthem	• Early involvement of palms and soles • Duskiness of blistering (often initially in the center of lesions) • Painful/tender skin • Mucosal erosions (oral, nasal, ocular, genital)
RMSF/other rickettsial spotted fevers	Viral exanthem	• Potential exposure to ticks (e.g., season [spring to late summer for RMSF], geographic location) • High fever, myalgias, headache (often for 2–5 days prior to rash) • Rash begins on wrists/ankles, spreads centripetally (± palms/soles) • Petechiae within erythematous macules/papules
Meningococcemia	Viral exanthem	• Petechiae → retiform purpura • Fever with chills, myalgias • Headache, stiff neck
Kawasaki disease	Viral exanthem, morbilliform/urticarial drug eruption, erythema multiforme, "diaper dermatitis" (for early perineal eruption)	• Early perineal erythema → desquamation • Conjunctival injection • "Chapped" lips, "strawberry" tongue • Acral erythema and edema • Continued high-spiking fever ≥5 days • Prominent unilateral lymphadenopathy
Staphylococcal scalded skin syndrome	Seborrheic dermatitis, viral exanthem	• Painful/tender skin • Periorifacial (around mouth and eyes) edema and (later) radial scale-crusts • Confluent erythema → superficial erosions/peeling, especially in intertriginous sites
Toxic shock syndrome	Scarlatiniform exanthem	• Strawberry tongue • Mucositis • Rapid evolution • Hypotension
Necrotizing fasciitis	Cellulitis	• Tense, "woody" induration • Extreme pain or (later) anesthesia • Rapid evolution • Erythema → dusky gray color • Watery, malodorous discharge

*In general, begins ≥2 wk after the drug is initiated and has a relatively limited set of culprit medications.
DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; RMSF, Rocky Mountain spotted fever.
Modified from Bolognia J, Schaffer JV, Duncan KO, Ko CJ. Fever and rash. In: Bolognia J, Schaffer JV, Duncan KO, Ko CJ, eds. *Dermatology Essentials*. Oxford: Saunders; 2014:35. Table 3.1.

Streptococcal Toxic Shock Syndrome

Confirmed case: isolation of group A streptococci from a normally sterile site (blood, cerebrospinal, pleural, or peritoneal fluid, tissue biopsy, surgical wound); or
Probable case: isolation of group A streptococci from a nonsterile site (throat, sputum, vagina, superficial skin lesion), and
Clinical signs of severity:

1. Hypotension: systolic blood pressure ≤ 90 mm Hg in adults or below 5th percentile for age in children, and
2. Two or more of the following signs:
   - Renal impairment: creatinine ≥177 μmol/L (≥2 mg/dL) for adults or ≥2 times the upper limit of normal for age; in patients with preexisting renal disease, a 2-fold or greater elevation over the baseline level
   - Coagulopathy: platelets ≤100 × 10^9/L (≤100,000/mm^3) or DIC defined by prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products
   - Liver involvement: serum aspartate aminotransferase, alanine aminotransferase, or total bilirubin levels greater than or equal to 2 times the upper limit of normal for age; in patients with

TABLE 40.7 Clinical and Laboratory Features of Kawasaki Disease

Epidemiologic Case Definition (Classic Clinical Criteria)*

Fever persisting at least 5 days† *and*
Presence of at least 4 principal features:
- Changes in extremities:
  - Acute: Erythema of palms, soles; edema of hands, feet
  - Subacute: Periungual peeling of fingers, toes in 2 and 3 wk
- Polymorphous exanthem
- Bilateral bulbar conjunctival injection without exudate
- Changes in lips and oral cavity: erythema, lip cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosa
- Cervical lymphadenopathy (>1.5 cm in diameter), usually unilateral

Exclusion of other diseases with similar findings

Other Clinical and Laboratory Findings

Cardiovascular findings:
- Congestive heart failure, myocarditis, pericarditis, valvular regurgitation
- Coronary artery abnormalities
- Aneurysms of medium-size noncoronary arteries
- Raynaud phenomenon
- Peripheral gangrene

Musculoskeletal system:
- Arthritis, arthralgias

Gastrointestinal tract:
- Diarrhea, vomiting, abdominal pain
- Hepatic dysfunction
- Hydrops of gallbladder

Central nervous system:
- Extreme irritability
- Aseptic meningitis
- Sensorineural hearing loss

Genitourinary system:
- Urethritis/meatitis

Other findings:
- Erythema, induration at bacille Calmette-Guérin inoculation site
- Anterior uveitis (mild)
- Desquamating rash in groin

Laboratory Findings in Acute Kawasaki Disease

Leukocytosis with neutrophilia and immature forms
Elevated erythrocyte sedimentation rate
Elevated C-reactive protein
Anemia
Abnormal plasma lipids
Hypoalbuminemia
Hyponatremia
Thrombocytosis after 1 wk‡
Sterile pyuria
Elevated serum transaminases
Elevated serum gamma-glutamyl transpeptidase
Pleocytosis of cerebrospinal fluid
Leukocytosis in synovial fluid

*Patients with fever for at least 5 days and <4 principal criteria can be diagnosed with Kawasaki disease when coronary artery abnormalities are detected by 2-dimensional echocardiography or angiography.
†In the presence of ≥4 principal criteria, Kawasaki disease diagnosis can be made on day 4 of illness. Experienced clinicians who have treated many patients with Kawasaki disease may establish diagnosis before day 4.
‡Some infants present with thrombocytopenia and disseminated intravascular coagulation.
From Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease. *Pediatrics*. 2004;114:1708-1733.

FIGURE 40.10 Erythema multiforme in a child with Kawasaki disease. (From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology*. 5th ed. Philadelphia: Elsevier; 2016.)

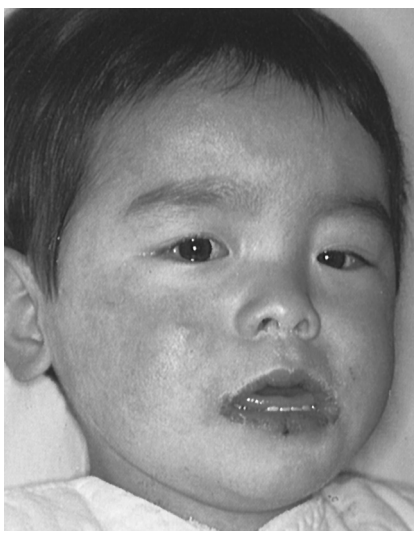


FIGURE 40.11 Kawasaki disease. Note characteristic facies with congestion of the bulbar conjunctivae and hemorrhagic crusts and erosions of the lips. (Courtesy Tomisaku Kawasaki, MD.)

FIGURE 40.12 Indurative edema of the hands in Kawasaki disease. (From Kliegman RM, Stanton BF, St Geme JW III, et al, eds. *Nelson Textbook of Pediatrics.* 20th ed. Philadelphia: Elsevier; 2016.)

FIGURE 40.14 Beau lines, a horizontal groove on the nails of a patient with Kawasaki disease, convalescent stage. (From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology.* 5th ed. Philadelphia: Elsevier; 2016.)

FIGURE 40.13 Desquamation of the fingers in a patient with Kawasaki disease, convalescent stage. (From Kliegman RM, Stanton BF, St Geme JW III, et al, eds. *Nelson Textbook of Pediatrics.* 20th ed. Philadelphia: Elsevier; 2016.)

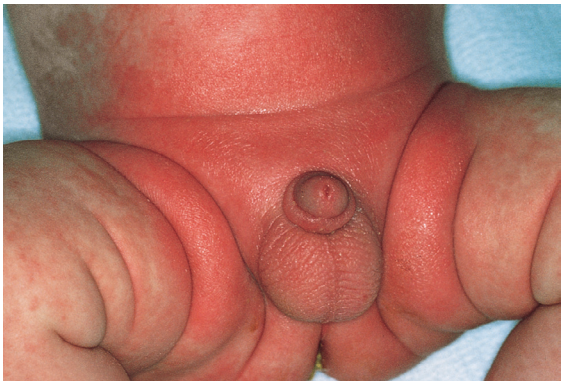


FIGURE 40.15 A scarlet fever–like rash in a child with Kawasaki disease. (From Habif TP. *Clinical Dermatology.* 6th ed. Philadelphia: Elsevier; 2016.)

preexisting liver disease, a 2-fold or greater elevation over the baseline level
- Acute respiratory distress syndrome defined by acute onset of diffuse pulmonary infiltrates and hypoxemia in the absence of cardiac failure, or evidence of diffuse capillary leak manifested by acute onset of generalized edema, or pleural or peritoneal effusions with hypoalbuminemia
- A generalized erythematous macular rash that may desquamate
- Soft tissue necrosis, including necrotizing fasciitis or myositis, or gangrene

Erythema Multiforme

Erythema multiforme (EM) is a self-limited immune reaction that occurs in the setting of infection. It is characterized by the abrupt onset of fixed erythematous papules that evolve into target lesions (see Fig. 40.10). It was previously thought to be related to SJS, but it is now clear that EM is a distinct disease. The basic lesions are round macular targets symmetrically distributed especially over the palms, soles, and extensor surfaces of the extremities. EM is typically associated with infection, most often HSV. *M. pneumoniae* has also been associated with EM. Drugs and systemic disease are rare causes of EM.

Stevens–Johnson Syndrome, Toxic Epidermal Necrolysis, and Staphylococcal Scalded Skin Syndrome

SJS and TEN are rare, life-threatening mucocutaneous exfoliative dermatoses that are usually drug related. They are thought to be associated with an immune response to an antigenic complex formed by the reaction of intermediate drug metabolites with host tissues. Several drug-related HLA alleles have been found to increase susceptibility for the development of SJS and TEN. SJS and TEN are characterized by diffuse cutaneous erythema and full-thickness necrosis of the epidermis with detachment of the skin at the dermal-epidermal junction. They differ in the percentage of involved total body surface area (BSA); SJS involves ≤10% BSA, SJS/TEN overlap involves between 10% and 30% BSA, and TEN involves ≥30% BSA. They are usually associated with exposure to drugs and differ histopathologically from SSSS, which also manifests clinically with diffuse erythema and blistering, in its cleavage plane. In SSSS, blistering is produced more superficially by disruption of the epidermal granular cell layer in response to 1 of 2 staphylococcal exfoliative toxins (ET-A or ET-B). This results in easy disruption of skin with firm rubbing (Nikolsky sign). SSSS is usually seen in infants and young children, whereas SJS and TEN are seen in older children. The key feature that distinguishes SJS and TEN is the presence of blistering lesions which may involve the lips, eyes, nasal mucosa, genitalia, or rectum (Figs. 40.17 and 40.18). Extensive ocular involvement, including corneal ulceration, uveitis, and panophthalmitis, may develop. Pulmonary and renal involvement have also been reported. Representative medications frequently associated with SJS and TEN include aminopenicillins, carbamazepine, phenytoin, trimethoprim-sulfamethoxazole, and nonsteroidal antiinflammatory medications. Prognosis is related to the speed with which the culprit medication is withdrawn, so a timely diagnosis is critical.

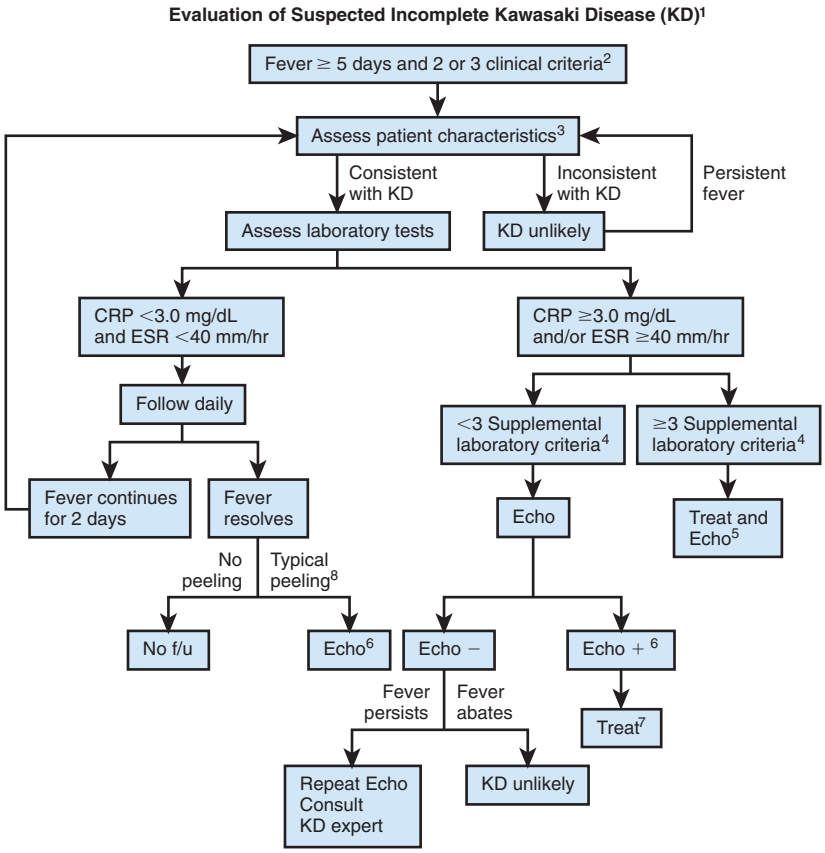


FIGURE 40.16 Algorithm for evaluation of suspected incomplete Kawasaki disease (KD). (1) In the absence of a gold standard for diagnosis, this algorithm cannot be evidence based, but rather represents the informed opinion of an expert committee. Consultation with an expert should be sought anytime assistance is needed. (2) Infants ≤6 months old on day 7 of fever or later without other explanation should undergo laboratory testing and, if evidence of systemic inflammation is found, given an echocardiogram (Echo), even if they have no clinical criteria. (3) Characteristics suggesting disease other than KD include exudative conjunctivitis, exudative pharyngitis, discrete intraoral lesions, bullous or vesicular rash, and generalized adenopathy. Consider alternative diagnoses. (4) Supplemental laboratory criteria include albumin ≤3.0 g/dL, anemia for age, elevation of alanine aminotransferase, platelet count after 7 days ≥450,000/mm^3, white blood cell count ≥15,000/mm^3, and urine white blood cell count ≥10/high-power field. (5) Can treat before performing echocardiogram. (6) Echocardiogram findings are considered positive (Echo+) for purposes of this algorithm if any of 3 conditions are met: z-score of the left anterior descending coronary artery (LAD) or right coronary artery (RCA) ≥2.5; coronary arteries meet Japanese Ministry of Health criteria for aneurysms; ≥3 other suggestive features exist, including perivascular brightness, lack of tapering, decreased left ventricle (LV) function, mitral regurgitation, pericardial effusion, or z-scores in LAD or RCA of 2-2.5. (7) If echocardiogram findings are positive, treatment should be given to children within 10 days of fever onset and to those beyond day 10 with clinical and laboratory signs (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]) of ongoing inflammation. (8) Typical peeling begins under nail beds of fingers and then toes. Echo–, negative echocardiogram findings; f/u, follow-up. (From Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease. *Pediatrics*. 2004;114:1708-1733; Son MBF. Kawasaki disease. In: *Nelson Textbook of Pediatrics*. Philadelphia: Elsevier; 2016:1209.e1-1214.e1, Chapter 166.)

Serum Sickness and Serum Sickness-Like Reaction

Serum sickness is a systemic hypersensitivity condition resulting from immune complex deposition in tissue and blood vessels that causes tissue damage through complement activation. It is classically associated with the administration of animal serum proteins, but the availability of alternative therapies, including monoclonal antibodies of human origin, has decreased the incidence of true serum sickness. A serum sickness-like reaction can be triggered by antibiotics or other drugs (particularly cefaclor, penicillins, sulfonamides, phenytoin, carbamazepine) and presents 1-2 weeks after exposure. Symptoms include fever, rash, arthralgia or arthritis, and lymphadenopathy. The rash of serum sickness-like reaction is morbilliform or large fixed serpiginous and cyclic urticarial plaques; it can be confused with other circular rashes such as giant urticaria and EM (Fig. 40.19). Serum sickness-like reactions do not exhibit the hypocomplementemia, vasculitis, circulating immune complexes, and renal lesions that are seen in serum sickness. Critical to making the diagnosis is identification of exposure to a drug in the preceding 1-2 weeks. A watchful waiting approach may support the diagnosis, inasmuch as the syndrome should resolve within approximately 4 weeks if exposure to the purported offending agent has been curtailed. Persistence of findings beyond this period indicates another disorder associated with immune complex–mediated vasculitis.

Henoch-Schonlein Purpura

HSP is usually a self-limited IgA-mediated vasculitis representing the most common vasculitis of childhood. It affects vessels in the skin, joints, gastrointestinal tract, and kidneys. The clinical manifestations include a rash, which initially is urticarial and then frequently evolves into a maculopapular eruption; after this eruption, petechiae and then purpuric plaques distributed predominantly on the buttocks and over the lower extremities develop (Fig. 40.20). These plaques usually are raised from the skin surface, which gives the rash its characteristic feature of "palpable purpura." Associated findings that are variably present include arthralgias and arthritis; edema of the feet, hands, face, scrotum, and scalp; melena, which may accompany intussusception; and an abnormal urinalysis that demonstrates hematuria and proteinuria. Fever, if present, is low grade and not a dominant feature of HSP. Laboratory testing is not necessary but can be of use to the clinician in excluding the infectious or hematologic causes of purpura if the patient does not present with classic features. Specifically, the results of both the platelet count and the coagulation profile are normal, and blood cultures are sterile. A Gram stain of the lesion is not usually needed, but the results are negative. Skin biopsy demonstrates the characteristic leukocytoclastic vasculitis involving the vessels in the dermis with IgA deposition. This finding is not specific for HSP, nor is it required for clinical confirmation.

Other Disorders

The diagnosis of other disorders manifesting with fever and rash is also based on formal syndromic criteria. SJIA (see Chapter 33), acute rheumatic fever (see Chapter 8), hemophagocytic lymphohistiocytosis (see Chapter 41), and SLE are examples. Representative diagnoses usually necessitating tissue confirmation are sarcoidosis and other vasculitides, such as polyarteritis nodosa or Wegener granulomatosis.

◆ Management

Treatment of patients with fever and rash includes both anticipatory guidance and specific interventions. Anticipatory guidance alone

FIGURE 40.17 Stevens–Johnson syndrome. Mucous membrane involvement with severe swelling and hemorrhagic crusting of the lips. (From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology*. 5th ed. Philadelphia: Elsevier; 2016.)

FIGURE 40.18 Stevens–Johnson syndrome. Confluent erythema, blisters, and exfoliation of the epidermis are present. (From Hurwitz S. *Clinical Pediatric Dermatology: A Textbook of Skin Disorders of Childhood and Adolescence*. 2nd ed. Philadelphia: WB Saunders; 1993:528.)

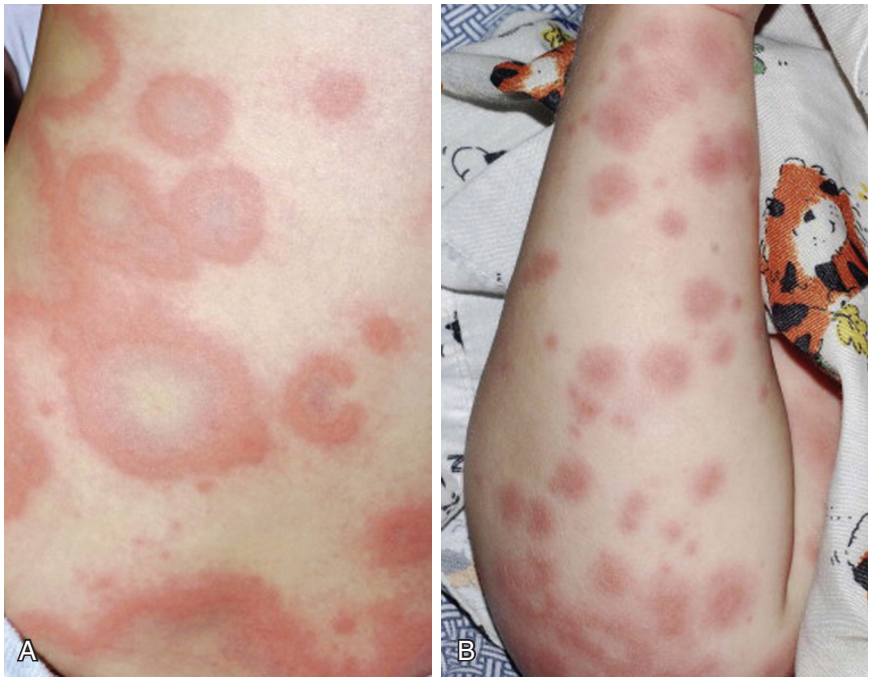


FIGURE 40.19 Urticaria and serum sickness-like reaction. *A,* Giant annular urticaria (urticaria "multiforme") in a young child with a recent viral upper respiratory tract infection. Individual lesions last <24 hours, but they often resolve with a dusky purplish hue that can lead to misdiagnosis as erythema multiforme. *B,* Serum sickness-like reaction due to amoxicillin. Some of the urticarial papules and annular plaques have a purpuric component, and the eruption was accompanied by high fevers, lymphadenopathy, arthralgias, and acral edema. (From Schaffer JV. Fever and rash. In: Bolognia JL, ed. *Dermatology Essentials*. Philadelphia: Elsevier; 2014;3:28-38.)

FIGURE 40.20 Henoch–Schönlein purpura (anaphylactoid purpura). Hemorrhagic macules, papules, and urticarial lesions appear in a symmetric distribution over the buttock. (From Kliegman RM, Stanton BF, St Geme JW III, et al, eds. *Nelson Textbook of Pediatrics.* 20th ed. Philadelphia: Elsevier; 2016:Fig. 167-2.)

usually suffices for patients who have a clearly identifiable, acute, self-limited, and noninvasive infectious or hypersensitivity disorder. Parents should be informed of the probable duration of illness, the expected evolution of clinical manifestations, potential complications and how to recognize them, and when to recontact the physician (see Tables 40.4 and 40.5).

The use of antipyretics as supportive therapy for patients with fever remains controversial. Arguments in favor of such therapy include decreasing symptomatic discomfort associated with the febrile state and reducing the undesirable metabolic and cardiopulmonary effects. Inadvertent overdose or unwanted side effects of over-the-counter antipyretics argue against their routine use.

Empirical therapy with antibiotics is an appropriate strategy for patients with focal cutaneous infection, such as cellulitis and erythema migrans, for patients with petechial or purpuric rash who are thought to have invasive infectious disorders, or for patients who appear toxic or manifest signs of cardiovascular instability. If epidemiologic evidence or clinical features are suggestive of rickettsial infection, the antimicrobial regimen should include doxycycline, even for children younger than 8 years. Suspected neonatal HSV infection should be treated with parenteral acyclovir.

Patients for whom a diagnosis is established by pattern recognition, case finding, syndromic aggregation, biopsy, or exclusion of other disorders may receive definitive interventions, as available, if the treatment benefits outweigh the risks. SSSS should be treated with an intravenous antistaphylococcal antibiotic. Staphylococcal TSS should be treated by removing vaginal foreign material if present, and administering intravenous vancomycin; toxin and cytokine production should be curtailed with a bacterial protein synthesis inhibitor such as clindamycin. If methicillin-sensitive *S. aureus* is confirmed by vaginal culture, an antistaphylococcal penicillin plus clindamycin is appropriate. Streptococcal TSS should be treated with surgical debridement if indicated, and parenteral penicillin and clindamycin. Intravenous immune globulin (IVIG) may be used as adjunctive therapy for streptococcal TSS to neutralize bacterial exotoxins. Treatment of acute rheumatic fever is directed at group A streptococcus with treatment-dose penicillin followed by prophylactic doses of penicillin to decrease the risk of recurrent rheumatic fever. Diseases caused by drug toxicity are treated by discontinuing the offending medication. SJS and TEN are treated with supportive care, often in a burn center, meticulous skin care, and IVIG.

Infections with HSV or varicella-zoster virus may be treated with oral or intravenous acyclovir. Intravenous therapy is particularly appropriate for immunocompromised patients. The benefits of acyclovir therapy for HSV or varicella-zoster virus in immunocompetent hosts are less clear.

Pharmacologic interventions in the systemic inflammatory disorders include antiinflammatory agents, such as the nonsteroidal agents, and corticosteroids and immunosuppressant or modulating agents. Administration of IVIG is a definitive intervention in all patients with KD to reduce coronary aneurysm formation. The most effective treatment regimen for patients with KD of less than 10 days' duration is 1 dose of IVIG (2 g/kg) given over 12 hours with adjunctive aspirin therapy for at least 6-8 weeks to prevent thrombotic complications. Because 10% of patients may have persistent fever (>48 hours) or recrudescence of fever after the 1-dose IVIG regimen, repeated treatment with IVIG is often necessary. Treatment of IVIG nonresponders is more controversial and may consist of corticosteroids, infliximab, or other immunosuppressant agents.

SUMMARY AND RED FLAGS

Most childhood episodes of fever and rash represent benign, self-limited viral illnesses with little or no sequelae. Diseases with potentially significant sequelae, such as meningococcemia, Rocky Mountain spotted fever, acute rheumatic fever, KD, SJS, DRESS, TSS, and SSSS require efficient evaluation and timely treatment. Red flags include toxic appearance, unstable vital signs, meningismus, or fever with petechiae or purpura.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

American Academy of Pediatrics. *Lyme Disease. Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:516-525.

American Academy of Pediatrics. Rickettsial Disease. *Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:677-680.

Avner JR. Acute fever. *Pediatr Rev*. 2009;30(1):5-13.

Baker RC, Seguin JH, Leslie N, et al. Fever and petechiae in children. *Pediatrics*. 1989;84(6):1051-1055.

Bialecki C, Feder HM Jr, Grant-Kels JM. The six classic childhood exanthems: a review and update. *J Am Acad Dermatol*. 1989;21(5 Pt 1):891-903.

Biesbroeck L, Sidbury R. Viral exanthems: an update. *Dermatol Ther*. 2013;26(6):433-438.

Bolognia J, Schaffer JV, Duncan KO, et al. Fever and rash. In: Bolognia J, Schaffer JV, Duncan KO, et al., eds. *Dermatology Essentials*. Oxford: Saunders/Elsevier; 2014:28-38.

Burns JC, Wiggins JW Jr, Toews WH, et al. Clinical spectrum of Kawasaki disease in infants younger than 6 months of age. *J Pediatr*. 1986;109(5):759-763.

Chang FY, Hwang B, Chen SJ, et al. Characteristics of Kawasaki disease in infants younger than six months of age. *Pediatr Infect Dis J*. 2006;25(3):241-244.

Chapman AS, Bakken JS, Folk SM, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis–United States: a practical guide for physicians and other health-care and public health professionals. *MMWR Recomm Rep*. 2006;55(RR-4):1-27.

French LE, Prins C. Erythema Multiforme, Stevens-Johnson syndrome and Toxic Epidermal Necrolysis. In: Bolognia J, Jorizzo JL, Schaffer JV, eds. *Dermatology*. 3rd ed. Philadelphia: Elsevier Saunders; 2012:319-333.

Gewitz MH, Baltimore RS, Tani LY, et al. Revision of the Jones Criteria for the Diagnosis of Acute Rheumatic Fever in the Era of Doppler Echocardiography A Scientific Statement From the American Heart Association. *Circulation*. 2015;131(20):1806-1818.

Goodyear HM, Laidler PW, Price EH, et al. Acute infectious erythemas in children: a clinico-microbiological study. *Br J Dermatol*. 1991;124(5):433-438.

Gowdie PJ, Tse SM. Juvenile idiopathic arthritis. *Pediatr Clin North Am*. 2012;59(2):301-327.

Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: part I. Clinical perspectives. *J Am Acad Dermatol*. 2013;68(5):693.e1-693.e14, quiz 706-708.

Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: part II. Management and therapeutics. *J Am Acad Dermatol*. 2013;68(5):709.e1-709.e9, quiz 18-20.

Kaye ET, Kaye KM. Fever and rash. In: Kasper D, Fauci A, Hauser S, et al., eds. *Harrison's Principles of Internal Medicine*. 19th ed. New York: McGraw-Hill; 2015.

Klassen TP, Hartling L, Wiebe N, et al. Acyclovir for treating varicella in otherwise healthy children and adolescents. *Cochrane Database Syst Rev*. 2005;(4):Cd002980.

Ladisch S. Histiocytosis syndromes of childhood. In: Kliegman R, Stanton B, St. Geme JW, III, et al., eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia, PA: Elsevier; 2016:2484-2489.

Lee Y-C, Kuo H-C, Chang J-S, et al. Two new susceptibility loci for Kawasaki disease identified through genome-wide association analysis. *Nat Genet*. 2012;44(5):522-525.

Macias ES, Pereira FA, Rietkerk W, et al. Superantigens in dermatology. *J Am Acad Dermatol*. 2011;64(3):455-472.

Mandl KD, Stack AM, Fleisher GR. Incidence of bacteremia in infants and children with fever and petechiae. *J Pediatr*. 1997;131(3):398-404.

Markowitz M, Kaplan EL. Reappearance of rheumatic fever. *Adv Pediatr*. 1989;36:39-65.

Mathur AN, Mathes EF. Urticaria mimickers in children. *Dermatol Ther*. 2013;26(6):467-475.

Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation*. 2004;110(17):2747-2771.

Noguera-Morel L, Hernández-Martín Á, Torrelo A. Cutaneous drug reactions in the pediatric population. *Pediatr Clin North Am*. 2014;61(2):403-426.

Onouchi Y. Genetics of Kawasaki disease: What we know and don't know. *Circ J*. 2012;76(7):1581-1586.

Scuccimarri R. Kawasaki disease. *Pediatr Clin North Am*. 2012;59(2):425-445.

Sidoroff A. Acute generalized exanthematous pustulosis. *Chem Immunol Allergy*. 2012;97:139-148.

Solomon AR, Rasmussen JE, Varani J, et al. The Tzanck smear in the diagnosis of cutaneous herpes simplex. *JAMA*. 1984;251(5):633-635.

Sood SK. Lyme disease in children. *Infect Dis Clin North Am*. 2015;29(2):281-294.

Streptococcal Toxic-Shock Syndrome (STSS) (Streptococcus pyogenes) 2010 Case Definition [08/16/2015]. Available from: <http://wwwn.cdc.gov/nndss/conditions/streptococcal-toxic-shock-syndrome/case-definition/2010/>.

Toxic Shock Syndrome (Other Than Streptococcal) (TSS) 2011 Case Definition. Available from: <http://wwwn.cdc.gov/nndss/conditions/toxic-shock-syndrome-other-than-streptococcal/case-definition/2011/>.

Woods CR. Rocky Mountain spotted fever in children. *Pediatr Clin North Am*. 2013;60(2):455-470.

Ye Q, Shao WX, Shang SQ, et al. A comprehensive assessment of the value of laboratory indices in diagnosing Kawasaki disease. *Arthritis Rheumatol*. 2015;67(7):1943-1950.

Yellen ES, Gauvreau K, Takahashi M, et al. Performance of 2004 American Heart Association recommendations for treatment of Kawasaki disease. *Pediatrics*. 2010;125(2):e234-e241.

41

Recurrent Fever, Infections, Immune Disorders, and Autoinflammatory Diseases

James W. Verbsky and John R. Routes

The immune system functions to prevent and retard the local establishment or systemic dissemination of bacteria, viruses, fungi, and protozoa. Furthermore, it must accomplish this task without excessive inflammation or the development of autoimmunity. The immune system has four primary components:

1. **Antibody-mediated immunity (humoral or B cell immunity)** is mediated by bone marrow-derived B lymphocytes and plasma cells (differentiated antibody-producing cells), which release antibodies (immunoglobulins) into secretions, plasma, and interstitial spaces. Antibodies work to opsonize and promote phagocytosis of organisms, neutralize toxins, and lyse pathogens (with the aid of complements).
2. **Cell-mediated immunity (T cell immunity)** is mediated by thymus-derived T lymphocytes (i.e., CD4 and CD8 T cells) that are activated by antigen-presenting cells (e.g., dendritic cells, macrophages) and antigens. Although T cells do not produce immunoglobulin, CD4 T cells are necessary for optimal B cell function. CD4 T cells also express cytokines that activate phagocytes to efficiently clear intracellular pathogens. CD8 T cells lyse virally infected cells.
3. The **phagocytic system** consists of tissue macrophages and dendritic cells, as well as blood-borne monocytes and neutrophils. In response to specific signals, phagocytes ingest and kill invading microorganisms. Dendritic cells also serve as antigen-presenting cells for T cells.
4. The **complement system** acts synergistically with antibodies and the remainder of the immune system to help clear microbial infections both directly (complement-mediated cytolysis) and indirectly (recruitment of phagocytic cells, opsonization of microbes).

The differential diagnosis for patients with recurrent infections is formidable in view of the complexity of the immune system. The different arms of the immune system are interconnected, thus similar infections may occur as a manifestation of phagocyte, humoral, cell-mediated, or complement disorders that can be inherited or acquired (Table 41.1). Alternatively, highly characteristic infections can point to a defect in a particular arm of the immune system (Table 41.2). Most patients with recurrent infections do not have an underlying identifiable primary immunodeficiency, but they frequently have allergic rhinitis, asthma, or other risks for recurrent infections (Table 41.3). Because of the low probability of identifying a discrete immune defect, the primary physician faces the difficult decision about the extent of the evaluation and which patients merit a complete evaluation. In addition, other genetic defects in the immune system result in recurrent episodes of spontaneous inflammation (i.e., **autoinflammatory disorders**), or immune dysregulation and **autoimmunity**, and these can often be mistaken as recurrent infections.

Although there are no established rules regarding immunologic work-up of a patient with infections, an evaluation should be considered for at least 1 of the following: (1) more than 2 systemic bacterial infections (sepsis, meningitis, osteomyelitis); (2) 2 or more serious respiratory infections (pneumonia, sinusitis) or bacterial infections (cellulitis, draining otitis media, lymphadenitis) per year; (3) the presence of an infection at an unusual site (hepatic or brain abscess); (4) infections with unusual pathogens (*Aspergillus* pneumonia, disseminated candidiasis, or infection with *Serratia marcescens*, *Nocardia* species, or *Burkholderia cepacia*); (5) infections of unusual severity; and (6) recurrent mycobacterial infections or invasive infections with atypical mycobacteria.

HISTORY AND PHYSICAL EXAMINATION

◆ History

The clinician must determine (1) the frequency, location, severity, and complications of the infections; (2) the accuracy of how infections were documented; (3) the presence or absence of a symptom-free interval; (4) the microbiologic features of any isolate; and (5) the response to antibiotic therapy. A single chronic infection may wax and wane with intermittent, inadequate treatment and may manifest as a series of infections. Furthermore, a detailed history can elucidate other risk factors for recurrent infections. Many nonimmune disorders are characterized by an increased susceptibility to infection that must also be considered (see Table 41.3). A detailed history can provide clues as to the likelihood and nature of a primary immune deficiency (Table 41.4).

Perinatal History

The clinician should determine if there was exposure to maternal viral infection during gestation (human immunodeficiency virus [HIV], cytomegalovirus (CMV), herpes simplex virus, rubella), or a history of prematurity, blood transfusions, respiratory distress syndrome (with bronchopulmonary dysplasia), or other pertinent neonatal illnesses. Infants previously placed on ventilators may develop chronic obstructive lung disease (bronchopulmonary dysplasia), predisposing them to recurrent pulmonary infections. Most perinatal HIV infections are seen in children whose mother or mother's partner has engaged in high-risk behavior (i.e., multiple sex partners or use of cocaine or intravenous drugs). Attention should be paid to the time of umbilical cord separation since infants with a history of delayed umbilical cord separation and recurrent episodes of sepsis or pneumonia should be evaluated for **leukocyte adhesion deficiency**.

Medical History

A variety of nonimmune medical issues can result in recurrent infections (see Table 41.3). Approximately 30% of children with recurrent sinopulmonary symptoms can be categorized as **atopic** (allergic on a hereditary basis). These subjects have normal growth and development, and episodes of recurrent illness may be afebrile,

TABLE 41.1 Cause and Mechanism of Recurrent Infection in Immunodeficiency States

Disorder	Pathogen	Deficiency
Primary Immunodeficiencies		
Humoral immunodeficiency syndromes (predominantly B cell defects)	Bacterial pathogens, enteroviruses	Reduced phagocytic efficiency, failure of lysis and agglutination of bacteria, inadequate neutralization of virus and bacterial toxins
Cellular immunodeficiency syndromes (predominantly T cell defects)	CMV, VZV, *Strongyloides stercoralis; Mycobacterium, Listeria, Nocardia; Cryptococcus, Candida* species; *Pneumocystis carinii*	Absence of or impaired delayed hypersensitivity response; absence of T cell cooperation for B cell synthesis of antibodies to T cell–specific antigens; absence of T cell cytokines that activate mononuclear phagocytes, failure of T cell clearance of viruses
Complement Deficiencies		
C1, C2, C3, C4, and factor B	*Streptococcus pyogenes, Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Klebsiella* species	Defective chemotaxis and opsonization of microbes
C5-C8 and properdin deficiencies	*Neisseria meningitidis, Neisseria gonorrhoeae*	Defective membrane attack mechanism
Phagocyte Defects		
Neutropenia (ANC < 500/mm^3)	Pyogenic bacteria or fungi, *Pseudomonas* species, *Staphylococcus aureus*	Decreased neutrophil numbers
Chronic granulomatous disease	Catalase-positive organisms, e.g., *S. aureus, Serratia* species, *Burkholderia cepacia, Nocardia* species, *Candida* species, *Aspergillus* species	Impaired neutrophil bactericidal activity secondary to impaired production of hydrogen peroxide
Secondary Immunodeficiencies		
AIDS	CMV, VZV, adenovirus, HBV, *Giardia lamblia, Entamoeba histolytica, Mycobacterium avium–intracellulare, Toxoplasma gondii, Mycobacterium tuberculosis, Cryptococcus neoformans, Pneumocystis jirovecii; Campylobacter, Candida, Isospora, Aspergillus, Nocardia, Strongyloides,* and *Cryptosporidium* species	Retrovirus infections transmitted by bodily fluid impair T cell response, reduced T helper cell numbers
Cancer	VZV, HSV, *Escherichia coli; Pseudomonas, Klebsiella, Listeria, Cryptococcus, Pneumocystis,* and *Mycobacterium* species	Neutropenia, lymphopenia, impaired cellular immunity
Immunosuppression	HSV, VZV, CMV, EBV, hepatitis virus, *Pseudomonas* species, *E. coli; Klebsiella, Acinetobacter, Serratia, Candida, Aspergillus, Mucor,* and *Cryptococcus* species	Dependent on agent used, leads often to impaired cellular immunity and neutropenia, lymphopenia
Transplantation	CMV, HSV, VZV, hepatitis virus, *S. aureus; Pseudomonas, Klebsiella, Candida, Aspergillus, Nocardia,* and *Pneumocystis* species; EBV	Related to use of immunosuppressive agents
Malnutrition	Measles, HSV, VZV, *Mycobacterium* species	Impaired T cell function, reduction in complement activity

AIDS, acquired immunodeficiency syndrome; ANC, absolute neutrophil count; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HSV, herpes simplex virus; VZV, varicella-zoster virus.

respond poorly to antibiotics, and be accompanied by upper respiratory symptoms such as coughing, sneezing, or wheezing. There may be a family history of atopic disease, and the patient's past medical history may include episodic wheezing, protracted cough after upper respiratory tract infection (URI) hay fever, allergies to foods, or eczema. The physical examination of allergic school-aged children may reveal typical characteristics including the following: dark circles under the eyes; open mouth with dry lips; coated tongue; evidence of nasal obstruction; transverse nasal crease; boggy, pale nasal mucosa; mucus in the pharynx; posterior pharyngeal "cobblestoning"; and postnasal drip.

Malnutrition and specific vitamin deficiencies may alter immune cell function. Protein-losing states due to gastrointestinal (e.g., inflammatory bowel disease, protein-losing enteropathy) or renal disease (e.g., nephrotic syndrome) may lead to hypocomplementemia, hypogammaglobulinemia, and recurrent infections. Chronic treatment with corticosteroids and other immunosuppressants can result in acquired immunodeficiency and recurrent infections.

Anatomic Abnormalities

Recurrent infections in primary immune deficiencies typically affect different anatomic locations. Structural or anatomic defects often result in recurrent infections that are generally localized to the affected organ system. Approximately 10% of children with recurrent infections have an underlying chronic disease or a structural defect that predisposes them to recurrent infections (see Table 41.3).

TABLE 41.2 Characteristic Pathogens Affecting Immunocompromised Patients

I. Humoral Defects

A. Antibody Deficiency (B Cell Defects)
1. Bacteria
Staphylococcus aureus (sepsis, sinopulmonary infection)
Haemophilus influenzae (sepsis, meningitis, arthritis, sinopulmonary infection)
Streptococcus pneumoniae (sepsis, meningitis, arthritis)
Pseudomonas aeruginosa (sepsis, pneumonia)
Mycoplasma species (arthritis, pneumonia)
Salmonella species (enteritis)
Campylobacter species (enteritis)
2. Viruses
Enterovirus, including polio vaccine (encephalitis, paralysis, myositis, arthritis)
Rotavirus (enteritis)
3. Protozoa
Giardia lamblia (enteritis)

B. Complement Deficiencies
1. C1, C2, C3, C4, factor B
S. pyogenes
S. pneumoniae, S. aureus, H. influenzae, Neisseria meningitidis, Klebsiella species (sepsis, meningitis, arthritis)
2. C5-8, properdin deficiency
N. meningitidis, N. gonorrhoeae (meningitis, sepsis, arthritis)

II. Combined B and T Cell Defects (Congenital, Acquired Immunodeficiency Syndrome, Immunosuppression Malignancies)

A. Bacteria
Listeria monocytogenes (sepsis, meningitis)
Salmonella (sepsis)
Mycobacterium tuberculosis (pneumonia, disseminated disease)
Atypical mycobacteria (*Mycobacterium avium, Mycobacterium intracellulare*) (sepsis, pneumonia, disseminated disease)
Nocardia species (pneumonia, CNS infection)
Legionella species (pneumonia)

B. Fungi
Cryptococcus neoformans (sepsis, meningitis)
Histoplasma capsulatum (pneumonia, disseminated disease)
Coccidioides immitis (pneumonia, meningitis)

C. Viruses
Varicella-zoster (cutaneous and CNS infection, pneumonia, hepatitis)
Cytomegalovirus (bone marrow infection, pneumonia, retinitis, esophagitis, colitis, CNS infection)
Herpes simplex (CNS infection, pneumonia, esophagitis, hepatitis, disseminated disease)
Epstein-Barr virus (lymphoma)
Measles (pneumonia, encephalitis)
Polyomavirus BK (hemorrhagic cystitis, ureteric stenosis, renal insufficiency)
Polyomavirus JC (progressive multifocal leukoencephalopathy)

D. Protozoa
Pneumocystis carinii (pneumonia, rare extrapulmonary spread)
Toxoplasma gondii (CNS infection, myocarditis)
Cryptosporidium species (enteritis)

E. Helminths
Strongyloides stercoralis (enteritis, pneumonia, sepsis, meningitis)

III. Neutropenia (Severe Chronic Neutropenia, Aplastic Anemia, Myelosuppression, Myelophthisis Myelosuppressive Agents, Bone Marrow Transplantation)

A. Bacteria
Escherichia coli (sepsis, pneumonia, pyelonephritis)
Klebsiella pneumoniae (sepsis, pneumonia)
P. aeruginosa (sepsis, pneumonia, cutaneous lesions)
Mixed anaerobic and aerobic enteric bacteria (typhlitis, perianal abscess)
S. aureus (sepsis, cellulitis, soft tissue infection)
Staphylococcus epidermidis (line infection)
Corynebacterium JK strain (sepsis)
α-Hemolytic streptococci (sepsis)

B. Fungi
Candida species (sepsis, pneumonia, ophthalmitis, liver and spleen abscesses)
Aspergillus species (sepsis, pneumonia, sinusitis, CNS infection, cutaneous lesions)
Mucor (pneumonia, sinusitis, CNS infection)
Fusarium species (sepsis, cutaneous lesions, pneumonia)
Alternaria species (sepsis, cutaneous lesions)

IV. Phagocytic Dysfunction

A. Chronic Granulomatous Disease
Bacteria (soft tissue, lymphadenitis, pneumonia, osteomyelitis)
Catalase-positive organisms, e.g., *S. aureus, Serratia marcescens, Burkholderia cepacia, Nocardia* species
Fungi (pneumonia, liver infection, soft tissue), *Candida* species, *Aspergillus* species)

B. Other Phagocyte Defects (Leukocyte Adhesion Deficiency Hyperimmunoglobulin E, Chédiak-Higashi syndrome, specific granule deficiency, Rac-2 deficiency)
Bacteria (soft tissue, pneumonia, lymphadenitis)
Pseudomonas species, *S. aureus, E. coli, Klebsiella, Enterobacter* species
Fungus (pneumonia)
Candida infection if diabetic

V. Splenic Dysfunction (e.g., Asplenia, Sickle Cell Anemia)

A. Bacteria
S. pneumoniae (sepsis, meningitis)
H. influenzae type b (sepsis, meningitis)
N. meningitidis (sepsis, meningitis)
Capnocytophaga canimorsus

B. Protozoa
Babesiosis
Malaria

CNS, central nervous system.

TABLE 41.3 Infections in Patients without Primary Immunodeficiency Syndromes

Predisposing Causes	Organism and Type of Infection
Alteration of Mucocutaneous Barriers	
Indwelling Catheter	
Central venous catheter (Broviac, Hickman)	*Staphylococcus aureus*; *S. epidermidis*; and *Bacteroides*, *Candida*, *Pseudomonas* species: bacteremia, fungemia
Urinary catheter	*Escherichia coli*, *Enterococcus* species, *Staphylococcus saprophyticus*: pyelonephritis
Tenckhoff catheter (continuous ambulatory peritoneal dialysis)	*Staphylococcus epidermidis*, *S. aureus*, *E. coli*, *Pseudomonas aeruginosa*, *Candida* species: peritonitis
Cerebrospinal fluid shunts	*S. epidermidis*, *S. aureus*, diphtheroid, *Bacillus* species: meningitis
Aspirated pulmonary foreign body	*S. aureus*, anaerobes: pneumonia, pulmonary abscess, empyema
Burns	*P. aeruginosa*, *S. epidermidis*, *Candida* species: cutaneous lesions, sepsis
Inhalation Therapy: Contaminated Solutions	*P. aeruginosa, Serratia marcescens, Legionella* species: pneumonia
Surgical Wounds	
Abdominal	Gram-negative bacteria, *S. aureus, S. epidermidis, Candida* species: peritonitis
Nongastrointestinal	*S. aureus, S. epidermidis,* streptococci, gram-negative bacteria: wound abscess, sepsis
Fistula-Sinus Communications	
Neurocutaneous fistula	*S. aureus, S. epidermidis, E. coli*: meningitis
Neuroenteric fistula	Gram-negative bacteria: meningitis
Otic, facial sinus-meningeal sinus tract	Pneumococcus: meningitis
Facial sinus fracture (CSF rhinorrhea)	Pneumococcus: meningitis
Intravenous Drug Abuse	*S. aureus, P. aeruginosa,* streptococci: endocarditis, osteomyelitis Hepatitis B, C, D viruses: AIDS
Prosthetic Devices	
Cardiac valves	*S. epidermidis,* streptococci, *S. aureus*, diphtheroid, *Candida* species: endocarditis
Pacemaker	*S. epidermidis, S. aureus, Candida* species: subcutaneous pocket or endocardial infection
Chronic Disease	
Malnutrition	Measles; tuberculosis; herpes simplex virus; bacterial, parasitic, and viral diarrhea, gram-negative bacteria: sepsis, pneumonia
Cystic fibrosis	*S. aureus, Haemophilus influenzae,* mucoid *P. aeruginosa, Burkholderia cepacia;* pneumonia
Diabetes mellitus	Urinary tract infections, *Mucor,* and other fungi: sinus-orbital infection
Nephrotic syndrome	Pnemococcus, *E. coli:* peritonitis
Uremia	*S. aureus,* gram-negative bacteria, fungi: sepsis, soft tissue infection
Cirrhosis, ascites	Pnemococcus, *E. coli:* peritonitis
Prolonged broad-spectrum antibiotic therapy	*Candida* species, *Enterococcus* species, multidrug-resistant gram-negative or gram-positive bacteria: sepsis
Spinal cord injury	Gram-negative or gram-positive bacteria: pneumonia, pyelonephritis, pressure sores, abscesses, osteomyelitis
Sickle cell anemia	Pnemococcus: sepsis, meningitis, osteoarticular infection *Salmonella* species, *S. aureus:* osteomyelitis
Congenital heart disease	*S. aureus, Streptococcus viridans* group: endocarditis
Urinary tract anomaly	*E. coli, S. saprophyticus, Enterococcus* species: pyelonephritis
Kartagener syndrome (dysmotile cilia)	*H. influenzae, Moraxella catarrhalis,* pnemococcus: pneumonia, sinusitis
Eczema/atopic disease	*S. aureus, Streptococcus* species, varicella, herpes simplex, molluscum: cutaneous infection, cellulitis
Protein-losing enteropathy (lymphangiectasia)	Pneumococcus: sepsis, peritonitis *Giardia* species: diarrhea
Periodontitis	*Fusobacterium* species: cellulitis, facial space infection

AIDS, acquired immunodeficiency syndrome; CMV, cytomegalovirus; CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HHV-6, human herpesvirus 6.

TABLE 41.4 Clinical Aids to the Diagnosis of Immunodeficiency

Suggestive of B Cell Defect (Humoral Immunodeficiency)
- Recurrent bacterial infections of the upper and lower respiratory tracts
- Recurrent skin infections, meningitis, osteomyelitis secondary to encapsulated bacteria *(Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Neisseria meningitidis)*
- Paralysis after vaccination with live attenuated poliovirus
- Reduced levels of immunoglobulins

Suggestive of T Cell Defect (Combined Immunodeficiency)
- Systemic illness after vaccination with any live virus or bacille Calmette-Guérin (BCG)
- Unusual life-threatening complication after infection with benign viruses (giant cell pneumonia with measles; varicella pneumonia)
- Chronic oral candidiasis after 6 months of age
- Chronic mucocutaneous candidiasis
- Graft-versus-host disease after blood transfusion
- Reduced lymphocyte counts for age
- Low level of immunoglobulins
- Absence of lymph nodes and tonsils
- Small thymus
- Chronic diarrhea
- Failure to thrive
- Recurrent infections with opportunistic organisms

Suggestive of Macrophage Dysfunction
- Disseminated atypical mycobacterial infection, recurrent *Salmonella* infection
- Fatal infection after BCG vaccination

Congenital Syndromes with Immunodeficiency
- Ataxia-telangiectasia: ataxia, telangiectasia
- Autoimmune polyglandular syndrome: hypofunction of 1 or more endocrine organs, chronic mucocutaneous candidiasis
- Cartilage-hair hypoplasia: short-limbed dwarfism, sparse hair, neutropenia
- Wiskott–Aldrich syndrome: thrombocytopenia, male gender, eczema
- Chédiak–Higashi syndrome: oculocutaneous albinism, nystagmus, recurrent bacterial infections, peripheral neuropathies
- DiGeorge syndrome (22q deletion syndrome): unusual facies, heart defect, hypocalcemia

Suggestive of Asplenia
- Heterotaxia, complex congenital heart disease, Howell–Jolly bodies on blood smear, sickle cell anemia

Eustachian tube abnormalities or cleft palate result in recurrent or chronic otitis media; congenital heart disease results in an increased risk of endocarditis; and posterior urethral valves, vesicoureteral reflux, or ureteral pelvic junction obstruction results in recurrent urinary tract infections. Recurrent pneumonia may result from congenital malformations (trachea-esophageal fistulas, cystic adenomatoid malformation, or sequestration), from aspiration of a foreign body (peanut, small toys) or chronic aspiration (gastroesophageal reflux or swallowing disorders), and from bronchopulmonary dysplasia. Repeated pneumonias in dependent lobes warrant evaluation for recurrent aspiration. Chronic illnesses that result in recurrent pulmonary infections include cystic fibrosis, primary ciliary dyskinesia, or α_1-antitrypsin deficiency. Recurrent sinus infections can occur due to anatomic defects of the sinuses (polyps, stenotic os). Endotracheal intubation predisposes the patient to recurrent pulmonary infections with nosocomial organisms. Right middle lobe syndrome and sequestered lung can appear as recurrent pneumonia in the same anatomic location.

Any direct communication to the cerebrospinal fluid that bypasses the blood–brain barrier predisposes patients to a central nervous system infection. Basilar skull fractures and dermal sinus tracts or fistulas may communicate with the subarachnoid space or neural tissue. Other conditions predisposing patients to opportunistic infections of the central nervous system include penetrating foreign body, cerebrospinal fluid shunts, myelomeningocele, and encephalocele. Local infections of the sinuses or of the middle ear may spread to contiguous structures to form cerebral abscesses or subdural-epidural empyema. Intravenous drug abuse, bacterial endocarditis, and heart disease with right-to-left shunt are associated with an increased risk of central nervous system infections.

Family History

Specific patterns of inheritance have been determined for a variety of immunologic defects. Genetic defects of immunity can be inherited as X-linked, autosomal recessive, or autosomal dominant disorders. Monogenic primary immunodeficiencies may exhibit reduced penetrance (some people with the genetic abnormality do not exhibit a clinical phenotype) and variable expressivity (different signs and symptoms with same genetic defect). A family history of unexplained infant deaths or serious infection should be sought, particularly in male infants since a number of important immune deficiencies are X-linked. Evidence of consanguinity should be sought as many serious primary immune deficiencies are autosomal recessive. Since allergic diseases can appear as recurrent infections, a family history of atopy is important. A child who has 1 allergic parent or 2 allergic parents is predisposed to allergic reactions by 25% and 50%, respectively.

Environmental History

The incidence of respiratory disease is increased in children exposed to cigarette or marijuana smoke or other noxious fumes (wood-burning stove) in the home. Respiratory and dermatologic findings are seen as a result of exposure to environmental allergens and toxins. Specific bacteriologic and parasitic exposures are associated with certain pets (i.e., *Salmonella* organisms and iguanas or turtles; psittacosis and birds; *Bartonella* organisms in kittens). A travel history may suggest exposure to unusual organisms that are regionally endemic, such as certain parasites and specific insect or animal bites, or to contaminated water. A move to a new house or to a new nursery school or exposure to a new babysitter, pet, or housekeeper may suggest possible allergic and infectious risks.

◆ Physical Examination

The physical examination may provide important clues to the diagnosis of a primary immune deficiency (see Table 41.4). Longitudinal evaluation of height and weight are crucial in identifying infants with failure to thrive or acute weight loss. Chronic upper respiratory infections are suggested by scarred tympanic membranes, postnasal drip, and cervical adenopathy. Transverse nasal creases, circles under the eyes, and posterior pharyngeal "cobblestoning" suggest respiratory allergy. Recurrent cough, wheezing, digital clubbing, and chest deformity are suggestive of pulmonary disease. Mouth ulceration or stomatitis can be a sign of immune deficiency or autoinflammatory disorder. Auscultation of the apex of the heart in the right side of the thorax (dextrocardia) may be accompanied by ciliary motility abnormalities or asplenia. Lymphadenopathy, hepatosplenomegaly, pallor, wasting, and recent weight loss are suggestive of systemic disease. Absence of lymph tissue (tonsils and lymph nodes) is suggestive of a B cell

deficiency, while absence of thymic tissue on chest radiograph in an infant is suggestive of T cell deficiency. Parotid enlargement with lymphadenopathy and hepatosplenomegaly is suggestive of HIV infection. Skin abnormalities including alopecia, eczema, pyoderma, and telangiectasia can be important clues. Evidence of hematologic disease, such as pallor, petechiae, and jaundice can be associated with immunodeficiencies. Generalized lymphadenopathy and splenomegaly may be suggestive of HIV disease, a phagocyte disorder with recurrent infections, or a lymphoproliferative disorder.

◆ Diagnostic Categories

The information obtained from the history and physical examination is usually sufficient to make a tentative classification:

1. The patient who is probably healthy.
2. The atopic or allergic patient.
3. The patient with a nonimmunologic defect in host defense (see Table 41.3).
4. The patient with hereditary inflammatory disorders (Table 41.5).
5. The immunodeficient patient.

Patient Who Is Probably Healthy

Many healthy children have repeated minor infections, or have a relatively brief history of repeated infections, or a single prolonged illness from which recovery has been delayed. Most upper respiratory tract infections last less than 7 days, and duration of longer than 14 days is unusual. Most children younger than 1 year who have a large family or who attend daycare develop respiratory or gastrointestinal infections about 6 times during the 1st year of life. The onset of the recurrent infection may coincide with entry into day care, preschool, or kindergarten. The healthy child has normal growth and development before the illness and usually a normal physical examination finding. When a discrepancy exists between the severity of an illness as reported by the parent and the child's physical appearance, it is often prudent to delay a detailed evaluation until more objective findings are documented by repeat examinations during acute episodes. Laboratory testing might include a complete blood cell count, inflammatory markers (i.e., erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]) to exclude rheumatic disorders or occult infections, and measurement of immunoglobulin levels and vaccine specific titers as a screen. Cultures and imaging of the affected area may provide additional data. With reassurance of the parents, these children recover spontaneously. Simple measures, rather than a complex set of laboratory studies, are often the only treatment required.

Patient with Hereditary Inflammatory Disorders

Autoinflammatory syndromes, formerly known as **periodic fever syndromes**, are a heterogeneous and ever increasing group of rare inflammatory disorders that manifest with recurrent fevers and/or inflammatory episodes (see Table 41.5). Recurrent fevers or inflammation can often be mistaken for recurrent infections. Patients exhibit characteristic physical findings during these episodes, such as fever, various rashes, lymphadenopathy, aphthous stomatitis, arthritis, and serositis with abdominal, chest, or testicular pain. These episodes can be periodic or sporadic, but the characteristic features occur with each episode. Laboratory evaluation may show elevated white blood cell (WBC) counts and elevated inflammatory markers during the episode that typically resolve between episodes. Importantly, infectious work-ups are often repeatedly negative, and the patient is typically well between febrile episodes.

There are also an increasing number of disorders of **immune dysregulation** that have been described (Table 41.6). Unlike autoinflammatory disorders, these disorders result in a failure to control T and B cell responses, resulting in **autoimmunity**. These disorders are not typically episodic, and once autoimmunity develops it continues until treated. Many of these disorders are *also* associated with immune deficiency and recurrent infection, thus patients experience recurrent infections simultaneously with autoimmune manifestations.

Immunodeficient Patient

Approximately 5-10% of children with recurrent infections have an underlying immunodeficiency. Frequently, the onset of infections occurs between the ages of 6 and 12 months, but delays in diagnosis are not uncommon. In addition, certain immune deficiencies such as common variable immunodeficiency disease (CVID) can present in adolescence or young adulthood; thus it is critical to consider immune defects in children of any age. Infections in patients with primary immune deficiencies often vary in type, location, and severity, although sinopulmonary infections are common. Failure to thrive may occur and can be a sign of a serious immune defect. Patients with primary immune defects often require repeated courses of antibiotics or intravenous antibiotics, or may have infections with unusual organisms or exhibit unexpected complications. Such children may respond to antibiotics but become ill when the medications are discontinued.

◆ Diagnostic Approach to the Patient with Recurrent Infections

Patients with recurrent, severe, or unusual infections involving multiple sites or organ systems should be investigated for an immunodeficiency (Fig. 41.1). Initial tests are recommended for patients suspected of a primary immune deficiency, although a variety of immune defects can occur despite normal screening tests. *Thus it is recommended that advanced testing be performed in consultation with a clinical immunologist.*

A complete blood count with *manual* differential should always be obtained in the evaluation of any child suspected of immunodeficiency. A neutrophil count below 500/mm^3 might indicate severe congenital neutropenia, cyclic neutropenia, idiopathic neutropenia, marrow failure, or replacement of marrow by leukemia or a tumor if other hematopoietic cell lines are affected. Analysis of the peripheral blood smear is important as this can detect neutrophil abnormalities (e.g., abnormal granules in Chédiak-Higashi) or evidence of asplenia (i.e., Howell-Jolly bodies).

Serum immunoglobulin levels (IgG, IgA, IgM, IgE) are essential to the work-up of suspected primary immunodeficiency. Antibody levels vary with age, with normal adult values of IgG at birth from transplacental transfer of maternal IgG, a physiologic nadir occurring between 3 and 6 months of age, and a gradual increase to adult values over several years. IgA and IgM are low at birth and levels increase gradually over several years, with IgA taking the longest to reach normal adult values. When IgG levels are low, albumin levels should be measured because increased loss of proteins, as in protein-losing enteropathy or nephrotic syndrome, can result in hypogammaglobulinemia. High immunoglobulin levels suggest intact B cell immunity and can be found in diseases with recurrent infections, such as chronic granulomatous disease (CGD), immotile cilia syndrome, cystic fibrosis, HIV infection, autoimmune diseases (lupus), and other disorders leading to chronic inflammation. Elevated IgE levels can be found in a number of immune deficiencies such as hyper-IgE syndrome, but more likely represent atopic diseases (atopic dermatitis).

Specific antibody titers after childhood vaccination (tetanus, diphtheria, *Haemophilus influenzae* type b, or *Streptococcus pneumoniae*) reflect the capacity of the immune system to synthesize specific antibodies and to develop memory B cells. If titers are low, immunization

TABLE 41.5 Autoinflammatory Disorders

Disease	Genetic Defect/ Presumed Pathogenesis	Inheritance	Affected Cells	Functional Defects	Associated Features
Familial Mediterranean fever	Mutations of *MEFV* (lead to gain of pyrin function, resulting in inappropriate IL-1β release)	AR	Mature granulocytes, cytokine-activated monocytes	Decreased production of pyrin permits ASC-induced IL-1 processing and inflammation following subclinical serosal injury; macrophage apoptosis decreased	Recurrent fever, serositis, and inflammation responsive to colchicine. Predisposes to vasculitis and inflammatory bowel disease
Mevalonate kinase deficiency (hyper 0 IgD syndrome)	Mutations of *MVK* (lead to a block in the mevalonate pathway). Interleukin-1β mediates the inflammatory phenotype	AR		Affecting cholesterol synthesis; pathogenesis of disease is unclear	Periodic fever and leukocytosis with high IgD levels
Muckle–Wells syndrome	Mutations of *NLRP3* (also called PYPAF1 or NALP3) lead to constitutive activation of the NLRP3 inflammasome	AD	PMNs, monocytes	Defect in cryopyrin, involved in leukocyte apoptosis and NF-κB signaling and IL-1 processing	Urticaria, SNHL, amyloidosis
Familial cold autoinflammatory syndrome	Mutations of *NLRP3* (see above) Mutations of NLRP12	AD	PMNs, monocytes	Same as above	Nonpruritic urticaria, arthritis, chills, fever, and leukocytosis after cold exposure
Neonatal-onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous and articular syndrome (CINCA)	Mutations of *NLRP3* (see above)		PMNs, chondrocytes	Same as above	Neonatal-onset rash, chronic meningitis, and arthropathy with fever and inflammation
TNF receptor–associated periodic syndrome (TRAPS)	Mutations of *TNFRSF1A* (resulting in increased TNF inflammatory signaling)	AD	PMNs, monocytes	Mutations of 55-kDa TNF receptor leading to intracellular receptor retention or diminished soluble cytokine receptor available to bind TNF	Recurrent fever, serositis, rash, and ocular or joint inflammation
Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome	Mutations of *PSTPIP1* (also called C2BP1) (affects both pyrin and protein tyrosine phosphatase to regulate innate and adaptive immune responses)	AD	Hematopoietic tissues, upregulated in activated T cells	Disordered actin reorganization leading to compromised physiologic signaling during inflammatory response	Destructive arthritis, inflammatory skin rash, myositis
Blau syndrome	Mutations of *NOD2* (also called CARD15) (involved in various inflammatory processes)	AD	Monocytes	Mutations in nucleotide binding site of CARD15, possibly disrupting interactions with lipopolysaccharides and NF-κB signaling	Uveitis, granulomatous synovitis, camptodactyly, rash, and cranial neuropathies, 30% develop Crohn disease
Chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majeed syndrome)	Mutations of *LPIN2* (increased expression of the proinflammatory genes)	AR	Neutrophils, bone marrow cells	Undefined	Chronic recurrent multifocal osteomyelitis, transfusion-dependent anemia, cutaneous inflammatory disorders

TABLE 41.5 Autoinflammatory Disorders—cont'd

Disease	Genetic Defect/ Presumed Pathogenesis	Inheritance	Affected Cells	Functional Defects	Associated Features
Early-onset inflammatory bowel disease	Mutations in *IL-10* (results in increase of many proinflammatory cytokines)	AR	Monocyte/ macrophage, activated T cells	IL-10 deficiency leads to increase of TNFγ and other proinflammatory cytokines	Enterocolitis, enteric fistulas, perianal abscesses, chronic folliculitis
Early-onset inflammatory bowel disease	Mutations in *IL-10RA* (see above)	AR	Monocyte/ macrophage, activated T cells	Mutation in IL-10 receptor alpha leads to increase of TNFγ and other proinflammatory cytokines	Enterocolitis, enteric fistulas, perianal abscesses, chronic folliculitis
Early-onset inflammatory bowel disease	Mutations in *IL-10RB* (see above)	AR	Monocyte/ macrophage, activated T cells	Mutation in IL-10 receptor beta leads to increase of TNFγ and other proinflammatory cytokines	Enterocolitis, enteric fistulas, perianal abscesses, chronic folliculitis

AD, autosomal dominant; AR, autosomal recessive; Ig, immunoglobulin; IL, interleukin; NF-κB, nuclear factor-κB; PMN, polymorhonuclear neutrophil; SNHL, sensorineural hearing loss; TNF, tumor necrosis factor.

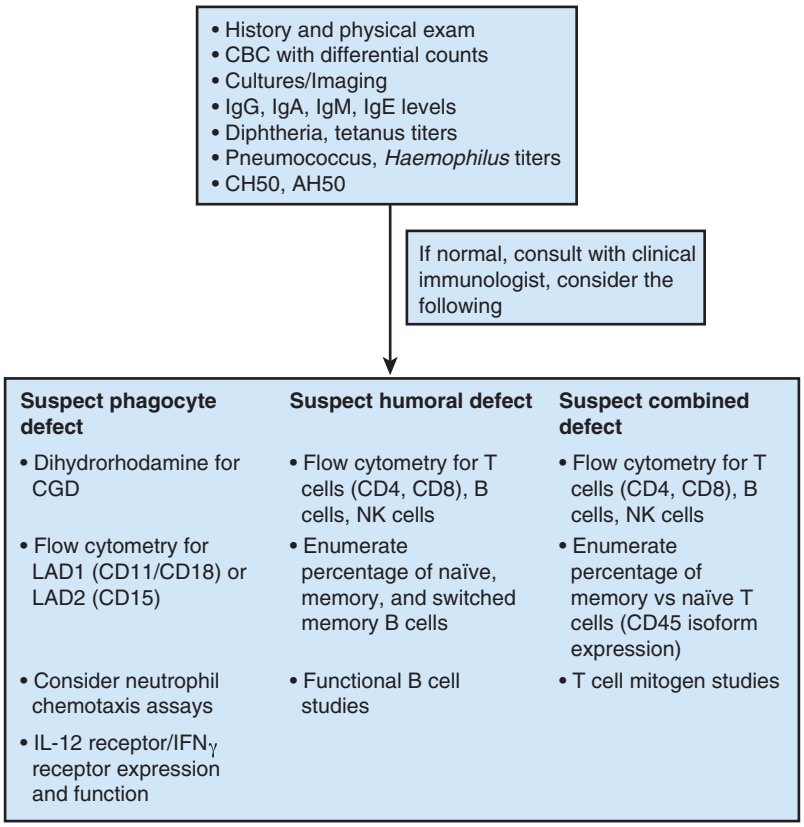


FIGURE 41.1 Initial work-up and follow-up studies of patients with suspected immune deficiency. Consultation with a clinical immunologist is recommended to guide advanced testing and interpret results. CBC, complete blood count; CGD, chronic granulomatous disease; LAD, leukocyte adhesion defect; NK, natural killer cell; IL, interleukin; IFN, interferon.

with a specific vaccine and obtaining titers 4-6 weeks later should be performed to confirm a response to the immunization. Poor response to bacterial polysaccharide antigens is often found before 24 months of age; even in older individuals the antibody response to polysaccharide vaccines is typically less robust and less long-lived than protein antigens. The development of protein-conjugate polysaccharide vaccines to *Streptococcus pneumoniae* and *Haemophilus influenzae* has dramatically reduced invasive infections with these organisms in early childhood by improving the response to vaccination. Antibody responses to the *S. pneumoniae* serotypes found in the 23-valent polysaccharide vaccine, but not in the conjugate vaccine, can be used to test antibody responses to polysaccharide antigens.

Complement assays include the CH50 test, which measures the presence of proteins in the classical pathway of complement (C1, C2,

TABLE 41.6 Disorders of Immune Regulation

Disease	Genetic Defect/Presumed Pathogenesis	Inheritance	Circulating T Cells	Circulating B Cells	Functional Defect	Associated Features
Perforin deficiency (FHL2)	Mutations in *PRF1*; perforin is a major cytolytic protein	AR	Increased activated T cells	Normal	Decreased to absent NK and CTL activities (cytotoxicity)	Fever, hepatosplenomegaly (HSMG), hemophagocytic lymphohistiocytosis (HLH), cytopenias
UNC13D/Munc13-4 deficiency (FHL3)	Mutations in *UNC13D*; required to prime vesicles for fusion	AR	Increased activated T cells	Normal	Decreased to absent NK and CTL activities (cytotoxicity and/or degranulation)	Fever, HSMG, HLH, cytopenias
Syntaxin 11 deficiency (FHL4)	Mutations in *STX11*, required for secretory vesicle fusion with the cell membrane	AR	Increased activated T cells	Normal	Decreased NK activity (cytotoxicity and/or degranulation)	Fever, HSMG, HLH, cytopenias
STXBP2/Munc18-2 deficiency (FHL5)	Mutations in *STXBP2*, required for secretory vesicle fusion with the cell membrane	AR	Increased activated T cells	Normal	Decreased NK and CTL activities (cytotoxicity and/or degranulation)	Fever, HSMG, HLH, cytopenias
Chediak–Higashi syndrome	Mutations in *LYST*, Impaired lysosomal trafficking	AR	Increased activated T cells	Normal	Decreased NK and CTL activities (cytotoxicity and/or degranulation)	Partial albinism, recurrent infections, fever, HSMG, HLH, giant lysosomes, neutropenia, cytopenias, bleeding tendency, progressive neurologic dysfunction
Griscelli syndrome, type 2	Mutations in *RAB27A* encoding a GTPase that promotes docking of secretory vesicles to the cell membrane	AR	Normal	Normal	Decreased NK and CTL activities (cytotoxicity and/or degranulation)	Partial albinism, fever, HSMG, HLH, cytopenias
SH2D1A deficiency (XLP1)	Mutations in *SH2D1A* encoding an adaptor protein regulating intracellular signaling	XL	Normal or increased activated T cells	Reduced memory B cells	Partially defective NK cell and CTL cytotoxic activity	Clinical and immunologic features triggered by EBV infection: HLH, lymphoproliferation, aplastic anemia, lymphoma, hypogammaglobulinemia, absent iNK T cells
XIAP deficiency (XLP2)	Mutations in *XIAP* encoding an inhibitor of apoptosis	XL	Normal or increased activated T cells; low/normal iNK T cells	Normal or reduced memory B cells	Increased T cells susceptibility to apoptosis to CD95 and enhanced activation-induced cell death (AICD)	EBV infection, splenomegaly, lymphoproliferation, HLH, colitis, IBD, hepatitis, low iNK T cells
IPEX, immune dysregulation, polyendocrinopathy, enteropathy X-linked	Mutations in *FOXP3*, encoding a T cell transcription factor	XL	Normal	Normal	Lack of (and/or impaired function of) CD4+ CD25+ FOXP3+ regulatory T cells (Tregs)	Autoimmune enteropathy, early-onset diabetes, thyroiditis, hemolytic anemia, thrombocytopenia, eczema, elevated IgE, IgA
CD25 deficiency	Mutations in *IL2RA*, encoding IL-2Rα chain	AR	Normal to decreased	Normal	No CD4+ C25+ cells with impaired function of Tregs	Lymphoproliferation, autoimmunity. Impaired T cell proliferation

STAT5b deficiency	Mutations in *STAT5B*, signal transducer, and transcription factor, essential for normal signaling from IL-2 and IL-15, key growth factors for T and NK cells	AR	Modestly decreased	Normal	Impaired development and function of γδ T cells, Tregs, and NK cells, low T cell proliferation	Growth hormone–insensitive dwarfism, dysmorphic features, eczema, lymphocytic interstitial pneumonitis, autoimmunity
LRBA deficiency	Mutations in *LRBA* (lipopolysaccharide responsive beige like anchor protein)	AR		Reduced I IgG and IgA in most	Defect CTLA4 expression on surface	Recurrent infections, inflammatory bowel disease, autoimmunity; EBV infections
CTLA4	Mutations or deletions in *CLTA4*	AD	Variable	IgG reduced	Hypogammaglobulinemia	Recurrent infections, autoimmune cytopenia, brain inflammation
APECED (APS-1), autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy	Mutations in *AIRE*, encoding a transcription regulator needed to establish thymic self-tolerance	AR	Normal	Normal	AIRE/1 serves as checkpoint in the thymus for negative selection of autoreactive T cells and for generation of Tregs	Autoimmunity: hypoparathyroidism hypothyroidism, adrenal insufficiency, diabetes, gonadal dysfunction, and other endocrine abnormalities, chronic mucocutaneous candidiasis, dental enamel hypoplasia, alopecia areata, enteropathy, pernicious anemia
ALPS–FAS	Germinal mutations in *TNFRSF6,* encoding CD95/Fas cell surface apoptosis receptor	AR	Increased $CD4^-$ $CD8^-$ TCRα/β double negative (DN) T cells	Normal, low memory B cells	Apoptosis defect FAS mediated	Splenomegaly, adenopathies, autoimmune cytopenias, increased lymphoma risk, IgG and IgA normal or increased, elevated FasL and IL-10, vitamin B_{12}
ALPS–FASLG	Mutations in *TNFSF6*, Fas ligand for CD95 apoptosis	AR	Increased DN T cells	Normal	Apoptosis defect FAS mediated	Splenomegaly, adenopathies, autoimmune cytopenias, SLE, soluble FasL is not elevated
ALPS–caspase 10	Mutations in *CASP10*, intracellular apoptosis pathway	AD	Increased DN T cells	Normal	Defective lymphocyte apoptosis	Adenopathies, splenomegaly, autoimmunity
ALPS–caspase 8	Mutations in *CASP8*, intracellular apoptosis, and activation pathways	AR	Slightly increased DN T cells	Normal	Defective lymphocyte apoptosis and activation	Adenopathies, splenomegaly, bacterial and viral infections, hypogammaglobulinemia
FADD deficiency	Mutations in *FADD* encoding an adaptor molecule interacting with FAS, and promoting apoptosis	AR	Increased DN T cells	Normal	Defective lymphocyte apoptosis	Functional hyposplenism, bacterial and viral infections, recurrent episodes of encephalopathy and liver dysfunction

AD, autosomal dominant; AR, autosomal recessive; CTL, cytotoxic T lymphocyte; IBD, inflammatory bowel disease; NK, natural killer cell; XL, X-linked.

C3, C4), and the AH50 test, which tests the proteins of the alternative pathway of complement (C3, factor B, properdin). In patients with deficiencies in complement protein, the CH50 levels or AH50 levels are generally zero, whereas they are low but not absent in disorders leading to complement consumption (e.g., systemic lupus erythematosus). If both the CH50 and AH50 levels are abnormal, a defect in the common pathway is likely (C5-C9). Specialized laboratories can measure the presence or function of specific complement proteins.

If the above studies are normal but a primary immune deficiency is still suspected, advanced studies can be performed. One such advanced study is **flow cytometry** to enumerate the percentage and absolute numbers of T cells, B cells and markers of B cell maturation, and NK cell subsets. Flow cytometry can also test for the presence of surface proteins that are necessary for normal immunity, such as major histocompatibility complex molecules or adhesion molecules. Functional T cell tests include T cell proliferation assays in response to mitogens (phytohemagglutinin or concanavalin A) or antigens (tetanus toxoid or *Candida*). These in vitro assays assess the capacity of T cells to proliferate in response to a nonspecific stimulus (mitogens) or antigen-specific memory T cells (antigens). T cell proliferation in response to specific antigens requires a prior exposure to that unique antigen. Delayed-type hypersensitivity skin tests to protein antigens such as tetanus, diphtheria, *Candida,* or mumps demonstrate the presence and function of both antigen-specific T cells and antigen-presenting cells. If delayed-type hypersensitivity skin test results are negative, one may consider a booster vaccination and retesting 4 weeks later.

Tests for **neutrophil function** include the nitroblue tetrazolium (NBT) or dihydrorhodamine 123 (DHR) test for CGD. In the NBT test, oxygen radicals generated by activated neutrophils oxidize NBT to an insoluble dark blue dye that can be detected in neutrophils by microscopic examination. In the DHR test, oxygen radicals generated by activated neutrophils oxidize DHR, which results in the emission of light that is detected by flow cytometry. Neutrophils that are activated in patients with CGD cannot generate oxygen radicals and therefore have an abnormal NBT test (no blue neutrophils) or DHR test (no increase in light emitted from activated neutrophils).

Genetic testing to confirm the diagnosis of a primary immunodeficiency disease can be performed in specialized laboratories and may be helpful for deciding on a course of treatment, determining the natural history and prognosis of the disease, and to allow for genetic counseling. Chromosomal deletion/duplication microarrays are increasingly used to diagnose specific syndromic disorders that may have immunodeficiency due to genomic copy number variants (CNV) such as DiGeorge Syndrome. Specific gene or multiple gene sequencing is available commercially. With the advent of next generation sequencing techniques, it is now possible to sequence nearly all the genes in a subject. Because there are hundreds of genes known to cause primary immune deficiencies, this technology is being used in the diagnosis of primary immune deficiencies.

HUMORAL IMMUNE DISORDERS

Immune disorders that result in impaired immunoglobulin production can result in recurrent infections, typically of the sinopulmonary tract (pneumonia, sinusitis, otitis media), although more disseminated infections can occur (meningitis, sepsis, cellulitis) (Table 41.7). These individuals do not typically have infections with opportunistic pathogens such as *Cryptosporidium, Pneumocystis,* or fungi that are characteristic of combined immune deficiencies (T cell or cell-mediated defects).

X-Linked Agammaglobulinemia (XLA)

X-linked agammaglobulinemia (Bruton agammaglobulinemia) is caused by mutations in the gene that encodes Bruton tyrosine kinase (BTK) and accounts for approximately 85% of all inherited forms of agammaglobulinemias (see Table 41.7). BTK is a cytoplasmic tyrosine kinase that is essential for pre-B cell differentiation into mature B cells. Affected children exhibit severe reductions in serum immunoglobulins and a serious risk for recurrent and sometimes life-threatening infections. Expression of the BTK gene also occurs in myeloid cells, which may account for the **neutropenia** associated with this condition, which typically occurs at the time of their initial presentation.

Although some affected children are asymptomatic until the age of 2 years, most show symptoms between 6 and 9 months of age when maternal transplacental acquired antibodies disappear. Affected individuals develop recurrent infections (recurrent otitis media, sinusitis, pneumonia, meningitis) with pyogenic bacteria, such as pneumococci, staphylococci, streptococci, and *Haemophilus* species. They also have an unusual susceptibility to infection by enteroviruses, which can lead to chronic diarrhea, hepatitis, pneumonitis, and persistent meningoencephalitis. Most live attenuated viral or bacterial vaccines are contraindicated in patients with XLA. The live attenuated polio vaccine is particularly problematic and has caused paralysis in some XLA patients. XLA patients have marked hypoplasia of lymphoid tissue (adenoids, tonsils, lymph nodes) with absence of germinal centers and rare plasma cells. The diagnosis should be considered if the serum IgG, IgM, and IgA levels are less than 5% of age-adjusted control values in a patient with normal T cell function. In the majority of patients, the number of B cells in the peripheral blood is severely reduced or absent. Treatment includes aggressive antibiotic management of infections and replacement immunoglobulin therapy, although chronic pulmonary and gastrointestinal diseases may still occur.

A variety of genetic defects involved in B cell development also lead to agammaglobulinemia, including μ heavy chain, λ5, Igα, Igβ, *PI3KR1*, and *BLNK* (see Table 41.7). These are inherited in an autosomal recessive manner and exhibit similar hypogammaglobulinemia, lack of B cells, and infectious complications.

Common Variable Immunodeficiency

CVID is a heterogeneous immunodeficiency characterized by hypogammaglobulinemia developing after an initial period of normal immune function, most commonly in the 2nd and 3rd decades of life (see Table 41.7). The etiology of CVID in the majority of cases is unknown, although a minority of patients has mutations in the genes encoding for ICOS ("inducible costimulator" on activated T cells), TACI (transmembrane activator and calcium-modulating cyclophilin ligand interactor), CD19, CD21, CD81, or BAFF-R (see Table 41.7).

Patients with CVID are susceptible to frequent respiratory tract infections due to *Streptococcus pneumoniae, Haemophilus influenzae* type b, and *Mycoplasma*. Bronchiectasis due to recurrent pyogenic lung infections is a frequent complication. Gastrointestinal infections with *Giardia*, *Campylobacter*, *Salmonella*, *Helicobacter,* and enteroviruses are common. Bacterial overgrowth in the gut may lead to diarrhea, steatorrhea, malabsorption, and protein-losing enteropathy. Patients exhibit normal-sized or enlarged tonsils and lymph nodes, and frequently have splenomegaly.

In addition to the infectious complications of CVID, **autoimmune complications** are common and an increasing cause of morbidity and mortality. Autoimmune hemolytic anemia and autoimmune thrombocytopenia occur frequently. Multisystemic granulomatous disease occurs in approximately 20-30% of patients, with noncaseating granulomas occurring most frequently in the liver, spleen, lungs, and skin.

TABLE 41.7 Humoral Immune Deficiencies

Severe Reduction in All Serum Immunoglobulin Isotypes with Profoundly Decreased or Absent B Cells

Disease	Genetic Defect/Presumed Pathogenesis	Inheritance	Serum IgG	Associated Features
BTK deficiency	Mutations in *BTK*, a cytoplasmic tyrosine kinase activated by cross-linking of the BCR	XL	All isotypes decreased in majority of patients; some patients have detectable immunoglobulins	Severe bacterial infections; normal numbers of pro-B cells
μ Heavy chain deficiency	Mutations in *IGHM*; essential component of the pre-BCR	AR	All isotypes decreased	Severe bacterial infections; normal numbers of pro-B cells
λ5 Deficiency	Mutations in *IGLL1*; part of the surrogate light chain in the pre-BCR	AR	All isotypes decreased	Severe bacterial infections; normal numbers of pro-B cells
Igα deficiency	Mutations in *CD79A*; part of the pre-BCR and BCR	AR	All isotypes decreased	Severe bacterial infections; normal numbers of pro-B cells
Igβ deficiency	Mutations in *CD79B*; part of the pre-BCR and BCR	AR	All isotypes decreased	Severe bacterial infections; normal numbers of pro-B cells
BLNK deficiency	Mutations in *BLNK*; a scaffold protein that binds to BTK	AR	All isotypes decreased	Severe bacterial infections; normal numbers of pro-B cells
PI3 kinase deficiency	Mutations in *PIK3R1*; a kinase involved in signal transduction in multiple cell types	AR	All isotypes low	Severe bacterial infections; normal numbers of pro-B cells

Severe Reduction in at Least Two Serum Immunoglobulin Isotypes with Normal or Low Number of B Cells

Disease	Genetic Defect/Presumed Pathogenesis	Inheritance	Serum IgG	Associated Features
Common variable immunodeficiency disorders	Unknown	Variable	Low IgG and IgA and/or IgM	Clinical phenotypes vary: most have recurrent infections, some have polyclonal lymphoproliferation, autoimmune cytopenias, and/or granulomatous disease
ICOS deficiency	Mutations in *ICOS*; a co-stimulatory molecule expressed on T cells	AR	Low IgG and IgA and/or IgM	Recurrent infections; autoimmunity, gastroenteritis, granuloma in some
CD19 deficiency	Mutations in *CD19*; transmembrane protein that amplifies signal through BCR	AR	Low IgG and IgA and/or IgM	Recurrent infections; may have glomerulonephritis
CD81 deficiency	Mutations in *CD81*; transmembrane protein that amplifies signal through BCR	AR	Low IgG, low or normal IgA and IgM	Recurrent infections; may have glomerulonephritis
CD20 deficiency	Mutations in *CD20*; a B cell surface receptor involved in B cell development and plasma cell differentiation	AR	Low IgG, normal or elevated IgM and IgA	Recurrent infections
CD21 deficiency	Mutations in *CD21*; also known as complement receptor 2 and forms part of the CD19 complex	AR	Low IgG; impaired antipneumococcal response	Recurrent infections
TACI deficiency	Mutations in *TNFRSF13B* (TACI); a TNF receptor family member found on B cells and is a receptor for BAFF and APRIL	AD or AR or complex	Low IgG and IgA and/or IgM	Variable clinical expression
BAFF receptor deficiency	Mutations in *TNFRSF13C* (BAFF-R); a TNF receptor family member found on B cells and is a receptor for BAFF	AR	Low IgG and IgM	Variable clinical expression
AID deficiency	Mutations in *AICDA* gene	AR	IgG and IgA decreased; IgM increased	Bacterial infections, enlarged lymph nodes, and germinal centers

Continued

TABLE 41.7 Humoral Immune Deficiencies—cont'd

Disease	Genetic Defect/Presumed Pathogenesis	Inheritance	Serum IgG	Associated Features
UNG deficiency	Mutations in *UNG*	AR	IgG and IgA decreased; IgM increased	Bacterial infections, enlarged lymph nodes, and germinal centers
Selective IgA deficiency	Unknown	Variable	IgA decreased/absent	Usually asymptomatic; may have recurrent infections with poor antibody responses to carbohydrate antigens; may have allergies or autoimmune disease. A very few cases progress to CVID, others coexist with CVID in the family

AD, autosomal dominant; AR, autosomal recessive; BCR, B cell receptor; CVID, common variable immunodeficiency disease; Ig, immunoglobulin; TNF, tumor necrosis factor; XL, X-linked.

When the disease affects the lungs it causes an interstitial lung disease known as granulomatous and lymphocytic interstitial lung disease (GLILD). GLILD is frequently misdiagnosed as sarcoidosis and may lead to significant pulmonary fibrosis. The enteropathy that occurs in CVID can be confused with celiac disease and can lead to chronic diarrhea, protein loss, and poor nutrition. Patients with CVID are also at increased risk for inflammatory bowel disease. Liver disease, in particular nodular regenerative hyperplasia, is an important cause of morbidity and mortality in patients with CVID. There is also a markedly increased susceptibility to B cell lymphomas in patients with CVID. GLILD, enteropathy, lymphoma, and liver disease are independent risk factors for early mortality in CVID.

The diagnosis of CVID requires that age-adjusted serum IgG levels be less than 2 standard deviations (SD) below normal values together with low serum IgA levels (mg/dL) and/or low serum IgM levels. Specific antibody production following immunization with polysaccharide antigens (e.g., unconjugated pneumococcal vaccine) is low or absent, and responses to protein antigens (e.g., tetanus and diphtheria) may be impaired. T cell numbers and function are highly variable, and B cell numbers are usually normal but may be low. It is important to exclude X-linked agammaglobulinemia, X-linked lymphoproliferative disease, or hyper-IgM syndrome as well as other causes of hypogammaglobulinemia, such as hypogammaglobulinemia associated with thymoma, hypogammaglobulinemia secondary to protein-losing enteropathy or other protein-losing states, or hypogammaglobulinemia secondary to medications before making the diagnosis of CVID.

Transient Hypogammaglobulinemia of Infancy

The fetus is capable of producing IgM or IgG by the 20th week of gestation when adequately stimulated (intrauterine infection), but under normal conditions neonatal levels of IgG are a reflection of prior maternal immunity via transplacental passage of maternal IgG. Significant antibody production does not normally begin until the 2nd or 3rd month of life; elevated IgA and IgM in a newborn can be a sign of an intrauterine or perinatal infection. Because maternal antibodies have a half-life of approximately 30 days, the term infant may develop a variable *physiologic* hypogammaglobulinemia between the ages of 4 and 9 months. In *transient* hypogammaglobulinemia of infancy, the immunoglobulin nadir at 6 months of age is accentuated, with immunoglobulin levels less than 200 mg/dL. Immunoglobulin levels remain diminished throughout the 1st year of life and usually increase to normal, age-appropriate levels, generally by 2-4 years of age. If the hypogammaglobulinemia is profound in extent or duration, recurrent viral and pyogenic infections can occur. The diagnosis is supported by normal levels of both B and T cells, and normal antibody responses to protein antigens such as diphtheria and tetanus toxoids. The transient nature of this disorder cannot be confirmed, however, until immunoglobulin levels return to normal ranges. Most patients do not require immune globulin replacement therapy.

Immunoglobulin A Deficiency

Selective IgA deficiency is defined as serum IgA levels less than 10 mg/dL with normal levels of other immunoglobulins. The diagnosis cannot be confirmed until the patient is at least 4 years of age when IgA levels should reach adult levels. Selective IgA deficiency is the most common immune disorder, occurring in approximately 1 in 500 individuals. Most patients with selective IgA deficiency are asymptomatic. In others, it is associated with recurrent sinopulmonary infections, food allergy, autoimmune disease, or celiac disease. IgA deficiency rarely occurs in families, and can exhibit either autosomal recessive or autosomal dominant inheritance with variable penetrance. Antibody replacement therapy is not indicated for IgA deficiency. In patients with IgA deficiency and increased infections, other reasons for recurrent infection should be sought (atopic disease). Blood products often contain IgA and IgA-deficient patients may develop antibodies against IgA. Therefore, IgA-deficient patients may be prone to anaphylactic reactions upon administration of blood products containing IgA; this is a relatively rare complication of IgA deficiency.

Specific Antibody Deficiency

Specific antibody deficiency syndrome is characterized by recurrent sinopulmonary infections with normal immunoglobulin levels and normal lymphocyte numbers and subsets, but a decreased ability to make specific antibodies in response to polysaccharide vaccines, such as to the 23-valent pneumococcal vaccine. Children less than 2 years of age may not respond well to polysaccharide vaccines, so interpreting these results must include consideration of the age of the child. The pathogenesis of this disorder is unknown. Lack of specific antibody titers to polysaccharide vaccines and recurrent sinopulmonary infections with encapsulated bacteria may necessitate the use of prophylactic antibiotics or uncommonly replacement antibody therapy. Specific antibody deficiency many times resolves as the child becomes older.

Hyperimmunoglobulin M Syndrome

Hyper-IgM syndrome results from a failure of B cells to undergo class switching from IgM to IgA, IgG, or IgE. The failure to efficiently class switch can result in recurrent infections. Hyper-IgM syndrome was first described as a result of defects in CD40 ligand or CD40, although these disorders are actually combined immunodeficiency disorders and are discussed later. Deficiencies in AID and UNG, 2 enzymes involved in class switch recombination, can result in hyper-IgM syndrome without cell-mediated defects (see Table 41.7).

COMBINED IMMUNODEFICIENCY DISORDERS

Disorders of T lymphocytes result in defects in both cell-mediated and humoral immunity since T cells are required to activate macrophages and to optimally activate B lymphocytes, and thus these disorders are often referred to as combined immune deficiencies. Patients with combined defects in T and B cell function have infections with the usual community acquired pathogens as well as opportunistic or unusual pathogens, and infections may be more severe or in unusual anatomic sites compared to normal individuals (see Table 41.2). In many cases they may have other associated problems such as autoimmune problems, malignancies, or failure to thrive.

Severe Combined Immunodeficiency

Severe combined immunodeficiency (SCID) is a primary immunodeficiency caused by mutations in 1 of several genes whose function is essential for the normal development of T cells (Table 41.8). In all forms of SCID there are profound abnormalities in T cells and subsequently B cell function is abnormal. Clinical manifestations of SCID generally begin within the first 4 months of life with the waning of maternal antibody and include failure to thrive, severe bacterial, viral, or fungal infections, and intractable diarrhea. Infections with opportunistic pathogens such as *Pneumocystis jiroveci (carinii)* and *Cryptosporidium* are common. Infections with *Candida* frequently involve the mucous membranes (mouth, esophagus, vagina), face, and diaper area, which are difficult to treat. Chronic viral infections including pneumonitis caused by adenovirus or CMV, disseminated varicella and measles infections occur. Chronic infection following immunization with live viral vaccines (measles, mumps, rubella, varicella, rotavirus) are frequent. Fatal, disseminated mycobacterial infection following bacille Calmette-Guérin (BCG) vaccination is frequently seen in parts of the world that use the BCG vaccine.

Patients with SCID may have skin disease similar to eczema due to graft-versus-host disease (GVHD) from engraftment of maternal lymphocytes or Omenn syndrome. **Omenn syndrome**, a variant form of SCID, is characterized by erythroderma and desquamation, lymphadenopathy, hepatosplenomegaly, marked eosinophilia, elevated serum IgE, and impaired T cell function and is caused by hypomorphic mutations that preserve limited function in SCID-causing genes, usually *RAG1, RAG2,* or Artemis *(DCLRE1C)*. Patients with Omenn syndrome have T cells in the periphery, but these T cells are typically expanded oligoclonal T cells. Omenn syndrome is fatal unless corrected by bone marrow transplantation. Patients with SCID are extremely susceptible to fatal GVHD from lymphocytes in blood transfusions, and these patients should always receive irradiated blood products.

Patients with SCID exhibit severe deficits in immunoglobulin synthesis and the responses to specific antigens are impaired. B cells may be absent or increased, but a profound decrease in naive T cells is always present. The number of T cells in the peripheral blood is generally fewer than 10% of normal (<200 cells/mm^3), and T cells show decreased proliferative responses to mitogens, decreased cytotoxicity, and decreased immunoregulatory activity. SCID is uniformly fatal without definitive treatment, which is hematopoietic stem cell transplantation (HSCT) or in some cases gene therapy. **Newborn screening for SCID** using the T cell receptor excision circle (TREC) assay has been implemented in several states in the United States and in an increasing number of countries on a pilot basis. TRECs are formed during DNA recombination of the T cell receptor, are biomarkers of naive T cells, and can be enumerated on the dried blood spots obtained for routine newborn screening tests. The TREC assay is highly sensitive at detecting SCID in newborns before life-threatening infectious complications occur. Early detection and treatment of newborns with SCID improves long-term survival to greater than 90%.

X-linked recessive SCID, which is caused by mutations in the common gamma chain of the IL-2 receptor gene *(IL2RG)*, is the most common form of SCID (see Table 41.8). The IL2RG protein is shared by several interleukin receptors (IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21). The lack of T and NK cells is due to defective signaling through the IL-7 and IL-15 receptors, respectively. IL-21 is required for efficient B cell function. Female carriers can be identified because lymphocytes and natural killer cells exhibit nonrandom inactivation of the X chromosome.

Autosomal recessive SCID is less common than X-linked SCID, and is caused by many different genetic defects that can be broken down based on the cell types that are lacking. A lack of T cells but not B cells is seen in genetic defects in T cell signaling proteins including *JAK3*, *IL7R*, and CD3 subunits (see Table 41.8). A lack of T and B cells is seen in defects in genes that affect DNA recombination, which is required to generate T and B cell receptors, including *RAG1*, *RAG2*, and *DCLRE1C* (artemis) (see Table 41.8). **Adenosine deaminase (ADA) deficiency**, an autosomal recessive trait, results in an inability to catalyze the conversion of adenosine and deoxyadenosine to inosine and deoxyinosine, respectively. Deficiency of ADA results in the accumulation of deoxyadenosine and deoxy-ATP which is toxic to lymphocytes, resulting in loss of T, B, and NK cells. Regardless of the genetic cause of SCID, all patients have extremely low numbers of naive T cells and all exhibit the typical clinical features in terms of susceptibility to infection, failure to thrive, and 100% mortality without definitive treatment.

COMBINED IMMUNE DEFICIENCIES

Combined immunodeficiencies are genetic defects that result in defective T cell function with or without intrinsic B cell abnormalities (Table 41.9). Because T cell function is abnormal, B cell function is also compromised leading to a combined immunodeficiency, albeit less severe than SCID.

Hyperimmunoglobulin M (hyper-IgM) syndrome is characterized by normal or increased concentrations of IgM and IgD but decreased levels or absence of IgG, IgA, and IgE (see Table 41.9). The most common form of these disorders is X-linked hyper-IgM syndrome, which is due to a mutation in the gene encoding the T cell surface protein CD40 ligand *(CD40L)*. A rarer, autosomal recessive form of this disorder is caused by mutations in the *CD40* gene, which is expressed on the surface of B cells and antigen-presenting cells (see Table 41.9). The CD40/CD40L pathway is essential for B cell isotype switching, which allows a B cell to maintain antigen specificity while altering immunoglobulin function. This switching is directed by cytokines and interaction between CD40 ligand on CD4 T cells and CD40 on B cells. All patients with hyper-IgM syndrome due to genetic defects in CD40L or CD40 have increased susceptibility to sinopulmonary infections with pyogenic bacteria. These individuals are also susceptible to opportunistic infections including *P. jiroveci (carinii)* and *Cryptosporidium parvum.* Signaling via CD40 on B cells accounts for the defects in antibody production and class switching, while defective CD40 signaling in phagocytes and antigen-presenting cells accounts for the susceptibility to opportunistic pathogens. In addition, as many as 50% of patients with CD40L deficiency will exhibit neutropenia.

Signal transduction via CD40 activates several signaling molecules and transcription factors, including nuclear factor-κB (NF-κB), and 2 enzymes, activation-induced cytidine deaminase (AID) and uracil DNA-glycosylase (UNG), which are also required for class switching. Damaging mutations in AID or UNG cause a failure of

TABLE 41.8 Severe Combined Immunodeficiency (SCID)

Disease	Genetic Defect/ Pathogenesis	Inheritance	Circulating T Cells	Circulating B Cells	Serum Ig	Associated Features
γc Deficiency	Mutation of *IL-2RG:* defect in γ chain of receptors for IL-2, -4, -7, -9, -15, -21	XL	Markedly decreased	Normal or increased	Decreased	Markedly decreased NK cells
JAK3 deficiency	Mutation of *JAK3:* defect in Janus-activating kinase 3	AR	Markedly decreased	Normal or increased	Decreased	Markedly decreased NK cells
IL7Rα deficiency	Mutation of *IL7RA:* defect in IL-7 receptor α chain	AR	Markedly decreased	Normal or increased	Decreased	Normal NK cells
CD45 deficiency	Mutation of *PTPRC:* defect in CD45	AR	Markedly decreased	Normal	Decreased	Normal γ/δ T cells
CD3δ deficiency	Mutation of *CD3D;* defect in CD3δ chain of T cell antigen receptor complex	AR	Markedly decreased	Normal	Decreased	Normal NK cells, no γ/δ T cells
CD3ε deficiency	Mutation of *CD3E:* defect in CD3ε chain of T cell antigen receptor complex	AR	Markedly decreased	Normal	Decreased	Normal NK cells, no γ/δ T cells
CD3ζ deficiency	Mutation of *CD3Z:* defect in CD3ζ chain of T cell antigen receptor complex	AR	Markedly decreased	Normal	Decreased	Normal NK cells, no γ/δ T cells

SCID Characterized by Lack of T and B Cells (DNA Recombination Defects)

Disease	Genetic Defect/ Pathogenesis	Inheritance	Circulating T Cells	Circulating B Cells	Serum Ig	Associated Features
RAG 1 deficiency	Mutation of *RAG1:* defective VDJ recombination; defect of recombinase activating gene (RAG) 1	AR	Markedly decreased	Markedly decreased	Decreased	
RAG 2 deficiency	Mutation of *RAG2:* defective VDJ recombination; defect of recombinase activating gene (RAG) 2	AR	Markedly decreased	Markedly decreased	Decreased	
DCLRE1C (artemis) deficiency	Mutation of *ARTEMIS:* defective VDJ recombination; defect in artemis DNA recombinase repair protein	AR	Markedly decreased	Markedly decreased	Decreased	Radiation sensitivity
DNA PKcs deficiency	Mutation of *PKRDC:* defective VDJ recombination; defect in DNA PKcs recombinase repair protein	AR	Markedly decreased	Markedly decreased	Decreased	Radiation sensitivity, microcephaly, and developmental defects
Reticular dysgenesis, AK2 deficiency	Mutation of *AK2:* defective maturation of lymphoid and myeloid cells (stem cell defect)	AR	Markedly decreased	Decreased or normal	Decreased	Granulocytopenia and deafness
Adenosine deaminase (ADA) deficiency	Mutations in *ADA:* defective ADA activity	AR	Absent from birth or progressive	Decreased or normal	Decreased	Decreased NK cells, often with costochondral junction defects, neurologic features, partial ADA activity may result in delayed or milder presentation

AR, autosomal recessive; Ig, immunoglobulin; NK, natural killer cell; XL, X-linked.

TABLE 41.9 Combined Immune Deficiencies

Disease	Genetic Defect/ Presumed Pathogenesis	Inheritance	Circulating T Cells	Circulating B Cells	Serum Ig	Associated Features
CD40L deficiency	Mutations in *CD40LG* (also called TNFSF5 or CD154)	XL	Normal	B cell numbers may be normal or increased	IgG and IgA decreased; IgM may be normal or increased	Bacterial and opportunistic infections, neutropenia, autoimmune disease
CD40 deficiency	Mutations in *CD40* (also called TNFRSF5)	AR	Normal	B cell numbers may be normal or increased	IgG and IgA decreased; IgM may be normal or increased	Bacterial and opportunistic infections, neutropenia, autoimmune disease
Purine nucleoside phosphorylase (PNP) deficiency	Mutation of *PNP*, absent PNP, and T cell and neurologic defects from elevated toxic metabolites, especially dGTP	AR	Progressive decrease	Normal	Normal or decreased	Autoimmune hemolytic anemia, neurologic impairment
ZAP70 deficiency	Mutation in *ZAP70* intracellular signaling kinase, acts downstream of TCR	AR	Decreased CD8, normal CD4 cells	Normal	Normal	Autoimmunity in some cases
MHC class I deficiency	Mutations in *TAP1, TAP2,* or *TAPBP* (tapasin) genes giving MHC class I deficiency	AR	Decreased CD8, normal CD4	Normal	Normal	Vasculitis; pyoderma gangrenosum
MHC class II deficiency	Mutation in transcription factors for MHC class II proteins (*CIITA, RFX5, RFXAP, RFXANK* genes)	AR	Normal number, decreased CD4 cells	Normal	Normal or decreased	Failure to thrive, diarrhea, respiratory tract infections, liver/biliary tract disease
AD hyperimmunoglobulin E syndrome (HIES) (Job syndrome)	Dominant negative heterozygous mutations in STAT3	AD; often de novo defect	Normal Th-17 and T follicular helper cells decreased	Normal; switched and nonswitched memory B cells are reduced; BAFF level increased	Elevated IgE; specific antibody production decreased	Distinctive facial features (broad nasal bridge), eczema, osteoporosis, and fractures, scoliosis, delay of shedding primary teeth, hyperextensible joints, bacterial infections (skin and pulmonary abscesses, pneumatoceles) due to *Staphylococcus aureus*, candidiasis, aneurysm formation
DOCK8 deficiency	Mutations in *DOCK8* – regulator of intracellular actin reorganization	AR	Decreased impaired T lymphocyte proliferation	Decreased, low CD27+ memory B cells	Low IgM, increased IgE	Low NK cells with impaired function, hypereosinophilia, recurrent infections; severe atopy, extensive cutaneous viral and bacterial (staph.) infections, susceptibility to cancer
Omenn syndrome	Hypomorphic mutations in *RAG1, RAG2, artemis, IL7RA, RMRP, ADA, LIG4, IL2RG, AK2,* or associated with DiGeorge syndrome; some cases have no defined gene mutation	Variable	Present; restricted T cell repertoire, and impaired function	Normal or decreased	Decreased, except increased IgE	Erythroderma, eosinophilia, adenopathies, hepatosplenomegaly
ITK deficiency	Mutations in ITK encoding IL-2-inducible T cell kinase required for TCR-mediated activation	AR	Progressive decrease	Normal	Normal or decreased	EBV-associated B cell lymphoproliferation, lymphoma, normal or decreased IgG
Activated PI3K-δ	Mutation in *PIK3CD*, PI3K-δ	AD; gain of function			High IgM, low IgA or IgG. Reduced IgG2 and impaired antibody to pneumococci and *Haemophilus*	Respiratory infections, bronchiectasis; autoimmunity; chronic EBV, CMV infection; lymphoma

AD, autosomal dominant; AR, autosomal recessive; Ig, immunoglobulin; IL, interleukin; MHC, major histocompatibility complex; TCR, T cell receptor; XL, X-linked.

immunoglobulin isotype switching without opportunistic infections since these proteins function only in isotype class switching and not cell-mediated immunity.

The hyper-IgM phenotype is seen in a number of primary immune deficiencies including an X-linked immunodeficiency associated with ectodermal dysplasia resulting from defects in the gene encoding the **NF-κB essential modulator (NEMO)**. NF-κB signaling is important for function of both innate and adaptive immune systems. Therefore, patients with defects in NEMO have a combined immunodeficiency and are susceptible to a wide spectrum of viruses and bacteria, in particular pyogenic bacteria (e.g., *S. pneumoniae, H. Influenzae)* and atypical mycobacteria. Gain-of-function mutations in the catalytic domain of PI3 kinase *(PIK3CD)* can also lead to a hyper-IgM phenotype. PIK3CD is expressed in B cells and T cells, and therefore gain-of-function mutations in PIK3CD lead to the constitutive activation of PI3 kinase resulting in impaired T cell and B cell function. These patients present with recurrent sinopulmonary infections and have an increased susceptibility to infection with herpes viruses. Autoimmunity, lymphoproliferation (including an increased incidence of B cell lymphomas), and structural lung diseases commonly occur.

Purine Nucleoside Phosphorylase Deficiency

Purine nucleoside phosphorylase (PNP) is an enzyme that follows adenosine deaminase in the purine salvage pathway and catalyzes the conversion of inosine and guanosine to hypoxanthine and guanine, respectively (see Table 41.9). PNP deficiency, which is inherited as an autosomal recessive disorder, leads to the intracellular buildup of deoxy-guanosine triphosphate (deoxy-GTP), which is toxic to rapidly dividing cells. Although PNP is ubiquitously expressed, PNP deficiency affects T cells and not B cells and leads to T cell lymphopenia with preserved numbers of B cells. Although serum immunoglobulins are usually normal, specific antibody production is impaired. A low serum uric acid level is suggestive of PNP deficiency. Patients with PNP deficiency are predisposed to infection with common and opportunistic pathogens. Autoimmunity and neurologic manifestations are also common. The only curative treatment for PNP deficiency is HSCT.

Hyperimmunoglobulin E Syndrome

Classic hyperimmunoglobulin E syndrome (HIES), also known as **Job syndrome** is an autosomal dominant disorder caused by mutations in STAT3, an important signaling molecule required for the signaling of several cytokines such as IL-6 and IL-10 (see Table 41.9). Classic HIES is characterized by markedly elevated levels of serum IgE, early onset, severe eczematous dermatitis, recurrent bacterial infections (skin, respiratory tract, bone), and chronic candidiasis (thrush, onychomycosis). Other associated features include coarse facial features, manifested by a broad nasal bridge, prominent nose, dental abnormalities, and irregular proportional cheeks and jaw. The eczematous rash is typically papular and pruritic, involving the face and extensor surfaces of arms and legs and may start at birth or soon thereafter. The skin abscesses typically due to *S. aureus* are remarkable for their absence of surrounding erythema or warmth, leading to term of "cold abscesses." By 5 years of age, all patients have had a history of recurrent skin abscesses and recurrent pneumonias with pneumatoceles, along with chronic otitis media and sinusitis. Patients may also develop septic arthritis, cellulitis, or osteomyelitis. Fungal infections with *Candida albicans* and *Aspergillus* species occur. Serum IgE levels typically exceed 2500 IU/mL. Usually, patients with HIES have normal concentrations of IgG, IgA, and IgM, and frequently have eosinophilia. The clinical manifestations of **DOCK8 deficiency** display considerable overlap with classic HIES, with high IgE levels, eczema, and recurrent infections (see Table 41.9). However, patients with DOCK8 deficiency typically lack pneumatoceles, and bone and tooth abnormalities. The optimal treatment of classic HIES is largely supportive and includes antimicrobial therapy and, in selected patients, replacement antibody. In contrast, HSCT is curative for DOCK8 deficiency.

IMMUNODEFICIENCIES WITH SYNDROMIC FEATURES

Several genetic defects that affect the immune system also affect other organ systems and thus represent a clinical syndrome (Table 41.10). A careful history and exam can lead a clinician to the diagnosis. Most of these conditions present with combined T and B cell defects.

Wiskott-Aldrich Syndrome

Wiskott-Aldrich syndrome (WAS) is an X-linked recessive disorder caused by mutation in the gene that encodes the protein Wiskott-Aldrich syndrome protein or WASP. WASP controls the assembly of actin filaments and intracellular vesicle transport in lymphocytes and megakaryocytes. WAS is characterized by abnormalities in lymphocyte, platelet, and phagocyte function (see Table 41.10). Classic WAS is characterized by the triad of recurrent infections involving encapsulated bacteria and opportunistic pathogens, hemorrhage secondary to thrombocytopenia and platelet dysfunction, and atopic dermatitis. Mutations in the WAS gene can also cause X-linked neutropenia and X-linked thrombocytopenia. The clinical manifestations of WAS begin in early infancy with pneumonia, otitis media, meningitis, and bleeding. Patients are susceptible to recurrent and severe infections with encapsulated bacteria and viruses (herpes simplex virus, varicella, EBV, CMV). Fungal and pneumocystis infections may occur as well. Autoimmunity is common and includes cytopenias, vasculitis, arthritis, and inflammatory bowel disease. Patients are also susceptible to malignancy, in particular lymphoreticular malignancies. In classic WAS there is thrombocytopenia with abnormally small platelets. Deficiency of this protein results in elevated levels of IgE and IgA, decreased IgG and/or IgM, poor responses to polysaccharide antigens, and waning T cell function. One-third of patients with Wiskott-Aldrich syndrome die as a result of hemorrhage, and two-thirds die as a result of recurrent infection caused by bacteria, cytomegalovirus, *P. jiroveci (carinii),* or herpes simplex virus. In classic WAS the only curative therapy is hematopoietic stem cell transplantation.

Ataxia-Telangiectasia

Ataxia-telangiectasia (AT) is an autosomal recessive disorder characterized by neurologic dysfunction, endocrine abnormalities, oculocutaneous telangiectasia, immunodeficiency, and radiation sensitivity with a high rate of malignancy (see Table 41.10). The defective gene is the ataxia-telangiectasia mutated gene *(ATM)* that encodes for a phosphatidylinositol 3-kinase involved in sensing DNA damage and DNA repair. Cerebellar ataxia is usually the 1st clinical manifestation, occurring when the child begins to walk. The patient's neurologic status often worsens, and choreoathetosis and oculomotor abnormalities develop. Telangiectasias first appear in the bulbar conjunctivae between 2 and 5 years of age and later spread to areas of trauma. Endocrine abnormalities, such as insulin-resistant diabetes mellitus and hypogonadism are common. There is a 15% risk of malignancy with non-Hodgkin lymphoma being the most common. Patients with ataxia-telangiectasia are extremely sensitive to ionizing radiation, and radiographic studies should be avoided if possible. Radiation sensitivity accounts for the high incidence of chromosomal translocations involving chromosomes 7 and 14 at the site of T cell receptor genes and immunoglobulin heavy-chain genes.

TABLE 41.10 Combined Immune Deficiencies with Syndromic Features

Disease	Genetic Defect/ Presumed Pathogenesis	Inheritance	Circulating T Cells	Circulating B Cells	Serum Ig	Associated Features
Wiskott–Aldrich Syndrome (WAS)	Mutations in *WAS*; cytoskeletal, and immunologic synapse defect affecting hematopoietic stem cell derivatives	XL	Progressive decrease, abnormal lymphocyte responses to anti-CD3	Normal	Decreased IgM: antibody to polysaccharides particularly decreased; often increased IgA and IgE	Thrombocytopenia with small platelets; eczema; lymphoma; autoimmune disease; IgA nephropathy; bacterial and viral infections. XL thrombocytopenia is a mild form of WAS, and XL neutropenia is caused by missense mutations in the GTPase binding domain of WASP
Ataxia–telangiectasia	Mutations in *ATM*; disorder of cell cycle checkpoint; and DNA double-stranded break repair	AR	Progressive decrease	Normal	Often decreased IgA, IgE, and IgG subclasses; increased IgM monomers; antibodies variably decreased	Ataxia; telangiectasia; pulmonary infections; lymphoreticular and other malignancies; increased α-fetoprotein and increased radiosensitivity
Cartilage-hair hypoplasia	Mutations in *RMRP* (RNase MRP RNA) involved in processing of mitochondrial RNA and cell cycle control	AR	Varies from severely decreased (SCID) to normal; impaired lymphocyte proliferation	Normal	Normal or reduced; antibodies variably decreased	Short-limbed dwarfism with metaphyseal dysostosis, sparse hair, bone marrow failure, autoimmunity, susceptibility to lymphoma and other cancers, impaired spermatogenesis, neuronal dysplasia of the intestine
CHARGE syndrome	Variable defects of the thymus and associated T cell abnormalities often due to deletions or mutations in *CHD7, SEMA3E,* or as yet unknown genes	De novo defect (majority) or AD	Decreased or normal; some have <1500 CD3 T cells/μL	Normal	Normal or decreased	Coloboma, heart anomaly, choanal atresia, retardation, genital and ear anomalies
DiGeorge anomaly	Contiguous gene defect in 90% affecting thymic development; may also be due to heterozygous mutation in *TBX1* (chromosome 22q11.2 deletion or TBX1 haploinsufficient syndrome)	AD; often de novo	Decreased or normal; 5% have <1500 CD3 T cells/μL	Normal	Normal or decreased	Hypoparathyroidism, conotruncal malformation; abnormal facies; large deletion (3 Mb) in 22q11.2 (or rarely a deletion in 10p)

AD, autosomal dominant; AR, autosomal recessive; Ig, immunoglobulin; XL, X-linked.

The degree of immunodeficiency in AT is quite variable and may include abnormalities in T cells and B cells. Respiratory tract disease is an important cause of morbidity and mortality and includes sinopulmonary infection with encapsulated organisms, interstitial lung disease, and lung disease associated with neuromuscular deficits including recurrent aspiration. Opportunistic respiratory tract infections are uncommon. There is no curative therapy for AT, although antimicrobial prophylaxis and intravenous immunoglobulin (IVIG) replacement is used to prevent infections.

DiGeorge Syndrome (22q Deletion Syndrome) and Other Thymic Defects

DiGeorge syndrome is a disorder caused in the majority of cases by microdeletion at chromosome 22q11.2, although a deletion at a 2nd loci at chromosome 10p13 results in a similar clinical picture. DiGeorge syndrome, also known as velocardiofacial syndrome or CATCH 22 syndrome (cardiac anomalies, abnormal facies, thymic hypoplasia, cleft palate, and hypocalcemia), is characterized by a constellation of clinical features that include dysmorphic facies, hypoparathyroidism, congenital heart defects, and T cell lymphopenia (see Table 41.10). The clinical anomalies are caused by maldevelopment of structures derived from the 1st through the 6th branchial pouches during embryogenesis, resulting in variable hypoplasia of the thymus, parathyroid glands, face, ears, aortic arch, and heart. Congenital heart defects include truncus arteriosus, ventricular septal defect, interrupted aortic arch, and tetralogy of Fallot. Hypocalcemia with tetany is often the initial problem in the 1st and 2nd months after birth. Facial abnormalities include microstomia, hypertelorism, and low-set ears.

The degree of immunodeficiency is highly variable and related to the extent of residual thymic function. In complete DiGeorge syndrome, which occurs in less than 1% of patients, severe T cell deficiency leads to a disorder resembling SCID with failure to thrive, and recurrent infections with opportunistic organisms (*P. jiroveci*, viruses, and fungi). In contrast, many other patients with DiGeorge exhibit relatively normal immune function or relatively minor immunodeficiency (incomplete DiGeorge syndrome). Autoimmunity, including autoimmune cytopenias, is common. The total T cell count may vary from severely depressed to normal. No correlation has been shown between severity of congenital defects and the severity of immunodeficiency, and immune function often improves with age.

The diagnosis is established by chromosomal microarray or fluorescent in situ hybridization to detect the usual deleted region in chromosome 22q11.2. Approximately 10% of patients have hypogammaglobulinemia with a minority requiring antibody replacement therapy. Importantly, due to intrinsic defects in the thymus, patients with DiGeorge syndrome cannot be treated with hematopoietic stem cell transplantation, although transfer of mature T cells during transplant may confer some immune function.

CHARGE syndrome (coloboma, heart anomaly, choanal atresia, retardation, genital and ear anomalies) is related to DiGeorge syndrome since both involve thymic aplasia. Mutations in *CHD7* are the most common known cause of CHARGE syndrome, although mutations in *SEMA3E* are found in a minority of patients (see Table 41.10). The degree of immunodeficiency is related to the extent of thymic hypoplasia and T cell numbers, and can be highly variable. Similar to DiGeorge syndrome, some mutations of CHD7 are a cause of SCID with a profound T cell lymphopenia.

Cartilage-Hair Hypoplasia

Cartilage-hair hypoplasia (CHH) is an autosomal recessive disease caused by mutations in the ribonuclease mitochondrial RNA-processing (RMRP) gene. CHH is characterized by metaphyseal dysostosis, sparse and thin hair, and variable immunodeficiency (see Table 41.10). Lymphocyte counts over time become low in all patients due to low numbers of T cells. Proliferative responses to mitogens are generally depressed, and immune function may deteriorate with time. The immunodeficiency can range from mild to severe, but in many affected patients it is relatively mild. Patients benefit most from replacement immunoglobulin. Patients may have moderate to severe neutropenia, making them susceptible to both viral and bacterial infections.

COMPLEMENT SYSTEM DEFICIENCIES

The complement system consists of plasma and membrane proteins that function in the innate immune response as well as facilitating adaptive immunity. Complement proteins can kill pathogens with or without antibodies, opsonize pathogens to facilitate their uptake by phagocytes, or mediate inflammation. The complement system can be activated through 3 pathways—the classical, alternative, or lectin pathways—that involve the sequential activation of complement factors resulting in an amplified response. Disorders of the complement system predispose to recurrent infection, autoimmunity, and angioedema (Table 41.11).

The 3 pathways for complement activation are initiated by different mechanisms. The classical pathway is activated by antigen-antibody complexes. The alternative pathway may be activated by C3b generated through the classical pathway or by spontaneous hydrolysis of C3 on microbial surfaces. The lectin pathway is initiated by the interaction of mannose-binding lectin with microbial carbohydrate. Activation of the classical pathway by an antigen-antibody complex is initiated by the binding of C1q to the Fc portion of an antibody molecule in the immune complex. C1r autoactivates and cleaves C1s, which cleaves C4 and then C2, forming the C3 convertase, C4b2b. C4b2b is activated by the lectin pathway when mannose-binding protein binds to sugar residues on the surface of pathogens, and mannose-binding protein–associated proteases (MASP) cleave C4 and C2. The alternative pathway is always active at a low level and is amplified when active C3 binds to a surface that lacks regulatory proteins. C3b generated from C3 binds to factor B, which is cleaved by factor D to form the alternative pathway C3 convertase, C3bBb. Properdin binds to and stabilizes the C3 convertase. The C3 convertase can cleave C3 resulting in further C3b deposition and activation of the alternative pathway, which acts as an amplification loop by generating more C3b, or it can form the C5 convertase, which initiates the formation of a membrane attack complex (MAC). The MAC is a complex of C5b, C6, C7, C8, and several C9 molecules that is common to all 3 pathways. The MAC generates pores in the cell membrane, leading to lysis of the cells.

C3a and C5a produced by cleavage of C3 and C5 respectively, release histamine from mast cells and basophils, leading to increased vascular permeability and smooth muscle contraction. In addition, C5a has chemotactic activity, attracting phagocytes to the site of complement activation, and it can cause degranulation of phagocytic cells. C3b acts as an opsonin when attached to the surface of a pathogen by binding to phagocytes.

The complement system is under tight regulation because it has potent inflammatory activity and the potential to cause significant damage to host cells, and therefore there are a number of complement regulatory proteins. C1 inhibitor regulates the cascade by blocking active sites on C1r, C1s, and the MASP. Factor I destabilizes C3 convertase complexes and degrades the active fragments. Other inhibitors include membrane proteins, such as decay accelerating factor (DAF), CR1, membrane cofactor protein (MCP), and plasma proteins such as C4 binding protein. Formation of the MAC can be blocked by cell surface CD59. Deficiency of any of these regulatory proteins can result

TABLE 41.11 Complement Defects

Disease	Genetic Defect/Presumed Pathogenesis	Inheritance	Functional Defect	Associated Features
C1q deficiency	Mutation in *C1QA, C1QB, C1QC:* classical complement pathway components	AR	Absent CH50 hemolytic activity; defective activation of the classical pathway, diminished clearance of apoptotic cells	SLE, infections with encapsulated organisms
C1r deficiency	Mutation in *C1R:* classical complement pathway component	AR	Absent CH50 hemolytic activity; defective activation of the classical pathway	SLE, infections with encapsulated organisms
C1s deficiency	Mutation in *C1S:* classical complement pathway component	AR	Absent CH50 hemolytic activity; defective activation of the classical pathway	SLE, infections with encapsulated organisms
C4 deficiency	Mutation in *C4A, C4B:* classical complement pathway components	AR	Absent CH50 hemolytic activity; defective activation of the classical pathway, defective humoral immune response to carbohydrate antigens in some patients	SLE, infections with encapsulated organisms
C2 deficiency	Mutation in *C2:* classical complement pathway component	AR	Absent CH50 hemolytic activity; defective activation of the classical pathway	SLE, infections with encapsulated organisms, atherosclerosis
C3 deficiency	Mutation in *C3:* central complement component	AR, gain-of-function AD	Absent CH50 and AH50 hemolytic activity; defective opsonization, defective humoral immune response	Infections; glomerulonephritis, aHUS with gain-of-function mutations
C5 deficiency	Mutation in *C5:* terminal complement component	AR	Absent CH50 and AH50 hemolytic activity; defective bactericidal activity	Neisserial infections
C6 deficiency	Mutation in *C6:* terminal complement component	AR	Absent CH50 and AH50 hemolytic activity; defective bactericidal activity	Neisserial infections
C7 deficiency	Mutation in *C7:* terminal complement component	AR	Absent CH50 and AH50 hemolytic activity; defective bactericidal activity	Neisserial infections
C8 α–γ deficiency	Mutation in *C8A, C8G:* terminal complement components	AR	Absent CH50 and AH50 hemolytic activity; defective bactericidal activity	Neisserial infections
C8b deficiency	Mutation in *C8B:* terminal complement component	AR	Absent CH50 and AH50 hemolytic activity; defective bactericidal activity	Neisserial infections
C9 deficiency	Mutation in *C9:* terminal complement component	AR	Reduced CH50 and AH50 hemolytic activity; deficient bactericidal activity	Mild susceptibility to neisserial infections
C1 inhibitor deficiency	Mutation in *C1NH:* regulation of kinins and complement activation	AD	Spontaneous activation of the complement pathway with consumption of C4/C2; spontaneous activation of the contact system with generation of bradykinin from high molecular weight kininogen	Hereditary angioedema
Factor B	Mutation in *CFB:* activation of the alternative pathway	AD	Gain-of-function mutation with increased spontaneous AH50	aHUS
Factor D deficiency	Mutation in *CFD:* regulation of the alternative complement pathway	AR	Absent AH50 hemolytic activity	Neisserial infections
Properdin deficiency	Mutation in *CFP:* regulation of the alternative complement pathway	XL	Absent AH50 hemolytic activity	Neisserial infections
Factor I deficiency	Mutation in *CFI:* regulation of the alternative complement pathway	AR	Spontaneous activation of the alternative complement pathway with consumption of C3	Infections, neisserial infections, aHUS, preeclampsia, membranoproliferative glomerulonephritis
Factor H deficiency	Mutation in *CFH:* regulation of the alternative complement pathway	AR	Spontaneous activation of the alternative complement pathway with consumption of C3	Infections, neisserial infections, aHUS, preeclampsia, membranoproliferative glomerulonephritis
MASP1 deficiency	Mutation in *MASP1:* cleaves C2 and activates MASP2	AR	Deficient activation of the lectin activation pathway, cell migration	Infections, 3MC syndrome

AD, autosomal dominant; aHUS, atypical hemolytic uremic syndrome; AR, autosomal recessive; SLE, systemic lupus erythematosus; XL, X-linked.

in an inflammatory response, tissue damage, or excessive complement consumption. Deficiency in the expression of CD59 results in paroxysmal hemoglobinuria. Deficiencies in the complement regulatory proteins (factor H, factor I, and MCP) result in atypical hemolytic uremic syndrome, membranoproliferative glomerulonephritis type II, and have been linked to age-related macular degeneration (see Table 41.11).

Although protein deficiencies or abnormalities have been identified for components in the classical complement pathway, the severity and the type of infection vary because of the considerable overlap between the 2 pathways (see Table 41.11). Disorders of complement proteins can result from inherited deficiency or can be secondary to increased consumption. Deficiencies of early components of the classical pathway (C1, C2, or C4) are not usually associated with severe infections, although patients with C2 deficiency may present with recurrent respiratory tract infections with encapsulated bacteria. Patients with C1, C2, or C4 deficiency are susceptible to autoimmune diseases, especially systemic lupus erythematosus. The exact mechanism of this susceptibility is not known but is thought to arise from the role of these early components in clearing immune complexes. Deficiency of C3, the major opsonin, due to a genetic defect or secondary to excessive consumption or protein loss (e.g., nephrotic syndrome, systemic lupus erythematosus) predisposes patients to infections, especially with encapsulated organisms. Deficiency of 1 of the terminal components that compose the MAC or properdin predisposes patients to invasive infections (e.g., meningitis, septicemia) with *Neisseria meningitidis* and *Neisseria gonorrhoeae.* Complement deficiency may be found in 40% of patients presenting with recurrent neisserial infections, particularly with meningococcal disease caused by uncommon serogroups (see Table 41.11).

C1 inhibitor deficiency causes **hereditary angioedema**, an autosomal dominant disorder that results in dysregulation of the classical complement pathway. After minor trauma, affected patients develop local angioedema without urticaria, pain, or erythema. The angioedema may be severe and untreated leads to significant morbidity and mortality. Angioedema involving the larynx or upper airways can be life-threatening, and involvement of the bowel leads to abdominal pain, vomiting, and diarrhea. Lack of inhibition of plasma kallikrein by C1 inhibitor and dysregulated production of bradykinin is the cause of the angioedema. Treatment of hereditary angioedema includes administration of C1 inhibitor, administration of a pharmacologic inhibitor of plasma kallikrein (ecallantide), or administration of a bradykinin β_2-antagonist (icatibant).

Diagnosis of Complement Deficiencies

The CH50 test is a widely available test of classical complement pathway function based on an antibody-dependent hemolytic assay. The CH50 test depends on the function of all 9 complement proteins, C1 through C9. The AH50 test, which activates the alternative pathway, depends on the alternative pathway components and C5-C9. An abnormal CH50 but not AH50 are consistent with defects in C1, C2, or C4. Alternatively, an abnormal AH50 but normal CH50 indicates a defect in properdin or factor B. Abnormal results of both tests indicate a deficiency in a terminal component common to both pathways (C3, C5-C9). If the CH50 or AH50 levels are abnormal, individual components can be analyzed in specialized laboratories. In hereditary angioedema, C4 levels are generally low, but C3 levels are normal. Determination of C1 inhibitor levels and/or function is needed to definitively diagnose hereditary angioedema. Low C3 and C4 levels are seen when the classical pathway is activated (e.g., systemic lupus erythematosus), whereas activation of the alternative pathway characteristically results in low C3 levels and normal C4 levels.

Specific treatment of complement deficiencies with component replacement is not available. Frequent courses of antibiotics or prophylactic antibiotics have been utilized. Immunization of patients and close contacts with pneumococcal and meningococcal vaccines may be useful, but infections may still occur in immunized complement-deficient patients. Replacement of complement proteins by plasma transfusion has been used in some patients with C2 deficiency, factor H deficiency, or factor I deficiency. MCP deficiency presenting with atypical hemolytic uremic syndrome is treated with renal transplantation since it is a membrane protein.

PHAGOCYTE DISORDERS

Neutrophils are important in protecting the skin, mucous membrane, and the lining of the respiratory and gastrointestinal tracts. They form the 1st line of defense against microbial invasion. During the critical 1st 2-4 hours after tissue invasion by pathogenic organisms, the arrival of phagocytic cells at the site of infection is crucial for the containment of the infection, limiting the size of the local lesion, and preventing dissemination. Monocytes/macrophages are also important in cell-mediated immunity, and in response to T cell cytokines (IFN-γ), these cells become effective killers of intracellular pathogens.

Neutrophils develop in the bone marrow from hematopoietic stem cells, and upon leaving the bone marrow mature neutrophils are found in the circulation or roll along the endothelium (known as the marginating pool). Adhesion molecules are necessary for neutrophils to roll and adhere to vascular endothelium and extravasate from the blood into sites of infection, where they phagocytose and kill pathogens, especially those coated by complement or antibodies. Chemotactic factors, including the complement fragment C5a, IL-8, leukotriene B_4, and bacterial formylated peptides (fMLP) mobilize neutrophils to enter tissues and sites of infections. Once in tissues these cells ingest the offending organisms (phagocytosis), and activate biochemical pathways important in intracellular microbial killing (degranulation and oxidative metabolism). The respiratory burst consists of the de novo synthesis of highly toxic and often unstable derivatives of molecular oxygen. Degranulation is the process by which lysosomal granules, containing preformed polypeptide antibiotics and proteases, fuse with the phagocytic vacuoles containing the ingested microbes.

Patients with neutrophil disorders are susceptible to a variety of bacterial infections and certain fungi. Infections associated with neutrophil disorders include infections of mucosal surfaces (e.g., respiratory tract infections, rectal and vaginal infections, gingivostomatitis), abscesses in the skin and viscera, lymphadenitis, poor wound healing, delayed umbilical cord separation, or absence of pus.

Disorders of Neutrophil Numbers

Neutropenia is defined as an absolute neutrophil count (ANC) less than 1500/mm^3 for children 1 year of age or older, although African-American children can have lower neutrophil numbers. The susceptibility to infection is minimally increased until the ANC is less than 1000/mm^3. Most patients do well with an ANC greater than 500/mm^3. At these levels, localized infections are more common than generalized bacteremia. Serious bacterial infections are more common with an ANC less than 200/mm^3. Neutropenia may be congenital and caused by mutations in several genes (Table 41.12) or acquired (e.g., autoimmune neutropenia, drug reactions, marrow replacement with cancer cells).

Inherited Forms of Neutropenia

Severe congenital neutropenia (Kostmann syndrome) is an autosomal recessive disorder caused by mutations in the HCLS-associated protein

X-1 *(HAX1)* gene and is characterized by severe persistent neutropenia (absolute neutrophil count <500 cells/mm^3) and recurrent bacterial infections (Table 41.12). Affected patients often have increased plasma concentrations of granulocyte colony-stimulating factor (G-CSF) as well as circulating eosinophils and monocytes. In severe congenital neutropenia, the neutrophil counts increase in response to exogenous G-CSF despite the elevated level of G-CSF at baseline.

Autosomal dominant inherited mutations in the elastase 2 gene *(ELA2)* are the most common cause of **cyclic neutropenia** although the disorder may present as persistent neutropenia as well. In the cyclic form of neutropenia, there are periodic episodes of profound neutropenia (absolute neutrophil counts <200 cells/mm^3), generally lasting 3-6 days and occurring in 21-day cycles (see Table 41.12). During the episodes of neutropenia, individuals develop aphthous ulcers, gingivitis, stomatitis, and cellulitis. Death from overwhelming infection with *Clostridium perfringens* occurs in about 10% of patients.

Severe congenital neutropenia, which may be either persistent or cyclic, is also seen in **Shwachman-Diamond syndrome**, an autosomal recessive syndrome of pancreatic insufficiency accompanying bone marrow dysfunction. Metaphyseal dysostosis and dwarfism may occur. A gain-of-function mutation in the Wiskott-Aldrich syndrome protein has also been associated with an X-linked form of severe congenital neutropenia. Severe congenital neutropenia may be associated with SCID in reticular dysgenesis, a disorder of hematopoietic stem cells affecting all bone marrow lineages due to mutations in the *AK2* gene.

The mainstay of treatment of all congenital neutropenias is recombinant human granulocyte colony-stimulating factor (rhG-CSF). Approximately 10% of patients with the diagnosis of severe congenital neutropenia and Shwachman-Diamond syndrome develop myelodysplasia/acute myelogenous leukemia. No cases of malignant transformations have been observed in patients with either cyclic or idiopathic neutropenia.

Acquired Neutropenia

Isoimmune neutropenia occurs in neonates as the result of transplacental transfer of maternal antibodies to fetal neutrophil antigens. The mother produces antibodies to specific neutrophil antigens on the surface of fetal leukocytes that are inherited from the father and are not present on maternal cells. Isoimmune neonatal neutropenia, similar to isoimmune anemia and thrombocytopenia, is a transient process that resolves as maternal antibodies wane. Cutaneous infections are common, and sepsis is rare. Early treatment of infection while the infant is neutropenic is the major goal of therapy. Intravenous immune globulin may decrease the duration of neutropenia. *Autoimmune neutropenia* usually develops in children 5-24 months of age. Neutrophil autoantibodies may be IgG, IgM, IgA, or a combination of these. Usually, the condition spontaneously resolves in 6 months to 4 years. Although intravenous immune globulin and corticosteroids have been used, most patients respond to G-CSF.

Disorders of Neutrophil Adhesion and Chemotaxis

Leukocyte adhesion deficiency type 1 (LAD-1) is an autosomal recessive inherited disorder resulting from mutations in the gene encoding the β_2 integrin CD18. CD18 is the common β-subunit of lymphocyte function-associated antigen-1 (LFA-1) (CD11a/CD18), Mac-1 (CD11b/CD18), and P150,95 (CD11c/CD18), proteins that are expressed on lymphocytes, monocytes/macrophages, and neutrophils, respectively. Diminished or absent surface expression of these proteins accounts for a profound impairment of neutrophil and monocyte cell migration and phagocytosis. The severity of the immunodeficiency is dependent on the level of expression of CD18. Infants affected with this disorder may present in early infancy with failure of separation of the umbilical cord (often 2 months after birth) with attendant omphalitis and sepsis (see Table 41.12). Cutaneous, respiratory, gingival, and mucosal infections are common, and sepsis may lead to death in early childhood. Due to a failure of neutrophils to adhere normally to vascular endothelium (marginate), absolute neutrophil counts are usually greater than 20,000/mm^3 even when patients are not infected. The diagnosis of LAD-1 can be made measuring the amount of LFA-1 on the surface of lymphocytes by flow cytometry. Hematopoietic stem cell transplantation is curative.

Leukocyte adhesion deficiency type 2 (LAD-2) is an autosomal recessive congenital disorder of glycosylation (type iic) caused by mutations in the *SLC35C1* gene. The *SLC35C1* gene encodes a GDP-fucose transporter, and mutation in this gene results in the absence of sialylated Lewis X blood group on the surface of neutrophils and other leukocytes, resulting in failure to roll and subsequently adhere to vascular endothelium. Patients with LAD-2 manifest with growth retardation, dysmorphic features, and neurologic deficits in addition to the increased susceptibility to infection. LAD-3 is a rare disorder caused by defects in the KINDLIN-3 protein resulting in defective neutrophil adhesion as well as platelet defects. Patients with LAD-3 present similar to LAD-1 with recurrent severe infections as well as a bleeding disorder.

Depressed neutrophil chemotaxis has been observed in a wide variety of clinical conditions (see Table 41.12). In addition to LAD-1 and LAD-2, defective migration of neutrophils has been described in hyper-IgE syndrome due to STAT3 mutations and with mutations in the *RAC2* gene (see Table 41.12). RAC2 is the predominant GTPase in human neutrophils, and it is integral to the function of the actin cytoskeleton. Deficiency in RAC2 is associated with decreased neutrophil chemotaxis, superoxide generation, and decreased degranulation in response to formylated peptides.

Disorders of Neutrophil Function

Chronic granulomatous disease (CGD) is a disorder of phagocytes due to mutations in any 1 of the subunits of the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (see Table 41.12). NADPH oxidase consists of 4 subunits (gp91^{phox}, p22^{phox}, p47^{phox}, and p67^{phox}) and is responsible for the generation of the respiratory burst, which involves the catalytic conversion of molecular oxygen to superoxide (O_2^-) that is essential for the killing of a variety of bacterial and fungal pathogens by neutrophils and macrophages. Mutations in the gene encoding the gp91^{phox} protein are inherited in an X-linked manner and account for approximately 65% of CGD. All other forms of CGD are inherited in in an autosomal recessive manner.

Although the clinical manifestations are variable, several clinical features suggest the diagnosis of CGD. The onset of clinical signs and symptoms may occur from early infancy to young adulthood, and the attack rate and severity of infections are dependent on the amount of residual oxidase activity generated by NADPH oxidase in affected individuals. Affected patients may have recurrent lymphadenitis, bacterial hepatic abscesses, or osteomyelitis. Infections also occur in the lungs, the middle ear, gastrointestinal tract, skin, and urinary tract. Patients characteristically exhibit lymphadenopathy, hypergammaglobulinemia, hepatosplenomegaly, dermatitis, failure to thrive, anemia, chronic diarrhea, and abscesses. Granulomas are prominent and may obstruct the pylorus or ureters or lead to inflammatory bowel disease. The most common pathogen is *S. aureus*, and infection with *S. marcescens, B. cepacia, Aspergillus* sp., *C. albicans,* or *Salmonella* sp. can occur. The diagnosis of CGD is made by either the DHR test or the NBT dye test.

The treatment of CGD is rapidly evolving. CGD is traditionally treated with prophylactic trimethoprim-sulfamethoxazole, itraconazole, long-term continuous interferon-γ therapy, and bactericidal

TABLE 41.12 Phagocyte Disorders

Disease	Genetic Defect/ Presumed Pathogenesis	Inheritance	Affected Cells	Affected Function	Associated Features
Severe congenital neutropenia 1 (ELANE deficiency)	Mutation in *ELANE:* misfolded protein response, increased apoptosis	AD	N	Myeloid differentiation	Susceptibility to MDS/ leukemia
SCN2a (GFI1 deficiency)	Mutation in *GFI1:* loss of repression of ELANE	AD	N	Myeloid differentiation	B/T lymphopenia
SCN3 (Kostmann disease)	Mutation in *HAX1:* control of apoptosis	AR	N	Myeloid differentiation	Cognitive and neurologic defects in patients with defects in both HAX1 isoforms, susceptibility to MDS/leukemia
SCN4 (G6PC3 deficiency)	Mutation in *G6PC3:* abolished enzymatic activity of glucose-6-phosphatase, aberrant glycosylation, and enhanced apoptosis of N and F	AR	N + F	Myeloid differentiation, chemotaxis, O^- production	Structural heart defects, urogenital abnormalities, inner ear deafness, and venous angiectasias of trunks and limbs
SCN5	Mutation in *VPS45:* controls vesicular trafficking	AR	N + F	Myeloid differentiation, migration	Extramedullary hematopoiesis, bone marrow fibrosis, nephromegaly
Cyclic neutropenia	Mutation in *ELANE:* misfolded protein response	AD	N	Differentiation	Oscillations of other leukocytes and platelets
X-linked neutropenia/ myelodysplasia	Mutation in *WAS:* regulator of actin cytoskeleton (loss of autoinhibition)	XL, gain-of-function	N + M	Mitosis	Monocytopenia
Leukocyte adhesion deficiency type 1 (LAD1)	Mutation in *ITGB2:* adhesion protein (CD18)	AR	N + M + L + NK	Adherence, chemotaxis, endocytosis, T/NK cytotoxicity	Delayed cord separation, skin ulcers, periodontitis, leukocytosis
Leukocyte adhesion deficiency type 2 (LAD2)	Mutation in *SLC35C1* GDP-fucose transporter	AR	N + M	Rolling, chemotaxis	Mild LAD type 1 features plus hh-blood group plus mental and growth retardation
Leukocyte adhesion deficiency type 3 (LAD3)	Mutation in *KINDLIN3:* Rap1-activation of β1–3 integrins	AR	N + M + L + NK	Adherence, chemotaxis	LAD type 1 plus bleeding tendency
Rac 2 deficiency	Mutation in *RAC2:* regulation of actin cytoskeleton	AD	N	Adherence, chemotaxis, O^- production	Poor wound healing, leukocytosis
X-linked chronic granulomatous disease (CGD)	Mutation in *CYBB:* electron transport protein (gp91phox)	XL	N + M	Killing (faulty O^- production)	Recurrent bacterial infection, susceptibility to fungal infection, inflammatory gut manifestations; McLeod phenotype in patients with deletions extending into the contiguous Kell locus
Autosomal recessive CGD – p22 phox deficiency	Mutation in *CYBA:* electron transport protein (p22phox)	AR	N + M	Killing (faulty O^- production)	Recurrent bacterial infection, susceptibility to fungal infection, and inflammatory gut manifestations
Autosomal recessive CGD – p47 phox deficiency	Mutation in *NCF1:* adapter protein (p47phox)	AR	N + M	Killing (faulty O^- production)	Recurrent bacterial infection, susceptibility to fungal infection, and inflammatory gut manifestations

TABLE 41.12 Phagocyte Disorders—cont'd

Disease	Genetic Defect/ Presumed Pathogenesis	Inheritance	Affected Cells	Affected Function	Associated Features
Autosomal recessive CGD – p67 phox deficiency	Mutation in *NCF2:* activating protein (p67phox)	AR	N + M	Killing (faulty O^- production)	Recurrent bacterial infection, susceptibility to fungal infection, and inflammatory gut manifestations
Autosomal recessive CGD – p40 phox deficiency	Mutation in *NCF4:* activating protein (p40phox)	AR	N + M	Killing (faulty O^- production)	Inflammatory gut manifestations only
IL-12 and IL-23 receptor β1 chain deficiency	Mutation in *IL-12RB1:* IL-12 and IL-23 receptor β1 chain	AR	L + NK	IFN-γ secretion	Susceptibility to *Mycobacteria* and *Salmonella*
IL-12p40 deficiency	Mutation in *IL-12B:* subunit p40 of IL-12/IL-23	AR	M	IFN-γ secretion	Susceptibility to *Mycobacteria* and *Salmonella*
IFN-γ receptor 1 deficiency	Mutation in *IFNGR1:* IFN-γR ligand binding chain	AR, AD	M + L	IFN-γ binding and signaling	Susceptibility to *Mycobacteria* and *Salmonella*
IFN-γ receptor 2 deficiency	Mutation in *IFNGR2:* IFN-γR accessory chain	AR	M + L	IFN-γ signaling	Susceptibility to *Mycobacteria* and *Salmonella*
STAT1 deficiency (AD form)	Mutation in *STAT1* (loss of function)	AD	M + L	IFN-γ signaling	Susceptibility to *Mycobacteria*

AD, autosomal dominant; AR, autosomal recessive; B/T, B and T cells; IFN, interferon; IL, interleukin; L, lymphocyte; M, monocyte/macrophage; MDS, myelodysplasia syndrome; N, neutrophil; NK, natural killer cell; XL, X-linked.

antibiotics. Steroids and antibiotics are used to treat granulomatous complications of the gastrointestinal, urinary, and respiratory tracts. Definitive treatment of CGD by HSCT in properly HLA-matched patients has achieved excellent outcomes (>90% survival) even for patients at high risk for transplant-associated morbidity and mortality.

Chédiak-Higashi syndrome (CHS), an abnormality of secondary granules, is an autosomal recessive disorder caused by a mutation in the *LYST* gene, which encodes a cytoplasmic protein thought to be involved in organellar protein trafficking resulting in fusion of the primary and secondary granules in neutrophils. Despite normal ingestion of particles and normal production of superoxide, neutrophils and macrophages in patients with CHS have delayed killing of microorganisms. Large azurophilic lysosomal granules are present in all granule-bearing cells including neutrophils and melanocytes. A smear of peripheral blood can demonstrate these giant granules in neutrophils and are virtually pathognomonic of CHS when other features are present.

Recurrent infections affect the skin, respiratory tract, and mucous membranes and are caused by both gram-positive and gram-negative bacteria as well as by fungi. *S. aureus* is the most common organism. Despite normal platelet counts, patients with Chédiak-Higashi syndrome have prolonged bleeding times due to a platelet storage pool abnormality. Patients usually have partial oculocutaneous albinism. Most patients progress to an accelerated phase associated with Epstein-Barr virus infection and characterized by a lymphoproliferative syndrome with generalized lymphohistiocytic infiltrates, fever, jaundice, hepatomegaly, lymphadenopathy, and pancytopenia (see Table 41.6). Neuropathy, which can be sensory or motor, and ataxia may be present.

DISORDERS OF MACROPHAGE FUNCTION

The interferon-γ (IFNγ)/interleukin-12 (IL-12) axis is crucial to host defense against intracellular pathogens, including mycobacteria, *Listeria*, and *Salmonella* species. Dendritic cells and macrophages produce interleukin-12 in response to bacterial pathogens that in turn stimulate the secretion of IFNγ by T cells and natural killer cells. IFNγ binds to receptors on macrophages, stimulating the production of tumor necrosis factor-α and inducible nitric oxide synthetase, promoting antigen presentation, and augmenting the respiratory burst and bactericidal activities of macrophages.

The classic members of this group of disorders involve mutations in the IFNγ receptor, the IL-12 receptor, or IL-12. The IFNγ receptor contains 2 chains: IFNγ receptor 1 (IFNγ-R1), which binds ligand, and IFNγ receptor 2 (IFNγ-R2), which is necessary for ligand-induced signaling. Complete absence of IFNγ-R1 or IFNγ-R2 is inherited in an autosomal recessive manner and causes the most severe disease, manifesting early in infancy often with disseminated atypical mycobacterial infection, recurrent *Salmonella* infection, or fatal infection after bacille Calmette-Guérin vaccination. Partial IFNγ-R1 or IFNγ-R2 defects typically have milder disease, present often in early childhood, but nonetheless with increased susceptibility to nontuberculous mycobacterial disease. Patients with partial IFNγ-R1 deficiency are especially prone to osteomyelitis due to atypical mycobacteria. Mutations leading to a deficiency in the production of the p40 subunit of IL-12 or in the expression of the IL-12Rβ1 receptor are inherited in an autosomal recessive manner. These patients have an increased susceptibility to serious infection with environmental mycobacteria, BCG, and *Salmonella* sp. Unexpectedly, these patients are also susceptible to skin and, rarely, invasive infections with *Candida albicans.* Mutations in STAT1, which mediates the signal transduction following the binding of IFNγ with the IFNγ receptor, also causes susceptibility to mycobacterial infections and is inherited in an autosomal recessive pattern. In addition, these patients are susceptible to a variety of viral pathogens since STAT1 is required for signal transduction of IFN-α/β in addition to IFN-γ.

ASPLENIA

The spleen plays a particularly important role in preventing invasive infections, especially during the 1st year of life before specific immunity to certain bacteria has developed. The spleen is able to bind and phagocytose unopsonized encapsulated bacteria, and produces natural antibodies against polysaccharides, demonstrating the critical role of the spleen in preventing sepsis in immunologically immature subjects

from encapsulated bacteria. The spleen is also an important location for the phagocytosis of complement and antibody opsonized bacteria, and a key location for the production of antibodies.

Functional asplenia occurs in children with sickle cell disease, initially as a result of vascular occlusion by the sickle cells in the splenic circulation. Congenital absence of the spleen may occur alone or as part of an asplenia syndrome with congenital heart disease. Mutations in NKX2 and ribosomal protein SA have been found in a small number of patients with congenital asplenia. Trauma and surgical splenectomy are also important causes of asplenia.

Individuals without spleens (anatomic or functional) are subject to a severe form of sepsis that is rapid in onset and can lead to sudden death if it is not recognized and treated promptly. Pneumococci are responsible for more than 50% of such infections; infections with *H. influenzae*, *S. aureus*, group A streptococci, gram-negative enteric bacilli, and meningococci also occur (see Table 41.1).

The diagnosis of anatomic or functional asplenia is suggested by the presence of red blood cell inclusions, particularly Howell-Jolly bodies on peripheral blood smear. Failure of uptake of technetium 99–sulfur colloid, which is normally taken up by the entire reticuloendothelial system or the lack of erythrocyte pitting are also noted in asplenic patients. Lack of a spleen by ultrasonography of the abdomen is suggestive of asplenia, but accessory splenic tissue may still be present. Functional tests of splenic tissue are a better indicator of asplenia.

The risk of fulminant infection in patients who have undergone splenectomy (from surgery or trauma), or in those with functional asplenia or congenital asplenia is highest in the 1st few years. The risk is lower in older children and in adults, probably because they have developed opsonizing antibodies through previous exposure. The management of functional or anatomic asplenia lies mainly in prevention. When splenectomy becomes necessary, partial protection against life-threatening infections can be obtained by immunizing patients with conjugated and polyvalent pneumococcal, *H. influenzae* type b, and meningococcal vaccines. Booster immunization may be needed because of waning immunity with time. Prophylactic antibiotics may be given continuously in a single daily dose for 1-3 years or up to the age of 16 years (some authorities suggest longer periods or even for life) after splenectomy. Parents of older asplenic children are advised to have their children seen by a physician or to administer the antibiotics at the 1st sign of a febrile illness.

AUTOINFLAMMATORY DISORDERS

Autoinflammatory disorders are genetic defects in the immune system with predominant inflammatory complications in the absence of significant infectious complications. Autoinflammatory disorders present with spontaneous, episodic, or persistent inflammation, but without the development of autoantibodies or autoreactive lymphocytes. Autoinflammatory disorders were formerly known as periodic fever syndromes, but this term has fallen out of favor since fever is a frequent but not universal finding.

Familial Mediterranean Fever

Familial Mediterranean fever (FMF) is caused by mutations in the *MEFV* gene that encodes the protein pyrin and was the 1st autoinflammatory disorder in which a genetic defect was elucidated. Although FMF is considered a recessive disorder, a substantial percentage of patients with clinical FMF have only 1 demonstrable mutation in *MEFV*. FMF is characterized by short episodes of fever (i.e., 1-3 days), serositis/peritonitis, prominent arthritis, and erythematous rash. Early in life fever may be the only symptom. However, more classic features typically appear within 3 years. The arthritis is typically monoarticular, and aspirates of affected joints are sterile with a predominance of neutrophils. In some cases, splenomegaly and even systemic vasculitis can ensue. The most serious long-term comorbidity with FMF is amyloidosis, which occurs frequently in patients who are not compliant with colchicine prophylaxis. Pyrin interacts with the inflammasome, a macromolecular complex involved in the processing of IL-1β, and mutations that result in FMF result in greater IL-1 production. Daily colchicine prophylaxis prevents many of the long-term complications of this disorder.

Pyogenic Arthritis, Pyoderma Gangrenosum, and Acne Syndrome

Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) is an autosomal dominant inherited syndrome caused by mutations in *PSTPIP1* (see Table 41.5), which leads to hyperphosphorylation of PSTPIP1, increased interaction with pyrin, leading to increased IL-1β production. PAPA begins in childhood with episodes of sterile monoarticular arthritis, and later in life pyoderma gangrenosum-like ulcerative skin lesions and cystic acne. The episodes of arthritis are the most common presentation, start in early childhood, and typically affect 1-3 joints at a time. The joint effusions are typically neutrophil-rich and sterile. Treatment of the arthritis with surgical drainage, or treatment with intraarticular or systemic steroids has shown benefit in resolving arthritis. Several reports demonstrated successful treatment with an IL-1 receptor antagonist (anakinra) or tumor necrosis factor (TNF)-α inhibitors (etanercept and infliximab).

Cryopyrin-Associated Periodic Syndromes

Cryopyrin-associated periodic syndromes (CAPS) are a spectrum of autoinflammatory disorders that are inherited in an autosomal dominant manner due to mutations in the *NLRP3* gene (see Table 41.5). *NLRP3* encodes cryopyrin, a protein that is part of the inflammasome. Mutations that cause CAPS prevent autoinhibition of the cryopyrin protein, resulting in spontaneous activation of the inflammasome and excessive production of IL-1β.

CAPS consists of 3 diseases: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disorder (NOMID), which represent a spectrum of disorders that present with recurrent or continual systemic inflammation, rash, fevers, arthritis, neurologic deficits, and amyloidosis. FCAS is the mildest form of this disorder that presents with fevers, an evanescent rash, headache, conjunctivitis, and joint pain after generalized cold exposure. Although the rash can have some visual features of urticaria, it lacks angioedema or signs of mast cell degranulation, and is histologically characterized by a neutrophilic infiltrate. MWS presents similar to FCAS but cold exposure is not necessary for symptoms to occur. Unlike FCAS, chronic meningitis occurs with papilledema and sensorineural hearing loss, joint pain and swelling is more severe, and untreated, amyloidosis develops over time. NOMID is the most severe variant of CAPS. Like MWS, all patients with NOMID exhibit a rash at or shortly after birth. Neurologic symptoms, such as aseptic meningitis, headache, cerebral atrophy, uveitis, hearing loss, and intellectual disability, are common and severe. In NOMID and MWS, chronic inflammation of the joints leads to a chronic arthropathy with epiphyseal and patellar overgrowth. FCAS, MWS, and NOMID exhibit laboratory evidence of acute-phase response with leukocytosis, neutrophilia, anemia, thrombocytosis, and elevated erythrocyte sedimentation rate and CRP levels.

Historically, a variety of immunosuppressive treatments, including corticosteroids and colchicine, have been used to treat CAPS. IL-1 inhibitors (anakinra, rilonacept, canakinumab) are now the treatment

of choice for these disorders based on their ability to induce rapid and sustained clinical response. Laboratory abnormalities typically normalize in days, and the rash responds rapidly. Importantly, IL-1 blockade improves long-term morbidity such as hearing loss, joint deformity, and amyloidosis.

Hyperimmunoglobulin D Syndrome

Hyperimmunoglobulin D syndrome (HIDS) is an autoinflammatory disorder caused by mutations in the mevalonate kinase *(MVK)* gene (see Table 41.5). MVK is an enzyme involved in the biosynthesis of cholesterol and isoprenoids. Patients with HIDS have low but detectable MVK enzyme activity resulting in elevated levels of mevalonic acid in the urine during attacks. Complete absence of MVK results in mevalonic aciduria, an inborn error of metabolism, which is also associated with fevers. It is unclear how mutations in MVK lead to an autoinflammatory disease.

The clinical manifestations of HIDS occur at an early age with recurrent fevers with lymphadenopathy, abdominal pain, arthralgia and arthritis, and painful migratory erythematous macules. These episodes may last 4-7 days and are often triggered by stress, trauma, or vaccination. Serum IgD and IgA levels are usually elevated but may be normal. Acute-phase reactants are elevated during attacks. Although high-dose corticosteroids and TNF-α antagonists have been used with variable success, IL-1β inhibitors appear more effective at preventing the inflammatory episodes. Amyloidosis may occur but is relatively rare.

Deficiency of the Interleukin-1 Receptor Antagonist

Deficiency of the IL-1 receptor antagonist (DIRA) is an autosomal recessive disorder due to mutations in the IL-1 receptor antagonist gene *(IL-1RN)* (see Table 41.5). IL-1 receptor antagonist (IL-1RA) is a decoy protein that binds to the IL-1 receptor but does not result in signaling, and the absence of IL-1RA in patients with DIRA leads to cellular hyperesponsiveness to IL-1β.

The clinical manifestations of DIRA occur within the 1st 2 weeks of life and include pustular rash, osteopenia, lytic bone lesions, and prominent systemic inflammation. All patients develop cutaneous pustulosis, and biopsies of the skin lesions revealed a neutrophilic predominance. Respiratory distress, aphthous ulcers, hepatomegaly, and failure to thrive occurred, with approximately one-third of infants expiring prior to effective treatment. Bone is prominently involved, with osteopenia, multiple osteolytic lesions, and rib widening. Laboratory abnormalities reflect an acute-phase response with elevated ESR and CRP, leukocytosis, anemia, and thrombocytosis.

Anakinra, a recombinant IL-1RA, is highly effective in the treatment of DIRA. Anakinra essentially replaces the IL-1RA that patients with DIRA cannot synthesize. Longer-acting anti-IL1 agents, canakinumab and rilonacept, also work with the advantage of less frequent dosing compared to anakinra but are considerably more expensive.

TNF Receptor–Associated Periodic Syndrome (TRAPS)

TNF receptor–associated periodic syndrome (TRAPS) is an autosomal dominant disease associated with missense mutations in the extracellular domain of the TNF receptor 1 gene *(TNFRSF1A)* (see Table 41.5). The clinical manifestations of TRAPS patients include recurrent and often prolonged fevers, abdominal pain, and arthralgias. A migratory rash with underlying fascial inflammation and myalgia can be seen, as well as conjunctivitis and periorbital edema. Increased serum levels of CRP, ESR, leukocytosis, and thrombocytosis are evident during and in between attacks. Initial insights into the pathophysiology of this disorder came when patients with TRAPS exhibited low serum levels of soluble TNFR1, suggesting that shedding of TNF receptors acts as a natural antagonist to TNF-α. In support of this, the TNF-α antagonist etanercept has been shown to reduce the severity of symptoms in some cases of TRAPS. However, not all patients with TRAPS have low serum TNFR1 levels, and TNF-α inhibition is not completely effective. Reports have also shown the beneficial effects of IL-1 inhibition and the anti–IL-6 receptor antibody tocilizumab.

Deficiency of Adenosine Deaminase 2

Deficiency of adenosine deaminase 2 (DADA2) is an autosomal recessive disorder due to null mutations in *CECR1*, which encodes adenosine deaminase 2 (ADA2) (see Table 41.5). The clinical manifestations of DADA2 begin in childhood with intermittent fevers, recurrent lacunar strokes, organomegaly, hypogammaglobulinemia, and systemic vasculitides. The lacunar strokes begin before the age of 5 years and typically occur during inflammatory episodes. A livedo-like rash is a prominent feature with biopsies showing a predominance of neutrophils and macrophages as well as vasculitis in medium-sized vessels. Some of these patients are diagnosed with early-onset polyarteritis nodosa. Treatment with glucocorticoids, TNF-α inhibitors, and IL-1 blockers has been utilized with some benefit.

Blau Syndrome

Blau syndrome is an autosomal dominant disease caused by mutation in *NOD2* (see table 41.5) that result in spontaneous activation of the NOD2 protein, activation of NF-κB, and production of proinflammatory cytokines. Blau syndrome was originally described as a granulomatous disease affecting the skin, joints, and uveal tract, and should be considered in any individual presenting with early-onset sarcoidosis. Blau syndrome presents with a boggy synovitis of large joints, particularly the wrist and ankles, and an erythematous papular rash similar to erythema nodosum. Biopsy of these lesions demonstrates noncaseating granulomas. Unlike sarcoidosis, respiratory involvement and hilar adenopathy are rare, although granulomatous liver disease, cranial neuropathies, and large vessel vasculitis can occur. Laboratory studies in Blau syndrome are typically normal, although elevated ESR and angiotensin-converting enzyme levels can be seen, and hypergammaglobulinemia can occur. Most patients with Blau syndrome have been treated with corticosteroids, although limited reports have shown effectiveness of infliximab, thalidomide, and possibly anakinra.

Majeed Syndrome

Majeed syndrome is an autosomal recessive disorder caused by mutations in the *LPIN2* gene (see Table 41.5). The clinical manifestations of Majeed syndrome begin in childhood with recurrent fevers, sterile osteomyelitis, congenital dyserythropoietic anemia (CDA), neutrophilic dermatosis, failure to thrive, and hepatomegaly. Treatment of Majeed syndrome has included nonsteroidal antiinflammatory drugs, corticosteroids, and IL-1 receptor antagonists. How mutations in the *LPIN2* gene lead to an autoinflammatory disorder is not known.

IMMUNE DYSREGULATION SYNDROMES

Immune dysregulation disorders are genetic defects in the regulation of the adaptive immune system (T and B cells) resulting in early-onset inflammatory bowel disease, eczema, autoimmune cytopenias, and other autoimmune or inflammatory complications. Abnormalities of immune regulation are frequently important components of the clinical manifestations in patients with primary immune deficiencies, which have been described previously in this chapter. Unlike autoinflammatory disorders, these disorders are not episodic and are associated with autoimmune manifestations. Additionally, the clinical phenotype includes varying degrees of susceptibility to infection.

Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is caused by mutations in the gene encoding perforin or genes encoding other proteins involved in the cytotoxic function of NK cells and CD8 cells, such as Munc13-4, syntaxin11, and syntaxin11 binding protein (see Table 41.6). HLH is a life-threatening disorder of infants and is characterized by high fever, rash, hyperferritinemia, coagulopathy, and hematologic cytopenias. HLH is typically triggered in response to viral infections, in particular EBV and CMV. The various molecular defects that underlie HLH all result in ineffective clearance of viral infections by NK cells and CD8 T cells, resulting in prolonged antigen exposure and protracted activation of CD8 T cells and NK cells. CD8 T cells and NK cells produce large amounts of IFNγ that activate macrophages, resulting in phagocytosis of bone marrow elements and end-organ damage. This disorder is fatal if not treated aggressively with combined immunosuppressive medications and chemotherapy. HSCT is the only curative treatment.

X-Linked Lymphoproliferative Disease Type 1 and Type 2

X-linked lymphoproliferative disease type 1 (XLP-1) is caused by a mutation in the gene called *SH2D1A*, which encodes for an adapter protein involved in signal transduction of T cells and NK cells. XLP-2 is a similar disorder caused by mutations in *XIAP*. XLP-1 is characterized by fulminant infection with Epstein-Barr virus (EBV) with immunodysregulation and/or lymphoma. Boys with this disease may be relatively normal until infected with EBV, which is acutely fatal in 80% of patients and due to the development of HLH. Boys who survive the initial EBV infection develop hypogammaglobulinemia and are at high risk for developing aplastic anemia and B cell lymphomas. XLP-2 presents similarly with HLH following EBV infection, but can also present with early onset colitis. Definitive therapy of both forms of XLP is HSCT.

Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-Linked and Related Disorders

The maintenance of peripheral tolerance is critically dependent on T regulatory cells, CD4-positive T cells that prevent autoimmunity and excessive immune responses. These cells are generated in the thymus to self-antigens, express the transcription factor Foxp3, and constitutively express high levels of the IL-2 receptor (CD25). T regulatory cells express numerous immunosuppressive molecules including CTLA4, which inhibits T cell activation, and IL-10 and TGF-β.

Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) is caused by mutations in the *FOXP3* gene, an X-linked transcription factor essential for the production and function of T regulatory cells (see Table 41.6). In males with a null mutation in FOXP3, the clinical manifestations begin at birth or soon thereafter, and consist of inflammatory gastrointestinal tract disease, failure to thrive, autoimmune diabetes mellitus, thyroiditis, Addison disease, severe food allergies, eczema, and autoimmune cytopenias. Hypomorphic mutations in Foxp3 that encode a protein with residual functional activity lead to a later onset and milder clinical phenotype, but allergic disease and failure to thrive are common. Patients with this disorder are aggressively immunosuppressed to be stabilized, but bone marrow transplantation is the only curative therapy.

CD25 Deficiency

CD25 (α chain of the high-affinity IL-2 receptor) deficiency is an autosomal recessive disorder due to mutations in the *IL2RA* gene (see Table 41.6). T regulatory cells constitutively express CD25 and respond to IL-2 generated by T cells during an immune response for their immunoregulatory functions. CD25 deficiency results in a syndrome similar to IPEX with severe enteropathy, diabetes mellitus, autoimmune hemolytic anemia, eczema, and lymphoproliferation. Importantly, patients with CD25 deficiency exhibit several unique features not seen in IPEX, namely chronic herpetic viral infections and an increased susceptibility to infections.

Signal Transducer and Activator of Transcription Protein 5B Deficiency

Signal transducer and activator of transcription protein 5b (STAT5b) deficiency is an autosomal recessive disorder due to mutations in the STAT5b gene, 1 of 2 STAT5 proteins involved in IL-2 signaling (see Table 41.6). Similar to CD25 deficiency, STAT5b deficiency results in T regulatory cell dysfunction leading to a syndrome of immune deficiency with autoimmunity. These infants also suffer from autoimmune diseases such as autoimmune thrombocytopenia and hemolytic anemia, eczema, and arthritis. Unlike IPEX or CD25 deficiency, growth failure occurs in STAT5b since this signaling protein is required for growth hormone signaling. Additionally, patients with STAT5b deficiency also develop pulmonary disease that pathologically resembles interstitial lymphocytic pneumonia, although whether this represents an autoimmune phenomenon or a response to infectious episodes is unclear.

Cytotoxic T Lymphocyte Antigen 4 Deficiency

Cytotoxic T lymphocyte antigen 4 (CTLA4) deficiency is an autosomal dominant inherited disorder due to mutations of the gene encoding for the CTLA4 protein (see Table 41.6). Null mutations or point mutations that encode a nonfunctional protein can result in haploinsufficiency. Not all patients who have damaging mutations in CTLA4 develop any clinical phenotype (i.e., reduced penetrance) and the onset of the disease and clinical manifestations are variable as well (variable expressivity). The clinical manifestations of CTLA4 deficiency may occur in early childhood or adulthood. The most common clinical manifestations include enteropathy; granulomatous and lymphocytic lung infiltration; lymphocytic infiltration of the bone marrow, brain, kidney, or liver; respiratory tract infections; splenomegaly; lymphadenopathy; and immune cytopenias. Patients frequently have hypogammaglobulinemia, which explains their propensity to infection. Autoimmune thyroiditis and psoriasis also occur. Treatment of CTLA4 deficiency includes the use of replacement immunoglobulin therapy for patients with hypogammaglobulinemia and recombinant CTLA4 for the autoimmune manifestations.

A phenotypically similar disorder is caused by mutations in the LPS-responsive vesicle trafficking, beach and anchor containing *(LRBA)* gene, which regulates the expression of CTLA4 on the surface of T cells. CTLA4 is essential for the function of T regulatory cells, which explains the common autoimmune and autoinflammatory features of both LRBA deficiency and CTLA4 deficiency.

Autoimmune Polyendocrinopathy-Candidiasis–Ectodermal Dystrophy

Autoimmune polyendocrinopathy-candidiasis–ectodermal dystrophy (APECED) is an autosomal recessive disorder caused by mutations in the gene encoding the autoimmune regulator *(AIRE)* gene (see Table 41.6). AIRE is a transcription factor that is essential for expression of peripheral tissue antigens in the thymus, allowing for deletion of self-reactive T cells in the thymus (i.e., negative selection) and for the production of T regulatory cells with the correct antigen specificity. The clinical manifestation of APECED includes chronic or recurrent *Candida* infections of the mucous membranes, skin, and nails;

autoimmune hypoparathyroidism; and Addison disease. Other autoimmune disorders, such as vitiligo, thyroiditis, and pernicious anemia may occur. The insidious and variable onset of the endocrinopathies requires the need for frequent evaluation for autoimmune endocrine disorders. The propensity to develop fungal infections is explained by autoantibodies to certain immune cytokines, such as IL-17, that are critical to the defense of fungal infections.

Autoimmune Lymphoproliferation Syndrome

Autoimmune lymphoproliferation syndrome (ALPS) is a group of disorders most commonly caused by mutations in the *FAS* gene or less commonly the FAS ligand *(FASL)* gene (see Table 41.6). Other genetic causes of ALPS have been described. FAS is a protein that is involved in the normal apoptotic pathway of lymphocytes, and defective apoptosis due to defects in FAS or FASL underlies the autoimmune manifestations of this disorder. The clinical manifestations of ALPS include lymphoproliferation (i.e., splenomegaly and lymphadenopathy) and autoimmune manifestations, particularly autoimmune thrombocytopenia and autoimmune hemolytic anemia, and an increased susceptibility to lymphoma. Autoimmune manifestations are usually responsive to immunosuppressive medication.

SUMMARY AND RED FLAGS

Recurrent *benign* infections are common, especially in large families or in day care settings, in which children may manifest 6-10 upper respiratory tract infections or gastroenteritis episodes a year. These infections usually last less than 1 week. The child continues to grow and develop normally, and his or her activities are not restricted. Screening tests to evaluate immune function are typically normal. Red flags to consider disorders of the immune system include absent lymphoid tissue, failure to thrive, digital clubbing, chronic diarrhea, prolonged infections, infections with unusual organisms, repeated serious infections, eczematous dermatitis, a family history of early childhood deaths (presumably from infection), and other diseases associated with increased risks for infection (sickle cell anemia, malignancy, asplenia). In these cases, immunologic workup, genetic testing, and consultation with a clinical immunologist can lead to a diagnosis and definitive treatment.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Overview, History, Exam, and Diagnostic Approach

Bonilla FA, Khan DA, Ballas ZK, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *J Allergy Clin Immunol*. 2015;136:1186-1205.

Buckley RH. Primary immunodeficiency diseases due to defects in lymphocytes. *N Engl J Med*. 2000;343:1313.

Picard C, Al-Herz W, Bousfiha A, et al. Primary Immunodeficiency Diseases: An Update on the Classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency, 2015. *J Clin Immunol*. 2015;35:696-726.

Puck JM. Primary immunodeficiency diseases. *JAMA*. 1997;278:1835.

Sullivan KE, Stiehm ER, eds. *Stiehm's Immune Deficiencies*. London: Academic Press; 2014.

Complement System Deficiency

Colten HR, Rosen FS. Complement deficiencies. *Annu Rev Immunol*. 1992;10:809.

Frank MM. Complement disorders and hereditary angioedema. *J Allergy Clin Immunol*. 2010;125(2 suppl 2):S262-S271.

Ratnoff WD. Inherited deficiencies of complement in rheumatic diseases. *Rheum Dis Clin North Am*. 1996;22:75.

Phagocyte Disorders

Borregaard N, Boxer LA. Disorders of neutrophil function. In: Kaushansky K, Lichtman M, Beutler E, et al., eds. *Williams Hematology*. 8th ed. New York: McGraw-Hill; 2010:951.

Boztug K, Klein C. Genetics and pathophysiology of severe congenital neutropenia syndromes unrelated to neutrophil elastase. *Hematol Oncol Clin North Am*. 2013;27(1):43-60.

Bustamante J, Boisson-Dupuis S, Abel L, et al. Mendelian susceptibility to mycobacterial disease: genetic, immunological, and clinical features of inborn errors of IFN-gamma immunity. *Semin Immunol*. 2014;26(6):454-470.

Dale DC, Person RE, Bolyard AA, et al. Mutations in the gene encoding neutrophil elastase in congenital and cyclic neutropenia. *Blood*. 2000;96:2317.

Gately MK, Renzetti LM, Magram J, et al. The interleukin-12/interleukin-12-receptor system: Role in normal and pathologic immune responses. *Annu Rev Immunol*. 1998;16:495.

Harris ES, Weyrich AS, Zimmerman GA. Lessons from rare maladies: leukocyte adhesion deficiency syndromes. *Curr Opin Hematol*. 2013;20(1):16-25.

Kuhns DB, Alvord WG, Heller T, et al. Residual NADPH oxidase and survival in chronic granulomatous disease. *N Engl J Med*. 2010;363(27):2600-2610.

Lekstrom-Himes JA, Gallin JI. Immunodeficiency diseases caused by defects in phagocytes. *N Engl J Med*. 2000;343:1703.

Winkelstein JA, Marino MP, Johnston RB Jr, et al. Chronic granulomatous disease. Report on a national registry of 368 patients. *Medicine (Baltimore)*. 2000;79:155.

Asplenia

Bolze A, Mahlaoui N, Byun M, et al. Ribosomal protein SA haploinsufficiency in humans with isolated congenital asplenia. *Science*. 2013;340(6135):976-978.

Koss M, Bolze A, Brendolan A, et al. Congenital asplenia in mice and humans with mutations in a Pbx/Nkx2-5/p15 module. *Dev Cell*. 2012;22(5):913-926.

Price VE, Blanchette VS, Ford-Jones EL. The prevention and management of infections in children with asplenia or hyposplenia. *Infect Dis Clin North Am*. 2007;21(3):697-710.

Spelman D. Prevention of overwhelming sepsis in asplenic patients: Could we do better. *Lancet*. 2001;357:2002.

Humoral Immune Defects

Angulo I, Vadas O, Garcon F, et al. Phosphoinositide 3-kinase delta gene mutation predisposes to respiratory infection and airway damage. *Science*. 2013;342(6160):866-871.

Bates CA, Ellison MC, Lynch DA, et al. Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency. *J Allergy Clin Immunol*. 2004;114:415-421.

Conley ME, Dobbs AK, Farmer DM, et al. Primary B cell immunodeficiencies: comparisons and contrasts. *Annu Rev Immunol*. 2009;27:199-227.

Lucas CL, Kuehn HS, Zhao F, et al. Dominant-activating germline mutations in the gene encoding the PI(3)K catalytic subunit p110delta result in T cell senescence and human immunodeficiency. *Nat Immunol*. 2014;15(1):88-97.

Resnick ES, Moshier EL, Godbold JH, et al. Morbidity and mortality in common variable immune deficiency over 4 decades. *Blood*. 2012;119(7):1650-1657.

Yel L. Selective IgA deficiency. *J Clin Immunol*. 2010;30(1):10-16.

Yong PF, Thaventhiran JE, Grimbacher B. "A rose is a rose is a rose," but CVID is Not CVID common variable immune deficiency (CVID): what do we know in 2011? *Adv Immunol*. 2011;111:47-107.

Combined Immune Deficiencies

Fischer A, Hacein-Bey Abina S, Touzot F, et al. Gene therapy for primary immunodeficiencies. *Clin Genet*. 2015;88:507-515.

Gennery AR, Slatter MA, Rice J, et al. Mutations in CHD7 in patients with CHARGE syndrome cause T-B + natural killer cell + severe combined immune deficiency and may cause Omenn-like syndrome. *Clin Exp Immunol*. 2008;153(1):75-80.

Kavadas FD, Giliani S, Gu Y, et al. Variability of clinical and laboratory features among patients with ribonuclease mitochondrial RNA processing endoribonuclease gene mutations. *J Allergy Clin Immunol*. 2008;122:1178-1184.

Leung DYM, Geha RS. Clinical and immunologic aspects of the hyperimmunoglobulin E syndrome. *Hematol Oncol Clin North Am*. 1988;2:81.

Pai SY, Logan BR, Griffith LM, et al. Transplantation outcomes for severe combined immunodeficiency, 2000-2009. *N Engl J Med*. 2014;371(5):434-446.

Routes JM, Grossman WJ, Verbsky J, et al. Statewide newborn screening for severe T-cell lymphopenia. *JAMA*. 2009;302(22):2465-2470.

Shearer WT, Dunn E, Notarangelo LD, et al. Establishing diagnostic criteria for severe combined immunodeficiency disease (SCID), leaky SCID, and Omenn syndrome: The Primary Immune Deficiency Treatment Consortium experience. *J Allergy Clin Immunol*. 2014;133(4):1092-1098.

Autoinflammatory and Immune Dysregulation Disorders

Filipovich AH, Chandrakasan S. Pathogenesis of hemophagocytic lymphohistiocytosis. *Hematol Oncol Clin North Am*. 2015;29(5):895-902.

Kuehn HS, Ouyang W, Lo B, et al. Immune dysregulation in human subjects with heterozygous germline mutations in CTLA4. *Science*. 2014;345(6204):1623-1627.

Lo B, Zhang K, Lu W, et al. Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy. *Science*. 2015;349(6246):436-440.

Oliveira JB, Bleesing JJ, Dianzani U, et al. Revised diagnostic criteria and classification for the autoimmune lymphoproliferative syndrome (ALPS): report from the 2009 NIH international workshop. *Blood*. 2010;116(14):e35-e40.

Park H, Bourla AB, Kastner DL, et al. Lighting the fires within: the cell biology of autoinflammatory diseases. *Nat Rev Immunol*. 2012;12(8):570-580.

Schubert D, Bode C, Kenefeck R, et al. Autosomal dominant immune dysregulation syndrome in humans with CTLA4 mutations. *Nat Med*. 2014;20(12):1410-1416.

Verbsky JW, Chatila TA. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) and IPEX-related disorders: an evolving web of heritable autoimmune diseases. *Curr Opin Pediatr*. 2013;25(6):708-714.

42

Disorders of Puberty

Peter M. Wolfgram

Puberty is defined by both biologic and social standards. Puberty is the time when there is an increase in sex steroid production, resulting in physical changes such as breast development in girls and testicular enlargement in boys, as well as maturation of processes required for future fertility. Puberty, also known as adolescence, is the time when children make the transition to adult patterns of behavior, which involve maturity, responsibility, and sexuality.

NORMAL PUBERTAL DEVELOPMENT

Terminology

Various terms are used to discuss puberty (Table 42.1). **Bone age** refers to the degree of epiphyseal calcification, width, and proximity to adjacent metaphyses and is a marker of physical maturity that normally corresponds to chronologic age. **Dental age** generally correlates with bone age. Bone age is usually determined from a radiograph of the left hand and wrist, with comparison to gender-appropriate standards in Greulich and Pyle's bone age atlas. In infants and toddlers, a more accurate assessment of bone age can be determined from a radiograph of the hemiskeleton, with primary attention to epiphyses of the long bones. Delayed or advanced bone age occurs in many conditions; bone age is strongly influenced by sex steroid production. The timing of the onset of puberty is usually more closely linked to the bone age than to the chronologic age when the 2 are significantly discordant. Regardless of chronologic age, linear growth ceases when the bone age reaches 15 years in females and 18 years in males.

Anatomy

Puberty is controlled by the production of gonadotropin-releasing hormone (GnRH) in the anterior hypothalamus. GnRH-containing cell bodies project axons to the median eminence, where they terminate on the hypothalamic portal vessels. This system is referred to as the **GnRH pulse generator**. After GnRH reaches the anterior pituitary gland via the portal vasculature, it stimulates the production of both follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the gonadotroph cells. In females, both FSH and LH are required for estrogen production by ovarian granulosa cells. The regulated secretion of FSH and LH is also required for follicle growth, ovulation, and maintenance of the corpus luteum. In males, FSH regulates spermatogenesis by Sertoli cells within the seminiferous tubules, and LH activates Leydig cells to produce testosterone. Androgens cause development of male internal and external reproductive organs and secondary sexual characteristics in both sexes by binding to receptor proteins in the cells of target tissues. Sex steroids also exert a negative feedback effect on the pituitary gland and hypothalamus.

Physiology

Perinatal Period and Infancy

Maternal estrogens stimulate breast development in both male and female fetuses. Maternal estrogens also stimulate uterine developmental and endometrial growth; at birth, withdrawal of the high levels of maternal estrogen and placental progesterone causes the infant endometrium to regress or even slough and manifests as vaginal bleeding.

At birth, levels of LH and FSH in both sexes rise markedly and remain elevated for several months. In the girl, FSH stimulates ovarian granulosa cells to produce 17β-estradiol sufficient to maintain prenatal breast development for up to 8 months of life. Estrogen-induced vaginal cornification is generally evident as abundant vaginal discharge at birth and is maintained as long as estrogens are produced. Ovarian size from birth to 3 months ranges from 0.7-3.6 cm^3, decreasing to 2.7 cm^3 by 12 months and to 1.7 cm^3 by 24 months; this size persists until the onset of puberty. Ultrasound studies of the ovaries in normal infants show many microcysts.

Male breast development regresses rather quickly after birth. Elevated LH levels after birth stimulate Leydig cell production of testosterone for 6-12 months, leading to further genital development. Penis length increases from 3-5 cm in the full-term newborn to 4.5-6 cm by 2-3 years.

Childhood

By 2 years of age, serum gonadotropin levels decrease, and thus serum sex steroid levels also decrease, frequently to levels undetectable by conventional assays.

Beginning approximately at ages 6-7 years in females and 7-8 years in males, adrenal androgen production begins to increase and can be detected by the presence of increasing concentrations of the weak adrenal androgen dehydroepiandrosterone (DHEA) and its sulfated derivative, DHEA sulfate (DHEAS). Despite these serum levels, there is initially no secondary sexual (pubic or axillary) hair development.

Adolescence

Beginning on average at about 10.5 years in females and 11.5 years in males, there is the return of activity of the hypothalamic GnRH pulse

(See *Nelson Textbook of Pediatrics,* p. 2655.)

TABLE 42.1

Puberty Terminology

Gonadarche: maturation of the gonads under the control of the hypothalamus (GnRH) and pituitary gland (FSH and LH)
Thelarche: presence of breast development in girls
Gynecomastia: presence of breast development in boys
Adrenarche or development of androgen-regulated pubarche: secondary sexual characteristics, including pubic hair, axillary hair, apocrine (underarm) odor, and acne, in both sexes
Menarche: time of the first menstrual period
Spermarche: time when a boy is first able to produce sperm

generator, leading to increased serum levels of FSH and LH. The trigger mechanism for this resurgence is unknown, but it may be linked to attainment of a critical body mass or fat mass. Leptin, a hormone produced by fat cells, may be the connection between weight (fat mass) and pubertal events. In early puberty, the activity of the hypothalamic GnRH pulse generator is mostly evident overnight (sleep-entrained), with pulses increasing in number and amplitude and eventually occurring every 60-90 minutes. Over time, this process begins to occur during the daytime; there is always greater gonadotropin secretion at night. Because of the longer half-life of sex steroids, serum levels of estradiol and testosterone show little, if any, diurnal variation. Testosterone levels may be slightly higher in the morning with advancing puberty. There is central sensitivity to the negative feedback effects of sex steroids, leading to significant elevations of gonadotropins when sex steroid production is impaired. The function of the hypothalamic GnRH pulse generator can be accelerated in the setting of obesity, and LH and FSH secretion can revert to the prepubertal pattern in the setting of significant weight loss, as occurs in females with anorexia nervosa.

Usually within 6 months of the onset of this heightened GnRH pulse generator activity in females, there is also increasing production of androgens by the adrenal glands, the major source of androgens in females. In males, the testes are the main source of androgens, although male adrenarche also begins about 6 months after gonadarche.

Sex Steroid Effects

In response to FSH, both testes and ovaries enlarge, starting gonadarche. Ovarian granulosa cells produce 17β-estradiol, which causes estrogen effects that generally occur in a fixed order (Table 42.2). Growth increase is one of the early effects of estrogen. Growth is stimulated by estrogen-stimulated increased production of growth hormone and insulin-like growth factor 1. Estrogens along with growth hormone and thyroid hormones increase bone mineralization and growth.

In response to LH, testicular Leydig cells produce testosterone, which is converted to dihydrotestosterone, leading to androgen effects that generally occur in the same order (Table 42.3).

Note that growth is not stimulated early in puberty by rising testosterone; in fact, during the phase when testosterone levels are beginning to rise, growth is usually slowed perceptibly from a prepubertal height velocity of perhaps 5 cm/yr to a velocity as slow as 4 cm/yr for 12-18 months. As levels of testosterone increase closer to 400 ng/dL and testis volume increases to between 10 and 12 cm^3, males make the transition to rapid growth. Rapid growth for males thus occurs for about 2 years in middle puberty, and slower growth continues for 2-3 more years.

Benign adolescent gynecomastia occurs in as many as 40-60% of normal males; enough estrogen relative to the amount of testosterone is produced so that breast development occurs. Gynecomastia usually starts in early to middle puberty (peak age, 13 years), before adult male concentrations of testosterone are achieved. It typically starts on one side and resolves within 2 years. Gynecomastia is more common in obese males, although true breast tissue in this setting is often difficult to distinguish from fat tissue (lipomastia).

TABLE 42.2 Estrogen Effects

Vaginal and urethral cornification
Breast development, often asymmetric
Linear growth
Fat development
Uterine development
Menarche: 2-2.5 yr after breast buds

TABLE 42.3 Androgen Effects

Psychologic changes
Skin and hair oils, sweat odors
Areolar growth and pigment
Sexual skin pigment and folding
Phallic growth
Voice change
Sexual hair growth
Hairline recession
Statural growth
Muscle mass/strength

Chronology of Puberty

Females

Females begin puberty at an average age of 10.5 years (range, 8-13 years; mean ± 2.5 standard deviations [SD]). There are data suggesting that female puberty begins at an earlier age and that African-American females begin puberty about 1 year earlier than white females, but this is not universally accepted. In 85% of females, the first clinically detectable sign of puberty is breast development (thelarche), although ovarian enlargement, which is not clinically detectable in a strict sense, occurs first. Breast buds appear as small nodules either directly underneath the nipples or slightly off center, causing the areolae and nipples to be pushed out and sometimes cause minor, transient discomfort as the skin around the nipple is stretched. Breast development may be unilateral and asymmetric in its earliest stages. Pubic hair usually begins to develop within the next 6 months; in approximately 15% of females, pubic hair precedes breast development. Such discordance has no clinical significance. The female adolescent growth spurt commences near the onset of thelarche, generally spanning a 2-year period between the ages of 11 and 13 years. Axillary hair generally begins, on average, between 12 and 13 years. Menarche, a rather late event in female puberty, occurs on average between 12.2 and 12.8 years, typically 2-2.5 years following thelarche. Menarche is often preceded by a whitish, non–foul-smelling vaginal discharge (physiologic leukorrhea) for up to 6 months. At the time of menarche, an adolescent female has reached 96.5% of her adult height potential. However, more linear growth may remain in clinical situations in which menarche occurs at a younger bone age than is typical for the average adolescent female. Menstrual cycles for the 1st 2 years after menarche are often anovulatory and irregular in frequency.

Males

Males begin puberty at an average age of 11.5 years (range, 9-14 years; mean ± 2.5 SD). The 1st clinically detectable sign of puberty is

(See *Nelson Textbook of Pediatrics,* p. 2735.)

testicular enlargement, a fact generally unknown to patients and their parents. From birth to the start of puberty, male testicular volumes range between 1 and 2 mL as determined by the use of an orchidometer (a series of ellipsoid models of varying volumes). Stretched penile length (measured with a rigid tape measure on the dorsum of the penis from the pubic symphysis to the tip of the nonerect penis without considering any foreskin tissue) averages about 3.5 cm (range, 2.8-4.2 cm) at birth and grows by an average of 2.5 cm until the start of puberty. The onset of male puberty is considered to have begun when at least 1 of the 2 testicles reaches 4 mL in volume. It takes approximately 5-6 years for the testicles to reach the average adult volume of 18 mL. Approximately 75-80% of the adult testicle consists of seminiferous tubules; testosterone-producing Leydig cells make up the remainder.

Within 6 months after the start of testicular enlargement, pubic hair can be found; pubic hair precedes testicular enlargement in approximately 15%. The presence of pubic hair is incorrectly considered the 1st evidence of puberty in boys by both patients and parents. Pubic hair is followed by the development of axillary hair at approximately 14 years of age. During this time, penile enlargement also occurs, reaching a mean adult length of 12.4 ± 1.6 cm at 20 years of age. The male adolescent growth spurt typically occurs between the ages of 13 and 15 years, commencing when the testicular volumes reach 12 mL. By age 15 years, a male has attained 98% of his final adult height. The ability of adolescent boys to produce sperm, as evidenced by detection of spermatozoa in urine samples, begins between 13.5 and 15 years.

Clinical Staging of Puberty

Standardized staging of pubertal development in both sexes allows for comparison between children, as well as longitudinal monitoring of individual children.

Breast development in females, genitalia in males, and pubic hair in both sexes are scored according to 5-stage systems originally devised by James M. Tanner and referred to as Tanner stages 1-5. Axillary hair in both sexes is rated by a 3-stage system referred to as stages 1-3. Puberty itself is not staged because different components of puberty may occur at different stages.

Females

For breast development, Tanner stage 1 refers to no breast development; Tanner stage 2, to the presence of just breast buds (1 or 2); Tanner stage 3, to the beginning of formation of the peripheral mound with elevation of the breast; Tanner stage 4, to a further increase in breast size, with the formation of the so-called "double contour," in which the areola and papilla are both raised off the surface of the whole breast; and Tanner stage 5, to adult size, with a return to the single contour in which the surface of the areola is again flush with that of the breast. It may be difficult to differentiate between Tanner stages 3 and 5 because the only difference between these 2 stages is breast size (determined mostly by fat content). Thus, small breasts, especially in an older adolescent female, should not necessarily be construed as Tanner stage 3, especially if she has already menstruated, which typically occurs when the breasts have reached Tanner stage 4 and/or if women in the family typically have small breasts.

Males

For external genitalia, Tanner stage 1 refers to the prepubertal state (testes < 4 mL in volume); Tanner stage 2, to slight enlargement of the testes and scrotum; Tanner stage 3, to lengthening of the penis and further enlargement of the testes and scrotum; Tanner stage 4, to continued penile growth in both length and width with development of the glans; and Tanner stage 5, to adult appearance. An alternative, simplified, and equally accurate approach involves only sizing of the testicles, whereby 4 mL represents the start of puberty, 12 mL correlates with the start of the growth spurt, and 18 mL is the average adult size. In some cases, the appearance of pubic hair does not occur until the testicular volumes reach 12-15 mL. Testicular volumes may differ at all stages between sides but not usually by more than one size on a standard orchidometer. It is important not to confuse a hydrocele with an enlarged testis.

Females and Males

Tanner staging of pubic hair is similar in both sexes. Tanner stage 1 is defined by having no pubic hair. Tanner stage 2 is characterized by the presence of a few, countable strands of curly, coarse, pigmented hair either in the mons area or perilabially along the midline in females or at the base of the penis and/or on the scrotum in males. Lighter, peach fuzz–like hair (lanugo) in the pubic region is not pubic hair. On occasion, especially in individuals from ethnic populations from Mediterranean countries or Northern India, there may be an extension of coarse body hair (hypertrichosis) to the pubic region that can be difficult to discern from pubic hair. Tanner stage 3 refers to the presence of coarser, darker, and curlier hairs, the number of which is no longer countable, which have spread more laterally. Tanner stage 4 refers to a thick, fully triangular pattern of hair growth, without spread to the thighs. Finally, Tanner stage 5 refers to the adult pattern in which there is spread of hair to the medial thighs. The designation Tanner stage 6 is used to describe hair growing up the linea alba, referring to the so-called male escutcheon.

Axillary hair is the simplest component of puberty to quantify. Stage 1 refers to the absence of any hair. Stage 2 refers to a countable number of curly, coarse, pigmented strands in at least 1 armpit. Stage 3 refers to the adult complement, which is merely more hair than is present in stage 2. For the individual with shaved axillae, it is safe to assume either stage 2 or stage 3 hair is present.

Family Patterns

The timing of puberty is affected by familial patterns; both parents' histories are important in assessing the child with early or late puberty. The following information is useful for establishing the parental effect:

- Age of their mother's menarche
- Age their father began shaving on a daily basis
- Age when their parents stopped growing

PRECOCIOUS PUBERTY

Definition

The onset of puberty, at least in females, may be occurring earlier than in the past; therefore, the definition of precocious puberty has been modified to refer to the appearance of any feature of puberty before 7 years of age in African-American females (and perhaps even before 6 years), before 8 years of age in white females (and perhaps even before 7 years), and before 9 years of age in males (regardless of race). If this conservative definition is applied, it remains important to consider pathologic causes in children who present with signs of puberty in the age range between the new and former definitions. The family pattern must also be considered; an early onset of puberty is frequently familial.

Normal Variants

Idiopathic Isolated Premature Thelarche

This common condition is the development of breast tissue in females before 8 years of age in white children and 7 years of age in African-American children, with no other manifestations of puberty

(See *Nelson Textbook of Pediatrics,* p. 2657.)

(Fig. 42.1). Elevated serum estrogen levels for age have been difficult to demonstrate, although higher levels than in age-matched normal females have been measured by an ultrasensitive estradiol assay. Development of breast tissue commonly begins between 2 and 3 years of age; it may be present from birth. The observed tissue may be asymmetric, unilateral, or bilateral. When asymmetric or unilateral, parents are typically concerned about the possibility of malignancy, an extremely rare occurrence in childhood. The early breast tissue frequently regresses without intervention, but it may persist. If it persists, the degree of development does not usually exceed Tanner stage 3. The bone age, if determined, is not frequently advanced, and there is no associated growth spurt. If these simple clinical criteria are met, no hormonal studies or additional radiologic procedures are necessary.

Physiologic breast enlargement also occurs in neonates from placental transfer of estrogens. Most marked in the 1st weeks of life, it usually regresses by 1-2 months.

Idiopathic Isolated Precocious Adrenarche

This common, normal variant is characterized by the development of pubic hair, axillary hair and odor, and/or a small amount of acne in white females before the age of 8 years, in African-American females before the age of 7 years, and in males before the age of 9 years. It appears to result from early production of adrenal androgens. Precocious adrenarche occurs much more commonly in females than in males and develops most often in obese and/or African-American females and in brain-injured children. There is no associated evidence of virilization (no growth spurt, no significant advancement of bone age, no increase in muscle bulk, no voice deepening, and no temporal hair recession). In females, there is no associated clitoromegaly and no evidence of estrogen-mediated components of puberty; in males, there is no phallic or testicular enlargement. If a child presents at a very young age, it is generally presumed that an organic cause (such as congenital adrenal hyperplasia) will be found. However, in infant males with isolated scrotal hair, typically no cause is found, and the hair subsequently falls out. In most cases of idiopathic precocious adrenarche (benign premature adrenarche), serum levels of DHEA and/or DHEAS are consistent with the reference range of Tanner staging of the hair growth, and the 8:00 A.M. 17-hydroxyprogesterone level is normal. If these criteria are met, no additional laboratory studies are indicated. This pubertal variant was considered benign and self-limited, but data suggest that at least in females with associated low birth weight, it may suggest an increased risk for **polycystic ovary disease**.

FIGURE 42.1 Two-year-old twin sisters with idiopathic isolated premature thelarche manifested by isolated breast development to Tanner stage 3.

Isosexual Central Precocious Puberty

Central sexual precocity results from activation of the hypothalamic-pituitary-gonadal axis at an earlier-than-normal age (Fig. 42.2). Isosexual development refers to pubertal changes appropriate for the sex of the child, such as breast budding in females and testicular enlargement in males. This is to be distinguished from contrasexual development, in which the pubertal features in females are mediated by male hormones (clitoromegaly) and those in males are mediated by female hormones (breast development).

Causes of isosexual precocious puberty are listed in Tables 42.4 and 42.5. The majority of cases in females, who are at least 10-fold more likely to be affected than males, are idiopathic, whereas only a small percentage of affected males have no definable cause. Ovarian size, as seen on a sonogram, is generally a reflection of ovarian estrogen production. In true central puberty, pituitary gonadotropins cause both ovaries to increase in size.

In true male central puberty, testes enlarge and androgen production increases. The size of testes enlargement sufficient to determine puberty is debatable. In general, prepubertal testes are less than 4 cm^3

FIGURE 42.2 A 3-year-old girl *(left)* with isosexual central precocious puberty characterized by both breast and pubic hair development, and tall stature, contrasted to a normal 5-year-old prepubertal girl *(right)*.

TABLE 42.4 Classification of Sexual Precocity

True Precocious Puberty or Complete Isosexual Precocity (GnRH-Dependent Sexual Precocity or Premature Activation of the Hypothalamic GnRH Pulse Generator)

Idiopathic true precocious puberty
CNS tumors
Optic glioma associated with neurofibromatosis type 1
Hypothalamic astrocytoma
Other CNS disorders
Developmental abnormalities including hypothalamic hamartoma of the tuber cinereum
Encephalitis
Static encephalopathy
Brain abscess
Sarcoid or tubercular granuloma
Head trauma
Hydrocephalus
Arachnoid cyst
Myelomeningocele
Vascular lesion
Cranial irradiation
True precocious puberty after late treatment of congenital virilizing adrenal hyperplasia or other previous chronic exposure to sex steroids
True precocious puberty due to gain-of-function mutations:
in the *KISS1R/GRP54* genes
in the *KISS1* gene

Incomplete Isosexual Precocity (Hypothalamic GnRH-Independent)

Males

Gonadotropin-secreting tumors
hCG-secreting CNS tumors (e.g., chorioepitheliomas, germinoma, teratoma)
hCG-secreting tumors located outside the CNS (hepatoma, teratoma, choriocarcinoma)
Increased androgen secretion by adrenal gland or testis
Congenital adrenal hyperplasia (CYP21 and CYP11B1 deficiencies)
Virilizing adrenal neoplasm
Leydig cell adenoma
Familial testotoxicosis (sex-limited autosomal dominant pituitary gonadotropin-independent precocious Leydig cell and germ cell maturation)
Cortisol resistance syndrome

Females

Ovarian cyst
Estrogen-secreting ovarian or adrenal neoplasm
Peutz–Jeghers syndrome

Both Sexes

McCune–Albright syndrome
Hypothyroidism
Iatrogenic or exogenous sexual precocity (including inadvertent exposure to estrogens in food, drugs, or cosmetics)

Variations of Pubertal Development

Premature thelarche
Premature isolated menarche
Premature adrenarche
Adolescent gynecomastia in boys
Macroorchidism

Contrasexual Precocity

Feminization in Males

Adrenal neoplasm
Chorioepithelioma
CYP11B1 deficiency
Late-onset adrenal hyperplasia
Testicular neoplasm (Peutz–Jeghers syndrome)
Increased extraglandular conversion of circulating adrenal androgens to estrogen
Iatrogenic (exposure to estrogens)

Virilization in Females

Congenital adrenal hyperplasia
CYP21 deficiency
CYP11B1 deficiency
3β-HSD deficiency
Virilizing adrenal neoplasm (Cushing syndrome)
Virilizing ovarian neoplasm (e.g., arrhenoblastoma)
Iatrogenic (exposure to androgens)
Cortisol resistance syndrome
Aromatase deficiency

CNS, central nervous system; CYP11B1, 11-hydroxylase; CYP21, 21-hydroxylase; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; 3β-HSD, 3β-hydroxysteroid dehydrogenase 4,5-isomerase; *KISS1R/GPR54*, kisspeptin/G protein–coupled receptor 54.
Modified from Grumbach MM. True or central precocious puberty. In: Kreiger DT, Bardin CW, eds. *Current Therapy in Endocrinology and Metabolism, 1985-1986*. Toronto, Canada: BC Decker; 1985:4-8.

in volume and 2 cm in length. If on examination both testes are enlarged and androgen signs are present, it is likely puberty is underway and testes-derived testosterone levels are increasing. If basal pituitary gonadotropins are increasing, or if LH levels increase markedly after GnRH stimulation, the diagnosis is central precocious puberty.

Hypothalamic hamartomas, which may be associated with ectopic secretion of GnRH or transforming growth factor-α, are common causes of precocious puberty. Approximately 3% of children with neurofibromatosis type I develop central precocity, usually caused by a hypothalamic optic glioma.

Central precocious puberty in the setting of untreated or undertreated peripheral causes of puberty, such as **virilizing congenital adrenal hyperplasia**, is caused by premature activation of the GnRH pulse generator, presumably as a result of continuous central nervous system exposure to high levels of androgens (or androgens aromatized to estrogens). Precocious puberty with thelarche and menarche in the setting of long-standing severe untreated **primary hypothyroidism** (Van Wyk–Grumbach syndrome) can occur, although the mechanism is not clear. It is clinically distinguished by the usual manifestations of hypothyroidism, including delayed growth and bone age, rather than the advanced bone age present with other causes of precocious puberty.

Incomplete Isosexual Precocity (Precocious Pseudopuberty)

Precocious pseudopuberty refers to gonadal or adrenal sex-steroid secretion *not* resulting from activation of the hypothalamic-pituitary-gonadal axis (pituitary-independent). It is caused by excessive production of or exposure to either androgens or estrogens (see Table 42.4).

TABLE 42.5 Differential Diagnosis of Sexual Precocity

Disorder	Plasma Gonadotropins	LH Response to GnRH	Serum Sex Steroid Concentration	Gonadal Size	Miscellaneous
Gonadotropin Dependent					
True precocious puberty	Prominent LH pulses (premature reactivation of GnRH pulse generator)	Pubertal LH response initially during sleep	Pubertal values of testosterone or estradiol	Normal pubertal testicular enlargement or ovarian and uterine enlargement	MRI of brain to rule out CNS tumor or other abnormality; skeletal survey for McCune–Albright syndrome (by US)
Incomplete Sexual Precocity (Pituitary Gonadotropin Independent)					
Males					
Chorionic gonadotropin-secreting tumor in males	High hCG, low LH	Prepubertal LH response	Pubertal value of testosterone	Slight-to-moderate uniform enlargement of testes	Hepatomegaly suggests hepatoblastoma; CT scan of brain if chorionic gonadotropin-secreting CNS tumor suspected
Leydig cell tumor in males	Suppressed	No LH response	Very high testosterone	Irregular, asymmetric enlargement of testes	
Familial testotoxicosis	Suppressed	No LH response	Pubertal values of testosterone	Testes symmetric and > 2.5 cm but smaller than expected for pubertal development; spermatogenesis occurs	Familial; probably sex-limited, autosomal dominant trait
Virilizing congenital adrenal hyperplasia	Prepubertal	Prepubertal LH response	Elevated 17-OHP in CYP21 deficiency or elevated 11-deoxycortisol in CYP11B1 deficiency	Testes prepubertal	Autosomal recessive; may be congenital or late-onset form, may have salt loss in CYP21 deficiency or hypertension in CYP11B1 deficiency
Virilizing adrenal tumor	Prepubertal	Prepubertal LH response	High DHEAS and androstenedione values	Testes prepubertal	CT, MRI, or US of abdomen
Premature adrenarche	Prepubertal	Prepubertal LH response	Prepubertal testosterone, DHEAS, or urinary 17-ketosteroid values appropriate for pubic hair stage 2	Testes prepubertal	Onset usually after 6 yr of age; more frequent in CNS-injured children
Females					
Granulosa cell tumor (follicular cysts may present similarly)	Suppressed	Prepubertal LH response	Very high estradiol	Ovarian enlargement on physical examination, CT, or US	Tumor often palpable on physical examination
Follicular cyst	Suppressed	Prepubertal LH response	Prepubertal to very high estradiol	Ovarian enlargement on physical examination, CT, or US	Single or recurrent episodes of menses and/or breast development; exclude McCune–Albright syndrome
Feminizing adrenal tumor	Suppressed	Prepubertal LH response	High estradiol and DHEAS values	Ovaries prepubertal	Unilateral adrenal mass
Premature thelarche	Prepubertal	Prepubertal LH, pubertal	Prepubertal or early estradiol response	Ovaries prepubertal	Onset usually before 3 yr of age
Premature adrenarche	Prepubertal	Prepubertal LH response	Prepubertal estradiol; DHEAS or urinary 17-ketosteroid values appropriate for pubic hair stage 2	Ovaries prepubertal	Onset usually after 6 yr of age; more frequent in brain-injured children

Continued

TABLE 42.5 Differential Diagnosis of Sexual Precocity—cont'd

Disorder	Plasma Gonadotropins	LH Response to GnRH	Serum Sex Steroid Concentration	Gonadal Size	Miscellaneous
Late-onset virilizing congenital adrenal hyperplasia	Prepubertal	Prepubertal LH response	Elevated 17-OHP in basal or corticotrophin-stimulated state	Ovaries prepubertal	Autosomal recessive
In Both Sexes					
McCune–Albright syndrome	Suppressed	Suppressed	Sex steroid pubertal or higher	Ovarian enlargement (visible on US); slight testicular enlargement	Skeletal survey for polyostotic fibrous dysplasia and skin examination for café-au-lait spots
Primary hypothyroidism	LH prepubertal; FSH may be slightly elevated	Prepubertal FSH may be increased	Estradiol may be pubertal	Testicular enlargement; ovaries cystic	TSH and prolactin elevated; T_4 low

CNS, central nervous system; CT, computed tomography; CYP, P450 cytochrome isoenzyme; DHEAS, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone; MRI, magnetic resonance imaging; 17-OHP, 17-hydroxyprogesterone; T_4, thyroxine; TSH, thyroid-stimulating hormone; US, ultrasonography.

Androgen Exposure or Overproduction

Anabolic steroids have been taken by males and females to improve muscle development and athletic performance. In males, if anabolic steroids are taken at the age of puberty, secondary sexual development will progress, but the testes will remain small. In females, anabolic steroids can produce clitoral enlargement (particularly in diameter), complexion problems, and hirsutism, as well as emotional lability.

Females. **Ovarian tumors** producing androgens (thecoma) and sometimes also estrogen may be palpable on physical examination and are usually easily seen on a pelvic sonogram. Arrhenoblastoma, a virilizing ovarian tumor, is rare in children. Gonadoblastomas, which are not always virilizing, typically occur in phenotypic females who have a Y chromosome. Granulosa cell tumors usually cause estrogen overproduction but occasionally cause virilization due to excessive androgen production.

Adrenal tumors can be detected with ultrasonography, computed tomography, or MRI. Androgens produced by adrenal tumors are not suppressed by dexamethasone. Excessive adrenal androgens may also be produced as a result of late-onset or nonclassic **congenital adrenal hyperplasia**, but the androgen production can be suppressed by dexamethasone. The enzymatic deficiency in late-onset congenital adrenal hyperplasia is mild, inasmuch as it does not cause ambiguity of genitalia at birth; however, it is associated with an accelerated growth rate and advanced bone age and may be clinically recognized any time after birth.

Males. If both testes are slightly increased in volume and testosterone levels are increased but LH and FSH levels are low, there are 2 possibilities: either the testes are being stimulated by human chorionic gonadotropin (hCG), which acts like LH and does not increase testicular volume, as with FSH, or the testes are functioning autonomously. hCG levels must be determined, and if they are increased, tumors producing hCG must be identified and removed; such tumors may include hepatoma, hepatoblastoma, teratoma, and chorioepithelioma.

If both testes are producing testosterone autonomously without gonadotropin stimulus, the condition of **testotoxicosis** is probable. Children with this autosomal dominant disorder have signs of puberty by 4 years of age (Fig. 42.3). Testosterone production and Leydig cell hyperplasia occur in the setting of prepubertal serum LH levels, because of a gain-of-function mutation in the gene for the LH receptor, resulting in its constitutive activation. Affected males are fertile. Females who carry this mutation do not develop precocious puberty.

If one testis is enlarged, a Leydig cell adenoma in that testicle is probably producing excess testosterone; the tumor must be removed. The high levels of testosterone suppress LH and FSH secretion, so the other testicle remains small. Depending on age, a testicular prosthesis may be inserted to replace the removed testicle.

If androgen signs are developing steadily but neither testis has enlarged, the androgen is presumed to be either from the adrenal glands or from an exogenous source. Inappropriate adrenal production of androgens results from tumors or abnormalities in steroid synthesis enzymatic activity. An adrenal tumor would have affected growth whenever the gland started to function, but not necessarily beginning at birth. A defect in steroid synthesis caused by an enzymatic deficiency (usually 21-hydroxylase) may be congenital, as in congenital adrenal hyperplasia, and the excess androgen production resulting from the enzymatic deficiency would have been produced from the time of birth, leading to increased growth velocity from early life. *Children with congenital adrenal hyperplasia may have severe adrenal crises during an illness or surgery*. A late-onset or nonclassic form of adrenal hyperplasia may also occur. A tumor can be identified by computed tomography, ultrasonography, or MRI and must be removed.

Estrogen Overproduction

The most common cause of premature progressive breast development is simple premature thelarche. In this case, a pelvic ultrasound study may show prepubertal ovaries varying from 1-3 cm^3 in volume with many small estrogen-producing follicular cysts. Some cysts may be larger (persistent follicular cysts). Estradiol is produced by the granulosa cells lining the follicles and causes vaginal discharge and breast development. Estradiol may cause uterine development as well but generally does not cause increased growth velocity. LH and FSH levels are low and if estradiol is measured, it might be elevated but minimally so. The follicular cysts regress spontaneously (90% of the time) within a few weeks to months, and the vaginal cornification is lost within 1 week of cyst regression. The breast tissue then softens but can remain for months, and may never completely regress. Typically premature thelarche due to persistent follicular cysts is usually benign and

FIGURE 42.3 A boy with familial testotoxicosis associated with significant penile enlargement, moderate pubic hair growth, and mild-to-moderate testicular enlargement over a 1.75-year period. *Left,* at 2 years of age. *Right,* at 3.75 years of age.

self-limited. However, 10% of the cysts may persist and enlarge, with some follicular cysts becoming large enough to threaten ovarian torsion and to necessitate surgical treatment.

Granulosa cell tumors are usually isolated occurrences but may occur as part of **Peutz–Jeghers syndrome** (oral melanosis and intestinal polyps). Aromatase is the enzyme that is responsible for conversion of androgen to estrogen; aromatase excess is an autosomal dominant disorder that can lead to increased estradiol levels.

McCune–Albright syndrome. This disorder (Fig. 42.4) consists of the clinical triad of polyostotic fibrous dysplasia, hyperpigmented macules (café-au-lait spots) with irregular borders ("coast of Maine"), and multiple autonomous endocrinopathies (most commonly gonadotropin-independent precocious puberty, but also hyperthyroidism, acromegaly, and hypercortisolemia) (Table 42.6). Precocious puberty occurs much more commonly in females than in males. Patients have a mutation in their $G_s a$ gene that occurs early in embryogenesis and results in constitutive activation of adenylyl cyclase only in affected tissues. This activation leads to the autonomous function of involved tissues, resulting, in the case of affected endocrine glands, in unregulated production of hormone. Precocity in females, often heralded by menstrual bleeding, frequently occurs before 2 years of age. The ovaries are enlarged and have many follicular cysts; the patient has elevated levels of estradiol. Later, when the GnRH pulse generator is activated subsequent to unabated sex steroid exposure, the patient may transition from gonadotropin-independent to central precocious puberty.

Vaginal Bleeding

The usual progression of puberty in females dictates that breast and uterine development begin about 2 years before the menses. When the rate of pubertal progression is accelerated, menses may start as early as 1-1.5 years after thelarche; if the rate is slow, menses may start perhaps 3-4 years after thelarche. In any case, vaginal bleeding is always a much later sign than breast development, and whenever vaginal bleeding occurs too early—especially if it ever occurs before breast development starts—it must be investigated thoroughly.

Gynecomastia

Breast tissue frequently develops in males during midpuberty, when the production of estrogen from testosterone in the testes temporarily overbalances the testosterone effects. Only rarely does breast tissue develop in prepubertal males, inasmuch as young males do not respond to transient gonadotropin stimulation with estrogen production. Differential diagnosis includes estrogen-producing tumors (gonadal or adrenal), exogenous estrogen, hCG-producing tumors, aromatase excess, certain types of male pseudohermaphroditism, and Klinefelter syndrome. Certain medications and illicit drugs are associated with gynecomastia. A **prolactinoma** should be considered, especially in the setting of **galactorrhea**.

Evaluation of gynecomastia in prepubertal males may include karyotyping and measurement of gonadotropins, estradiol, testosterone, hCG, and prolactin level. Imaging is dictated by the results.

◆ Diagnostic Approach to Precocious Puberty

In the initial evaluation of the child with precocious puberty, the clinician attempts to determine:

- Whether the process is a normal variant or pathologic
- The rate of progression of the pubertal changes
- Whether the process originates centrally or peripherally

FIGURE 42.4 A 12-year-old girl with McCune–Albright syndrome with a café-au-lait spot with an irregular border ("coast of Maine") on the back *(left)* and representative lesion of fibrous dysplasia involving the left humerus *(right)*.

TABLE 42.6 Clinical Manifestations of McCune–Albright Syndrome in 158 Reported Patients*

Manifestation	% OF PATIENTS			Mean Age at Diagnosis (yr) and Range	Comments
	Total (n = 158)	Male (n = 53)	Female (n = 105)		
Fibrous dysplasia	97	51	103	7.7 (0-52)	Polyostotic more common than monostotic
Café-au-lait lesion	85	49	86	7.7 (0-52)	Variable size and number of lesions, irregular border (coast of Maine)
Sexual precocity	52	8	74	4.9 (0.3-9)	Common initial manifestation
Acromegaly/gigantism	27	20	22	14.8 (0.2-42)	17/26 of patients with adenoma on MRI/CT
Hyperprolactinemia	15	9	14	16.0 (0.2-42)	23/42 of acromegalic patients with PRL
Hyperthyroidism	19	7	23	14.4 (0.5-37)	Euthyroid goiter is common
Hypercortisolism	5	4	5	4.4 (0.2-17)	All primary adrenal
Myxomas	5	3	5	34 (17-50)	Extremity myxomas
Osteosarcoma	2	1	2	36 (34-37)	At site of fibrous dysplasia, not related to prior radiation therapy
Rickets/osteomalacia	3	1	3	27.3 (8-52)	Responsive to phosphorus plus calcitriol
Cardiac abnormalities	11	8	9	(0.1-66)	Arrhythmias and CHF reported
Hepatic abnormalities	10	6	10	1.9 (0.3-4)	Neonatal icterus is most common

*Evaluations include clinical and biochemical data; other rarely described manifestations include metabolic acidosis, nephrocalcinosis, developmental delay, thymic and splenic hyperplasia, and colonic polyps.
CHF, congestive heart failure; CT, computed tomography; MRI, magnetic resonance imaging; PRL, prolactin.
Modified from Ringel MD, Schwindinger WF, Levine MA. Clinical implications of genetic defects in G proteins: the molecular basis of McCune-Albright syndrome and Albright hereditary osteodystrophy. *Medicine (Baltimore)*. 1996;75:171-184.

Initial evaluation should include:

- Medical history: growth patterns; excessive responses to illness (adrenal crisis); exposure to exogenous sex steroids; history of intracranial insults (hydrocephalus, meningitis, or encephalitis)
- Review of symptoms: growth records, head size since birth, vision problems, headache, age at onset of androgen signs (behavior changes, need for increased hair washing because of oiliness, need for deodorant), age at onset of estrogen signs (vaginal discharge or breast budding), café-au-lait spots ("coast of Maine" in McCune–Albright syndrome or "coast of California" in neurofibromatosis)
- Family history: timing of maternal and paternal growth and pubertal development; siblings and cousins with early development; neurofibromatosis
- Physical examination: vital signs, height, weight, head circumference, tooth age, café-au-lait spots, neurofibromata, pubic and axillary hair, body odor, skin and hair oils, visual fields, optic discs, breast development, vaginal cornification/discharge, penis/clitoris size, scrotal/labial development, testicular volume, pubic hair stages, facial asymmetry or bone abnormalities (fibrous dysplasia of McCune–Albright syndrome), neurologic status, affect or mood, intellectual ability

The 1st test is usually a determination of bone age; if the bone age is not significantly advanced (within 20% of the chronologic age in months) and not associated with an increase in height velocity, the results suggest a normal variant, a slowly progressive process, or a process of relatively short duration. If the bone age is significantly advanced, a workup is mandatory (Table 42.7). Clinical and laboratory findings in sexual precocity are listed in Table 42.5.

For females with breast development, pelvic ultrasonography and determination of central precocity are the initial diagnostic tests. Because of the pulsatile secretion of serum gonadotropins, random measurements of LH and FSH even by ultrasensitive immunochemiluminescent assay (ICMA) are occasionally low and appear prepubertal even in the setting of central activation. If this occurs and there is clinical suspicion nonetheless of maturation of the GnRH pulse generator, a GnRH stimulation test should be performed. With central precocity, as with normal puberty, endogenous GnRH that "primes" the pituitary gonadotrophs is being produced, so that after administration of a single pharmacologic dose of GnRH, there is copious release of LH. If, on the other hand, the precocity has a peripheral basis, the high levels of circulating estradiol, through central negative feedback, prevent the gonadotrophs from releasing LH in response to the exogenous GnRH bolus.

If a female with advanced bone age presents only with contrasexual androgenic effects (specifically, evidence of virilization), measurement of gonadotropins and estradiol is not indicated as an adrenal cause should be considered. Measurement of serum 17-hydroxyprogesterone is the diagnostic test for 21-hydroxylase deficiency, the most common enzyme abnormality associated with nonclassic or late-onset adrenal hyperplasia. On occasion, an adrenocorticotropic hormone (ACTH) stimulation test may need to be performed to determine the specific enzymatic deficiency. Screening for Cushing syndrome with a 24-hour urine collection with measurement of free cortisol (and creatinine to document completeness of the collection) or midnight salivary cortisol may also be indicated if the appropriate "cushingoid" body habitus is present. Generally, linear growth is attenuated with Cushing syndrome, which is in contrast to most other causes of precocious puberty. Given the typical lack of ovarian involvement in the pathology of virilization in girls, magnetic resonance imaging of the head is not usually indicated.

For males, the testicular examination guides the evaluation by suggesting whether there is a testicular or adrenal source of the androgens.

TABLE 42.7 Diagnostic Approach to Precocious Puberty

Girls with Breast Development, with or Without Androgen Effects

Random serum FSH and LH measurement by ICMA; estradiol measurement
GnRH stimulation test (if random FSH and LH levels are uninformative)
Pelvic ultrasonography
Prepubertal ovaries: ultrasonography (or other radiologic imaging) to image adrenal glands and question about exogenous sources
One enlarged ovary: either functioning ovarian cyst or solid granulosa-cell tumor
Bilaterally enlarged ovaries for age: GnRH test to distinguish between central precocity (usual) or McCune–Albright syndrome (rare)
Head MRI with contrast medium (if central precocity is confirmed biochemically and is progressive)

Girls with Contrasexual Androgen Effects (Virilization)

Serum total testosterone (provides an index of the severity of the process)
17-Hydroxyprogesterone (for CAH)
ACTH stimulation test (for CAH) (optional)
Midnight salivary cortisol or 24-hr urine free cortisol and creatinine (for Cushing syndrome)
Abdominal/pelvic MRI (if testing suggests either an adrenal or ovarian tumor)

Boys with Isosexual Precocity

Prepubertal testes: ultrasonography (or other radiologic imaging) of the adrenal glands; question about exogenous sources
One enlarged testis: ultrasonography (or other radiologic imaging) of this testis for an androgen-producing tumor
Bilaterally enlarged testes for age: GnRH test to distinguish between central precocity and other causes (familial testotoxicosis, hCG-producing tumor, CAH with adrenal rests, or hypothyroidism)
If central precocity is confirmed biochemically, head MRI with contrast

Tests to Consider, in Either Sex, Depending on Clinical Presentation

Serum hCG
Prolactin
T_4 and TSH

ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; ICMA, immunochemiluminescent assay; LH, luteinizing hormone; MRI, magnetic resonance imaging; T_4, thyroxine; TSH, thyroid-stimulating hormone.

Testotoxicosis and hCG-producing tumors cause some testicular enlargement but less than expected for the degree of virilization.

◆ Treatment of Precocious Puberty

General Issues

Not all cases of precocious puberty necessitate treatment. Cases of idiopathic precocious thelarche and adrenarche should be monitored, because their manifestations are not typically progressive and there is no significant early onset of the other components of puberty or short stature. In addition, not all children with central precocious puberty require treatment, inasmuch as a significant number of cases are either slowly progressive and/or transient. Unless there is rapid progression and/or significant psychosocial difficulties, most children with central precocity should be observed for a 3- to 6-month period before pubertal reversal therapy is initiated. The reasons that favor treatment

include preservation of acceptable final height, prevention of psychologic trauma (menstruation at an early age), reversal of mature physical appearance to decrease the risk of pregnancy in females (because other people assume that affected children are older than they appear), and reduction of aggressiveness and preoccupation with sexuality. Serious psychologic effects of early puberty are not usually encountered. If a decision is made to reverse puberty, the goal of therapy is to inhibit secretion and/or effects of estrogens in females and androgens in males (Table 42.8).

Central Precocious Puberty

The goal of therapy is to inhibit secretion of gonadotropins and reduce production of sex steroids by the administration of GnRH analogs with a prolonged duration of action (Table 42.9). This causes downregulation of pituitary GnRH receptors, preventing the response to endogenous GnRH and thus decreasing LH and FSH secretion. Several doses of GnRH are necessary to produce the antagonistic response because the treatment initially stimulates the axis and only later results in downregulation of pituitary GnRH receptors. Accurate verification of adequate suppression of the axis typically requires repeat GnRH testing, although random LH-ICMA levels may be sufficient.

Therapy is stopped at about 11 years in females and 12 years in males so that puberty can resume. Successful GnRH agonist treatment is associated with a stabilization of androgen effects in males and estrogen effects in females; there is no effect on androgen-mediated events in females as androgens are predominately produced by the adrenal glands. Complete reversal of physical changes to the prepubertal state is unusual. Height velocity and the rate of bone age maturation should slow; on some occasions, height velocity actually becomes subnormal. This is not necessarily problematic as long as bone age maturation slows commensurately. Final height is optimized with earlier initiation of therapy. Once GnRH analog therapy is discontinued, reactivation of the hypothalamic-pituitary-gonadal axis occurs within 12 months. Long-term fertility data in individuals treated with GnRH analogs as children continues to grow, but studies suggest successful childbearing in women and normal testicular function in young adult men following GnRH therapy.

Large tumors in the hypothalamic-pituitary region are surgically removed, and both the tumor or the surgery can precipitate central precocious puberty. However, hypothalamic hamartomas are benign and tend to grow very slowly; therefore, surgery is usually not recommended.

Precocious Pseudopuberty (Incomplete Isosexual Precocity)

Treatment is directed at the underlying cause (Table 42.10). The precocious puberty of McCune–Albright syndrome is treated with inhibitors (testolactone or anastrozole) of aromatase, the enzyme that converts androgen to estrogen. The results of this approach are variable, and sometimes a GnRH agonist must be added if central puberty is also present. Ketoconazole is an effective therapy for familial testotoxicosis (due to a constitutively active LH receptor) because it has the desirable and reversible side effect of interfering with sex steroid synthesis; spironolactone is an androgen receptor blocker.

DELAYED OR ABSENT PUBERTY

Delayed puberty is the failure of development of any pubertal feature by 13 years of age in females or by 14 years of age in males. A lower cutoff may be appropriate in a child with a strong familial pattern of early puberty.

◆ Differential Diagnosis

Delay or absence of puberty is caused by:

- Constitutional delay: a variant of normal
- Hypogonadotropic hypogonadism: low gonadotropin levels as a result of a defect of the hypothalamus and/or pituitary gland (Tables 42.11 and 42.12)
- Hypergonadotropic hypogonadism: high gonadotropin levels as a result of a lack of negative feedback because of a gonadal problem (see Tables 42.11 and 42.12). Girls may have isolated absence of adrenarche with normal breast development (see later discussion).

TABLE 42.8 Objectives for the Management and Treatment of True Precocious Puberty

Detection and treatment of an expanding intracranial lesion
Arrest of premature sexual maturation until the normal age at onset of puberty
Regression of secondary sexual characteristics already present
Attainment of normal mature height; suppression of the rapid rate of skeletal maturation
Prevention of emotional disorders and handicaps and alleviation of parental anxiety; promotion of understanding by counseling, early sex education, and acceleration of social age
Reduction of risk of sexual abuse and early sexual debut
Prevention of pregnancy in girls
Preservation of future fertility
Diminishment of the increased risk of breast cancer associated with early menarche

From Grumbach MM. True or central precocious puberty. In: Krieger DT, Bardin CW, eds. *Current Therapy in Endocrinology and Metabolism, 1985-1986.* Toronto, Canada: BC Decker; 1989:4-8.

TABLE 42.9 GnRH Analogs Used to Treat Precocious Puberty

Leuprolide acetate (Lupron Depot) given as an intramuscular injection every 1-3 mo*
Leuprolide acetate (Lupron) given as a daily subcutaneous injection
Nafarelin acetate (Synarel) given b.i.d. by an intranasal route

*Preferred because of infrequent dosing.
b.i.d., twice a day; GnRH, gonadotropin-releasing hormone.

TABLE 42.10 Treatment of Precocious Pseudopuberty (Incomplete Isosexual Precocity)

Tumors
Surgical removal
Chemotherapy and/or radiation as indicated
Illicit or unintentional administration of exogenous estrogens or androgens should be uncovered and eliminated
Familial testotoxicosis: ketoconazole or spironolactone and testolactone
Adrenal hyperplasia: exogenous glucocorticoid
Hypothyroidism: levothyroxine
McCune–Albright syndrome: testolactone or anastrozole
GnRH agonist therapy may need to be added to any of above medical therapies if central puberty becomes superimposed at an early age

GnRH, gonadotropin-releasing hormone.

(See *Nelson Textbook of Pediatrics,* p. 2643.)

TABLE 42.11 Classification of Delayed Puberty and Sexual Infantilism

Idiopathic (Constitutional) Delay in Growth and Puberty (Delayed Activation of Hypothalamic LRF Pulse Generator)

Hypogonadotropic Hypogonadism: Sexual Infantilism Related to Gonadotropin Deficiency

CNS Disorders

Tumors

Craniopharyngiomas
Germinomas
Other germ cell tumors
Hypothalamic and optic gliomas
Astrocytomas
Pituitary tumors (including MEN-1, prolactinoma)

Other Causes

Langerhans histiocytosis
Postinfectious lesions of the CNS
Vascular abnormalities of the CNS
Radiation therapy
Congenital malformations, especially associated with craniofacial anomalies
Head trauma
Lymphocytic hypophysitis

Isolated Gonadotropin Deficiency

Kallmann syndrome
- With hyposmia or anosmia
- Without anosmia

LHRH receptor mutation
Congenital adrenal hypoplasia (*DAX1* mutation)
Isolated LH deficiency
Isolated FSH deficiency
Prohormone convertase 1 deficiency (PCI)

Idiopathic and Genetic Forms of Multiple Pituitary Hormone Deficiencies Including *PROP1* Mutation

Miscellaneous Disorders

Prader–Willi syndrome
Laurence-Moon or Bardet-Biedl syndrome
Functional gonadotropin deficiency
Chronic systemic disease and malnutrition
Sickle cell disease
Cystic fibrosis
Acquired immunodeficiency syndrome (AIDS)
Chronic gastroenteric disease
Chronic renal disease
Malnutrition
Anorexia nervosa
Bulimia
Psychogenic amenorrhea
Impaired puberty and delayed menarche in female athletes and ballet dancers (exercise amenorrhea)
Hypothyroidism
Diabetes mellitus
Cushing disease
Hyperprolactinemia
Marijuana use
Gaucher disease

Hypergonadotropic Hypogonadism

Males

The syndrome of seminiferous tubular dysgenesis and its variants (Klinefelter syndrome)
Other forms of primary testicular failure
Chemotherapy
Radiation therapy
Testicular steroid biosynthetic defects
Sertoli-only syndrome
LH receptor mutation
Anorchia and cryptorchidism
Trauma/surgery

Females

The syndrome of gonadal dysgenesis (Turner syndrome) and its variants
XX and XY gonadal dysgenesis
Familial and sporadic XX gonadal dysgenesis and its variants
Familial and sporadic XY gonadal dysgenesis and its variants
Aromatase deficiency
Other forms of primary ovarian failure
Premature menopause
Radiation therapy
Chemotherapy
Autoimmune oophoritis
Galactosemia
Glycoprotein syndrome type 1
Resistant ovary
FSH receptor mutation
LH/hCG resistance
Polycystic ovarian disease
Trauma/surgery
Noonan or pseudo-Turner syndrome
Ovarian steroid biosynthetic defects

CNS, central nervous system; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone; LHRH, luteinizing hormone-releasing hormone; LRF, luteinizing hormone-releasing factor; MEN, multiple endocrine neoplasia.

Constitutional Delay of Growth and Puberty

This is the most common cause of delayed puberty and is thought to be a normal variant. It is usually diagnosed in males, probably as a result of ascertainment bias of referral patterns. The cause is unknown, but approximately 50% of affected patients have a 1st-degree relative with delayed puberty and/or late growth. This tendency can occur in a child of the same gender as the affected parent or in a child of the opposite gender. An affected child typically presents in early adolescence when peers are beginning to develop and having growth spurts but the patient is not. The patient's height is usually at or below the 3rd percentile (see Chapter 43). In the classic case, the affected child had a normal length at birth, a slowdown in height velocity between 6 months and 2 years of age that resulted in short stature, and a normal or near-normal height velocity thereafter along the child's current height percentile. The physical examination findings are unremarkable, and, depending on the age, the child may have delayed puberty. The cardinal diagnostic result is a bone age that is moderately delayed in comparison with chronologic age. There may also be a history of delayed dentition. Without intervention, final adult height usually

TABLE 42.12 Molecular Basis for Developmental Disorders Associated with Hypogonadotropic Hypogonadism

Gene	Phenotype	Complex Phenotype
Isolated Hypogonadotropic Hypogonadism		
Kallmann Syndrome or Normosmic IHH (With the Same Mutant Gene)		
KAL1 (Xp22.3)	X-linked Kallmann syndrome	Anosmia/hyposmia, renal agenesis, dyskinesia
FGFR1 (8p11.2)	Autosomal dominant Kallmann syndrome (± recessive)	Anosmia/hyposmia, cleft lip/palate
FGF8 (ligand for FGFR1) (10q25)		
NSMF (9p34.3)	Autosomal dominant/Oligogenetic Kallmann syndrome	
PROK2 (3p21.1)	Autosomal recessive Kallmann syndrome	
*PROKR2** (20p12.3)		
CHD7 (8p12.1)	Autosomal dominant (some)	CHARGE syndrome; includes hyposmia
Normosmic Isolated Hypogonadotropic Hypogonadism		
GNRH1 (8p21-11.2)	Autosomal recessive	
*GNRHR** (4q13.2-3)	Autosomal recessive (± dominant)	
*GPR54** (19p13.3)	Autosomal recessive	
SNRPN Lack of function of paternal 15q11-q13 region or maternal uniparental disomy		Prader–Willi syndrome, obesity
LEP (7q31.3)	Autosomal recessive	Obesity
LEPR (1p31)	Autosomal recessive	Obesity
NR0B1 (X21.3-21.2)	X-linked recessive	Adrenal hypoplasia
TAC3 (12q13-12)	Autosomal recessive	
TACR3 (4q25)	Autosomal recessive	
Multiple Pituitary Hormone Deficiencies		
PROP1 *POU1F1*	Autosomal recessive GH, PRL, TSH, and LH/FSH (less commonly, later-onset ACTH deficiency)	
HESX1	Autosomal recessive; and heterozygous mutations Multiple pituitary deficiencies including diabetes insipidus, but LH/FSH uncommon	Septo-optic dysplasia
LHX3	Autosomal recessive GH, PRL, TSH, FSH/LH	Rigid cervical spine
PHF6	X-linked; GH, TSH, ACTH, LH/FSH	Börjeson-Forssman-Lehmann: intellectual disability; coarse facies

*A G protein–coupled receptor.
ACTH, corticotrophin; CHD7, chromatin-remodeling factor; DAX1, dosage-sensitive sex reversal-adrenal hyperplasia congenita critical region on the X chromosome, gene 1; FGF, fibroblast growth factor; FSH, follicle-stimulating hormone; GH, growth hormone; GnRH, gonadotropin-releasing hormone; GPR54, kisspeptin G protein–coupled receptor 54; *HESX1*, homeobox gene expressed in ES cells; IHH, idiopathic hypogonadotropic hypogonadism; LEP, leptin; LH, luteinizing hormone; *LHX3*, lim homeobox gene 3; NELF, nasal embryonic luteinizing hormone–releasing factor; NR0B1, nuclear receptor family 0, group B, member 1; *PHF6*, plant homeodomain–like finger gene; PRL, prolactin; PROK2, prokineticin 2; PROP1, prophet of Pit-1; R, receptor; SNRPN, small nuclear ribonucleoprotein polypeptide SmN; TAC3, neurokinin 3; TSH, thyroid-stimulating hormone.

reaches or approximates the target height range. However, children with constitutional delay may have a blunted pubertal growth spurt in relation to their peers, and therefore may not reach their genetic target height range.

Hypogonadotropic Hypogonadism

A variety of central nervous system insults may disrupt production of gonadotropins. The GnRH pulse generator may be disrupted by an interfering substance, such as excess prolactin (with or without hypothyroidism), or by stress, chronic illness, malnutrition, or excessive physical activity. The hypothalamic arcuate nucleus may be damaged by trauma, radiation, infection, infiltration, increased intracranial pressure, or surgery. The most common mass lesions are craniopharyngiomas, gliomas, and cysts. Congenital conditions or malformations may have allowed enough GnRH for infantile development but not enough for pubertal needs.

Kallmann syndrome. This is the combination of an impaired or absent sense of smell and gonadotropin deficiency. Other features include color blindness, atrial septal defects, and renal structural anomalies (unilateral renal agenesis). The X-linked form is caused by a mutation of the *KAL* gene; there are autosomal recessive and autosomal dominant forms.

LH and FSH deficiencies may also be isolated or caused by multiple pituitary hormone deficiencies. The latter condition may be a result of pituitary damage from trauma, radiation, infection, sickle cell disease, compression by infiltrate or tumor, or autoimmune processes. In differentiating primary pituitary deficiency from that secondary to hypothalamic deficiency, the clinician should remember that all pituitary

hormones except prolactin are stimulated by hypothalamic releasing hormones; prolactin is inhibited by hypothalamic prolactin inhibitory factor. Therefore, if all pituitary hormones, including prolactin, are deficient, the problem is in the pituitary gland. If prolactin levels are present or even elevated but the other pituitary hormones are deficient, the problem is above the pituitary gland in the stalk or hypothalamus. In the case of isolated LH and FSH deficiencies, the primary abnormality may lie within the pituitary or hypothalamic neurons producing GnRH; however, increasingly there is evidence of primary abnormalities being further upstream. In particular, defects in molecules required for proper migration of GnRH neurons (including the *KAL* gene) or lack of necessary signaling to GnRH-producing neurons (e.g., defects in kisspeptin or neurokinin B and their receptors) can result in LH and FSH deficiency through inappropriate GnRH secretion.

Hypergonadotropic Hypogonadism: Males

If the testes are small, they may have been damaged by torsion, sickle cell disease, infection, autoimmune disease, chemotherapy, or radiation and may not be able to respond to LH and FSH stimulation. If the bone age is greater than 10 years and the hypothalamus has probably matured, the serum LH and FSH may then be high.

When the testis size is prepubertal and LH is present but testosterone is not increasing, there may be a problem with the LH receptor.

Klinefelter syndrome. This occurs in 1:500 males and is often associated with a 47,XXY karyotype; common features include reduced intelligence, adolescent gynecomastia (often pronounced), and small, firm testes. The testes rarely exceed 5 mL in volume (approximately 25% of the average adult volume). Patients, often tall and thin with an eunuchoid habitus, may have delayed puberty. Virilization may be incomplete, the phallus is often smaller than average, and infertility nears 100%.

Hypergonadotropic Hypogonadism: Females

In this condition, the ovary may be unable to synthesize estrogen (an inherited metabolic defect, possibly associated with excess adrenal mineralocorticoid and hypertension), the ovary may not be formed normally (dysgenesis), or the ovary may have been damaged by any of the factors listed for testicular damage and by galactosemia.

The ovary may be intact but may not be stimulated by gonadotropins. Gonadotropins are present but not effective if there is an FSH receptor problem.

Turner syndrome. The 2 most common features of Turner syndrome are short stature (involving the limbs to a greater degree than the trunk) and ovarian insufficiency (Fig. 42.5). Lymphedema and a webbed neck are diagnostic features present in a neonate. Additional features include a shield chest, increased carrying angle (cubitus valgus), short 4th metacarpal, hypoplastic nails, renal anomalies, and left-sided heart defects (coarctation of the aorta, bicuspid mitral valve, etc.). Approximately 50% of affected girls have no stigmata except short stature and thus are typically identified later. About 20% may have spontaneous puberty with functioning ovaries for at least a short period of time, which is in large part dependent on the child's karyotype, but the infertility rate is greater than 99%.

Females with Delayed or Absent Adrenarche

If a female has advanced breast development but no androgen signs, she may have a deficiency of androgen receptors, as occurs in **androgen insensitivity syndrome** (testicular feminization). In females, the androgens come predominantly from the adrenal glands (adrenarche). If the bone age has not passed 8 years, when DHEAS generally increases, adrenarche may simply be delayed (delayed adrenarche). If bone age is advanced, however, there is a deficiency in androgen production. In addition, there may be an inherited problem in androgen synthesis from an enzyme deficiency or the adrenal glands may be damaged secondary to autoimmune, infectious, or hypoxic injury. In these latter conditions, other signs of adrenal insufficiency would be evident.

FIGURE 42.5 A 16-year-old girl with Turner syndrome (45,XO), characterized by short stature, absence of thelarche, webbed neck, and increased carrying angles.

◆ Diagnostic Approach to Delayed Puberty

A normal growth rate with delayed, but not absent, puberty and a family history of "late blooming" suggests the diagnosis of constitutional delay of growth and puberty, which is the most commonly encountered cause (see Tables 42.11 and 42.12). A bone age that correlates with the patient's pubertal status confirms the clinical impression; no other testing is necessary.

Initial evaluation should include:

- Medical history: trauma, illness, medications (e.g., stimulants, chemotherapy), radiation, infection, malnutrition, autoimmune problems, sickle status, stresses, growth records, galactosemia
- Review of symptoms: vision problems, headache, vomiting, inability to detect odors (hyposmia or anosmia), age at onset of androgen signs, age at onset of estrogen signs, small genitalia at birth, signs of primary adrenal insufficiency such as hyperpigmentation, need for deodorant, need to wash hair more frequently
- Family history: timing of maternal and paternal growth and pubertal development; siblings and cousins with delayed development
- Physical examination: signs of chronic disease, temperature, blood pressure, height, weight, head circumference, dental age, tanning (hyperpigmentation), pubic and axillary hair, adult body odor, skin and hair oils, visual fields, optic discs, ability to detect odors, breast development, vaginal cornification/discharge, penis size, scrotal development, testicular volume, pubic hair stages, neurologic status, affect or mood, intellectual ability, dysmorphic features

Initial laboratory evaluation screens for chronic disease include (complete blood cell count, chemistry profile, sedimentation rate),

hypothyroidism (free thyroxine and thyroid-stimulating hormone), and hyperprolactinemia (prolactin level). If growth is slow, the clinician should measure insulin-like growth factor-1 level (a marker of basal growth hormone activity) and consider growth hormone testing. The clinician should measure testosterone levels in males and estradiol levels in females.

Measurements of random FSH and LH and results of a GnRH stimulation test may differentiate between hypogonadotropic hypogonadism and primary gonadal failure (Figs. 42.6 and 42.7). Elevated gonadotropin levels support a diagnosis of primary gonadal failure. Chromosomal karyotyping is then performed (Klinefelter syndrome in males and Turner syndrome in females). GnRH stimulation testing, with measurement of serum LH levels over 1-2 hours, is often employed. Its rationale is based on the fact that a child in puberty has a significant rise in serum LH over baseline. Unfortunately, the GnRH test is not helpful in distinguishing between constitutional delay and hypogonadotropic hypogonadism because in both cases, the LH response is blunted secondary to lack of endogenous GnRH priming of the gonadotrophs. However, the child with constitutional delay eventually develops an appropriate pubertal response to GnRH stimulation testing.

If **Kallmann syndrome** is being considered, a magnetic resonance imaging scan may show abnormalities in the olfactory region. If a 46,XX female has unexplained ovarian failure, antiovarian antibodies are obtained and müllerian-inhibiting substance can also be utilized in girls to assess ovarian follicle reserve and potential fertility. An hCG stimulation test to evaluate ability to produce testosterone and a serum level of müllerian-inhibiting substance (secreted by Sertoli cells) are useful for determining whether functional testicular tissue is present.

◆ Treatment of Delayed Puberty

If delayed puberty is **physiologic**, there is no medical necessity for initiating sex steroid replacement. "Watchful waiting" is usually the appropriate course of action. Adolescent males with constitutional

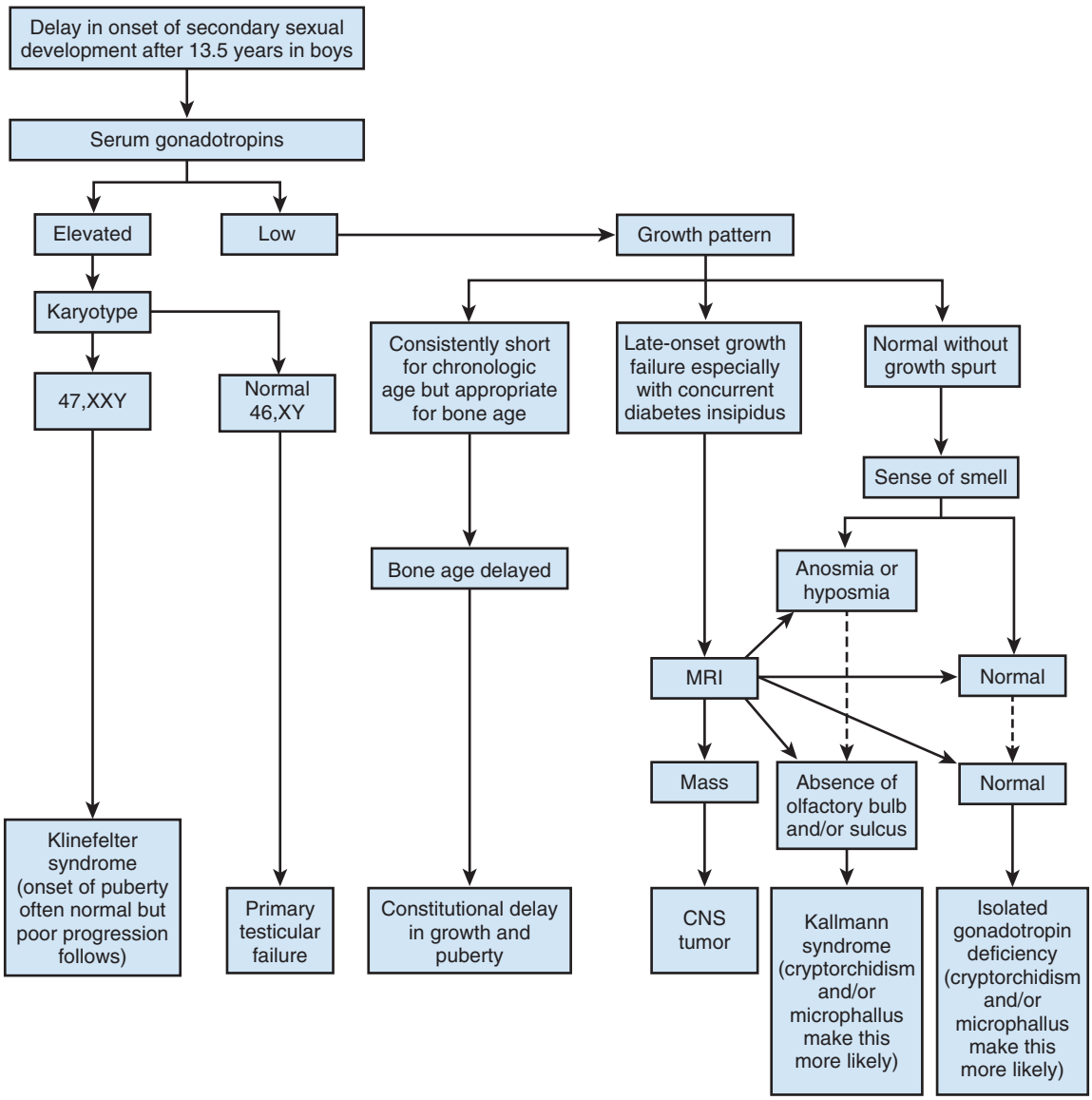


FIGURE 42.6 Flow chart for the evaluation of delayed puberty in males. A brain MRI with absent olfactory bulb and/or sulcus is consistent with Kallman syndrome, while a normal MRI suggests Isolated gonadotropin deficiency. CNS, central nervous system; MRI, magnetic resonance imaging. (From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors. *Williams Textbook of Endocrinology*. 13th ed. Philadelphia: Elsevier; 2016:1156.)

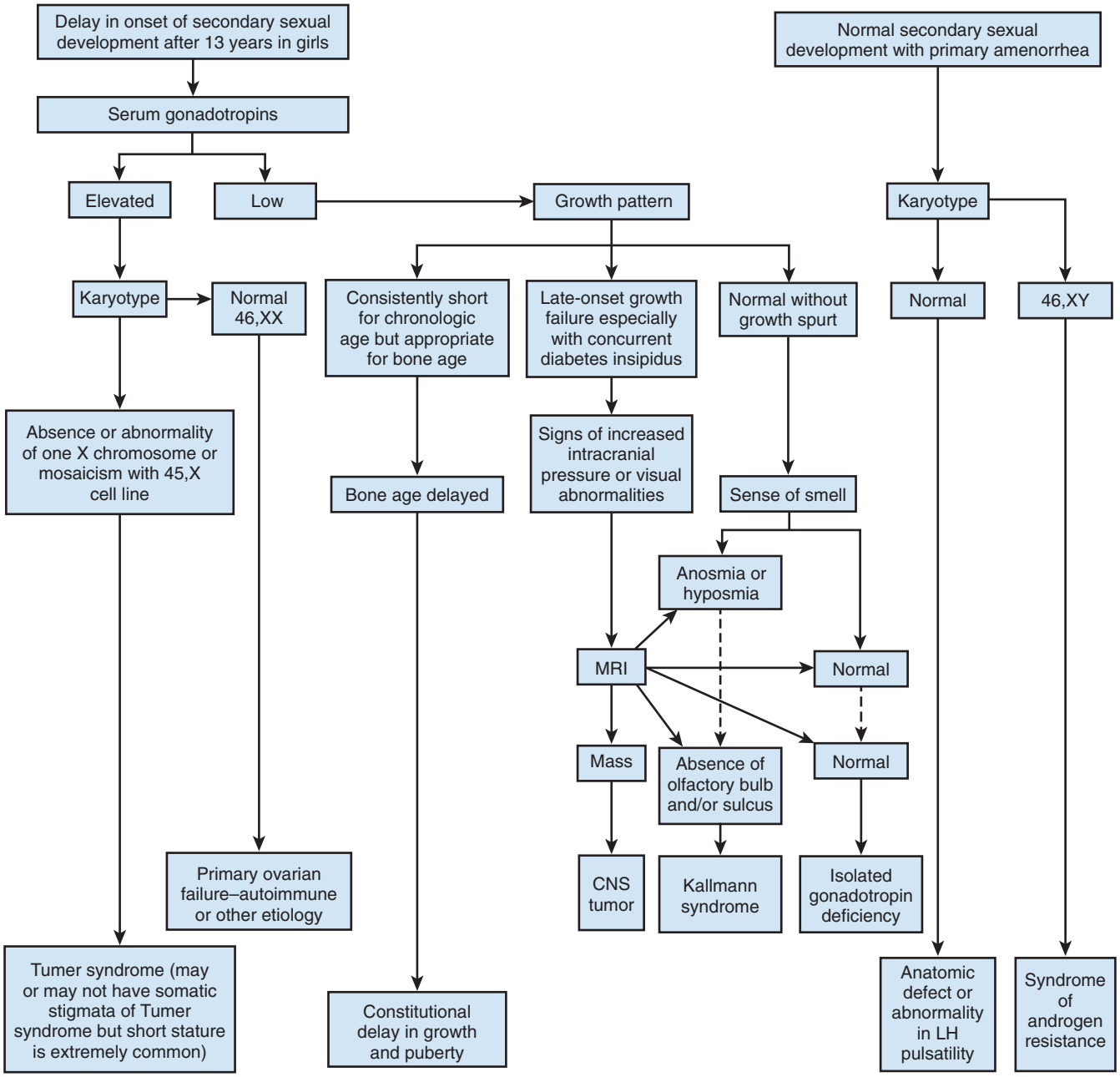


FIGURE 42.7 Flow chart for the evaluation of delayed puberty in females. A brain MRI with absent olfactory bulb and/or sulcus is consistent with Kallman syndrome, while a normal MRI suggests Isolated gonadotropin deficiency. CNS, central nervous system; LH, luteinizing hormone; MRI, magnetic resonance imaging. (From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors. *Williams Textbook of Endocrinology*. 13th ed. Philadelphia: Elsevier; 2016:1157).

delay of growth and puberty who are short, underdeveloped, and psychologically compromised frequently benefit from a short course of testosterone therapy. This is usually given as long-acting intramuscular testosterone at a dosage of 50-100 mg every 3-4 weeks for a course ranging between 3 and 12 months. Treatment is generally begun at about 13 years of age, and if possible, when the testes are about 6-8 mL in volume. These doses stimulate height and weight gain, allow adequate virilization (increased pubic and axillary hair growth and penile enlargement), and do not typically suppress pituitary FSH and LH secretion, thereby allowing simultaneous endogenous pubertal progression (testicular enlargement). This narrows the physical gap between the patient and peers without causing undue advancement of bone age. Acne is the principal side effect and the adult height is not altered. It is the hope that at the conclusion of treatment, the male will continue to grow and develop rapidly with the testosterone treatment perceived as a "jump starter" of endogenous puberty. A short course of low-dose anabolic steroids, such as oxandrolone or fluoxymesterone, can also be employed in prepubertal and pubertal males, and low-dose estradiol has been used in prepubertal and pubertal females with constitutional delay.

Treatment of **hypogonadism** is aimed at mimicking normal physiology with stepwise replacement of testosterone in males and estrogen and progesterone in females. For males with hypogonadism, low-dose parenteral testosterone is initiated at 50 mg every 3-4 weeks, with increases in 50-mg increments made over a 2- to 3-year period. Most adult men receive 200 mg every 3-4 weeks, which is based on the daily

TABLE 42.13 Red Flags Related to Puberty

Pubertal changes in African-American girls beginning before age 6 yr (excluding isolated thelarche from birth to 2 yr of age)
Pubertal changes in white girls beginning before age 7 yr (excluding isolated thelarche from birth to 2 yr of age)
Pubertal changes in all boys beginning before 9 yr of age
Absence of pubertal changes in girls by 13 yr of age
Absence of pubertal changes in boys by 14 yr of age
Neurologic signs and symptoms (headaches, visual disturbances)
Vaginal bleeding before breast development
Significantly asymmetric gonadal size in either sex (boys, by clinical examination; girls, by pelvic ultrasonography)
Testicular underdevelopment
Girls with advancing breast development but no androgen signs
Galactorrhea
Pelvic mass

TABLE 42.14 Things Not to Miss with Regard to Puberty

Dysmorphic features
Unusual thinness or obesity
Cutaneous findings
Penis or clitoris diameter and length
Size of testes in patients with gynecomastia
Other endocrine deficiencies or excesses

adult male testosterone production rate of 6 mg. Some adult men are treated with 300 mg every 2 weeks. Adult men can use testosterone by patch, which is often associated with local irritation, or by gel, but typically in growing adolescents, intramuscular testosterone is prescribed.

For females, daily estrogen therapy is given for 1 year. This can be either in the form of conjugated estrogens (Premarin) at 0.3 mg daily for the 1st 6 months and 0.625 mg daily for the 2nd 6 months, or with an analogous schedule of ethinyl estradiol replacement or through a weekly applied 17β-estradiol patch. This duration does not place the uterus at undue risk for hyperplasia and malignancy, but after 2 years of therapy (or if spotting occurs prior), progesterone should be added. Options to consider when adding progesterone include continuing the purely estrogen-containing pills (conjugated estrogens or ethinyl estradiol) or the 17β-estradiol patches in conjunction with oral medroxyprogesterone acetate (Provera) or switching the patient over to conventional oral contraceptives. If the patient is not put on a conventional oral contraceptive, the estrogen (pill or patch) is prescribed days 1-23 of the calendar month with addition of medroxyprogesterone acetate on days 10-23. With this approach, withdrawal bleeding generally occurs between day 23 and the end of the month, although there can be some variability in the timing between patients.

Patients of either sex with hypogonadotropic hypogonadism are potentially fertile, but sex steroid therapy alone is ordinarily not sufficient to initiate gametogenesis, although there are rare cases in males in which testosterone replacement alone has stimulated spermatogenesis. The general approach to fertility induction in either sex involves the addition of either cyclic gonadotropin therapy or pump-driven GnRH therapy at the age of desired conception. *Finally, if hypogonadotropic hypogonadism is present as 1 component of hypopituitarism, it is critical to adequately replace all deficient hormones.* In contrast, patients with primary hypogonadism have intrinsic gonadal damage and are normally infertile.

SUMMARY AND RED FLAGS

Early, late, or asynchronous puberty can indicate underlying pathology. Red flags related to puberty are listed in Table 42.13. Important findings not to miss are listed in Table 42.14.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Normal Pubertal Development

Bourguignon JP. The neuroendocrinology of puberty. *Growth Gen Horm*. 1995;11:1.

Caprio M, Fabbrini E, Isidori AM, et al. Leptin in reproduction. *Trends Endocrinol Metab*. 2001;12:65.

Conte FA, Grumbach MM, Kaplan SL. A diphasic pattern of gonadotropin secretion in patients with the syndrome of gonadal dysgenesis. *J Clin Endocrinol Metab*. 1975;40:670.

Herman-Giddens ME, Slora EJ, Wasserman RC, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research Office Settings network. *Pediatrics*. 1997;99:505.

Kaiserman KB, Nakamoto JM, Geffner ME, et al. Minipuberty of infancy and adolescent pubertal function in adrenal hypoplasia congenita. *J Pediatr*. 1998;133:300.

Kaplowitz PB, Oberfield SE. Reexamination of the age limit for defining when puberty is precocious in girls in the United States: implications for evaluation and treatment. Drug and Therapeutics and Executive Committees of the Lawson Wilkins Pediatric Endocrine Society. *Pediatrics*. 1999;104:936.

Nakamoto JM. Myths and variations in normal pubertal development. *West J Med*. 2000;172:182.

Pyle SI, Waterhouse AM, Greulich WW. *A Radiographic Standard of Reference for the Growing Hand and Wrist. Prepared for the United States National Health Examination Survey*. Chicago: Cleveland Press of Case Western Reserve University, Year Book Medical Publishers; 1971.

Rosenfield RL, Bachrach LK, Chernausek SD, et al. Current age of onset of puberty. *Pediatrics*. 2000;106:622.

Precocious Puberty

Blanco-Garcia M, Evain-Brion D, Roger M, et al. Isolated menses in prepubertal girls. *Pediatrics*. 1985;76:43.

Carel JC, Eugster EA, Rogol A. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics*. 2009;123:4.

Clemons RD, Kappy MS, Stuart TE, et al. Long-term effectiveness of depot gonadotropin-releasing hormone analogue in the treatment of children with central precocious puberty. *Am J Dis Child*. 1993;147:653.

Fenton C, Tang M, Poth M. Review of precocious puberty, part I: gonadotropin-dependent precocious puberty. *Endocrinologist*. 2000;10:107.

Feuillan PP, Jones JV, Barnes K, et al. Reproductive axis after discontinuation of gonadotropin-releasing hormone analog treatment of girls with precocious puberty: long term follow-up comparing girls with hypothalamic hamartoma to those with idiopathic precocious puberty. *J Clin Endocrinol Metab*. 1999;84:44.

Ibáñez L, Dimartino-Nardi J, Potau N, et al. Premature adrenarche—normal variant or forerunner of adult disease? *Endocr Rev*. 2000;21:671.

Kosugi S, Van Dop C, Geffner ME, et al. Characterization of heterogeneous mutations causing constitutive activation of the luteinizing hormone receptor in familial male precocious puberty. *Hum Mol Genet*. 1995;4:183.

Léger J, Reynaud R, Czernichow P. Do all girls with apparent idiopathic precocious puberty require gonadotropin-releasing hormone agonist treatment? *J Pediatr*. 2000;137:819.

Jung H, Carmel P, Schwartz MS, et al. Some hypothalamic hamartomas contain transforming growth factor alpha, a puberty-inducing growth factor, but not luteinizing hormone-releasing hormone neurons. *J Clin Endocrinol Metab*. 1999;84:4695.

Merke DP, Cutler GB Jr. Evaluation and management of precocious puberty. *Arch Dis Child*. 1996;75:269.

Schwindinger WF, Levine MA. McCune-Albright syndrome. *Trends Endocrinol Metab*. 1993;4:238.

Tang M, Fenton C, Poth M. Review of precocious puberty, part II: gonadotropin-independent precocious puberty. *Endocrinologist*. 2000;10:397.

Delayed or Absent Pubertal Development

Achermann JC, Jameson JL. Advances in the molecular genetics of hypogonadotropic hypogonadism. *J Pediatr Endocrinol Metab*. 2001;14:3.

Argente J. Diagnosis of late puberty. *Horm Res*. 1999;51(suppl 3):95.

Brook CGD. Treatment of late puberty. *Horm Res*. 1999;51(suppl 3):101.

Hagen CP, Aksglaede L, Sorensen K, et al. Serum levels of anti-mullerian hormone as a marker of ovarian function in 926 healthy females from birth to adulthood and in 172 Turner syndrome patients. *J Clin Endocrinol Metab*. 2010;95:11.

Topaloglu AK, Reimann F, Guclu M, et al. TAC3 and TACR3 mutations in familial hypogonadotrophic hypogonadism reveal a key role for neurokinin B in the central control of reproduction. *Nat Genet*. 2009;41:3.

43

Short Stature

Omar Ali

Short stature (usually defined as height >2 standard deviations [SD] below the mean for age) and growth failure (a subnormal height velocity that leads to a decline in growth percentiles, usually a height velocity >1.5 SD below the mean for age) are *symptoms, not diseases*. Of the 2, short stature is more likely to be noticed but growth failure is more likely to be pathologic.

Short stature may represent a normal variant or may be a signal of serious physical or emotional illness. Because linear growth is a crucial component of childhood, growth is in many ways an index of childhood well-being. Illnesses, even those not involving aberrations of growth-regulating hormones, often interfere with growth. Therefore, the measurement and charting of heights sequentially on standardized growth charts constitute a central part of a child's medical evaluation and the finding of short stature, particularly if associated with a subnormal height velocity, deserves close attention and appropriate evaluation.

DEFINITION

Short stature is defined as height more than 2 SD below the mean for age, which is at the 2.3 percentile (Fig. 43.1*A, B*). On growth charts (and in clinical practice) it is more common to define short stature as height below the 3rd percentile for age, which is −1.88 SD. Implicit in this definition is the understanding that height is a normally distributed characteristic; therefore, a proportion of normal individuals have heights >2 SD from the mean. Since height is strongly heritable (i.e., a large proportion of the observed variation between individuals is hereditary), stature that is inappropriately low for the child's genetic endowment may also be a cause for concern.

Growth failure is defined as a subnormal rate of growth, or a height velocity that is below the norm for that age. Since sustained height velocity below the 25th percentile is insufficient to maintain a child's position on the growth chart, growth failure is sometimes defined as a height velocity below the 25th percentile for age. Other authorities prefer to use >1.5 SD below the average height velocity for that age as the cutoff.

Short stature should be distinguished from "failure to thrive." The latter term refers primarily to *poor weight gain* in infants and young children (although linear growth may be secondarily affected), whereas short stature refers primarily to subnormal linear growth in childhood and adolescence.

NORMAL GROWTH

Height is highly heritable, but the genetic program underlying this regulation is not fully understood. The growth of individual organs as well as the growth of the skeleton as a whole is regulated by negative feedback mechanisms that slow and eventually stop growth as organs and the organism reach their final size. This gradual deceleration of growth with age does not appear to be driven primarily by changes in the endocrine system since levels of growth hormone (GH) and the insulin-like growth factors remain elevated even as growth slows in the latter part of puberty. The final height and growth pattern of any given individual are affected by subtle variations in large numbers of many genes, while more significant variants in *individual* genes cause the various genetic forms of short stature and **skeletal dysplasias**.

Fetal Growth and Birth Size

A human being experiences his or her most rapid linear growth in the *prenatal* period (growing from near zero to about 50 cm in length in just 9 months). While genetic factors play a major role in postnatal growth, *fetal* growth and birth size mainly reflect maternal and placental factors, including maternal or uterine size, parity, multiparity, nutrition, and placental function. Many congenital disorders such as Turner syndrome and congenital GH deficiency that markedly stunt postnatal growth have only minimal effects on prenatal growth and birth size. Therefore, birth size is generally a poor predictor of the eventual growth pattern in most children. An exception is the neonate who is small for gestational age (SGA) as a result of **intrauterine growth restriction (IUGR)**. While most infants with IUGR (caused by nutritional problems or poor placental function) show catch-up growth (a period of rapid growth that occurs spontaneously after relief from the adverse intrauterine condition that had suppressed the rate of growth), 10-20% remain shorter than expected beyond infancy and early childhood, making IUGR 1 of the possible causes of childhood short stature.

Postnatal Growth Patterns

Infancy is also a period of relatively rapid growth (faster than at any other time in postnatal life). Growth then gradually slows as the infant gets older, declining to its lowest point just before puberty, before accelerating again during the pubertal growth spurt, and finally ending with the completion of linear growth about 5 years after the onset of puberty (Table 43.1 and Fig. 43.2).

Since birth length is mostly determined by maternal and placental factors, size at birth may not reflect the infant's genetic growth potential. It is during the 1st 2 years of life that infants gradually transition from their birth size to their own genetically determined height potential. Therefore, it is normal for infants to shift linear growth percentiles during this period; 65% of infants will exhibit such shifts, moving up or down on the growth chart. By 24 months, these shifts are complete and most children have entered a specific "growth channel" or linear growth percentile in relation to peers and any significant deviation from this channel should evince concern.

After a period of slow but steady growth during childhood, many children experience a further "prepubertal dip" in height velocity,

(See *Nelson Textbook of Pediatrics,* p. 2642.)

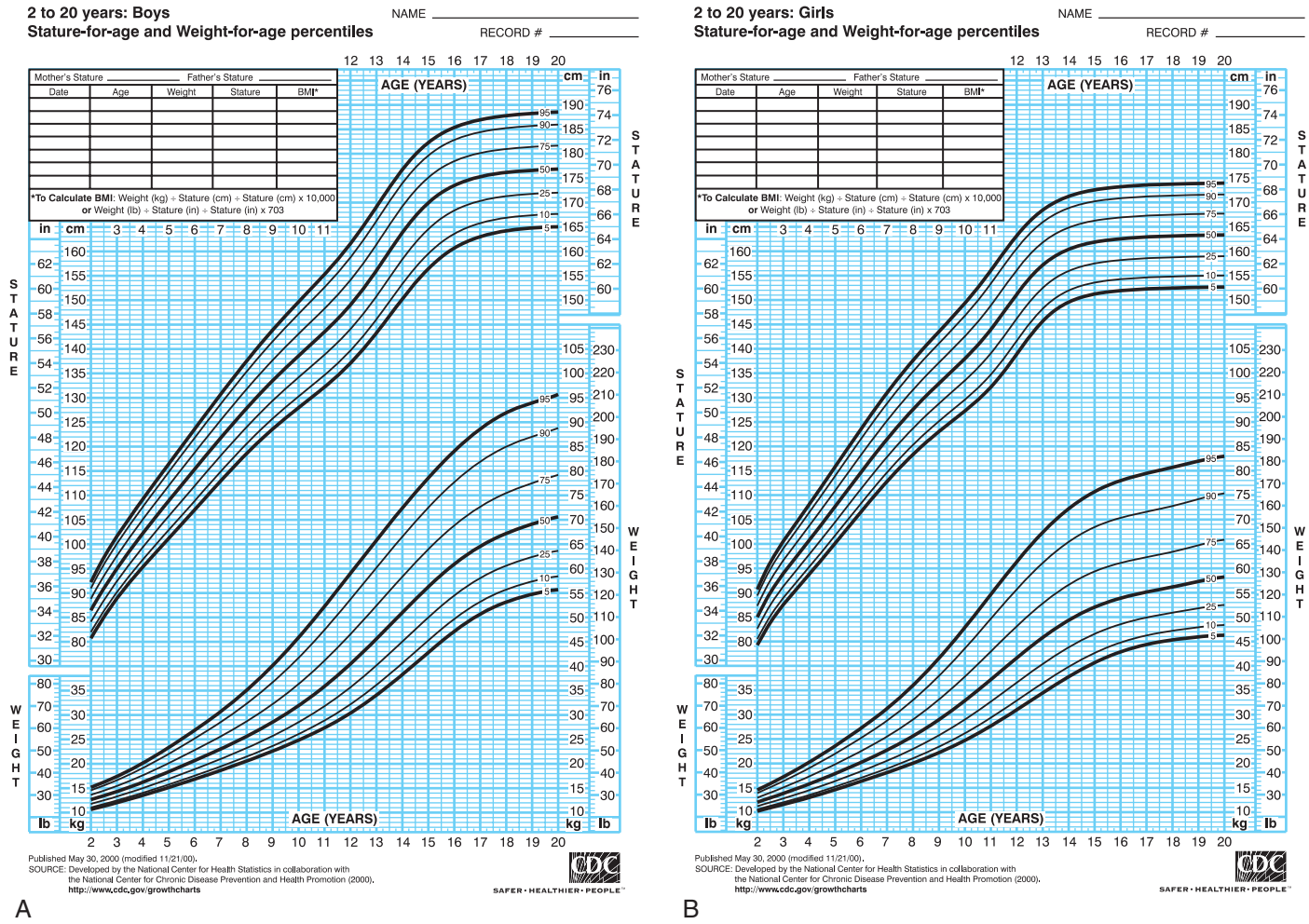


FIGURE 43.1 Centers for Disease Control and Prevention growth charts for the ages 2-20 years. *A,* Boys, stature for age. *B,* Girls, stature for age.

TABLE 43.1 Growth Velocity at Various Ages

Age Interval	Average Height Velocity
Prenatal	66 cm/yr
0-1 yr	25 cm/yr
1-2 yr	12 cm/yr
2-3 yr	8 cm/yr
3-5 yr	7 cm/yr
5–onset of puberty	5-6 cm/yr
Pubertal growth spurt	Girls 8-12 cm Boys 10-14 cm

reaching a nadir just before the onset of puberty. Height velocity then accelerates once again as puberty advances. This acceleration of growth during puberty reaches a peak known as the "pubertal growth spurt." The timing of the pubertal growth spurt differs between girls and boys. Females generally begin pubertal development at 10-11 years of age and their pubertal growth spurt starts coincidentally with breast development and peaks before menarche. For females with an average tempo of puberty, peak growth velocity (8-9 cm/yr) is reached at 11-12 years of age. After menarche (which generally occurs 2-2.5 years after the onset of puberty), the growth rate declines and growth finally stops about 2 years after menarche, with girls gaining an average of 7 cm in height after menarche.

In males, testicular enlargement is generally the 1st sign of puberty and occurs at approximately 11.5 years on average (range, 9-14.3 years). In males with an average tempo of pubertal development, peak growth velocity occurs about 2 years after the onset of puberty (so, later than girls in absolute terms, as well as in terms of the stage of puberty) at approximately 13-14 years, with an average rate of 10.3 cm (4 inches)/yr. It is worth noting that prepubertal males and females grow at very similar rates; the ultimate taller stature of males relative to females is mostly the result of a longer period of growth and a higher peak growth velocity during puberty.

These are the *average* timings of puberty and pubertal growth, but it should be kept in mind that there are large variations in the timing of puberty—and therefore, in growth rates—among individuals of the same age during the period of adolescence.

Because of these characteristic patterns of growth during childhood and adolescence, the rate of growth (centimeters per year or inches per year) is a key variable in evaluating a short child. Growth rates may vary somewhat with season and can be affected by transient illness, but a child should maintain a relatively set growth channel on the linear growth percentile charts after 2-3 years of age. A persistently slow rate of growth in relation to age-appropriate norms is alarming and is likely to reflect an underlying medical disorder.

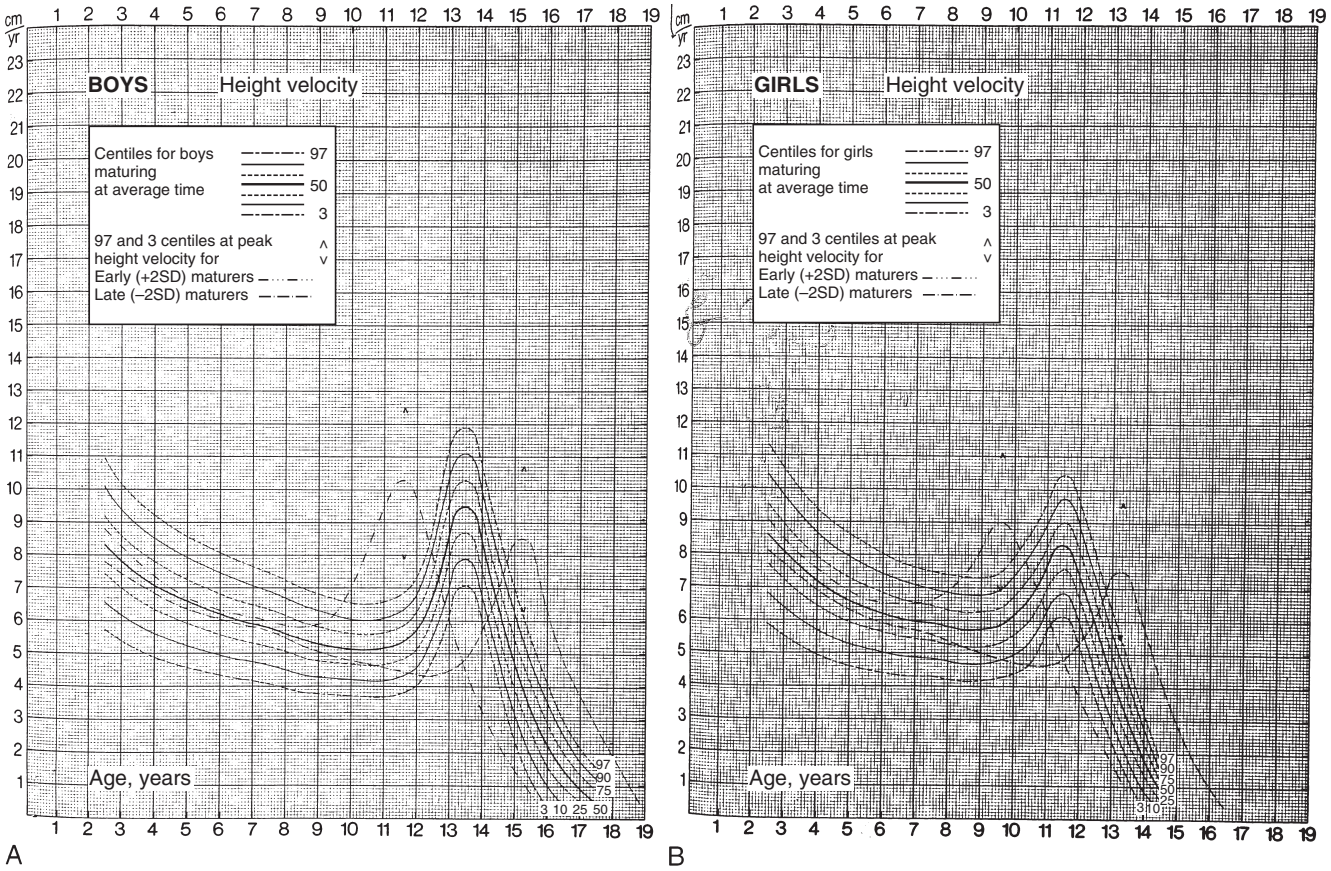


FIGURE 43.2. *A,* Height velocity for American boys. Lines with early velocity refer to the 50th percentile for boys 2 standard deviations (SD) early in growth tempo; lines with late or gradual velocity refer to the 50th percentile for boys 2 SD late in growth tempo. ^ and v, 97th and 3rd percentiles for peak velocities of early and late maturers, respectively. *B,* Height velocity for American girls. Lines with early velocity refer to the 50th percentile for girls 2 SD early in growth tempo; lines with late or gradual velocity refer to the 50th percentile for girls 2 SD late in growth tempo. ^ and v, 97th and 3rd percentiles for peak velocities of early and late maturers, respectively. (Modified from Tanner J, Davies P. Clinical longitudinal standards for height and height velocity in North American children. *J Pediatr.* 1985;107:317-329.)

MEASURING A CHILD

Stature is evaluated as supine length until 2 years of age and as standing height thereafter (Fig. 43.3). For measurement of supine length, an infant lies on an inflexible ruled horizontal surface, at 1 end of which 1 person holds the infant's head in contact with a fixed board; a 2nd person extends the infant's legs as much as possible and brings a movable plate in contact with the infant's heels. Recumbent measurements average 1 cm (0.4 inch) more than standing height.

After 2 years of age, children are measured standing and barefoot with a device such as a Harpenden stadiometer; a vertical metal bar is affixed to an upright board or wall, and height is measured at the top of the head by a sliding perpendicular plate or block. *Measurements of length using pen marks on the examining table at the head and foot of an infant are often grossly inaccurate, as are height measurements using a flexible metal rod atop a standard weight scale.*

With the use of optimal techniques, the variation in measurement among observers is less than 0.3 cm (0.1 inch). It is then possible to determine changes in height over 3- to 4-month intervals to estimate the annualized growth rate. However, because of normal seasonal variations in growth rates, a longer interval between measurements (6-12 months) is more reliable in the calculation of height velocity.

Measurements are then plotted on standard growth charts; it is recommended that World Health Organization (WHO) growth charts be used for infants from birth to 2 years of age and Centers for Disease Control and Prevention (CDC) growth charts for children from ages 2-18 years (see Fig. 43.1). These CDC and WHO growth charts are available at: http://www.cdc.gov/growthcharts/ and http://www.who.int/childgrowth/standards/en/.

Calculated growth rates (centimeters per year or inches per year) should be evaluated in relation to age-related norms with growth velocity charts for North American children for children over 2 years of age (see Fig. 43.2).

Body Proportions

Apart from linear height, it is also useful to assess the upper-to-lower segment ratio (U/L) (Fig. 43.4) and the arm span. The U/L is determined by measuring the lower segment (vertical distance between the symphysis pubis and the floor, with the child standing) and the upper segment (the difference between the lower segment and height). Arm span is the distance between the outstretched middle fingertips with the child standing against a flat board or wall. The U/L and arm span are used to determine whether the child is normally proportioned or not (in Europe, it is more common to assess sitting height versus standing height for the same purpose).

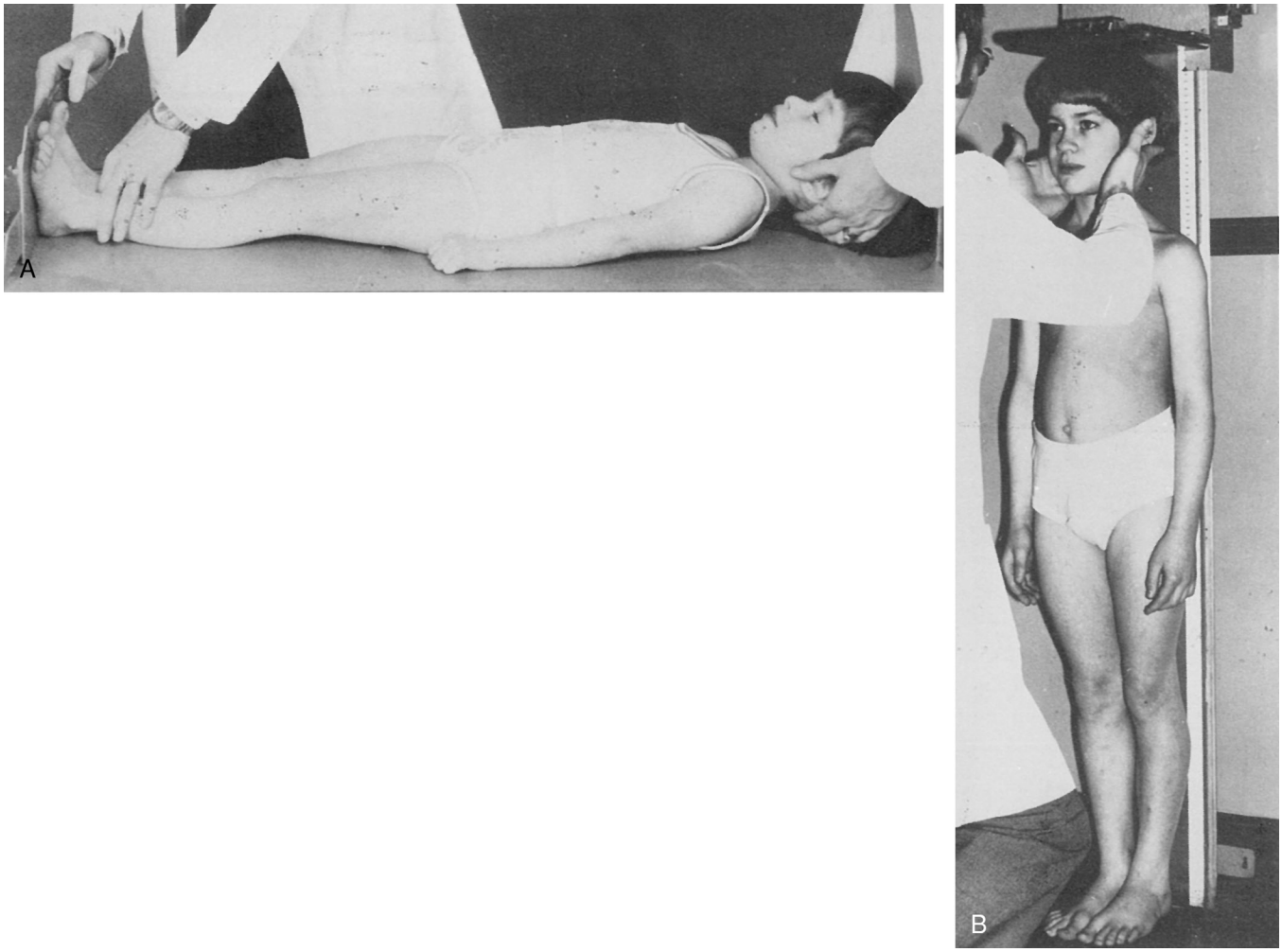


FIGURE 43.3 *A,* Technique for measuring length. *B,* Technique for measuring erect height. (From Wilson JD, Foster DW, eds. *Williams Textbook of Endocrinology*. 8th ed. Philadelphia: WB Saunders; 1992: 1106-1107.)

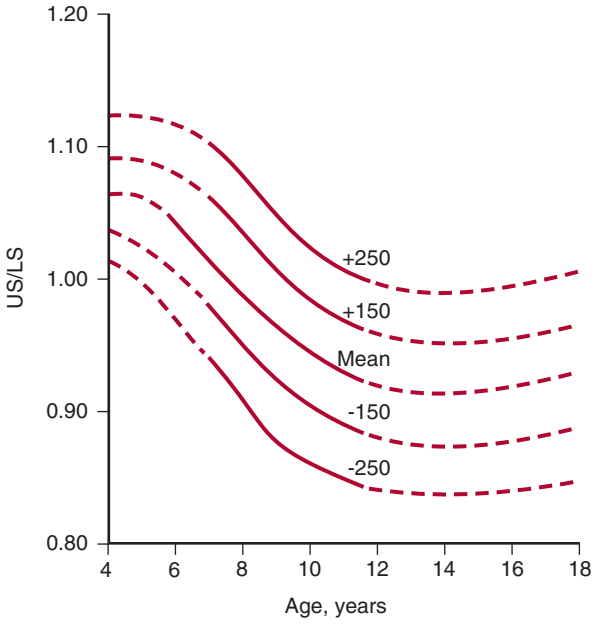


FIGURE 43.4. Normal upper-to-lower segment ratios (US/LS) for white children. (From McKusick V. *Hereditable Disorders of Connective Tissue*. 4th ed. St. Louis: CV Mosby; 1972.)

The U/L gradually declines with age throughout childhood. Since infants have relatively short legs, the U/L is high (an average of 1.7) at birth. It then declines throughout childhood as the legs increase in length relative to the upper body, decreasing to a mean of 0.9 by late puberty (in males; in females, the ratio may be closer to 0.95). The arm span as compared to the height is another measure of body proportions and is normally shorter than the height in younger children and increases to become slightly longer than the height by late puberty (about 5 cm more than height in boys, 1.2 cm more than height in girls). Deviations from the norm in the U/L and the arm span may point to conditions such as skeletal dysplasias, Turner syndrome, or long-standing hypothyroidism (increased U/L segment ratio, i.e., relatively short extremities) and radiation-induced spinal damage or genetic disorders such as Klinefelter or Marfan syndromes and homocystinuria (low U/L segment ratio, due to a relatively short trunk or unusually long extremities).

Weight should also be considered in relation to a child's stature. Undernutrition is generally caused by nonendocrine factors (poor nutritional intake, malabsorption, systemic illness) and typically leads to a decrease in weight before a decrease in linear growth. Obesity in childhood is usually exogenous; exogenous obesity is generally associated with an accelerated growth rate. In contrast, endocrine disorders that cause poor growth and short stature are often associated with weight gain and obesity (Cushing syndrome, hypothyroidism, and in

some instances, GH deficiency). Therefore, the obese child who has a slow growth velocity is more likely to have an endocrine cause of short stature, while the undernourished child with short stature likely has short stature secondary to poor weight gain and is unlikely to have an endocrine disorder.

Familial and Genetic Factors

Both parental height and parental pattern of growth are key determinants of a child's growth pattern. This strong familial influence on height is not detectable at birth but is manifested by 2-3 years of age. Final adult height is strongly heritable with heritability estimates ranging from 0.8-0.95 (i.e., 80-95% of the observed variation is explained by hereditary rather than environmental factors). The mid-parental height (MPH) is used as a measure of the child's genetic growth potential and is an average of the height of both parents *after correcting for sex*. Since the average adult male is taller than the average adult female by 13 cm (5 inches), 13 cm is added to the mother's height in the case of a male child, while 13 cm is subtracted from the father's height in the case of a female child; the parental heights, after correction for sex, are then averaged to obtain the MPH.

Thus MPH is determined in the following manner:

Males: [father's height in cm + (mother's height in cm + 13 cm)]/2

Females: [(father's height in cm − 13 cm) + mother's height in cm]/2

The MPH is a good index of the child's genetic height potential, but tends to become less accurate if 1 parent is unusually tall or short; that is, the offspring of an exceptionally tall parent or exceptionally short parent will be closer to the average height than is predicted by the MPH because of the phenomenon of *regression to the mean*.

In addition to the influence on final adult height, parents' *patterns* of growth are also often repeated in their children. In particular, many men who were "late bloomers" with delayed onset of puberty and delayed but normal growth spurts have sons with similar growth patterns.

Ethnic Factors and Secular Trend

The average height of various populations across the globe is not the same; in the current era, Northern European populations are taller than many (but not all) other ethnic groups, and it therefore seems to make sense to use population-specific standards of growth because a child from a generally short ethnic group may be labeled as "short stature" by Northern European standards, but may be normal for his or her own ethnic group. Two additional observations need to be kept in mind:

1. Migrants from countries where the average height is lower tend to have children who are taller than their parents when they move to a country with a higher standard of living. This indicates that at least some of the observed height difference may be environmental (most likely related to nutrition and childhood disease burden) and that this height difference may shrink or disappear in subsequent generations.
2. The Northern European populations were themselves much shorter in the 18th and 19th centuries and average heights have steadily increased as living standards improved (reflecting improvements in nutrition and other public health measures). This "secular trend" in height slows down and plateaus over time, but is much more marked in populations that have recently seen an improvement in living standards.

Thus practitioners should make allowances for ethnic differences in height when evaluating children from different ethnic backgrounds, but should not automatically assume such differences as the sole explanation for short stature in children from historically shorter populations. Growth velocity in particular should not be abnormal even in historically shorter populations, and a subnormal growth velocity should trigger an evaluation in the same way as it would in children from a Northern European background.

General Well-Being

Because growth is a barometer of a child's health, general well-being and freedom from serious illness are necessary for a child to achieve his or her genetic growth potential. Chronic illnesses that are not primarily problems of stature often interfere with growth secondarily, and short stature may be the presenting feature of such conditions as inflammatory bowel disease, celiac disease, and renal disease.

Psychologic Factors

Under normal circumstances, emotional and psychologic factors do not have a great effect on growth. However, in certain cases, emotional deprivation can lead to very significant growth failure (sometimes labeled "deprivation dwarfism" or "psychosocial dwarfism") via mechanisms that are still poorly understood.

Endocrine Regulation of Growth

GH is produced by the anterior pituitary under the control of GH-releasing hormone (GHRH) from the hypothalamus, and is essential for normal growth in childhood and adolescence (though it appears to play a relatively small role in prenatal growth). GH is secreted in brief pulses and peak secretion occurs during sleep, so random serum levels have little utility in the evaluation of GH deficiency except in the newborn period (when random GH levels are usually elevated, and a level below 7 ng/mL is very likely to reflect GH deficiency).

GH exerts its growth-promoting effect through stimulating the production of **insulin-like growth factor 1 (IGF-1)** (primarily in the liver, but also in some target tissues) as well as via direct actions of GH on bone. Most circulating IGF-1 is bound to IGF-binding proteins, with the largest proportion being bound in a ternary complex with **IGF-binding protein-3 (IGFBP-3)** and a protein named the acid-labile subunit (ALS). Because IGF-1 levels in the blood are stable throughout the day and reflect the integrated effect of GH secretion, measurement of IGF-1 is often used as a surrogate measure of GH secretion.

Thyroid hormone also has a relatively limited role in prenatal growth, but is absolutely essential for normal postnatal linear growth, both via direct actions on the epiphyseal growth plate and via a permissive effect on GH secretion. **Hypothyroidism** can therefore lead to very profound growth failure and an evaluation of thyroid hormone status is essential in the investigation of growth failure.

Glucocorticoids do not play any significant role in promoting growth, but are powerful inhibitors of growth when present in excess. Persistent exposure to excess corticosteroids (whether endogenous or exogenous) can lead to very severe growth failure (along with significant weight gain). Deficiency of glucocorticoids generally does not adversely affect growth if the child is otherwise healthy.

Sex steroids mediate the pubertal growth spurt (see Chapter 42). This involves direct effects of sex steroids on bone growth as well as steroid-induced amplification of GH secretion. Most of the bone-maturing action of sex steroids is mediated by estrogen in *both* sexes; while testosterone has some direct effects on bone strength and thickness, most of the effects of testosterone on linear growth and the maturation of growth plates in males occur via the action of estrogen produced by the peripheral conversion of testosterone. Consequently, even in males, bone maturation can be affected by genetic defects in the production or action of estrogen, as well as by pharmacologic inhibition of this pathway (e.g., by using aromatase inhibitors that block the conversion of testosterone to estrogen). **Sexual precocity** (true precocious puberty, exogenous exposure, or congenital adrenal

hyperplasia) tends to accelerate linear growth transiently as a result of premature or excessive production of sex steroids (or both) (see Chapter 42). But if left untreated, these conditions advance osseous maturation, leading to premature epiphyseal fusion and a short final adult height. The absence of sex steroids (hypogonadism) in the absence of other abnormalities blunts the pubertal growth spurt, but tends not to limit final height, as bone maturation and epiphyseal fusion are also delayed by the lack of estrogen in these patients.

Bone Age

Osseous maturation follows a very predictable pattern during the growth and development of the child, and a radiograph of the *non-dominant hand* can be used to assess bone age (i.e., the degree of maturation of the bones compared to age-matched standards). Bone age is usually estimated by comparing the child's radiologic findings with a standard set of radiologic images, or by using various scoring algorithms. These readings are subject to observer bias and error but are still useful as long as this inherent subjectivity is kept in mind. Bone age is very closely correlated with pubertal maturation and an assessment of bone age can be especially useful in cases of precocious puberty, delayed puberty, and constitutional growth delay. Except in cases of precocious puberty, bone age is rarely useful in the evaluation of short stature in a child less than 5 years of age.

CAUSES OF SHORT STATURE

Understanding the factors that influence childhood growth leads directly to an understanding of the causes of short stature and to the differential diagnosis of short stature for an individual child (Tables 43.2, 43.3, 43.4, 43.5, and 43.6). While a very large number of conditions can potentially lead to short stature and growth failure, the vast majority of children with short statures are either normal variants (familial short stature, constitutional delay of growth and puberty) or have no discernible cause (idiopathic short stature [ISS]). It is also important to remember that the child with *growth failure* is far more likely to have an underlying pathology than a child who happens to be short but has a normal growth velocity.

Normal Variants

The 2 most frequent causes of short stature in children are **familial short stature** and **constitutional delay of growth and puberty**. These are considered normal variants and their recognition can help avoid expensive and unnecessary testing and interventions.

Familial Short Stature

The term "familial short stature" is usually reserved for familial forms of mild-to-moderate short stature that do not have a specific identifiable genetic defect; since hundreds of genes play a role in growth, this height potential likely reflects the influence of multiple loci of small effect or a few loci of relatively moderate effect. Genetic disorders that result in severe short stature, or that are associated with other abnormal physical findings (syndromes), or that are caused by known genetic defects, are conventionally treated separately from familial short stature.

The child's height is in keeping with the genetic endowment, and the child is otherwise healthy. Typically, 1 or both parents (and often other family members) are about 1.5-2 SD below the mean in height. This relatively short genetic potential is reflected in the short MPH, and if the child continues to grow along his or her current percentile, he or she would fall within 9 cm of this height (approximately within 2 SD of the MPH); by age 2, the child is usually noted to be small in relation to peers. Although the growth channel is low, it should *parallel*

TABLE 43.2 Classification of Growth Retardation

- I. PRIMARY GROWTH ABNORMALITIES
  - A. Osteochondrodysplasias (see Table 43.3)
  - B. Chromosomal abnormalities
    - Turner syndrome
    - Noonan syndrome
    - Prader–Willi syndrome
    - Russell–Silver syndrome
    - SHOX haploinsufficiency
- II. SECONDARY GROWTH DISORDERS
  - A. Malnutrition
  - B. Chronic disease
    - Cardiac disorders
      - Left-to-right shunts
      - Congestive heart failure
    - Pulmonary disorders
      - Cystic fibrosis
    - Gastrointestinal disorders
      - Inflammatory bowel disease
      - Celiac disease
      - Malabsorption
      - Chronic diarrhea
    - Hematologic disorders
      - Chronic anemia (including sickle cell disease, thalassemias)
    - Renal disorders
      - Chronic renal failure
      - Renal tubular acidosis
    - Immunologic disorders
      - Congenital immunodeficiency
      - HIV
  - C. Intrauterine growth restriction
  - D. Endocrine disorders
    - Hypothyroidism
    - Cushing syndrome
    - Pseudohypoparathyroidism
    - Vitamin D–deficient or –resistant rickets
- III. IGF DEFICIENCY (see Tables 43.4, 43.5)
  - A. Secondary IGFD
    - GH deficiency due to hypothalamic dysfunction
    - GH deficiency due to pituitary GH deficiency
  - B. Primary IGFD (GH insensitivity)
    - Primary GH insensitivity–GH receptor (GHR) defects
    - Secondary GH insensitivity (STAT5B)–GHR signal transduction defects
    - Primary defects of IGF synthesis
    - Primary defects of IGF transport/clearance (ALS)
  - C. IGF resistance
    - Defects of the IGF-1 receptor
    - Postreceptor defects
- IV. IDIOPATHIC SHORT STATURE (ISS)
  - A. Constitutional delay of growth and puberty with normal height prediction
  - B. ISS with delayed bone age and tempo of puberty
  - C. ISS with normal bone age and tempo of puberty
  - D. ISS with a familial component
  - E. ISS without a familial component

GH, growth hormone; IGF, insulin-like growth factor; GHRH, growth hormone–releasing hormone; SHOX, Short Stature Homeobox; STAT5B, signal transduction and activator of transcription 5B; HIV, human immunodeficiency virus; ALS, acid labile subunit. Modified from Sperling MA. *Pediatric Endocrinology*. 4th ed. Philadelphia: Elsevier; 2014:325.

TABLE 43.3 Nosology and Classification of Genetic Skeletal Disorders (2015)

- FGFR3 chondrodysplasia group
- Type 2 collagen group
- Type 11 collagen group
- Sulphation disorders group
- Perlecan group
- Aggrecan group
- Filamin group and related disorders
- TRPV4 group
- Ciliopathies with major skeletal involvement
- Multiple epiphyseal dysplasia and pseudoachondroplasia group
- Metaphyseal dysplasias
- Spondylometaphyseal dysplasias (SMD)
- Spondylo-epi-(meta)-physeal dysplasias (SE[M]D)
- Severe spondylodysplastic dysplasias
- Acromelic dysplasias
- Acromesomelic dysplasias
- Mesomelic and rhizo-mesomelic dysplasias
- Campomelic dysplasia and related disorders
- Slender bone dysplasia group
- Dysplasias with multiple joint dislocations
- Chondrodysplasia punctata (CDP) group
- Neonatal osteosclerotic dysplasias
- Osteopetrosis and related disorders
- Other sclerosing bone disorders
- Osteogenesis imperfecta and decreased bone density
- Abnormal mineralization group
- Lysosomal Storage Diseases with Skeletal Involvement (Dysostosis Multiplex group)
- Osteolysis group
- Disorganized development of skeletal components group
- Overgrowth (tall stature) syndromes with skeletal involvement
- Genetic inflammatory/rheumatoid-like osteoarthropathies
- Cleidocranial dysplasia and related disorders
- Craniosynostosis syndromes
- Dysostoses with predominant craniofacial involvement
- Dysostoses with predominant vertebral with and without costal involvement
- Patellar dysostoses
- Brachydactylies (without extraskeletal manifestations)
- Brachydactylies (with extraskeletal manifestations)
- Limb hypoplasia–reduction defects group
- Ectrodactyly with and without other manifestations
- Polydactyly-Syndactyly-Triphalangism group
- Defects in joint formation and synostoses

From Bonafe L, et al. Nosology and classification of genetic skeletal disorders: 2015 revision. *Am J Med Genet A.* 2015;167A(12):2869-2892.

the normal growth curve from that point onward. Continued deviation away from the normal growth curve (indicating a subnormal growth velocity) is *not* typical and should raise concerns about a disorder other than familial short stature. Stature that is extremely low (2.5-3 or more SD below the mean) raises concerns even if the parents are short, since this degree of short stature may reflect a specific genetic cause of short stature (e.g., a mild defect in GH secretion or action, or a form of hypochondroplasia) in the parents as well as the child.

The review of systems is generally negative in the otherwise healthy child, as are the physical examination findings (aside from short stature). The height-to-weight ratio, body proportions, muscularity,

TABLE 43.4 Established Genetic Defects of the GH-IGF Axis Resulting in IGF Deficiency

Mutant Gene	Inheritance	Phenotype
HPA		Developmental abnormalities
HESX1	AR	Septo-optic dysplasia; variable involvement of pituitary hormones
PROP1	AR	GH, PRL, TSH, LH, FSH deficiencies; variable ACTH deficiency
POU1F1 (Pit1)	AR, AD	GH, PRL deficiency; variable degree of TSH deficiency
RIEG	AD	Rieger syndrome
LHX3	AR	GH, TSH, LH, FSH, prolactin deficiencies
LHX4	AD	GH, TSH, ACTH deficiencies
SOX3	XL	GH deficiency, intellectual disability
GLI2	AD	Holoprosencephaly, hypopituitarism
GLI3	AD	Pallister-Hall syndrome, hypopituitarism
Isolated Growth Hormone Deficiency		
GHRHR	AR	IGHD, type IB form of IGHD
GHS-R	AD	GHD and ISS
GH1	AR	Type IA form of IGHD
	AR	Type IB form of IGHD
	AD	Type II form of IGHD
	X-linked	Type III form of IGHD; hypogammaglobulinemia
	AD	Bioinactive GH molecule
Growth Hormone Insensitivity		
Growth Hormone Receptor		
Extracellular domain	AR, AD	IGF-1 deficiency; decreased or normal GHBP
Transmembrane	AR	IGF-1 deficiency; normal or increased GHBP
Intracellular domain	AD	IGF-1 deficiency; normal or increased GHBP
IGF		
IGF1	AR	IGF-1 deficiency; IUGR and postnatal growth failure
STAT5B	AR	IGF-1 deficiency, variable immune defect, hyperprolactinemia, chronic pulmonary infections, recurrent eczema
ALS	AR	IGF-1 deficiency; variable postnatal growth failure, delayed puberty

HPA, hypothalamic pituitary; ACTH, adrenocorticotropic hormone (corticotropin); AD, autosomal dominant; AR, autosomal recessive; FSH, follicle-stimulating hormone; GH, growth hormone; GHBP, GH-binding protein; GHD, growth hormone deficiency; GHRHR, GH-releasing hormone receptor; IGF, insulin-like growth factor; IGHD, isolated GHD; IUGR, intrauterine growth restriction; LH, luteinizing hormone; PRL, prolactin; TSH, thyroid-stimulating hormone; ALS, acid labile subunit.

From Sperling MA. *Pediatric Endocrinology*. 4th ed. Philadelphia: Elsevier; 2014:333.

and pubertal development are normal for age. Abnormalities found on review of systems or physical examination should prompt consideration of other diagnoses.

Laboratory studies are not mandatory, but if done are all normal. The bone age is also normal, and this suggests that the short child's "room for growth" is not greater than that of other children of the same age. Prediction of adult height can be made on the basis of bone age, but the accuracy is variable; the predicted height is within 9 cm of the MPH.

Constitutional Delay of Growth and Puberty

Constitutional delay of growth and puberty is a growth pattern that is also considered a variant of normal. These children appear to have a slowed maturational pattern and their bone age is delayed relative to their peers. As part of this slowed maturation, they also enter puberty later than their peers. This variant occurs in both sexes but is more common in males and is recognized predominantly in them for this reason, as well as for cultural reasons.

These children often begin to show moderate short stature (height, −1.5 to −2.5 SD) during early-to-middle childhood but are otherwise healthy. They have delayed onset of puberty and therefore a delayed growth spurt. One or both parents (or other family members) may have a history of delayed puberty and a late adolescent growth spurt, with eventual cessation of growth during late adolescence or even into the 3rd decade of life. The affected parent usually is of normal adult stature. Otherwise, the history and review of systems are negative. The physical examination findings are normal except for delayed onset of puberty in children of an appropriate age.

Laboratory tests are not mandatory but are normal if performed, with the important exception of a delayed bone age (bone age < chronologic age). It is important to note that IGF-1 levels normally increase with onset of puberty and should be compared with standards for the child's pubertal stage and bone age rather than his or her chronologic age. A delayed bone age suggests that the child has more "room to grow" than the average age-matched child and that the child is likely to reach an adult height taller than that suggested by the current height percentile. Some children have *mixed* familial short stature and constitutional delay in growth and development; they tend to have both delayed puberty and a short predicted adult height.

Chronic illness may mimic constitutional delay in growth and development and should be considered in the differential diagnosis. It is sometimes difficult to distinguish children with constitutional delay in growth and development from the more unusual condition of central (hypothalamic/pituitary) hypogonadism; a positive family history of delayed but normal puberty and growth, a normal sense of smell (to exclude Kallmann syndrome), and normal neurologic findings favor constitutional delay. Evaluation for permanent **central hypogonadism** is indicated if puberty fails to begin by the age of 13 years in females or 14 years in males, particularly if there is no family history of constitutional growth delay.

Females with delayed puberty are more likely to have an underlying pathologic cause, so the threshold for investigation is lower in females. On the other hand, benign constitutional delay is common in males,

TABLE 43.5 Proposed Classification of Growth Hormone (GH) Insensitivity

Primary GH Insensitivity (Hereditary Defects)

1. GH receptor defect (may be positive or negative for GH-binding protein)
   - Extracellular mutation (e.g., Laron syndrome)
   - Cytoplasmic mutation
   - Intracellular mutation
2. GH signal transduction defects (distal to the cytoplasmic domain of the GH receptor)
   - STAT5B mutations
3. Insulin-like growth factor-1 defects
   - IGF-1 gene deletion
   - IGF-1 transport defect (acid labile subunit [ALS] mutation)
   - IGF-1 receptor defect
4. Bioinactive GH molecule (responds to exogenous GH)

Secondary GH Insensitivity (Acquired Defects)

- Circulating antibodies to GH that inhibit GH action
- Antibodies to the GH receptor
- GH insensitivity caused by malnutrition, liver disease, catabolic states, diabetes mellitus
- Other conditions that cause GH insensitivity

From Sperling MA. *Pediatric Endocrinology*. 4th ed. Philadelphia: Elsevier; 2014:347.

TABLE 43.6 Genetic Syndromes Associated with Short Stature

Selected Genetic Disorders Associated with Short Stature

Condition	Genetics	Features (Not All Are Present in Every Case)
Turner syndrome	45,XO and variants	Short stature, lymphedema of hands and feet at birth, low posterior hairline, webbed neck, shield chest, cubitus valgus, clinodactyly, short 4th metacarpal, Madelung deformity
Noonan syndrome	*PTPN11, SOS1, RAF1, KRAS, SHOC2, BRAF, NRAS, RIT1, CBL, KATB6, LZTR1, SOS2*	Short stature, hypertelorism, downslanting eyes, low-set ears, webbed neck, chest deformity (pectus excavatum), cryptorchidism, intellectual disability, lymphedema
Prader–Willi syndrome	Paternal chromosome 15 (15q11.2-13) defects	Initial hypotonia and failure to thrive, then marked hyperphagia and obesity, hypogonadism, small hands and feet, thick saliva, intellectual disability
SHOX haploinsufficiency	SHOX gene mutations	Short stature, Madelung deformity, mesomelia, cubitus valgus, dislocation of the ulna
Russell–Silver syndrome	Imprinting control region on paternal chromosome 11p15.5; maternal uniparental disomy of chromosome 7	IUGR, age appropriate head circumference with short stature, triangular facies, downturned corners of the mouth, prominent forehead, 5th finger clinodactyly, limb length asymmetry

SHOX, Short Stature HomeoboX gene; IUGR, intra-uterine growth restriction; PTNP11. Protein Tyrosine Phosphatase Nor-receptor type 11.

and in the presence of a positive family history, further evaluation may be delayed even beyond the age of 14 years. The possibility of **central hypogonadism** becomes stronger the longer the onset of puberty is delayed, but it should be noted that cases of spontaneous development of normal puberty can occur up to and even beyond the age of 18.

In most cases, only reassurance and an explanation of the growth pattern are required, but if the parents *and* the child are eager to hasten pubertal development (usually because of involvement in sports or because of bullying and other psychosocial considerations), then a short course of low-dose sex steroids can accelerate the onset of puberty. Intervention does not change the final height but hastens the child's progression to that height. Treatment options are discussed in detail later in this chapter.

Idiopathic Short Stature

ISS is a clinical description rather than a disease. ISS is generally considered a normal variant of growth (since pathologic causes are excluded by definition). The exact definition varies from country to country; in the United States, the Food and Drug Administration (FDA) uses a definition of height >2.25 SD below the age mean (which is the 1st percentile for height) for children in whom no specific cause of short stature has been identified after a thorough evaluation. This corresponds to an adult height <160 cm (5 feet 3 inches) for males and <150 cm (4 feet 11 inches) for females.

In many cases, these children have familial short stature and their height is not inappropriate for parental height. But in most definitions, they are included in the category of ISS because the purpose of the definition was to identify children who may not have any pathology, but whose short stature per se constitutes a possible reason to treat them with GH. This notion remains controversial because there is no universal agreement about the possible psychosocial or economic impact of ISS. Those who support treatment of these children argue that such a degree of short stature may have adverse psychologic, social, and economic consequences and deserves to be treated even if no underlying pathology is identified. Opponents argue that there is no convincing evidence that short stature of this degree itself leads to any significant handicaps that would justify prolonged invasive therapy with an extremely expensive medication that may itself have future adverse health consequences. Third-party payers often regard such treatment as cosmetic and may not approve requests for therapy. It should be noted that in most cases, there are no consistent adverse effects of short stature on quality of life in children at or just below the 1st percentile; however, some studies do indicate that practical and psychosocial difficulties increase in those with extreme degrees of short stature.

ISS is a diagnosis of exclusion; history, physical examination, laboratory studies, and imaging studies do not reveal any specific cause of short stature in an otherwise normal child. How much investigation is needed before a child can be labeled ISS remains a matter of controversy and clinical practice can vary significantly within and between different countries. Treatment with GH was approved by the FDA in 2003 but remains controversial and may not be approved by third party payers. Treatment is more likely to be beneficial in those with more extreme degrees of short stature. A predicted adult height less than 136 cm (about 4 feet 6 inches) in females and less than 149 cm (about 4 feet 11 inches) in males is *very* likely to be associated with quality of life issues and certainly deserves treatment even in the absence of any underlying cause.

Small for Gestational Age

Children who are born SGA usually catch up with their peers by 2-3 years of age, but 10-20% of children born SGA will fail to catch up and will continue to be below the 3rd percentile. This is more likely in children who are born premature as well as SGA and in those most severely affected at birth. The mechanism underlying this failure of catch-up growth is not well understood. Children with IUGR also have an increased future risk of metabolic disorders such as type 2 diabetes. Children who were SGA typically have normal proportions and no other physical findings; in some cases, the IUGR is 1 component of a genetic syndrome (see Tables 43.2 and 43.6) and other features of the syndrome are present.

Children who were born SGA with poor postnatal growth typically have normal or even elevated GH levels but lower average values of IGF-1 and IGFBP-3 (though most are still in the normal range), indicating some degree of GH resistance in at least some of these children. GH treatment increases final height by about 1 SD on average (about 6 cm) if started early in life and continued for at least 7 years. In the United States, treatment is approved by the FDA for children who were born SGA and whose height remains >2 SD below the mean at age 2. In Europe, treatment is approved for children whose height is >2.5 SD below the mean by age 4. These children can be mildly GH-resistant and may therefore require GH doses at the higher end of the dose range. Since individual response varies, GH treatment can be started at the usual dose (30-50 μg/kg/day) and then increased if needed based on growth response and IGF-1 levels.

Endocrine Disorders

Growth Hormone Deficiency

GH is essential for postnatal growth, and children who lack it are extremely stunted. GH deficiency may be congenital or acquired. The **congenital** form may be associated with other pituitary hormone deficiencies (multiple pituitary hormone deficiency [MPHD]) and may be associated with **midline craniofacial defects** (absence of the septum pellucidum and optic nerve hypoplasia [septo-optic dysplasia], cleft palate, holoprosencephaly, single central incisor). Genetic testing has revealed underlying genetic mutations in transcription factors involved in the development of the anterior pituitary in many (but not all) of these cases (see Table 43.4). Isolated congenital GH deficiency is relatively rare (i.e., it is more common to see congenital GH deficiency as a component of MPHDs). Some of these isolated cases are related to genetic abnormalities in the GH-releasing hormone receptor (GHRHR mutations) and others to mutations in the GH gene itself. Mutations in the GH receptor or in downstream signaling molecules lead to various rare forms of GH resistance. Mutations in the IGF-1 gene, in the ALS protein (a component of the IGF–IGFBP-3–ALS ternary complex), and in the IGF-1 receptor can lead to growth failure on rare occasions. But most cases of GH deficiency discovered in the course of evaluation of short stature are not due to known genetic mutations in the GH-IGF axis and are regarded as **idiopathic**.

GH deficiency may also be **acquired** secondary to birth injury, head injury, midline tumors (most commonly craniopharyngioma), and cranial irradiation. Most such cases are associated with deficiencies of other pituitary hormones, but isolated GH deficiency may also occur after such insults. Injury to the anterior pituitary during childhood most likely affects GH secretion, followed by gonadotropins, thyroid-stimulating hormone (TSH), and adrenocorticotropic hormone (ACTH) in that order (in adults, gonadotropins may be affected more than GH). It is therefore possible to see isolated GH deficiency after a cranial injury, while it is very unusual to see central hypothyroidism or adrenal insufficiency in the absence of GH deficiency.

Growth Hormone Deficiency Presenting in the Neonatal Period

Isolated congenital GH deficiency that *presents* in the newborn period is uncommon. If GH deficiency presents in the newborn period, it

(See *Nelson Textbook of Pediatrics,* p. 2640.)

usually does so in the setting of MPHD. It may be associated with midline defects (central incisor, septo-optic dysplasia, holoprosencephaly, cleft palate). Affected infants are often normal in birth size, although statistical analysis suggests that as a group, they are somewhat small. These newborns have an increased incidence of **hypoglycemia** and may also have **jaundice** with a hepatitis-type picture. Males frequently have **micropenis**; cryptorchidism may be seen in cases with concomitant gonadotropin deficiency. Hypoglycemia may be worsened by associated ACTH deficiency, which may also lead to hypotension and hypothermia. Associated central **hypothyroidism** may also cause hypothermia, poor growth, poor feeding, and prolonged jaundice.

Laboratory testing reveals a low random GH level (this is the only stage in life at which a random GH level is useful; levels less than 7 ng/mL in the 1st week of life are considered abnormal), as well as low levels of IGF-1 (not very useful because the normal range overlaps with the deficient range) and low IGFBP-3. Associated central hypothyroidism, if present, is suggested by a low T_4 and an *inappropriately normal* (or even slightly elevated) TSH level; one would have expected the TSH level to be markedly elevated in a baby with low T_4, but instead it is either normal or just minimally elevated. A low cortisol level (especially in the face of hypoglycemia or other stressful situations) and low or low-normal ACTH level may hint at central ACTH deficiency; an ACTH stimulation test may be required to confirm the diagnosis. Gonadotropin levels may be affected, and if so, will remain low instead of rising in the 1st 2-3 months of life as they normally do in infants. GH stimulation testing is *not* required for the diagnosis of GH deficiency in the newborn period. Genetic testing may show mutations in 1 of several genes involved in the normal development of the pituitary and the GH-producing cells of the pituitary *(POUF1*, *PROP1*, *HESX1*, *LXH3*, *LHX4*, *SOX3)* (see Table 43.4). Treatment with GH (*and* with other pituitary hormones that are frequently deficient in these neonates) will permit normal growth and development and prevent hypoglycemia and other complications.

Growth Hormone Deficiency in Childhood

Most male children who are diagnosed with GH deficiency in childhood demonstrate no manifestations in the neonatal period. A very small proportion has specific genetic defects in GH secretion or action that did not present (or were not obvious) in the newborn period; these children will usually exhibit very profound growth failure by the 2nd or 3rd year of life. They typically look younger than their actual age and are classically described as chubby or cherubic; their heights are depressed more than their weights. They may have high-pitched voices, delayed dentition, and poor musculature. On testing, they are found to have very low IGF-1 and IGFBP-3 levels; GH stimulation testing reveals peak GH levels that are usually lower than 5 ng/mL. Bone age is typically delayed and an MRI of the brain may show a hypoplastic pituitary gland, an empty sella, or an abnormal pituitary bright spot. Genetic testing may show defects in the GHRH receptor gene or the GH gene. Defects in other genes involved in regulating GH secretion may be seen, but all are extremely rare. These children typically respond very dramatically to GH replacement therapy and will grow very poorly in the absence of such therapy.

Much more common is the phenomenon of the child who presents with short stature in childhood but does not have any known genetic or acquired cause of GH deficiency. These children are diagnosed as GH deficient based on a combination of auxologic and laboratory criteria and are candidates for GH therapy. But unlike children with neonatally apparent GH deficiency, or children with obvious causes of acquired GH deficiency (tumors, trauma, radiation), these children are frequently not GH-deficient when retested after puberty. This **idiopathic GH deficiency** may be due to multiple genetic loci of small effect or a few loci of moderate effect, but the exact cause remains unknown. Poor linear growth usually becomes evident by age 3 years, but many cases are not brought to the attention of physicians until later in childhood.

Diagnosis and treatment of children with idiopathic GH deficiency are based on consensus guidelines and expert opinion and may vary from country to country. In most cases, children are investigated for idiopathic GH deficiency if they are below the normal range for height (>2 SD below the mean, or <3rd percentile) or are extremely short for their genetic target height (projected adult height more than 9 cm below the MPH). A subnormal growth velocity (growth velocity <25th percentile or >1.5 SD below the mean) is seen and no other obvious cause of short stature can be found.

No single test can be regarded as the gold standard for making this diagnosis. Most children will have an IGF-1 level that is low for age (and in older children, for pubertal stage and bone age), but occasionally a child who meets all other criteria for GH deficiency will have a normal IGF-1 level, while in other cases the IGF-1 level may be low because of malnutrition or chronic disease in a child who is not GH deficient. IGFBP-3 level is also frequently used as a measure of GH secretion but is less sensitive than the IGF-1 level and may not be helpful in most cases. **Bone age is almost always delayed**. If the diagnosis is suspected as a result of auxologic findings (short stature, subnormal growth velocity), a delayed bone age, and low IGF-1 and/or IGFBP-3 levels, then most authorities recommend performing 2 GH stimulation tests. In these tests, GH secretion is provoked by 1 of several pharmacologic agents and multiple GH levels are drawn over the next 2-3 hours. Glucagon, arginine, L-dopa, and clonidine are the most commonly used agents in children; insulin-induced hypoglycemia is considered by many to be the gold standard test in adults, but is associated with the risk of life-threatening hypoglycemia and is not recommended in children. If all levels remain below an arbitrary cutoff (10 ng/mL in the United States), then the child is considered GH deficient. It should be noted that provocative testing is known to have both false-positive as well as false-negative results and should only be interpreted in the context of all available auxologic, laboratory, and imaging information. Because of these issues, some authorities recommend using auxologic criteria and growth factor levels to make the diagnosis of GH deficiency without performing any provocative tests of GH secretion.

Any child diagnosed as having GH deficiency should have cranial imaging performed to rule out intracranial pathology before treatment is started. Once imaging (usually an MRI of the brain with fine cuts through the pituitary region) has been performed, treatment can be started with GH. The usual starting dose ranges from 30-50 μg/kg/day, and this can then be increased in the case of poor response. Doses of 70 μg/kg/day or higher may be needed in some cases. IGF-1 levels can be used to assess the biochemical response and to see if there is room to increase the GH dose any further. Some authorities have recommended IGF-based dosing (adjusting the GH dose to keep the IGF-1 level in the high-normal range), but very high doses of GH may be required in some children to achieve such levels, and because of safety concerns this method has not been widely adopted.

Acquired Growth Hormone Deficiency

In acquired forms of GH deficiency, there may be a history of a precipitating event (cranial irradiation, head trauma) or a history suggestive of an intracranial lesion (headaches, vomiting, visual disturbances). Affected children often have normal growth until the onset of the disorder; thereafter, their growth is attenuated.

On physical examination, there may be evidence of the underlying disturbance (bitemporal hemianopsia, optic atrophy, or papilledema in midline tumors such as craniopharyngioma; dermatitis, scalp lesions, hepatosplenomegaly in Langerhans cell histiocytosis). The typical case will either be a child with a known history of conditions that can affect the anterior pituitary (head injury, irradiation, tumor) who shows deceleration of growth, or a child who was growing normally and then has an obvious growth failure. Laboratory tests will show decreased IGF-1 levels (and in some cases, abnormal levels of other pituitary hormones); cranial imaging (usually an MRI with and without contrast) should then be done in all such cases. Bone age may not be delayed if the onset of GH deficiency was relatively recent. The diagnosis of GH deficiency is usually confirmed by provocative testing and treatment can then be started with usual doses of GH. In patients with brain tumors, treatment is usually delayed for at least 1 year after completion of therapy because of the theoretical risk that GH therapy may increase the size of any tumor that is present.

Traditionally, GH therapy for GH deficiency was continued until linear growth was completed (i.e., until the closure of epiphyses), though it could be stopped at any point before that if the child is satisfied with his or her attained height. Because of the extremely high cost of GH therapy (50-100,000 dollars/year in the United States), many 3rd party payers require cessation of therapy once a reasonable adult height has been reached (exact targets vary depending on the plan).

Growth Hormone Insensitivity

GH action may be impaired due to mutations of the GH receptor (**Laron syndrome**), defects in postreceptor signaling, mutations in the IGF-1 gene, deficiency of the ALS protein, and defects in IGF-1 action (Table 43.7; see also Tables 43.2 and 43.5). All of these conditions are very rare and constitute only a tiny fraction of the cases of short stature and growth failure seen in clinical practice.

The GH receptor consists of an extracellular ligand-binding domain, a single membrane-spanning domain, and a cytoplasmic signaling component. Circulating GH-binding protein (GHBP) is just the extracellular domain of the GH receptor protein. Mutations in this receptor lead to various forms of **Laron syndrome**, characterized by GH resistance (hence elevated GH levels), low IGF-1 and IGFBP-3, and extreme degrees of growth failure. In some (but not all) cases, the extracellular domain of the receptor is involved, so GHBP level is also low.

Other clinical features of Laron syndrome include small head circumference, characteristic facies with saddle nose and prominent forehead, delayed skeletal maturation, small genitalia and testes, short limb length compared to trunk length, and abnormal body composition with osteopenia and obesity. Intellectual development is normal or only modestly impaired. Prenatal growth is near normal, but postnatal growth is profoundly affected, with heights as low as −10 SD.

It is worth noting that *untreated* children do not have a shortened life span and have a *lower* than average risk for cancer.

Defects in the post-GH receptor signaling pathway can also cause short stature. Several patients have been described as GH insensitivity caused by a homozygous missense mutation in the gene encoding the STAT5B protein, which is an essential component of the JAK-STAT signaling pathway that is activated by the GH receptor. These patients have severe postnatal growth failure as well as immune dysregulation related to the role of STAT5B in the immune system.

Mutations in the gene encoding IGF-1 cause profound prenatal as well as postnatal growth failure. A complete absence of IGF-1 is probably lethal in humans, but individuals have been described with deletions in the IGF-1 gene causing partial loss of function. These patients also have microcephaly, significant developmental delay, and hearing loss.

IGF-1 is carried in the bloodstream primarily as part of a ternary complex with IGFBP-3 and the ALS. **ALS deficiency** leads to low circulating IGF-1 levels (probably via accelerated IGF-1 metabolism) and leads to mild short stature and pubertal delay.

IGF-1 receptor mutations are extremely rare in liveborn babies and present with profound prenatal and postnatal growth failure. These children may have normal or only mildly abnormal cognitive development. Unlike the other GH insensitivity syndromes, circulating levels of IGF-1 are normal or elevated in these patients.

All forms of GH insensitivity (except rare IGF-1 receptor defects) lead to IGF-1 deficiency. The FDA has approved treatment of these disorders with recombinant IGF-1 in cases where height *and* IGF-1 levels are >3 SD below the mean with elevated or normal GH levels and no response to GH therapy. Commercial availability of this product has varied, and obtaining supplies for therapy may sometimes be a problem.

TABLE 43.7 Clinical Features of Growth Hormone Insensitivity

Growth and Development

- Birth weight: near normal
- Birth length: may be slightly decreased
- Bone age: delayed, but may be advanced relative to height age
- Genitalia: micropenis in childhood; normal for body size in adulthood
- Puberty: delayed 3-7 yr
- Sexual function and fertility: normal

Craniofacies

- Hair: sparse before the age of 7 yr
- Forehead: prominent; frontal bossing
- Skull: normal head circumference; craniofacial disproportion due to small facies
- Facies: small
- Nasal bridge: hypoplastic
- Orbits: shallow
- Dentition: delayed eruption
- Sclerae: blue
- Voice: high-pitched

Musculoskeletal/Metabolic/Miscellaneous

- Hypoglycemia: in infants and children; fasting symptoms in some adults
- Walking and motor milestones: delayed
- Hips: dysplasia; avascular necrosis of femoral head
- Elbow: limited extensibility
- Skin: thin, prematurely aged
- Osteopenia

From Sperling MA. *Pediatric Endocrinology*. 4th ed. Philadelphia: Elsevier; 2014:355.

Hypothyroidism

Hypothyroidism impairs linear growth (Fig. 43.5). Thyroid deficiency may be congenital or acquired (Fig. 43.6). In view of the usefulness of neonatal thyroid screening programs, it is very uncommon for congenital hypothyroidism to go untreated and cause short stature.

Acquired hypothyroidism in children usually results from **autoimmune thyroiditis**. Children with Turner syndrome, Down syndrome, Klinefelter syndrome, celiac disease, or diabetes mellitus are at increased risk for autoimmune hypothyroidism, as are children with a family history of autoimmune disease. Acquired hypothyroidism tends

(See *Nelson Textbook of Pediatrics,* p. 2665.)

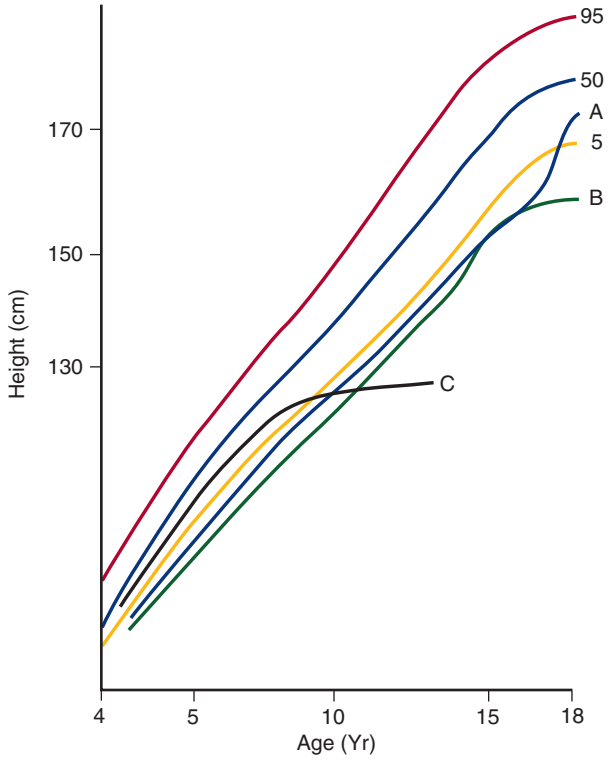


FIGURE 43.5 Patterns of linear growth. Normal growth percentiles (5th, 50th, 95th) are shown along with typical growth curves for constitutional delay of growth and adolescence *(A),* familial short stature *(B),* and acquired pathologic growth failure *(C)* (e.g., acquired primary hypothyroidism). (From Styne DM. Endocrine disorders. In: Behrman RE, Kliegman RM, eds. *Nelson Essentials of Pediatrics*. 2nd ed. Philadelphia: WB Saunders; 1994:616.)

to manifest most commonly in older children and teenagers. Often there are few complaints except for slow growth (after previously normal growth), weight gain, a goiter, or a combination of these. Other symptoms (dry hair or skin, constipation, cold intolerance) are less common. Postmenarchal females may have amenorrhea, or in rare cases, galactorrhea. School performance is generally not impaired. On physical examination, the major features are a height suggestive of deceleration from the previous growth curve, a goiter, and relative obesity (weight age > height age). The physical examination may also reveal bradycardia, dry hair or skin, and delayed reflexes.

In acquired hypothyroidism, the laboratory test results include a high level of TSH and a low or low-normal thyroxine (T_4) level or free thyroxine level (FT_4). The presence of positive thyroid antibodies (antithyroperoxidase and antithyroglobulin antibodies) is consistent with autoimmune thyroiditis. The bone age is often significantly delayed in hypothyroidism.

Central hypothyroidism is uncommon. In the newborn period, it usually (but not always) presents as a component of MPHD with TSH levels that are normal or even mildly elevated but that are inappropriately low for the decreased thyroxine level. Acquired central hypothyroidism is usually due to known injury to the anterior pituitary (e.g., central nervous system tumors, granulomas, irradiation, head trauma) and is associated with other pituitary hormone deficiencies. In practice, it is much more common to see low T_4 and normal or mildly elevated TSH levels in children who have another illness and have the syndrome of **nonthyroidal illness (NTI)** leading to temporarily abnormal thyroid function tests (previously known as euthyroid sick syndrome).

The treatment of hypothyroidism is thyroid replacement therapy (L-thyroxine).

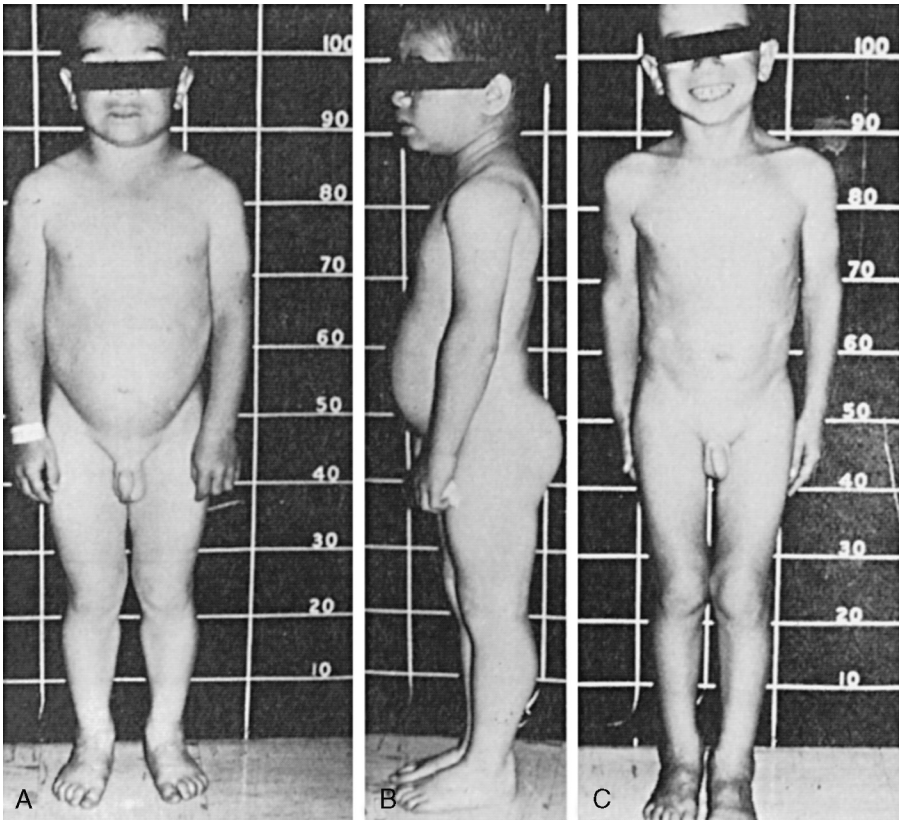


FIGURE 43.6 *A* and *B,* A 10-year-old boy with acquired hypothyroidism before treatment. Note the short stature, immature body proportions, sleepy expression, generalized myxedema, and protuberant abdomen. *C,* After 4 months of thyroid hormone therapy, the child has grown, has lost myxedema, and has a bright facial expression. (From Kaplan SA, ed. *Clinical Pediatric and Adolescent Endocrinology*. Philadelphia: WB Saunders; 1982:93.)

Glucocorticoid Excess (Cushing Syndrome)

Cushing syndrome results from excessive levels of glucocorticoids. Whether endogenous or exogenous, glucocorticoids markedly stunt growth. In general, because such conditions are acquired, the history reveals a child previously growing well whose growth velocity slows. The child typically continues to gain weight at a rapid rate, even though linear growth is attenuated. This is in contrast to exogenous obesity, in which affected children tend to grow at normal or rapid rates. The history may indicate that the child was treated with oral, topical (especially with occlusive dressings), or intradermal glucocorticoids at high doses or for long durations. Alternate-day oral glucocorticoids are much less likely to attenuate growth than are daily doses. Cushing syndrome is very unlikely with inhaled corticosteroids (ICS), but a small effect on linear growth may be seen with the use of high-potency ICS.

Physical findings in endogenous Cushing syndrome may include acne, virilization, and increased appetite. Hyperpigmentation may occur when Cushing syndrome is secondary to excessive ACTH levels. This may be caused by ACTH from a pituitary tumor (Cushing disease) or (less commonly) from a nonpituitary source (ectopic ACTH syndrome).

The physical examination usually reveals short stature with relative obesity. Many affected children have the moon face and plethora characteristic of Cushing syndrome. A buffalo hump, large purple striae, acne, and hypertension may also be present. Marked virilization is worrisome because it may indicate an adrenal tumor.

The diagnosis of endogenous Cushing syndrome is based on demonstrating abnormally high glucocorticoid production (on a 24-hour urine sample for free cortisol, normalized to creatinine) and failure to suppress cortisol production adequately in response to exogenous glucocorticoid. A screening test for capacity to suppress cortisol secretion in response to exogenous glucocorticoid is the overnight dexamethasone suppression test. This involves the child taking 0.3 mg/m^2 of dexamethasone at 11:00 P.M. (the standard dose of dexamethasone in adults is 1 mg), followed by a measurement of circulating cortisol the following morning; a normal cortisol level after dexamethasone suppression is less than 5 ng/mL. False-positive results may occur in the setting of obesity, chronic illness, or stress. If the child shows biochemical evidence of Cushing syndrome, further investigations including computed tomography, magnetic resonance imaging, and measurement of ACTH levels are needed to determine whether a pituitary tumor (the commonest cause), an adrenal tumor, or ectopic ACTH production is present. Exogenous Cushing syndrome is usually evident from the history and physical examination results.

Treatment involves the removal of excess glucocorticoids either by reducing or discontinuing exogenous steroids if medically feasible, or in the case of endogenous hypercortisolism caused by a pituitary or adrenal tumor, by surgery.

Other Endocrine Disorders

Diabetes mellitus, when poorly controlled, can lead to slow linear growth. The diagnosis should be apparent from the history. However, because of the risk of autoimmune thyroiditis and celiac disease, slow-growing children with diabetes should also be checked for hypothyroidism and celiac disease.

Diabetes insipidus, when poorly controlled or untreated, may lead to slow growth. High fluid intake in central diabetes insipidus is dramatically decreased with vasopressin; treatment of nephrogenic diabetes insipidus is more challenging (see Chapter 45).

Vitamin D deficiency rickets, hypophosphatemic rickets, and **pseudohypoparathyroidism** are also associated with short stature, but bony abnormalities and disorders of calcium and phosphate metabolism, rather than short stature, are the usual presenting features of these disorders.

Genetic Causes of Short Stature

Several chromosomal abnormalities, copy-number variants (microdeletions, duplications), and single-nucleotide variants that are associated with significant short stature are well described and more are being discovered, but apart from Turner syndrome, these are uncommon causes of short stature. Because of the relatively high prevalence of Turner syndrome, **a karyotype is indicated in the evaluation of all prepubertal girls with significant short stature**.

Turner syndrome. Turner syndrome is relatively common, with an incidence of 1/2500 liveborn females, and is caused by the absence or abnormality of an X chromosome. Short stature is the *single most common physical finding* in Turner syndrome and may occur in the absence of any other physical finding (Fig. 43.7). The mechanism by which short stature occurs in Turner syndrome is multifactorial, but haploinsufficiency (absence of 1 copy) of the **S**hort **S**tature **H**omeobo**X** gene *(SHOX)* is believed to play a major role. This gene is located within the pseudoautosomal region of the X chromosome, which escapes X-inactivation and is therefore normally expressed from both copies of the X chromosome. It is highly active in skeletal tissues, and its absence in Turner syndrome (where only 1 X chromosome is present, or if present, the 2nd X chromosome is abnormal) leads to haploinsufficiency and causes severe short stature.

Linear growth is only mildly affected in utero and birth size is normal or near normal. By early childhood, marked short stature is usually noted and there is progressive deviation of height away from the normal growth curve. Linear growth is further attenuated during the teenage years and the mean adult height ranges from 142-146 cm in various populations. Even in females with Turner syndrome, adult height is influenced by the height of the parents, and girls with Turner syndrome who are born to tall parents tend to be taller. Breast enlargement and menses generally fail to occur as a result of ovarian failure. However, the presence of pubertal development should not deter consideration of the diagnosis because approximately 10% of patients have some residual ovarian tissue rather than streak gonads. In a few cases, even fertility has been reported.

In addition to short stature and ovarian failure, there may be various dysmorphic features, including a webbed neck, low posterior hairline, lymphedema beginning in the neonatal period (manifesting mainly as puffy hands and feet), increased carrying angle of the arm, pigmented nevi, short 4th metacarpals, nail abnormalities, and renal and cardiac anomalies (coarctation of the aorta). But any or all of these may be absent, and short stature may be the only abnormality in some females with Turner syndrome (particularly in those with chromosomal mosaicism). Therefore, the absence of dysmorphic features should not preclude consideration of Turner syndrome in short females.

A karyotype analysis is necessary to confirm or rule out the diagnosis of Turner syndrome in any female with short stature of unknown origin. If 45,X0 is confirmed, additional screening in the laboratory should include a fluorescence in situ hybridization (FISH) probe for the Y chromosome as these individuals require removal of their streak gonads to reduce the risk for gonadoblastoma in the dysgenic gonadal tissue. Additional laboratory features may include abnormally high levels of the gonadotropins, luteinizing hormone, and follicle-stimulating hormone (FSH), which are indicative of ovarian failure; however, levels may be normal in middle childhood because of normal central nervous system suppression of gonadotropin secretion at that time.

(See *Nelson Textbook of Pediatrics,* p. 2723.)

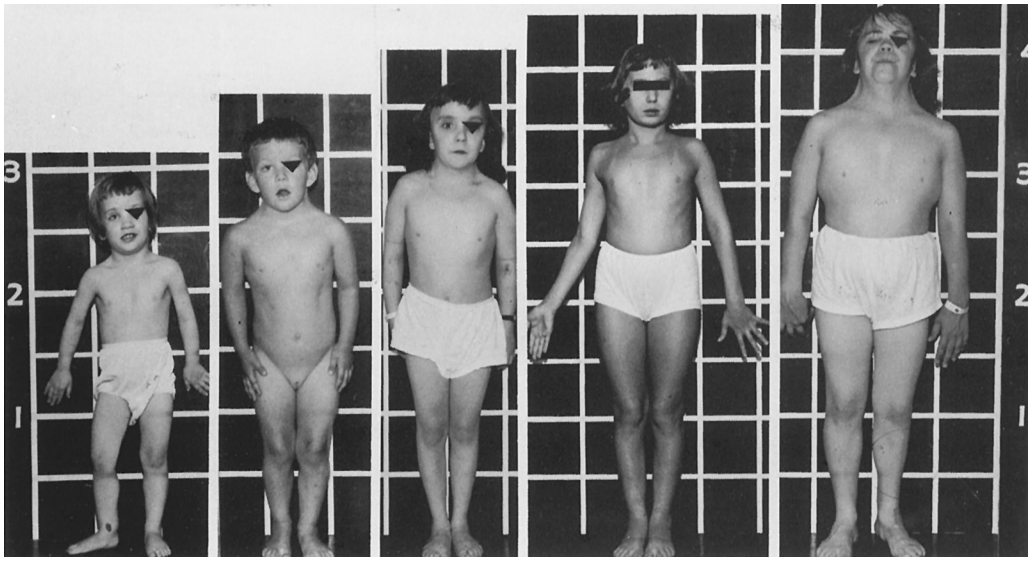


FIGURE 43.7 Five girls with 45,X0 syndrome illustrating the variability of features such as a webbed neck and broad chest. (From Lemli L, Smith D. The X0 syndrome. A study of the differentiated phenotype in 25 patients. *J Pediatr.* 1963;63:577-588.)

Although short stature in Turner syndrome is not believed to result from GH deficiency, treatment of Turner syndrome with GH therapy (typically in higher doses than those required for classic GH deficiency) increases final height and is recommended. The addition of low-dose oxandrolone may further increase the growth of females with Turner syndrome and is a useful adjunct in females who are diagnosed relatively late and who may not reach a normal height with GH therapy alone.

Down syndrome. Short stature is a prominent feature in Down syndrome, but the mechanism by which trisomy 21 causes impaired growth is not known. It is independent of the hypothyroidism that may also occur in this condition. Specific treatment for short stature is typically not recommended in this condition.

Prader–Willi syndrome (PWS). PWS is characterized by hypotonia, failure to thrive with poor sucking during infancy, hypogonadism (manifested as cryptorchidism in males), short stature with small hands and feet, hyperphagia leading to morbid obesity beginning in early childhood, developmental delay/intellectual disability, and behavioral concerns including obsessive-compulsive disorder. The average adult height is 147 cm (4 feet 9 inches) in females and 155 cm (5 feet 1 inch) in males. PWS is caused by the absence or inactivity of a segment of the paternally inherited chromosome 15 (15q11.2-13), whereas deletion of the same chromosomal segment in the maternally inherited chromosome causes **Angelman syndrome**. It is thus the classic example of genomic imprinting; a phenomenon in which the expression of a gene or genomic region differs depending on the chromosome's parent of origin.

PWS may be due to a deletion of the PWS region of the paternal chromosome (about 65% of cases), or the inheritance of 2 complete copies of the maternal chromosome 15 and the absence of the paternal chromosome (a condition labeled maternal uniparental disomy, responsible for 30-35% of the cases). In about 2% of the cases, it appears to be due to a defect in the imprinting center rather than the absence of the paternal genes. DNA methylation probes will detect almost all cases by revealing whether the patient has maternal and paternal methylation patterns (normal), absence of the paternal pattern (causing PWS), or absence of the maternal pattern (causing Angelman syndrome). Further genetic testing is then needed to determine whether the cause is a deletion, a disomy, or an imprinting center defect.

Early treatment with GH increases final height, but also improves body composition and the achievement of developmental milestones. It may also decrease the incidence of morbid obesity. Because of these reasons, most authorities consider early treatment with GH (starting between 4 months and 2 years of age) to be the standard of care in PWS. Because of some reports of a possible increase in the rate of sudden death from upper airway obstruction in the 1st months of treatment, a sleep study and/or an ears, nose, and throat (ENT) consult may be recommended before initiating treatment, with the sleep study repeated 6-12 weeks after starting treatment and annually thereafter.

Russell–Silver syndrome. Russell–Silver syndrome (RSS) is characterized by severe IUGR that persists in postnatal life. These children have proportionate short stature, a normal head circumference, triangular facies, downturned corners of the mouth, and a prominent forehead. Other features may include 5th finger clinodactyly and undergrowth of 1 or more limbs of the body (hemihypotrophy), leading to limb length discrepancy. These children usually have feeding difficulties and may exhibit mild developmental delay.

RSS is associated with methylation abnormalities in an imprinting control region on the paternal chromosome 11p15.5 in about 60% of subjects. In another 10%, it is caused by maternal uniparental disomy of chromosome 7 (absence of the paternal chromosome 7). No genetic cause is identified in the remaining children and the diagnosis is based on clinical criteria. Treatment with GH increases height, but the doses required may be higher than average because of some element of GH resistance.

Short stature HomeoboX gene mutations. The *SHOX* gene is located within the pseudoautosomal regions of the X and Y chromosomes. This region escapes X-inactivation and so it is normally expressed from both X chromosomes in females. In males, the gene is expressed from the X as well as the Y chromosomes. Haploinsufficiency of the *SHOX* gene (mutations affecting 1 copy of the gene) leads to short stature that may be associated with other skeletal findings such as the Madelung deformity (a dinner fork deformity of the distal forearm and wrist), mesomelia (shortening of the forearm and leg), cubitus valgus, and dislocation of the ulna. The combination of short stature and several of the above significant skeletal abnormalities is labeled **Léri-Weill-dyschondrosteosis** and is more common in females.

In other cases, the skeletal abnormalities may be relatively subtle and isolated short stature may be the only notable finding.

Screening for *SHOX* gene mutations is reserved for children with any combination of the following physical findings: increased U/L, reduced arm span/height ratio, increased sitting height/height ratio, above-average body mass index, Madelung deformity, cubitus valgus, short or bowed forearm, dislocation of the ulna at the elbow, or the appearance of muscular hypertrophy. In otherwise short children who do not have any of these associated findings, the yield from testing for *SHOX* mutations is very low. Treatment with GH can increase final height, though higher than average doses may be required.

Noonan syndrome. Noonan syndrome has an incidence of 1 in 1000-2500 live births. Approximately 50% of children with Noonan syndrome have a pathogenic variant in the *PTPN11* gene. There are currently 12 genes that have been identified in which pathogenic variants result in Noonan syndrome; these are much less common than *PTPN11* and include the genes: *SOS1, RAF1, KRAS, SHOC2, BRAF, NRAS, RIT1, CBL, KATB6, LZTR1,* and *SOS2*. The syndrome is characterized by minor facial dysmorphism (hypertelorism, downward eye slant, and low-set ears), proportionate short stature, and right-sided heart disease, most often pulmonic stenosis and hypertrophic cardiomyopathy. Other common findings include a short webbed neck, chest deformity (pectus excavatum), cryptorchidism, intellectual disability, bleeding diathesis, and lymphedema. Since some of these findings overlap with the findings seen in Turner syndrome, this syndrome was sometimes described as "pseudo-Turner," though Noonan syndrome occurs in both females and males and has its own specific phenotypic features and genetic etiology. GH therapy is recommended to treat short stature associated with Noonan syndrome and is an FDA-approved indication for the use of GH.

Malnutrition

Worldwide, malnutrition resulting from poverty is still the commonest cause of short stature. In North America, malnutrition may arise from inadequate intake secondary to poverty or deprivation, poor intake secondary to overt or occult chronic illness (e.g., inflammatory bowel disease, renal failure), or inability to utilize food intake (malabsorption). In all these conditions, weight tends to be depressed to a greater degree than height. The history should include a review of the child's food intake (often best obtained by a 3-day diet record), appetite, and detailed review of systems. Specific nutritional disorders, such as rickets, may also lead to short stature. Appropriate treatment leads to acceleration of linear growth, typically lagging a few weeks or months behind weight gain. Catch-up growth occurs, but may not compensate for all of the lost height potential in long-standing cases, leading to a permanent height deficit.

Chronic Illness

Chronic illnesses, such as inflammatory bowel disease, celiac disease, renal dysfunction, and chronic inflammation, can lead to short stature. The mechanisms of impaired growth include poor appetite or poor intake (e.g., inflammatory bowel disease, renal dysfunction), malabsorption (e.g., celiac disease), medications (e.g., chronic glucocorticoids for severe asthma), chronic acidosis (e.g., renal tubular acidosis), and secondary endocrine dysfunction (e.g., GH resistance associated with systemic inflammation). Although the primary disorder is evident in many cases, short stature is sometimes the presenting feature of the chronic disease. This occurs notably in inflammatory bowel disease, celiac disease, and renal dysfunction.

Gastrointestinal disease—Children usually have a greater deficit in weight than height. Gastrointestinal symptoms are frequently present, but short stature alone may be the initial presentations of celiac disease and inflammatory bowel syndrome. The growth failure in inflammatory bowel disease is due to a combination of decreased food intake, malabsorption, and the inflammatory process (mediated by proinflammatory cytokines). This may be further aggravated by the use of high-dose glucocorticoids for treatment. GH therapy has been shown to increase height velocity in some small trials in inflammatory bowel disease, but no consensus exists yet about its role in these children. Celiac disease responds to a gluten-free diet and height velocity normalizes with adequate treatment.

Renal disease—Children with chronic kidney disease may develop growth failure due to chronic metabolic acidosis, uremia, poor nutrition, anorexia, anemia, calcium and phosphorus imbalance, renal osteodystrophy, and impairment of GH action. It may also be aggravated by the use of high-dose glucocorticoids. GH therapy is recommended for children with profound growth failure and is typically continued until renal transplantation.

Pulmonary disease—Growth failure in cystic fibrosis is secondary to both its pulmonary and gastrointestinal manifestations. Chronic infection and systemic inflammation contribute to short stature.

Severe asthma may interfere with growth directly as well as via the effect of glucocorticoid therapy. Daily use of systemic glucocorticoids for any significant length of time will lead to growth suppression, but potent ICS may also have noticeable systemic effects in some cases (probably due to individual differences in technique and sensitivity). Alternate-day dosing and drug holidays can reduce this risk of growth suppression from oral corticosteroids. In the case of ICS, the use of the minimum effective potency and dose may help ameliorate systemic effects in children who exhibit signs of growth failure.

Cardiac disease—All forms of severe heart disease in childhood can be associated with growth failure. The underlying mechanism may be an increase in energy requirements, as well as anorexia and poor oral intake.

Immunodeficiencies—Both congenital and acquired immunodeficiencies (such as, human immunodeficiency virus [HIV] infection) are associated with growth failure. Mechanisms include anorexia, malabsorption, diarrhea, chronic infection, and systemic inflammation. The diagnosis is usually evident, but an occasional child with common variable immune deficiency may present with growth failure before clues in the history and physical examination lead to an evaluation of immune status. Successful treatment of the underlying disease will usually lead to an improvement in growth.

Other diseases—Childhood rheumatologic diseases, especially systemic juvenile idiopathic arthritis (JIA), are frequently associated with growth retardation. Children with childhood cancers may have poor weight gain and growth failure because of anorexia, gastrointestinal disturbances, and increased energy utilization. After diagnosis, chemotherapy and radiation may lead to poor growth, and radiation to the spine can lead to a permanent growth deficit and disproportionate growth failure (with short truncal height and longer limbs). Late growth failure may be the result of hypothalamic damage leading to GH and thyroid hormone deficiencies.

In most of these systemic illnesses, the history typically reveals that the child had been growing normally until some point. Then, the growth rate slowed, which is suggestive of the onset of an illness. The history may reveal a clear earlier diagnosis of chronic illness or may include symptoms suggestive of the underlying disorder (e.g., loss of appetite, diarrhea, mouth sores, fevers). The physical examination typically shows that the weight is more depressed than the height. There may also be features indicative of the underlying disorder (e.g., pallor in anemia, perianal findings in Crohn disease).

Laboratory studies that screen for chronic illness (complete blood cell count, erythrocyte sedimentation rate, chemistry profile,

urinalysis) may at times provide clues to the diagnosis. Screening for celiac disease with tissue transglutaminase immunoglobulin (Ig)A antibody testing may be indicated, especially if failure to thrive appears after a period of normal growth or if weight is affected more than height. If indicated by the clinical features and/or screening laboratory studies, definitive diagnosis requires directed tests (e.g., endoscopy and biopsy for inflammatory bowel disease or celiac disease, sweat chloride test for cystic fibrosis).

The management of these conditions rests on a specific therapy directed at the underlying condition (e.g., a gluten-free diet for celiac disease). When the disease is adequately treated, the growth rate often improves, but catch-up growth may not compensate for all of the lost height potential in long-standing cases, leading to a permanent height deficit. GH therapy may be indicated if the height deficit is severe and is unlikely to correct with treatment of the underlying disease alone. GH is specifically approved for the treatment of short stature in children with renal insufficiency.

Emotional Deprivation

Deprivation can stunt growth in 2 ways. First, a child may be deprived of food (an example of malnutrition); in this case, the child's weight is generally depressed more than the height. Second (and more rarely), a child who is emotionally deprived (and emotional deprivation, rather than actual physical abuse, seems to be key) may have profound short stature without apparent malnutrition (psychosocial dwarfism). In this case, the height is depressed more than the weight (Fig. 43.8). Such a child may (in some, but not all cases) have the clinical features of GH deficiency and may in fact show laboratory evidence of hypopituitarism, but when placed in a more nurturing environment, the child grows markedly, and the GH levels revert to normal. This disorder may be difficult to diagnose, and the social history is critical. The diagnosis ultimately rests on significant improvement of growth once the environment improves.

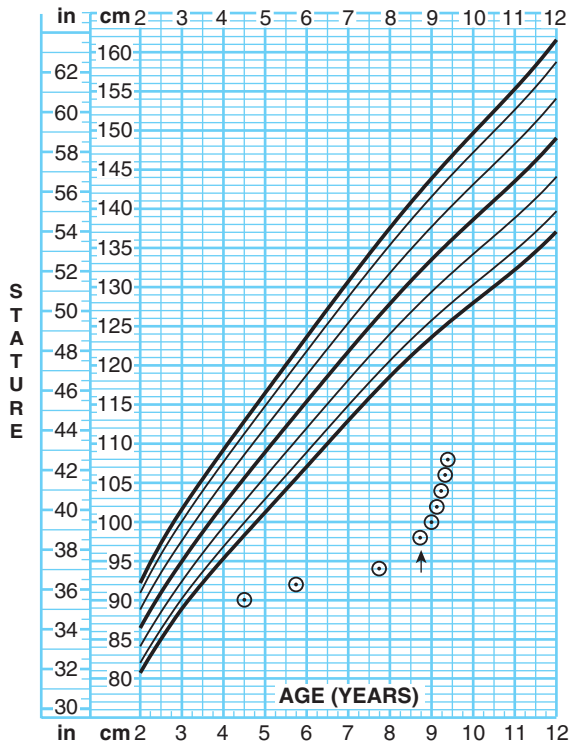


FIGURE 43.8 A growth chart of a boy with deprivation dwarfism (psychosocial dwarfism). Between the ages 6 and 8½ years, he had chemical evidence of growth hormone (GH) deficiency. After placement in a chronic care facility *(arrow),* his growth rate improved markedly, and his GH levels reverted to normal. NCHS, National Center for Health Statistics. (Data from the Centers for Disease Control and Prevention. Published May 30, 2000, and modified November 21, 2000. http: www.cdc.gov/growthcharts.)

Iatrogenic Causes

Treatments for medical conditions may secondarily impair growth. The classic example is **glucocorticoids.** This is obviously a risk with prolonged systemic steroid use, but even inhaled or topical steroids (especially if used over a wide area or under an occlusive cover) may suppress growth. A significant proportion of the dose of ICS is deposited in the oral cavity and oropharynx and after being swallowed is absorbed via the GI tract. Much of this is metabolized to inactive metabolites in the liver (1st-pass metabolism) but some still escapes inactivation and may have systemic effects. Systemic effects are generally mild, but long-term studies show that high-potency ICS (e.g., budesonide and fluticasone) do have a small but measurable impact on linear growth. The final adult height may be decreased by 1-2 cm in long-term users of ICS. Since poorly controlled asthma is a serious condition and may have an even bigger impact on growth, this relatively small effect should not prevent the use of ICS in asthma patients who need it. But an occasional child may have more significant slowing of growth based on individual differences in sensitivity, metabolism, and technique, and this possibility should be kept in mind as a possible cause of slow growth.

Spinal irradiation for treatment of malignancies may stunt growth by limiting further spinal growth; this is associated with a high U/L. Treatments for hyperactivity (**sympathomimetic agents** suppress appetite) may interfere with growth and cause a small but measurable decrease in final height in some children.

Bone Dysplasias

Skeletal dysplasias constitute a group of disorders in which there is an innate failure of the bone or cartilage to grow normally (see Table 43.3). Abnormal body proportions are characteristic of these conditions (disproportionate short stature), although there are some exceptions. Skeletal dysplasias are inherited disorders which, most often, impact the regulation of normal bone growth. Bone age is not a reliable indicator of osseous maturity in these conditions.

Achondroplasia

Achondroplasia is the classic example of an **autosomal dominant chondrodysplasia** (Fig. 43.9). The incidence is approximately 1/20,000. This condition is relatively unique in that near all affected individuals have a gain of function mutation in the fibroblast growth factor receptor 3 *(FGFR3)* gene at position 1138, which results in a glycine to arginine amino acid substitution in the protein (p.Gly380Arg). An estimated 80% of the cases are due to de novo mutations (i.e., the parents do not have the mutation). Short stature, body disproportion with short limbs, hypotonia, and a relatively large head with midface hypoplasia are often noted at birth. A progressive deceleration of growth rate begins in infancy, and the humerus and femur are particularly shortened (rhizomelia; i.e., proximal shortening of the limbs). The hands may show a 3-pronged configuration (trident hand). In addition, there may be hydrocephalus as a result of narrowing of the foramen magnum, kyphosis, stenosis of the spinal canal, and vertebral disk lesions. The diagnosis is clinical and is supported by characteristic radiologic features that include small cuboid vertebral bodies and anterior beaking of the 1st or 2nd lumbar vertebra. The average adult height is 125 cm (4 feet 1 inch) in girls and 131 cm (4 feet 3 inches) in boys. There is no effective treatment for short stature in this condition.

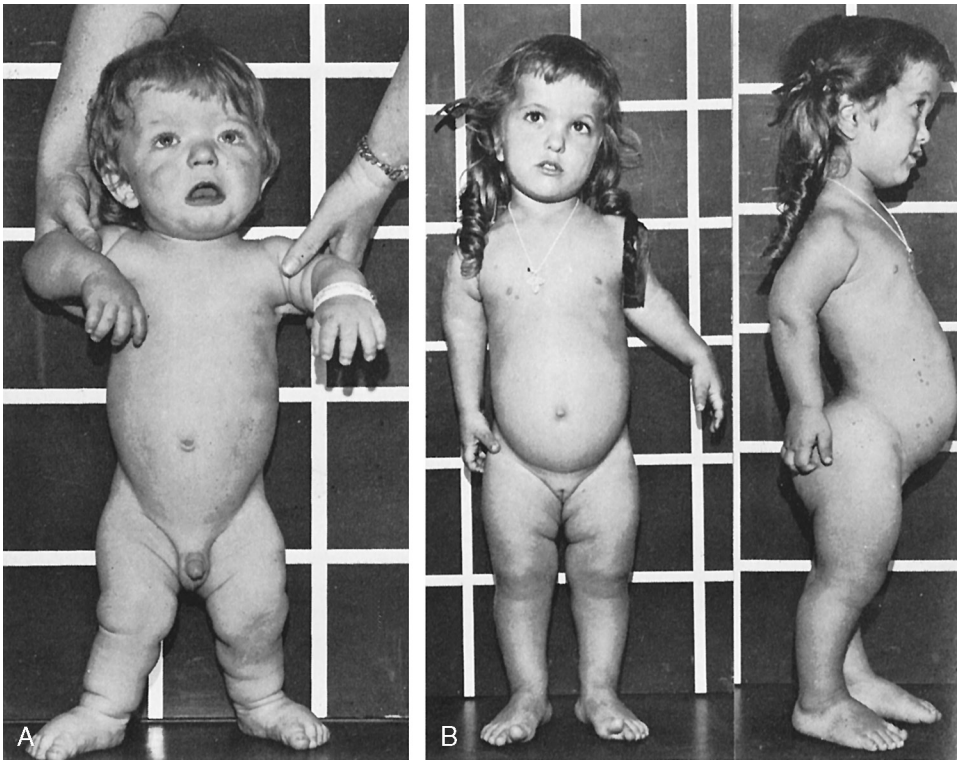


FIGURE 43.9 Achondroplasia. *A,* One-year-old boy with height age of 4 months. *B,* Four-year-old girl with a height age of 20 months. (*A,* from Smith DW. Compendium on shortness of stature. *J Pediatr.* 1967;70:504; *B,* from Jones KL, ed. *Smith's Recognizable Patterns of Human Malformation.* 4th ed. Philadelphia: WB Saunders; 1988.)

Hypochondroplasia

Hypochondroplasia is an allelic variant of achondroplasia and manifests with short stature and dysmorphic features that are often milder than in achondroplasia. In particular, there are few craniofacial abnormalities, and body disproportion may be subtle. Newborns may be slightly small, but short stature generally becomes apparent by age 3 years. The short stature is minimally disproportionate with relatively short limbs. The hands and feet are usually noted to show brachydactyly (shortening of the tubular bones). Genu varum may occur. Radiologic hallmarks include metaphyseal indentation and flaring as well as hypoplasia of the ilia with small greater sciatic notches. Some reports suggested a beneficial effect of GH, but this remains a nonstandard indication for GH treatment.

Spondyloepiphyseal dysplasias are a heterogeneous group of dysplasias that primarily affect the epiphyses and the vertebral bodies. Most forms are characterized by a shortened trunk and vertebral anomalies. These conditions may lead to spinal cord compression due to subluxation of the cervical spine. GH therapy is not recommended.

Osteogenesis Imperfecta

Moderate and severe forms of osteogenesis imperfecta are associated with proportional short stature. The diagnosis is usually evident and short stature is not a presenting feature.

EVALUATING THE CHILD WITH SHORT STATURE

Statistically, most children with short stature will turn out to have 1 of the normal variant causes of short stature (familial short stature or constitutional delay) or will have ISS. An extensive evaluation will *not* reveal a specific cause in most patients. On the other hand, short stature in general, and growth failure in particular, may the 1st sign of a serious systemic disease or endocrine disorder and appropriate evaluation is essential to make the correct diagnosis. It is best to start the evaluation with a thorough history (including a family history and direct measurement of the heights of both parents if possible) and physical examination (including careful measurement and plotting of height on appropriate growth charts) and then order laboratory tests and imaging studies based on this evaluation and specifically tailored to the particular child instead of simply ordering a certain panel of tests for every child with short stature.

At the 1st contact with a short child, the physician usually does not know if the height velocity is also abnormal. If the initial history and examination do not indicate that a specific cause may be present, it is best to schedule a 2nd visit in 4-6 months to reassess the height and to accurately measure the height velocity. But if the initial history and examination indicate possible pathology, or if the short stature is unusually severe (>2.5 SD below the mean is a good cutoff), then some immediate laboratory tests and a bone age radiograph may be performed at the 1st visit.

At any stage, the finding of a subnormal growth velocity is more concerning than the finding of short stature. Normal variants are not characterized by a subnormal growth velocity, and barring mismeasurement, a growth rate below the normal range is a cause of concern and should trigger an evaluation. A figure of 5 cm/yr is frequently used as a rough measure of the minimum height velocity in childhood (after age 3), though strictly speaking a normal height velocity may be as low as 4 cm/yr for males and 4.5 cm/yr for females in children between the age of 6 years and puberty.

Initial screening labs should include an IGF-1 level (to assess GH secretion), a TSH (to evaluate the thyroid gland), and a bone

age radiograph to assess bone maturation and obtain an estimate of the final adult height. A complete blood count (to rule out anemia) and a creatinine level (to assess renal function) as well as an erythrocyte sedimentation rate or C-reactive protein to identify systemic inflammation may be indicated. *A karyotype is mandatory in any female with significant short stature* because of the possibility of Turner syndrome. Beyond that, the testing will be guided by the history, the physical examination, and the results of initial screening labs.

◆ Important Considerations in the History

Pregnancy and Birth History

- Did the mother have illnesses or take medication during the pregnancy? Maternal illness or use of certain drugs can cause poor fetal growth.
- What was the birth weight and length? IUGR may lead to continuing small stature.
- Did the baby have perinatal problems such as unexplained hypoglycemia, prolonged jaundice, or in males, a small phallus? These are all suggestive of congenital GH deficiency.
- Did the neonate have other perinatal problems (birth asphyxia, puffy extremities)? These may provide clues to the underlying cause of short stature (significant hypoxia may lead to hypopituitarism; puffy extremities in a female are suggestive of Turner syndrome).

Infancy and Childhood

What was the child's growth pattern? The child who is short but growing at a normal rate and paralleling the 3rd percentile is more likely to have familial or constitutional short stature. The child whose height deviates progressively away from the normal curve (especially after 24 months of age) is much more likely to have an underlying medical disorder. When this progressive deviation occurs from early childhood and continues, it often represents a congenital disorder (e.g., Turner syndrome, congenital GH deficiency). However, growth attenuation that occurs after a sustained period of normal growth suggests that a disorder has been acquired (e.g., acquired GH deficiency, inflammatory bowel disease).

What were the child's developmental milestones? How is the school performance? Slow development or poor school performance may indicate a central disorder or may represent part of a syndrome (e.g., PWS). Hypothyroidism acquired after age 3 years usually does not interfere with school performance, although inadequately treated congenital hypothyroidism often leads to intellectual impairment. This question may also elicit a history of emotional problems.

Has the child had any serious illnesses or been on medication? Chronic illness often impedes growth, as do certain medications (glucocorticoids). A history of nonendocrine medical problems may also provide clues to the underlying disorder (e.g., the presence of aortic coarctation may be suggestive of Turner syndrome).

Review of Systems

How is the child's appetite? What does the child eat in a typical 3-day period (often best described by a formal diet record)? Adequate caloric intake is needed for growth. Inadequate intake may be a symptom of underlying chronic disease.

Does the child have abdominal pain, diarrhea, unexplained fevers, mouth or anal sores, or joint pain? These symptoms suggest occult inflammatory bowel disease.

Does the child have neck swelling, lethargy, constipation, cold intolerance, or weight gain without much increase in height? These are among the symptoms of acquired hypothyroidism.

Does the child have headaches, vomiting, or visual disturbances? Symptoms of central nervous system dysfunction, raised intracranial pressure, or both suggest the possibility of acquired hypopituitarism in association with a central lesion such as a tumor or hydrocephalus.

Has the child begun pubertal development? Puberty influences growth. Children with constitutional delay in growth and development have delayed puberty and often have an exaggerated nadir of growth velocity before puberty begins. However, the more puberty is delayed, the greater the likelihood of a medical disorder such as hypogonadism. Delayed puberty may also be a manifestation of hypogonadism (Turner syndrome), or it may be secondary to a growth-impeding disorder (hypothyroidism, malnutrition, chronic illness). Precocious puberty is not a cause of growth failure (it should accelerate growth), but it may lead to a short final adult height because of premature fusion of the epiphyses.

◆ Family History

What were the heights of the parents and other family members at the child's age, and when did they undergo puberty? What are the current heights of the parents and family members? The most frequent causes of short stature are familial short stature and constitutional delay in growth and development. In the former, a family history of short stature is elicited. In the latter, a family history of delayed puberty is elicited.

◆ Physical Examination

Height and weight should each be plotted carefully on growth charts. The degree of short stature in relation to peers is ascertained. Previous height measurements provide an index of the child's pattern of growth. Weight that is depressed more than height in a short child is suggestive of chronic illness or malnutrition. In contrast, a child who is short but chubby is more likely to have an endocrine disorder or syndrome (e.g., GH deficiency, hypothyroidism, Cushing syndrome, PWS).

Exogenous obesity is usually associated with a relatively tall stature. Disproportionate short stature is characteristic of skeletal dysplasias (short limbs in the case of achondroplasia and hypochondroplasia, short trunk in some rare forms of skeletal dysplasia) and may also be seen in long-standing hypothyroidism.

The presence of dysmorphic features is often suggestive of a syndrome or genetic disorder (e.g., Turner syndrome, Noonan syndrome). Midline craniofacial defects are suggestive of hypopituitarism.

Goiter, delayed dentition, bradycardia, dry hair or skin, or delayed reflexes may be suggestive of hypothyroidism.

A cherubic or doll-like appearance, high-pitched voice, delayed dentition, poor musculature, or relative adiposity may be suggestive of GH deficiency.

Bitemporal hemianopsia, papilledema, optic atrophy, or accelerating head circumference in a young child is suggestive of a central nervous system abnormality (craniopharyngioma) causing hypopituitarism.

The stage of puberty is noted. Delayed puberty is compatible with constitutional delay in growth and development, hypogonadism, panhypopituitarism, severe hypothyroidism, or chronic illness.

THERAPEUTIC OPTIONS

◆ Specific Treatment of the Primary Disorder

If a child is found to have a clear medical condition causing short stature and for which treatment is available (e.g., hypothyroidism, GH deficiency), the appropriate treatment (thyroid replacement therapy or GH therapy, respectively) improves growth markedly as long as the epiphyses remain open. Often, such children experience accelerated

(catch-up) growth for some time after appropriate treatment is instituted. Complete compensation for growth failure is unlikely to occur if the disorder was many years in duration or occurred very close to the onset of normal puberty.

Sex Steroids

Sex steroid treatments may be administered to adolescents with constitutional delay of growth and development. Males with delayed puberty may be treated with testosterone enanthate or cypionate (50-100 mg/month intramuscularly or subcutaneously for 3-6 months; smaller doses given more frequently may be more physiologic and are preferred by some practitioners) to gradually bring about secondary sexual characteristics and accelerated linear growth. This is often gratifying for males and is usually followed by spontaneous pubertal development. The low dose of testosterone is designed to avoid undue advancement of bone age and loss of growth potential. Oxandrolone is a testosterone derivative with fewer androgenic effects than testosterone, and does not aromatize to estrogen, so theoretically it may be preferable to depo-testosterone injections. Several small studies report beneficial effects of oxandrolone in males with constitutional delay of growth and puberty. The usual dose is 2.5 mg daily for anywhere from 3-12 months. Giving oxandrolone (in addition to GH therapy) to females with Turner syndrome leads to better height outcomes than GH alone, so this is frequently done at around age 8-10 in females who are still well short of a normal height. Females with Turner syndrome who started GH relatively early in life are less likely to require the addition of oxandrolone. The usual dose is 0.03-0.05 mg/kg/day. Side effects at this dose are rare, but signs of virilization should prompt a reduction in dose.

Estrogen—Just as males with constitutional delay are treated with androgens, females with pubertal delay and mild short stature may be treated with a short course of estrogen therapy. However, benign constitutional delay is less likely in females (who are more likely to have an underlying pathologic cause such as Turner syndrome) and such treatment is relatively rare. If it is contemplated, care should be taken to exclude other causes of pubertal delay and to use low doses of estrogens because estrogens promote epiphyseal closure.

Counseling

Reassurance and counseling should be available for all patients. For many children with familial short stature or constitutional delay in growth and development, it is reassuring to be told that they are normal and are likely to reach a normal adult height or 1 in keeping with the family heights. This is particularly true for children with delayed puberty, in whom the discrepancy in height in comparison with peers (who have gone through their pubertal growth spurts) is disconcerting. It is helpful if parents do not dwell on the child's height but focus on the child's strengths. Gymnastics, wrestling, soccer, and swimming are often activities at which short children are not at a disadvantage and in which they may excel.

Growth Hormone Therapy

There is a broad consensus for the use of GH therapy in children with short stature caused by classic GH deficiency, Turner syndrome, Noonan syndrome, *SHOX* haploinsufficiency, PWS, and chronic renal failure. Children who were born SGA and fail to catch up to the normal range of height by age 2 years (by 4 years of age in Europe) are also candidates for GH therapy. The U.S. FDA has approved GH for children with ISS, but this treatment remains controversial and the cost-benefit ratio remains uncertain.

Side effects of GH therapy include fluid retention that is usually mild and tends to resolve with continued treatment. Mild headaches are also common and are usually benign. Increased intracranial pressure (**pseudotumor cerebri**) is a rare but serious dose-related side effect. It usually resolves if treatment is stopped, and after resolution, treatment can frequently be restarted at a lower dose. The incidence of **slipped capital femoral epiphyses** is increased and scoliosis may be worsened during GH therapy, likely secondary to accelerated growth. GH-neutralizing antibodies may appear but are rarely of clinical significance. GH can accelerate the growth of existing nevi and can induce insulin resistance but this does not appear to be clinically significant.

Because of its growth-promoting effects, there has long been concern about a possible increase in the incidence of cancer. No significant increase in common childhood cancers has been noted yet in surveillance studies, but (somewhat unexpectedly) in 1 French study (the Safety and Appropriateness of Growth hormone treatments in Europe [SAGhE] study), the group treated with GH had a standardized mortality ratio (SMR) of 1.33 (95% CI, 1.08-1.64) compared to controls. Cardiovascular disease was responsible for most of the excess mortality. Although all-type cancer-related mortality was not increased in the French cohort, bone tumor–related mortality was increased. There were weaknesses in the design of this study and a smaller study from Belgium, the Netherlands, and Sweden did not show the same results, but the study did raise concerns about long-term safety. More long-term follow-up data are being collected to determine the true long-term safety profile of GH. Until more information becomes available, most authorities do not recommend any changes in current practice, but this may change if ongoing studies reveal new hazards. It should be kept in mind that GH therapy on a large scale did not begin until 1985, so even the earliest treated subjects are not very old at this time; impact on the risk of cancer or heart disease in the elderly (if any) may not be detectable in various study cohorts at this time.

◆ Other Treatments

Recombinant human IGF-1 is indicated for the treatment of extremely short children with primary IGF-1 deficiency (both height *and* IGF-1 >3 SD below the mean for age) caused by severe GH insensitivity (e.g., Laron syndrome and IGF-1 gene defects). Availability may be an issue. Possible side effects include hypoglycemia, increased intracranial pressure, and adenotonsillar hypertrophy.

SUMMARY AND RED FLAGS

Short stature may be a variant of normal development or may indicate a serious underlying problem (Tables 43.8 and 43.9). When short stature is associated with a slow growth velocity, progressive deviation from the child's previous growth channel, obesity, headache, vomiting, dysmorphic features, or a goiter, or if short height is inconsistent with

TABLE 43.8 Red Flags in the Evaluation of Short Stature

Height >2-2.5 standard deviations below the mean for age
Subnormal growth velocity
Abnormal body proportions
Abnormal height:weight ratio
Dysmorphic features
Goiter
Abnormal central nervous system and ophthalmologic examinations

TABLE 43.9 Conditions Not to Miss

Hypoglycemia in a child with no risk factors for hypoglycemia	Consider hypopituitarism in the differential
Hypoglycemia, jaundice, and microphallus in a newborn boy	Rule out growth hormone deficiency
Obesity in a child who is short	Rule out hypothyroidism, growth hormone deficiency, Cushing syndrome, Prader–Willi syndrome, Laurence- Moon–Biedl syndrome
Shortness in a child with a goiter	Rule out hypothyroidism
Shortness in a child with headache, vomiting, or visual disturbance	Rule out hypopituitarism secondary to a central nervous system lesion, including craniopharyngioma or hydrocephalus

the family history, a search for an underlying medical disorder should be undertaken. Understanding how to measure a child accurately, performing simple proportion measurements, and calculating growth velocity are skills that all pediatricians must have in order to diagnose short stature and identify associated disease states and syndromes.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Alatzoglou KS, Dattani MT. Genetic causes and treatment of isolated growth hormone deficiency—an update. *Nat Rev Endocrinol*. 2010;6(10):562-576.

Allen DB, Cuttler L. Clinical practice. Short stature in childhood—challenges and choices. *N Engl J Med*. 2013;368(13):1220-1228.

Ambler GR, Fairchild J, Wilkinson DJ. Debate: idiopathic short stature should be treated with growth hormone. *J Paediatr Child Health*. 2013;49(3):165-169.

Badaru A, Wilson DM. Alternatives to growth hormone stimulation testing in children. *Trends Endocrinol Metab*. 2004;15(6):252-258.

Bouali H, Latrech H. Achondroplasia: current options and future perspective. *Pediatr Endocrinol Rev*. 2015;12(4):388-395.

Chen EY, Liao YC, Smith DH, et al. The human growth hormone locus: nucleotide sequence, biology, and evolution. *Genomics*. 1989;4:479-497.

Cohen J, Blethen S, Kuntze J, et al. Managing the child with severe primary insulin-like growth factor-1 deficiency (IGFD): IGFD diagnosis and management. *Drugs R D*. 2014;14(1):25-29.

Cohen LE. Idiopathic short stature: a clinical review. *JAMA*. 2014;311(17):1787-1796.

Coste J, Pouchot J, Carel JC. Height and health-related quality of life: a nationwide population study. *J Clin Endocrinol Metab*. 2012;97(9):3231-3239.

Dauber A, Rosenfeld RG, Hirschhorn JN. Genetic evaluation of short stature. *J Clin Endocrinol Metab*. 2014;99(9):3080-3092.

de Paula FJ, Góis-Júnior MB, Aguiar-Oliveira MH, et al. Consequences of lifetime isolated growth hormone (GH) deficiency and effects of short-term GH treatment on bone in adults with a mutation in the GHRH-receptor gene. *Clin Endocrinol (Oxf)*. 2009;70(1):35-40.

Downie AB, Mulligan J, Stratford RJ, et al. Are short normal children at a disadvantage? The Wessex growth study. *BMJ*. 1997;314:97-100.

Ghigo E, Bellone J, Aimaretti G, et al. Reliability of provocative tests to assess growth hormone secretory status. Study in 472 normally growing children. *J Clin Endocrinol Metab*. 1996;81(9):3323-3327.

Hermanussen M, Staub K, Assmann C, et al. Dilemmas in choosing and using growth charts. *Pediatr Endocrinol Rev*. 2012;9(3):650-656.

Kayemba-Kay's S, Epstein S, Hindmarsh P, et al. Does plasma IGF-BP3 measurement contribute to the diagnosis of growth hormone deficiency in children? *Ann Endocrinol (Paris)*. 2011;72(3):218-223.

Larson A, Nokoff NJ, Meeks NJ. Genetic causes of pituitary hormone deficiencies. *Discov Med*. 2015;19(104):175-183.

Lee PA, Chernausek SD, Hokken-Koelega AC, et al. International Small for Gestational Age Advisory Board consensus development conference statement: management of short children born small for gestational age, April 24-October 1, 2001. *Pediatrics*. 2003;111(6 Pt 1):1253-1261.

Navarro R, Dunn JD, Lee PA, et al. Translating clinical guidelines into practice: the effective and appropriate use of human growth hormone. *Am J Manag Care*. 2013;19(suppl 15):s281-s289.

Oberfield SE. Growth hormone use in normal, short children—a plea for reason. *N Engl J Med*. 1999;340:557-559.

Pfäffle R. Hormone replacement therapy in children: the use of growth hormone and IGF-I. *Best Pract Res Clin Endocrinol Metab*. 2015;29(3):339-352.

Pinto G, Cormier-Daire V, Le Merrer M, et al. Efficacy and safety of growth hormone treatment in children with hypochondroplasia: comparison with an historical cohort. *Horm Res Paediatr*. 2014;82(6):355-363.

Ranke MB. Treatment with recombinant human insulin-like growth factor-1 in severe primary IGF deficiency and beyond. *Horm Res Paediatr*. 2015;83(5):358-360.

Rochira V, Kara E, Carani C. The endocrine role of estrogens on human male skeleton. *Int J Endocrinol*. 2015;2015:165215.

Sandberg DE, Colsman M. Growth hormone treatment of short stature: status of the quality of life rationale. *Horm Res*. 2005;63(6):275-283.

Saenger P, Wiklund KA, Conway GS, et al. Recommendations for the diagnosis and management of Turner syndrome. *J Clin Endocrinol Metab*. 2001;86:3061-3069.

Seaver LH, Irons M, American College of Medical Genetics (ACMG) Professional Practice and Guidelines Committee. ACMG practice guideline: genetic evaluation of short stature. *Genet Med*. 2009;11(6):465-470.

Swerdlow AJ, Cooke R, Albertsson-Wikland K, et al. Description of the SAGhE cohort: a large European study of mortality and cancer incidence risks after childhood treatment with recombinant growth hormone. *Horm Res Paediatr*. 2015;84:172-183.

Tanner J, Davies P. Clinical longitudinal standards for height and height velocity for North American children. *J Pediatr*. 1985;107:317-329.

Zahnleiter D, Uebe S, Ekici AB, et al. Rare copy number variants are a common cause of short stature. *PLoS Genet*. 2013;9(3):e1003365.

44

Hypoglycemia

Alvina R. Kansra

Hypoglycemia, although rare in children beyond the newborn period, is an acute, life-threatening medical emergency that may result in seizures, permanent brain damage, or even sudden death. In addition, hypoglycemia may be due to a serious underlying disorder. Various pathologic mechanisms, such as abnormal hormone secretion, metabolic defects, and drugs or toxins, have been attributed as causes of hypoglycemia. Therefore, to evaluate hypoglycemia either in a child or newborn, a comprehensive strategy for diagnosis and treatment is crucial. An important underlying cause of hypoglycemic disorders is a disruption in the normal response of the metabolic and endocrine systems during the transition from fed to fasted state. Hypoglycemia results from an imbalance in glucose homeostasis, either excessive glucose removal from the circulation or deficient glucose delivery into the circulation, or both. Obtaining plasma and urine specimens to evaluate the critical levels of various hormones and metabolic products at the time of hypoglycemia are essential for diagnosis and should be drawn immediately before treatment begins. However, treatment should never be delayed if there is uncertainty as to what critical labs are required. Obtaining a "red top" and "green top" blood collection tube will allow for most all studies to be run.

DEFINITION OF HYPOGLYCEMIA

The precise definition of hypoglycemia, one applicable to all age groups, is controversial. Historically, a working definition for significant hypoglycemia was initially developed based on the clinical manifestations of low blood sugars in neonates.

Attempts have been made to define hypoglycemia by using operational thresholds or a clinical approach. An operational threshold is based on the glucose in plasma or whole blood that prompts the intervention and is defined as blood glucose <40 mg/dL (plasma glucose levels <45 mg/dL); the clinical approach defines the blood glucose concentration threshold at which clinical signs and symptoms appear (and disappear by correcting the low glucose concentration). The wide range of blood glucose concentrations at which clinically overt signs may appear has led to uncertainty in definition.

Regardless of the wide fluctuations in glucose levels (between fed and fasting states), plasma blood glucose is normally maintained within a very narrow range of 70-100 mg/dL. A plasma glucose value below 40 mg/dL is commonly taken as the clinical definition of hypoglycemia. However, subtle signs and symptoms of neuroglycopenia can be documented at plasma glucose levels below 70 mg/dL and are more apparent at glucose levels below 60 or 50 mg/dL. For provocative tests, such as fasting studies, a glucose level of 50 mg/dL can be taken as sufficiently low for judging fuel and hormonal responsiveness. The response to a given level of plasma glucose can vary, depending on the underlying disorder. Patients with glucose-6-phosphatase deficiency (type 1 glycogen storage disease) may appear asymptomatic at glucose levels below 40 mg/dL because they have concomitant elevations of plasma lactate (and ketones), which can partially spare the glucose utilization by the brain. On the other hand, children with defects in fatty acid oxidation can become very ill at plasma glucose levels as high as 60 mg/dL because they have no alternative fuels (ketones) to glucose as a substrate for the brain, heart, and skeletal muscle.

When comparing reported glucose values, the clinician must recognize some technical factors. Unless a free-flow blood sample is obtained from the infant with minimal pain, the glucose values are likely to be unreliable. Second, whole blood glucose values are slightly lower than those of plasma because of the dilution by the fluid in the red blood cells. Finally, hematocrit also influences the blood glucose concentration. This is particularly important in newborns, whose hematocrit values are higher than older infants and children. A high hematocrit level results in lower blood glucose concentration; the opposite is true for low hematocrit values.

It was once common practice to accept lower standards for glucose levels in newborns because of the high frequency of low plasma glucose levels on the day of birth. It should be stressed that these lower values represent a purely "statistical" definition of normal; there is no evidence that the neonatal brain has less need for glucose than do the brains of older children or adults. Specific maturational delays in several of the fasting systems (metabolic, endocrine) adequately explain why neonates have such a high risk of hypoglycemia during the first 12-24 hours after delivery. The use of different glucose standards for newborns should be discouraged, and the same treatment goals for hypoglycemia should be applied to newborns and older children: that is, to maintain plasma glucose levels above 60 mg/dL.

REGULATION OF BLOOD GLUCOSE CONCENTRATION

The brain is solely dependent upon glucose as a primary source of energy. However, during the period of starvation it can also use ketones an alternative (but not sole) source for energy production. Glucose is derived either from the intestinal absorption of dietary carbohydrates (exogenous source) or endogenous production (glycogenolysis or gluconeogenesis). Within 2-3 hours after a meal, glucose absorption from the intestine ceases, and the liver becomes the major source of glucose for the brain and other tissues. The liver produces glucose through a combination of glycogenolysis and gluconeogenesis (Fig. 44.1). Gluconeogenesis provides approximately 25% of hepatic glucose production in the early phases of fasting; the rate of gluconeogenesis is determined largely by rates of proteolysis and remains constant throughout fasting. Hepatic glycogenolysis provides the majority of glucose production early in a fast, but by 12 hours, liver glycogen stores become depleted. The body must then begin to depend on release of fatty acids by lipolysis

(See *Nelson Textbook of Pediatrics,* p. 773.)

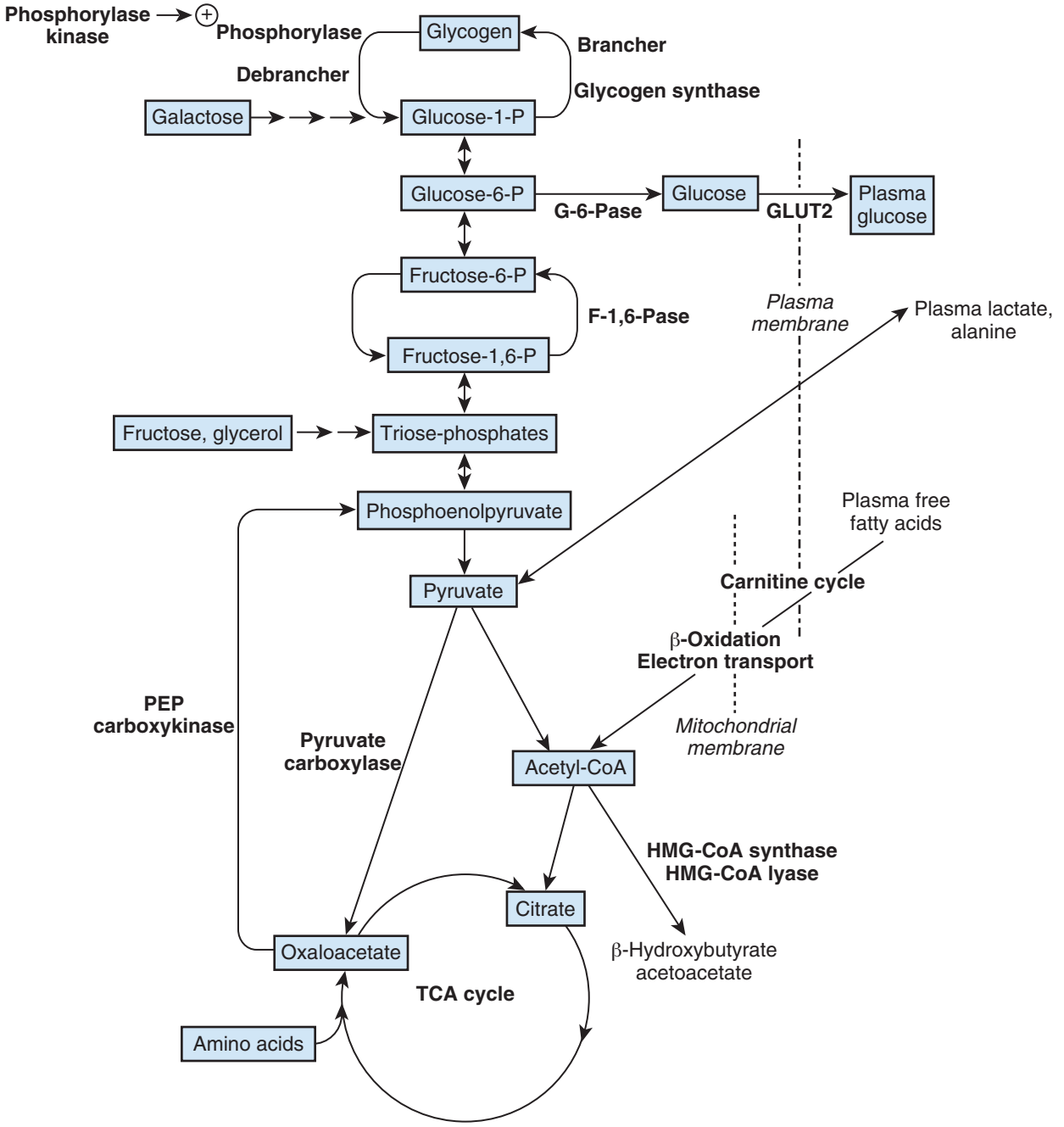


FIGURE 44.1 Metabolic systems of fasting adaptation. Shown are the pathways of hepatic gluconeogenesis, glycogenolysis, and ketogenesis. Key enzyme steps are in boldface. Enzyme steps in gluconeogenesis: pyruvate carboxylase, phosphoenolpyruvate (PEP) carboxykinase, fructose-1,6-bisphosphatase (F-1,6-Pase), glucose-6-phosphatase (G-6-Pase), and the plasma membrane glucose transporter 2 (GLUT2). Enzyme steps in glycogenolysis: glycogen synthase, glycogen brancher enzyme, glycogen phosphorylase kinase, glycogen phosphorylase, and glycogen debrancher enzyme. Steps in ketogenesis include a series of enzyme steps in the carnitine cycle for transporting fatty acids across the mitochondrial membrane, enzymes of the β-oxidation cycle, enzymes of electron transport, and enzymes of ketone synthesis (3-hydroxy-3-methylglutaryl-coenzyme A [HMG-CoA] synthase and HMG-CoA lyase). P, phosphate; TCA, tricarboxylic acid.

from stores of fat in adipose tissue. Most tissues can oxidize free fatty acids directly and thus minimize their use of glucose. The major exception is the brain, which is unable to directly oxidize free fatty acids, because they cannot cross the blood-brain barrier. Partial oxidation of free fatty acids in the liver produces ketones (β-hydroxybutyrate and acetoacetate), which are readily oxidized by the brain, thus sparing cerebral glucose consumption.

Metabolic systems and hormones normally prevent hypoglycemia during fasting (Tables 44.1 and 44.2). The integration of these systems is demonstrated by the changes in plasma concentrations of the major fuels and hormones during the course of fasting (Fig. 44.2). Plasma glucose concentrations gradually decline over the course of the fast as liver glycogen reserves are depleted. In infants and young children, with their larger ratio of brain to body mass, glucose levels fall faster than

in older children and adults and may reach 50 mg/dL by 24-30 hours of fasting. Plasma levels of lactate, a representative gluconeogenic precursor, decline during the course of fasting as hepatic gluconeogenesis is stimulated and protein turnover slows. Plasma free fatty acid levels begin to rise quickly after 12-20 hours of fasting in response to the fall in insulin concentrations as glucose levels decline. The increased availability of fatty acids is accompanied by a 10- to 20-fold rise in plasma ketone levels as hepatic oxidation of fatty acids is activated. Determining the circulating levels of these fuels and hormones at the point of hypoglycemia provides the most important information for diagnosing the cause of hypoglycemia.

TABLE 44.1 Metabolic Systems and Hormones Regulating Blood Glucose

Metabolic Systems
Hepatic gluconeogenesis
Hepatic glycogenolysis
Adipose tissue lipolysis
Fatty acid oxidation (liver and peripheral organs) and hepatic ketogenesis

Hormonal Systems
Insulin
Counter-regulatory hormones
- Glucagon
- Cortisol
- Growth hormone
- Epinephrine

CLINICAL MANIFESTATIONS

A variety of signs and symptoms may occur in patients with hypoglycemia (Table 44.3). They can be divided into 2 categories. Those in the 1st category result from activation of the autonomic nervous system and release of the counter-regulatory hormone epinephrine. Those in the 2nd category are secondary to inadequate delivery of glucose to the brain (neuroglycopenia).

CAUSES OF TRANSIENT NEONATAL HYPOGLYCEMIA

Hypoglycemia is a common problem in newborns. The majority of cases are transient, although the neonatal period is also the time when inherited disorders are most likely to manifest. The differential diagnosis of hypoglycemia is extensive (Table 44.4).

Normal Newborns

As many as 30% of normal, full-term newborns and those of size appropriate for gestational age may be unable to maintain plasma

TABLE 44.2 Hormonal Regulation of Fasting Metabolic Systems

Hormone	Hepatic Glycogenesis	Hepatic Glucogenesis	Adipose Tissue Lipolysis	Hepatic Ketogenesis
Insulin	Inhibits	Inhibits	Inhibits	Inhibits
Glucagon	Stimulates	—	—	—
Cortisol	—	Stimulates	—	—
Growth hormone	—	—	Stimulates	—
Epinephrine	Stimulates	Stimulates	Stimulates	Stimulates

From Sperling MA, ed. *Pediatric Endocrinology*. 2nd ed. Philadelphia: Elsevier; 2002.

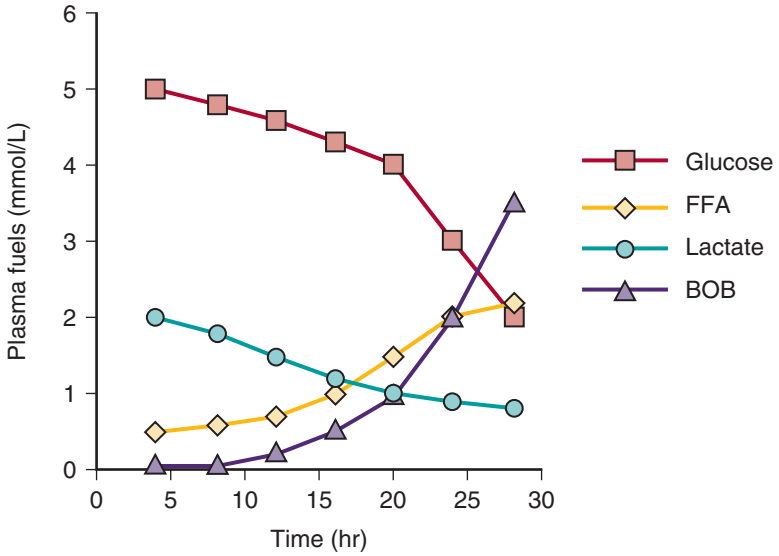


FIGURE 44.2 Changes in plasma levels of key fuels during fasting in a normal child. Note that plasma glucose declines toward hypoglycemic values by 24 hours as hepatic glycogen reserves become depleted. Plasma levels of lactate, a representative gluconeogenic substrate, decline gradually during the fast as hepatic gluconeogenesis is activated. Late in fasting, levels of plasma free fatty acids (FFA) increase as lipolysis is stimulated, followed by a dramatic rise in β-hydroxybutyrate that reflects the increase in the rates of hepatic fatty acid oxidation and ketone synthesis. BOB, β-hydroxybutyrate.

TABLE 44.3 Symptoms of Hypoglycemia

Neurogenic Symptoms Due to Activation of Autonomic Nervous System*
Sweating
Shakiness, trembling
Tachycardia
Anxiety, nervousness
Weakness
Hunger
Nausea, vomiting
Pallor
Hypothermia

Neuroglycopenic Symptoms Due to Decreased Cerebral Glucose Use
Headache
Visual disturbances
Lethargy, lassitude
Restlessness, irritability
Difficulty with speech and thinking, inability to concentrate
Mental confusion
Somnolence, stupor, prolonged sleep
Loss of consciousness, coma
Hypothermia
Twitching, convulsions, "epilepsy"
Bizarre neurologic signs
Motor disturbances
Sensory disturbances
Loss of intellectual ability
Personality changes
Bizarre behavior
Outburst of temper
Psychologic disintegration
Manic behavior
Depression
Psychoses
Permanent mental or neurologic damage

*Some features may be attenuated by β adrenergic blocking agents
From Langdon DR, Stanley CA, Sperling, MA. Hypoglycemia in the toddler and child. In: Sperling MA, ed. *Pediatric Endocrinology*. 4th ed. Philadelphia: Elsevier; 2014:922.

glucose levels above 50 mg/dL if they fast during the 1st 6 hours after delivery. By the 2nd day of life, the frequency of plasma glucose concentrations below 50 mg/dL decreases to less than 1%, which indicates a rapid maturation of fasting metabolic adaptation. The extremely poor fasting tolerance on the day of birth can be explained by lack of development of key enzymes in the pathways of both hepatic gluconeogenesis and ketogenesis. Transcription of these genes is delayed until after delivery but becomes well activated by the end of the first 24 hours. Glucagon and cortisol may be important for activation of enzymes involved in gluconeogenesis. Ingestion of long-chain fats (e.g., in colostrum) may be important for triggering transcription of the two enzymes of ketogenesis. Thus, on the day of birth, all newborns can be viewed as having impaired fasting adaptation. In the absence of other risk factors, hypoglycemia in the first day may necessitate only feeding and follow-up blood glucose determination to ensure that further workup is not necessary. Breast-fed babies are at special risk for hypoglycemia when there are problems initiating milk production.

Newborns Small for Gestational Age and Premature Infants

Hypoglycemia is significantly more common in premature infants and those small for gestational age because of decreased stores of glycogen, fat, and protein. In addition, the enzymes necessary for gluconeogenesis may be less developed than in normal full-term infants.

Infants of Diabetic Mothers

Infants born to mothers with any type of diabetes, including gestational diabetes, are at risk for hypoglycemia because of oversecretion of insulin during the first few days after delivery. This transient neonatal hyperinsulinemia occurs because maternal hyperglycemia stimulates fetal insulin secretion and, after delivery, affected infants have difficulty in downregulating insulin secretion to adapt to the withdrawal of the hyperglycemia. Because of the growth-stimulating effects of insulin on the fetus, infants of diabetic mothers are often large for gestational age. Blood glucose levels should be monitored after birth until they stabilize in the normal range. Enteral feedings should be initiated as soon as possible to prevent fasting hypoglycemia. Hypoglycemia should be treated with intravenous glucose; the problem should resolve promptly, within 1-2 days. Prolonged hyperinsulinism (HI) in infants of diabetic mothers should raise the suspicion of either a genetic form of HI or perinatal stress-induced HI.

Perinatal Stress-Induced Hyperinsulinism

Some infants with birth asphyxia or intrauterine growth restriction may have severe problems with hypoglycemia for prolonged periods, ranging from a few days to a few months after birth. This form of transient HI has not been well characterized, but it is probably not rare. The mechanism appears to be HI; oral diazoxide, which decreases insulin secretion, provides good control of hypoglycemia in these infants.

Erythroblastosis Fetalis

An association between hypoglycemia and erythroblastosis fetalis caused by Rh incompatibility occurs in infants who are anemic at birth (cord hemoglobin <10 g/dL). The low blood glucose levels in these infants have been attributed to high plasma insulin concentration. The cause of these high insulin levels remains undefined. The current prevention and management of Rh sensitization have markedly reduced the incidence of erythroblastosis and of fetal and neonatal anemia. Nonetheless, such infants require careful monitoring of plasma glucose concentration soon after birth.

Intrapartum Maternal Glucose Administration

Administration of excessive glucose quantities to the mother during labor results in maternal as well as fetal hyperglycemia. Increased fetal glucose concentration causes increased fetal insulin secretion and fetal HI. If the glucose has been administered to the mother immediately before the infant's birth, the infant is born with high insulin levels. In addition, high fetal blood glucose and insulin levels may also cause an increase in fetal blood lactate concentration and metabolic acidosis. These effects are more pronounced if the mother has received infusions of glucose for a prolonged time. An acute administration of large amounts of glucose-containing fluids to prevent hypotension in women receiving conduction anesthesia could result in acute fetal hyperglycemia, HI, and metabolic acidosis. This is a transient HI that leads to hypoglycemia in a fetus.

(See *Nelson Textbook of Pediatrics,* p. 897.)

TABLE 44.4 Classification of Hypoglycemia in Infants and Children

Neonatal Transitional (Adaptive) Hypoglycemia

Associated with Inadequate Substrate or Immature Enzyme Function in Otherwise Normal Neonates

Prematurity
Small for gestational age
Normal newborn

Transient Neonatal Hyperinsulinism

Infant of diabetic mother
Small for gestational age
Discordant twin
Birth asphyxia
Infant of toxemic mother

Neonatal, Infantile, or Childhood Hyperinsulinemic Hypoglycemias

Recessive K_{ATP} channel HI
Recessive HADH (hydroxyl acyl-CoA dehydrogenase) mutation HI
Recessive UCP2 (mitochondrial uncoupling protein 2) mutation HI
Focal K_{ATP} channel HI
Dominant K_{ATP} channel HI
Atypical congenital hyperinsulinemia (no mutations in *ABCC8* or *KCNJ11* genes)
Dominant glucokinase HI
Dominant glutamate dehydrogenase HI (hyperinsulinism/hyperammonemia syndrome)
Dominant mutations in *HNF-4A* and *HNF-1A* (hepatic nuclear factors 4α and 1α) HI with monogenic diabetes of youth later in life
Dominant mutation in SLC16A1 (the pyruvate transporter)—exercise-induced hypoglycemia
Acquired islet adenoma
Beckwith-Wiedemann syndrome
Factitious disorder: insulin administration (Munchausen syndrome by proxy)
Oral sulfonylurea drugs
Congenital disorders of glycosylation

Counter-Regulatory Hormone Deficiency

Panhypopituitarism
Isolated growth hormone deficiency
Adrenocorticotropic hormone deficiency
Addison disease
Epinephrine deficiency

Glycogenolysis and Gluconeogenesis Disorders

Glucose-6-phosphatase deficiency (GSD 1a)
Glucose-6-phosphate translocase deficiency (GSD 1b)
Amylo-1,6-glucosidase (debranching enzyme) deficiency (GSD 3)
Liver phosphorylase deficiency (GSD 6)
Phosphorylase kinase deficiency (GSD 9)
Glycogen synthetase deficiency (GSD 0)
Fructose-1,6-diphosphatase deficiency
Pyruvate carboxylase deficiency
Galactosemia
Hereditary fructose intolerance

Lipolysis Disorders

Fatty Acid Oxidation Disorders

Carnitine transporter deficiency (primary carnitine deficiency)
Carnitine palmitoyltransferase-1 deficiency
Carnitine translocase deficiency
Carnitine palmitoyltransferase-2 deficiency
Secondary carnitine deficiencies
Very-long-, long-, medium-chain acyl-CoA dehydrogenase deficiency

Other Etiologies

Substrate-Limited

Ketotic hypoglycemia
Poisoning—drugs
Salicylates
Alcohol
Oral hypoglycemic agents
Insulin
Propranolol
Pentamidine
Quinine
Disopyramide
Ackee fruit (unripe)—hypoglycin
Vacor (rat poison)
Trimethoprim-sulfamethoxazole (with renal failure)

Liver Disease

Reye syndrome
Hepatitis
Cirrhosis
Hepatoma

Amino Acid and Organic Acid Disorders

Maple syrup urine disease
Propionic acidemia
Methylmalonic acidemia
Tyrosinosis
Glutaric aciduria
3-Hydroxy-3-methylglutaric aciduria

Systemic Disorders

Sepsis
Carcinoma/sarcoma (secreting insulin-like growth factor II)
Heart failure
Malnutrition
Malabsorption
Anti-insulin receptor antibodies
Anti-insulin antibodies
Neonatal hyperviscosity
Renal failure
Diarrhea
Burns
Shock
Postsurgical
Pseudohypoglycemia (leukocytosis, polycythemia)
Excessive insulin therapy of insulin-dependent diabetes mellitus
Factitious
Nissen fundoplication (dumping syndrome)
Falciparum malaria

GSD, glycogen storage disease; HI, hyperinsulinemia; K_{ATP}, regulated potassium channel.
From Sperling MA. Hypoglycemia. In: Kliegman RM, Stanton BF, St. Geme JW III, et al., eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:776.

Maternal Drug Therapy

The various pharmacologic agents administered to the mother for the treatment of medical problems that can influence blood glucose levels in the newborn can be divided into 2 broad categories:

1. Some drugs, including oral hypoglycemic agents, can directly affect blood glucose. Oral hypoglycemic agents, such as chlorpropamide and sulfonylureas, are administered by some physicians for the treatment of gestational diabetes. Because these drugs are easily transported across the placenta, the infant is born with a certain amount of drug present in the circulation. These drugs, particularly those with prolonged effects, may result in profound hypoglycemia that tends to persist until the drug is removed, either by its own clearance or by exchange transfusion.
2. Some drugs are administered to the mother with indirect effects (the more common contributor to neonatal hypoglycemia). β-Sympathomimetic agents commonly used for the prevention and treatment of premature labor can result in maternal hyperglycemia by increasing hepatic glucose production and decreasing glucose utilization. Maternal hyperglycemia, in turn, can initiate fetal hyperglycemia and HI, which can cause hypoglycemia in the newborn.

Beckwith-Wiedemann Syndrome

The clinical features of infants born with Beckwith-Wiedemann syndrome (BWS) consist of macroglossia, abdominal wall defects (omphalocele, umbilical hernia), somatic gigantism, visceromegaly (liver, kidney, spleen), and hypoglycemia. Other possible features include ear anomalies, such as creases on the lobe; cardiac defects; renal abnormalities; hemihypertrophy; and neonatal polycythemia. These infants are prone to intraabdominal malignancies, including Wilms tumor, hepatoblastoma, rhabdomyosarcoma, and neuroblastoma. Most cases of BWS are sporadic, although approximately 15% have autosomal dominant inheritance. BWS appears to be caused by abnormal genomic imprinting involving multiple genes at chromosome 11p15.

Early recognition of hypoglycemia is extremely important for appropriate clinical management because there is an association in BWS between hypoglycemia and intellectual impairment. Any infant born with an omphalocele should be monitored for potential hypoglycemia. Approximately 50% of newborns with BWS have hypoglycemia; 80% of cases are mild and transient. The remaining 20% of cases are more prolonged and difficult to control. HI is the principal mechanism of the hypoglycemia. Hypertrophy and hyperplasia of the islet of Langerhans have been observed. Treatment depends on the severity of the hypoglycemia; it may include frequent feedings, intravenous dextrose, medications such as diazoxide or octreotide, and, rarely in severe cases, partial pancreatectomy. If managed medically, the hypoglycemia eventually resolves over weeks to months of care.

CAUSES OF PERSISTENT HYPOGLYCEMIA IN INFANTS AND CHILDREN

Hyperinsulinism

Congenital HI is the most common cause of persistent hypoglycemia in infants and children. Previously, this disorder was referred to as nesidioblastosis, leucine-sensitive hypoglycemia, or idiopathic hypoglycemia of infancy. Most affected patients present during infancy; macrosomia may be present at birth as a result of high fetal insulin levels, which act as a growth factor in utero. Excessive insulin secretion during fasting suppresses all of the fasting systems, including hepatic glucose production, lipolysis, and ketogenesis. Hypoglycemia results from both increased glucose utilization and underproduction of glucose. Because lipolysis and ketosis are inhibited, levels of alternative fuels remain low, which increases the risk of seizures and permanent brain injury. There are several genetic defects of pancreatic β-cell insulin secretion in children with HI (Fig. 44.3 and Table 44.5; see also Table 44.4).

Recessive KATP Channel Hyperinsulinism

This is the most severe form of congenital HI. Affected infants are usually large for gestational age and present with symptoms of hypoglycemia in the 1st days after birth. The hypoglycemia is often extremely severe, and treatment may require intravenous glucose infusions at 20-30 mg/kg/min (4-6 times normal) to maintain plasma glucose in the normal range of 70-100 mg/dL. This disorder is caused by genetic defects of the β-cell plasma membrane adenosine triphosphate-dependent potassium (KATP) channel (Fig. 44.4). The channel is encoded by 2 adjacent genes located on chromosome 11p: *ABCC8*, which encodes the sulfonylurea receptor type 1 (SUR1) protein subunit and *KCNJ11A*, which encodes the potassium channel, inwardly rectifying, Kir6.2 subunit. Common founder mutations of *ABCC8* have been identified in Ashkenazi Jews and in Finland, but most affected patients have 1 of a large number of "private" (rare and unique) mutations. Medical management with diazoxide or octreotide (which acts like somatostatin) may be tried (see Figs. 44.3 and 44.4) but is rarely effective. Most infants require surgical near-total (98%) pancreatectomy to achieve control of hypoglycemia. Approximately 50% of infants with severe HI who require surgery have diffuse disease caused by these recessive KATP channel mutations; the remainder has focal lesions that are potentially curable by partial surgical resection.

Focal KATP Channel Hyperinsulinism

Approximately half the infants with severe neonatal-onset HI have focal lesions of the pancreas that are potentially curable by surgical resection. The molecular defect in these infants involves the same KATP channel genes as in recessive KATP channel HI through a 2-hit mechanism: loss of heterozygosity for the maternal chromosome 11p and expression of a paternally derived *ABCC8* or *KCNJ11A* mutation. Histologically, the focal lesions usually appear as adenomatosis. The clinical features are identical to those of infants with recessive KATP channel HI, including diazoxide unresponsiveness and hypoglycemia that is extremely difficult to control. Methods to diagnose and localize focal pancreatic adenomatosis preoperatively include acute insulin response tests to secretagogues such as calcium and tolbutamide, selective pancreatic arterial calcium stimulation of insulin release with pancreatic venous sampling, and positron emission tomography.

Dominant KATP Channel Hyperinsulinism

One family has been reported with HI caused by a dominantly expressed mutation of the *ABCC8* gene, rather than the usual recessive disease described previously.

Dominant Glutamate Dehydrogenase Hyperinsulinism

Dominantly expressed gain-of-function mutations of glutamate dehydrogenase have been identified in children with the unusual combination of HI plus asymptomatic hyperammonemia (HI/HA). The majority of cases arise from de novo mutations, and only 20% are familial. Hypoglycemic symptoms often do not manifest in the neonatal period, and the disorder may not be recognized until the affected patient is an adult. Birthweights of affected infants are normal.

In addition to hypoglycemia, affected individuals have persistent but asymptomatic hyperammonemia in the range of 70-150 μmol/L (see Fig. 44.3). The mutations affect the pathway of leucine-stimulated insulin secretion, and patients can have protein-sensitive hypoglycemia, as well as fasting hypoglycemia. Diazoxide is effective in controlling hypoglycemia.

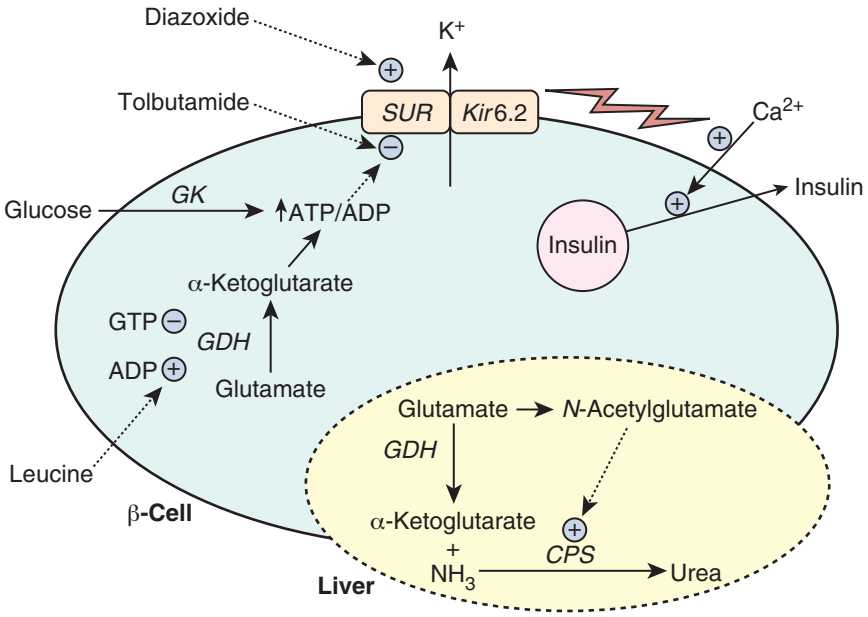


FIGURE 44.3 Pathways of pancreatic β-cell insulin secretion. Increases in plasma concentrations of glucose lead to increased pancreatic β-cell glucose oxidation rates and elevations of intracellular adenosine triphosphate (ATP). The increase in the ratio of ATP to adenosine diphosphate subsequently acts via the sulfonylurea receptor type 1 (SUR1) component of the ATP-sensitive potassium (KATP) channel to inhibit potassium efflux, resulting in membrane depolarization and activation of a voltage-gated calcium ion channel. The rise in intracellular calcium triggers the release of insulin from secretory granules into the plasma. Genes involved in congenital hyperinsulinism include glucokinase; glutamate dehydrogenase (GDH); SUR1; and the ion pore component of the KATP channel, Kir6.2. Note that leucine triggers β-cell insulin secretion by allosterically activating GDH to increase oxidation of glutamate, which subsequently leads to inhibition of the KATP channel. As shown in the *inset* of liver pathways of glutamate metabolism, in the hyperinsulinism/hyperammonemia syndrome, overactivity of GDH leads to excessive ammonia production from glutamate and also decreases the availability of glutamate for synthesis of *N*-acetylglutamate, a required allosteric activator of the 1st step in ureagenesis. Note that SUR1 mediates both tolbutamide activation of insulin release and diazoxide inhibition of insulin release. Somatostatin inhibits insulin release at a more distal site in the pathway. ADP, adenosine diphosphate; CPS, carbamyl phosphate synthetase; GK, glucokinase; GTP, guanosine triphosphate; SUR, sulfonylurea receptor.

Dominant Glucokinase Hyperinsulinism

This extremely rare disorder causes mild fasting hypoglycemia as a result of a dominant gain-of-function mutation of islet glucokinase (see Fig. 44.3). Birthweights of affected infants are normal, and the age at onset of hypoglycemic symptoms ranges from infancy to adulthood. Diazoxide therapy has been effective in controlling plasma glucose levels.

Insulinoma

Acquired **insulinomas** are the most common form of HI in adults but are rare in childhood, especially in early infancy. These are usually isolated, benign tumors, but multiple adenomas may occur in association with the familial multiple endocrine neoplasia syndromes. In contrast to focal congenital HI, insulinomas may be detectable by imaging procedures such as computed tomography, magnetic resonance imaging, radioactive octreotide scans, or transduodenal ultrasonography. Surgical resection is the treatment of choice.

Insulin Reaction, Oral Hypoglycemic Agents, and Surreptitious Insulin Administration

Insulin-induced hypoglycemia is a common occurrence in insulin-treated diabetic patients and may also occur in patients with type 2 diabetes who are taking oral hypoglycemic agents, such as glyburide, that stimulate insulin secretion. Surreptitious insulin administration should always be included in the differential diagnosis of unexplained hypoglycemia and, in young children, may occur as part of factitious disorder by proxy (Munchausen syndrome by proxy). Exogenous human or animal insulin use can be demonstrated by assays showing elevated plasma insulin values with simultaneous suppression of plasma C peptide (use of insulin lispro may not be detectable with some insulin immunoassays).

Counter-Regulatory Hormone Deficiencies

Hypopituitarism

Hypopituitarism with isolated deficiency of growth hormone, and particularly with deficiencies of both growth hormone and adrenocorticotropin hormone, predisposes to fasting hypoglycemia. In affected older infants, hypoglycemia may occur after 10-14 hours of fasting. Newborns with hypopituitarism sometimes present with much more severe hypoglycemia, which can closely mimic the KATP channel form of congenital HI, including increased glucose requirements of 10-20 mg/kg/min and an inappropriate glycemic response to glucagon when patients are hypoglycemic. Liver disease resembling progressive cholestatic jaundice may occur in these newborns and does not resolve until replacement therapy is begun for the deficient hormones. Hypotonia and, in affected boys, a small phallus may also be present.

A number of syndromes, such as midline craniofacial defects, septo-optic dysplasia, and Russell-Silver dwarfism, may be associated with hypopituitarism. Infant boys characteristically have microphallus, which is a useful diagnostic sign.

TABLE 44.5 Correlation of Clinical Features with Molecular Defects in Persistent Hyperinsulinemic Hypoglycemia in Infancy

Type	Macrosomia	Hypoglycemia/ Hyperinsulinemia	Family History	Molecular Defects	Associated Clinical, Biochemical, or Molecular Features	Response to Medical Management	Recommended Surgical Approach	Prognosis
Sporadic	Present at birth	Moderate/severe in 1st days to weeks of life	Negative	*ABCC8/KCNJ11A* mutations not always identified in diffuse hyperplasia	Loss of heterozygosity in microadenomatous tissue	Generally poor; may respond better to somatostatin than to diazoxide	Partial pancreatectomy if frozen section shows β-cell crowding with small nuclei—suggests microadenoma Subtotal >95% pancreatectomy if frozen section shows giant nuclei in β cells—suggests diffuse hyperplasia	Excellent if focal adenoma is removed, thereby curing hypoglycemia and retaining sufficient pancreas to avoid diabetes Guarded if subtotal pancreatectomy (>95%) is performed; diabetes mellitus develops in 50% of patients; hypoglycemia persists in 33%
Autosomal recessive	Present at birth	Severe in 1st days to weeks of life	Positive	*ABCC8/KCNJ11A*	Consanguinity a feature in some populations	Poor	Subtotal pancreatectomy	Guarded
Autosomal dominant	Unusual	Moderate onset usually post 6 mo of age	Positive	Glucokinase (activating) Some cases gene unknown	None	Very good to excellent	Surgery usually not required Partial pancreatectomy only if medical management fails	Excellent
Autosomal dominant	Unusual	Moderate onset usually post 6 mo of age	Positive	Glutamate dehydrogenase (activating)	Modest hyperammonemia	Very good to excellent	Surgery usually not required	Excellent
Beckwith–Wiedemann syndrome	Present at birth	Moderate, spontaneously resolves post 6 mo of age	Negative	Duplicating/ imprinting in chromosome 11p15.1	Macroglossia, omphalocele, hemihypertrophy	Good	Not recommended	Excellent for hypoglycemia; guarded for possible development of embryonal tumors (Wilms hepatoblastoma)
Congenital disorders of glycosylation	Not usual	Moderate/onset post 3 mo of age	Negative	Phosphomannose isomerase deficiency	Hepatomegaly, vomiting, intractable diarrhea	Good with mannose supplement	Not recommended	Fair

From Sperling MA. Hypoglycemia. In: Kliegman RM, Stanton BF, St. Geme JW III, et al., eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:778.

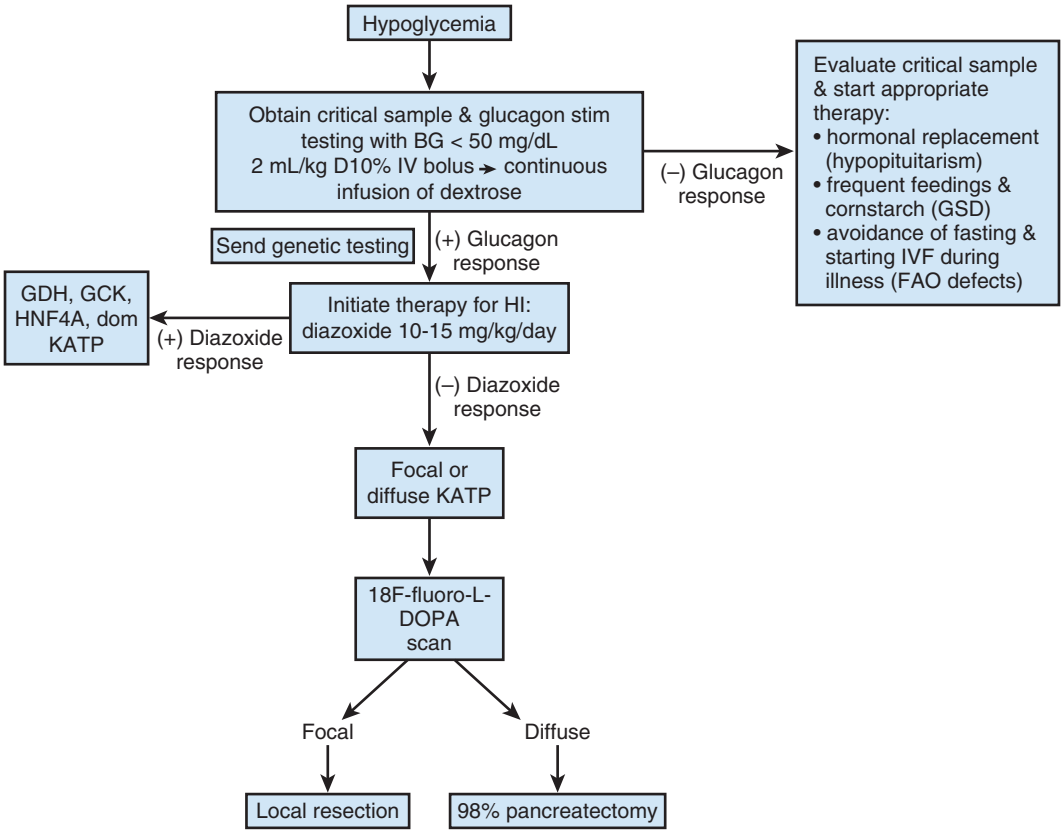


FIGURE 44.4 Diagnostic and treatment approach in cases of hyperinsulinism. BG, blood glucose; D, dextrose; dom, dominant; FAO, fatty acid oxidation; GCK, glucokinase; GDH, glutamate dehydrogenase; GSD, glycogen storage disease; HNF4A, hepatic nuclear factor 4-alpha; IV, intravenous; IVF, intravenous fluids; KATP, adenosine triphosphate-dependent potassium channel. (From De León DD, Thornton PS, Stanley CA, et al. Hypoglycemia in the newborn infant. In: Sperling MA, ed. *Pediatric Endocrinology*. 4th ed. Philadelphia: Elsevier; 2014:171, Fig. 6.8.)

Isolated Cortisol Deficiency

Fasting hypoglycemia may occur in infants and children with adrenal insufficiency of various causes, including adrenocorticotropin hormone deficiency and primary adrenal insufficiency (Addison disease), or as a consequence of adrenal suppression resulting from exogenous glucocorticoid administration. Hypoglycemia is uncommon in the presentation of newborns with congenital adrenal hyperplasia, but once glucocorticoid replacement treatment is begun, these children are also at risk for adrenal crises and hypoglycemia if not given supplemental doses during intercurrent illness.

Epinephrine Deficiency

Catecholamine deficiency is extremely rare and has been described as secondary to adrenal hemorrhage in infants small for gestational age. These patients may present for the 1st time during childhood with hypoglycemia during fasting. The diagnosis is confirmed by measurement of plasma or urinary catecholamine levels. Some affected children may show evidence, on abdominal films, of previous adrenal hemorrhage in the form of adrenal calcification.

Fasting hypoglycemia has been observed occasionally in children treated with **β-blocking agents**, such as propranolol. The mechanism appears to be suppression of lipolysis as a result of the interference with epinephrine stimulation of adipose tissue; this suppression impairs the 3rd stage of fasting adaptation. Hypoglycemia may occur after 12 or more hours of fasting. Hypoglycemic attacks may be associated with acute hypertension as a result of the unopposed α-adrenergic effects of epinephrine.

Metabolic Enzyme Defects

Hepatic Gluconeogenesis

The genetic metabolic defects in hepatic gluconeogenesis lead to fasting hypoglycemia associated with increased plasma concentrations of gluconeogenic precursors, such as lactate and alanine.

Glucose-6-phosphatase deficiency (Glycogen storage disease type 1a and type 1b). This is the most common form of the glycogen storage disorders, although (see Fig. 44.1) deficiency of glucose-6-phosphatase is actually a gluconeogenic defect as it blocks the release of glucose from both gluconeogenesis and glycogenolysis. Hypoglycemia occurs within 2-3 hours after a meal, as soon as intestinal carbohydrate absorption is complete. Affected infants usually do not present with symptomatic hypoglycemia, because the associated elevations of lactate provide an alternative fuel for the brain when the glucose level is low. Instead, the manifestation is usually growth failure late in the 1st year. The liver is massively enlarged as a result of fat and glycogen deposition and extends into the left upper quadrant and down into the pelvis. Associated abnormalities include elevations of plasma triglyceride (up to 2000-4000 mg/dL) and hyperuricemia. Treatment is aimed at correcting the frequent cycling into fasting that leads to growth failure by a combination of high-carbohydrate meals together with either uncooked cornstarch or continuous intragastric dextrose infusions. Carbohydrates that cannot be converted to glucose, such as galactose in milk, fructose in fruits, and sucrose, should be limited. The type 1b variant is caused by deficiency of the microsomal glucose-6-phosphate translocase and is associated with the additional problem of neutropenia, leading to mouth ulcers and skin infections.

Treatment with granulocyte colony-stimulating factor has been beneficial in these patients.

Glucose transporter 2 deficiency (Fanconi-Bickel syndrome). A small number of infants have been described with a combination of hepatomegaly, increased liver glycogen store, renal Fanconi syndrome, and galactose intolerance. This recessively inherited disorder is caused by pathogenic variants in the gene *SLC2A2*, which encodes glucose transporter 2 (GLUT2), a plasma membrane glucose transporter, which is expressed in liver, kidney, and pancreatic β cells. GLUT2 is necessary to export free glucose from the cytosol into the plasma (see Fig. 44.1). Deficiency of GLUT2 interferes with glucose release from the liver not only from glycogenolysis but also from gluconeogenesis and from other sugars, such as galactose and fructose.

Fructose-1,6-diphosphatase deficiency. This defect blocks gluconeogenesis immediately above the triose-phosphates (see Fig. 44.1). Affected children present in the 1st year or the neonatal period with life-threatening attacks of hypoglycemia and lactic acidemia provoked by fasting stress. Moderate fatty hepatomegaly is commonly seen together with hyperuricemia. Fructose ingestion can precipitate hypoglycemia and lactic acidemia. During controlled fasting, plasma glucose can be maintained in the normal range until 8-12 hours, because glycogenolysis remains normal. Treatment with avoidance of prolonged fasting and restriction of fructose-containing foods and glycerol is effective in avoiding hypoglycemia.

Pyruvate carboxylase deficiency. Pyruvate carboxylase is 1 of the 4 key gluconeogenic enzymes (see Fig. 44.1). It also plays an important role in pyruvate oxidation because it generates oxaloacetate needed to maintain tricarboxylic acid (TCA) cycle activity. The clinical features are often dominated by the defect in pyruvate oxidation and include those of Leigh syndrome and congenital lactic acidemia. However, affected infants are also susceptible to the development of symptomatic hypoglycemia after 8-10 hours of fasting.

Hepatic Glycogenolysis

Defects in hepatic glycogenolysis are associated with abbreviated fasting tolerance, leading to hypoglycemia and hyperketonemia. Defects can occur in either the synthesis or breakdown of hepatic glycogen (see Fig. 44.1). Debrancher enzyme deficiency is the most severe of these defects.

Debrancher enzyme deficiency (type 3 glycogen storage disease). Children with this disorder usually present in the 1st year of life with growth delay and massive hepatomegaly. Symptomatic hypoglycemia is not common, because plasma ketone levels are usually elevated and provide the brain with alternative substrate when the glucose level is low. Hypoglycemia develops quickly, often within 3-6 hours after a meal. Treatment with uncooked cornstarch to prolong glucose absorption is useful in preventing hypoglycemia and improving growth. Problems caused by hypoglycemia are ameliorated later in childhood as body mass increases. However, half or more of patients with debrancher enzyme deficiency are at risk for developing progressive muscle weakness and/or cardiomyopathy by the 2nd and 3rd decades of life.

Phosphorylase/phosphorylase kinase deficiency. The manifestations of either of these 2 enzyme defects clinically resemble a very mild form of debrancher enzyme deficiency. Affected infants present with enlarged livers, often in association with impaired growth. Symptomatic hypoglycemia is unusual. Fasting tests show a pattern of accelerated starvation with early onset of hyperketonemia. Treatment to reduce fasting intervals to less than 4-6 hours (e.g., with uncooked cornstarch) is helpful in correcting the failure to thrive. As in debrancher enzyme deficiency, the fasting disturbance becomes less apparent as body mass increases, and the hepatomegaly and growth delay may totally resolve by the end of the 1st decade. Liver phosphorylase deficiency is recessively inherited; both recessive inheritance and X-linked inheritance have been reported for phosphorylase kinase deficiency.

Glycogen synthase deficiency. A small number of patients with deficiency of glycogen synthase have been reported. They have presented with episodes of symptomatic, hyperketotic hypoglycemia after fasts of 10-12 hours. Mild hepatomegaly may be present as a result of the increased deposition of triglycerides that is common in all of the glycogenoses. Treatment with uncooked cornstarch at bedtime may be helpful in avoiding symptomatic episodes of early morning hypoglycemia.

Fatty Acid Oxidation Disorders

Genetic defects in fatty acid oxidation interfere with the ketotic phase of fasting adaptation. The most common of the disorders is medium-chain acyl-coenzyme A (CoA) dehydrogenase (MCAD) deficiency. Children with MCAD deficiency present with acute attacks of life-threatening coma and **hypoketotic hypoglycemia** that are usually precipitated by fasting stresses of 12 hours or longer. Attacks are triggered by intercurrent illnesses that impair feeding, especially gastroenteritis. The clinical features mimic Reye syndrome, with coma, elevated liver transaminase levels, and mild hepatomegaly with steatosis. More severe forms of fatty acid oxidation disorders also involve skeletal and cardiac muscle and may manifest with cardiomyopathy and chronic muscle weakness or acute episodes of rhabdomyolysis. More than 12 different defects in the pathway of fatty acid oxidation have been identified; all are recessively inherited. Many states have neonatal screening programs in which dual tandem mass spectrometry of blood spot acylcarnitine profiles are used to detect MCAD deficiency and several of the other fatty acid oxidation disorders. This is important for presymptomatic detection and treatment, because the mortality rate at the 1st presentation may be higher than 25%.

Other Metabolic Causes of Hypoglycemia

Glucose transporter 1 deficiency. Isolated hypoglycorrhachia (low cerebrospinal fluid glucose level) in association with normal concentrations of plasma glucose has been demonstrated in a number of infants with intractable seizures in early infancy caused by a deficiency of glucose transporter 1 (GLUT1). GLUT1 is the plasma membrane carrier protein responsible for glucose transport across the blood-brain barrier, as well as into red blood cells. Affected patients are heterozygous for a GLUT1 mutation and have persistently low levels of spinal fluid glucose, ranging from 20-30 mg/dL. Seizures may begin in the neonatal period and respond poorly to treatment with antiseizure drugs. Progressive brain damage, microcephaly, and developmental delay occur in untreated patients. Several patients have been reported to respond very well to treatment with a ketogenic diet, which restricts carbohydrates and keeps plasma levels of ketones elevated to 3-6 mEq/L.

Hereditary fructose intolerance. Hereditary fructose intolerance is caused by a recessively inherited deficiency of hepatic fructose-aldolase, which transforms fructose-1-phosphate to the triose-phosphates. Affected patients cannot metabolize dietary fructose or sucrose (table sugar) in the liver or intestinal mucosa for conversion to glucose. Chronic fructose intake in young infants may cause liver dysfunction, acidemia, failure to thrive, hyperuricemia, and, ultimately, liver failure. In affected older children, ingestion of fructose causes severe abdominal pain, and these children may learn by experience to avoid fructose and thus escape identification. Fasting tolerance is normal, but ingestion of large amounts of fructose may provoke postprandial hypoglycemia by tying up intracellular phosphate and thus blocking glycogenolysis. Treatment is avoidance of dietary sources of fructose.

Galactosemia (galactose-1-phosphate uridyl transferase deficiency). This is a serious inborn error of metabolism wherein many of the long-term consequences of the metabolic defect can potentially be prevented by early intervention. For this reason, all infants born in the United States are screened for galactosemia in the neonatal period. Absence of galactose-1-phosphate uridyl transferase prevents the conversion of galactose to glucose and results in accumulation of galactose-1-phosphate in the liver and other tissues. It has been suggested that accumulation of this metabolite inhibits the enzyme involved in the conversion of glucose-1-phosphate to glucose-6-phosphate and thus decreases the production of glucose from glycogen, thereby producing hypoglycemia. Depending on the magnitude of the defect, affected infants may present in the immediate neonatal period or later in infancy. The patients do not tolerate galactose or lactose. Intolerance to lactose in milk, the major nutrient containing galactose, is evident soon after birth when feedings are initiated. The infant may present with vomiting, failure to thrive, hepatomegaly, and indirect or direct hyperbilirubinemia. In severe or untreated cases, lenticular opacities, aminoaciduria, and intellectual disability may occur. In untreated patients, progressive hepatomegaly, cirrhosis, and hepatic failure may develop. Affected infants are at increased risk for *Escherichia coli* sepsis.

Any infant with persistent jaundice, hepatomegaly, and failure to thrive should be tested for galactosemia. A presumptive diagnosis can be made by the presence of reducing sugar (Clinitest positive) that is not glucose (i.e., the glucose enzyme test result is negative) in the urine. This test should be performed while the infant is being fed a galactose-containing formula. The diagnosis should be confirmed by measuring the enzyme activity in the red blood cells.

Treatment consists of elimination of galactose from the diet. In spite of treatment, which results in prevention of hepatic disease and of intellectual disability, many affected older children demonstrate learning and behavior problems.

Reactive Hypoglycemia

Reactive or postprandial hypoglycemia is extremely rare in the pediatric age range and, even in adults, may be overdiagnosed. Only 2 situations in infants and children present with reactive hypoglycemia:

Glutamate dehydrogenase-hyperinsulinism, hyperinsulinism/hyperammonemia syndrome. Affected children have fasting hypoglycemia, but because of their leucine sensitivity, may also develop symptomatic hypoglycemia within 30-90 minutes of eating a high-protein meal.

Post–Nissen fundoplication hypoglycemia (late dumping syndrome). Similar to patients who have had gastric surgery, infants who have undergone Nissen fundoplication procedures for gastroesophageal reflux can develop recurrent attacks of postprandial hypoglycemia. The hypoglycemia may be severe enough to produce seizures and permanent brain damage. The mechanism is thought to involve rapid gastric emptying that leads to a rapid rise in plasma glucose accompanied by a delayed but excessive insulin response, which is followed by a precipitous fall in plasma glucose to hypoglycemic levels 30-90 minutes after a meal.

Hereditary fructose intolerance. Patients with this disorder develop acute abdominal discomfort and hypoglycemia within a short period of time after an oral load of fructose (e.g., fruit, fruit juice, or sucrose).

DIAGNOSIS OF HYPOGLYCEMIA

Critical Samples

Tests on the specimens of blood and urine obtained at the time of hypoglycemia provide the key information for diagnosis (Table 44.6 and Fig. 44.5). Ideally, these specimens are collected during hypoglycemia, immediately before treatment is begun. It is best to collect some extra tubes of plasma and urine just before giving intravenous dextrose, to set aside for later decisions about which other tests to order. Tests should include plasma glucose measurement, various metabolic precursors and hormones involved in glucose counter-regulation, including glucose, bicarbonate, insulin, growth hormone, cortisol, lactate, pyruvate, ammonia, β-hydroxybutyrate, free fatty acid, carnitine, acylcarnitine profile, and a urine sample for organic acid analysis and ketones. Additional tests to consider include transaminases, uric acid, triglycerides, and creatinine kinase levels. Fig. 44.5 shows a paradigm for diagnosis of different hypoglycemic disorders that is based on analysis of the critical samples.

Fasting Study

In some cases, a formal fasting test is advised to establish the etiology of hypoglycemia. This should only be done in a well controlled setting with adequate monitoring by experienced medical and nursing staff.

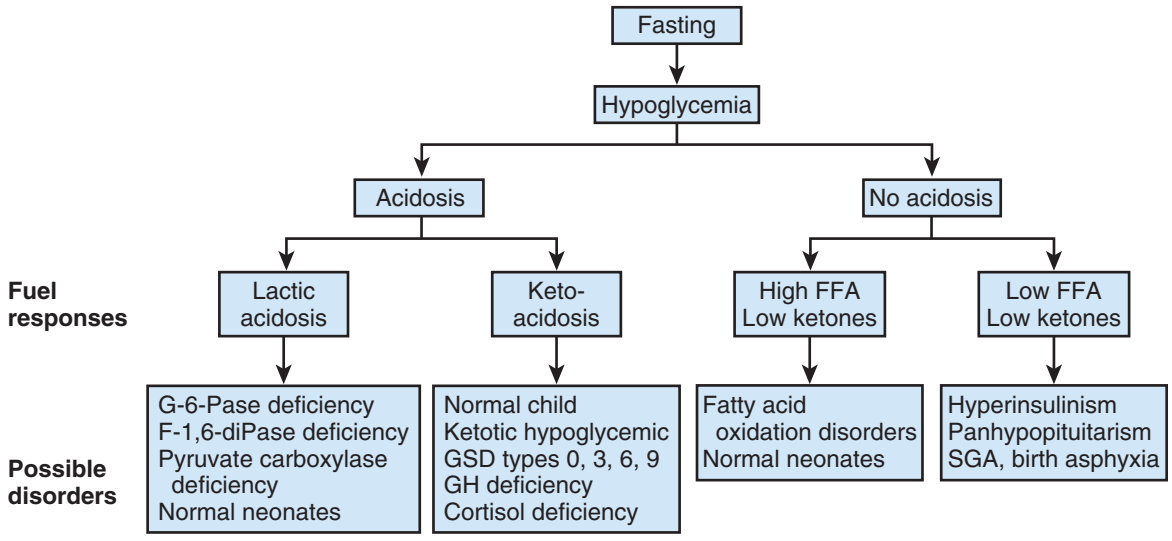


FIGURE 44.5 Algorithm for diagnosis of hypoglycemia, based on fasting fuel responses. F-1,6-diPase, fructose-1,6-diphosphatase; FFA, free fatty acid; G-6-Pase, glucose-6-phosphatase; GH, growth hormone; GSD, glycogen storage disease; SGA, small for gestational age.

TABLE 44.6 Clinical Manifestations and Differential Diagnosis in Childhood Hypoglycemia

				SERUM		EFFECT OF 24–36 hr FAST ON PLASMA					GLYCEMIC RESPONSE TO GLUCAGON		GLYCEMIC RESPONSE TO INFUSION OF	
Condition	Hypoglycemia	Urinary Ketones or Reducing Sugars	Hepatomegaly	Lipids	Uric Acid	Glucose	Insulin	Ketones	Alanine	Lactate	Fed	Fasted	Alanine	Glycerol
Normal	0	0	0	Normal	Normal	↓	↓	↑	↓	Normal	↑	↓		Not indicated
Hyperinsulinemia	Recurrent severe	0	0	Normal or ↑	Normal	↓↓	↑↑	↓↓	Normal	Normal	↑	↑		Not indicated
Ketotic hypoglycemia	Severe with missed meals	Ketonuria +++	0	Normal	Normal	↓↓	↓	↑↑	↓↓	Normal	↑	↓↓		Not indicated
Fatty acid oxidation disorder	Severe with missed meals	Absent	0 to + Abnormal liver function test results	Abnormal	↑		Contraindicated				↑	↓		Not indicated
Hypopituitarism	Moderate with missed meals	Ketonuria ++		Normal	Normal	↓↓	↓	↑↑	↓↓	Normal	↑	↓↓	↑	↑
Adrenal insufficiency	Severe with missed meals	Ketonuria ++	0	Normal	Normal	↓↓	↓	↑↑	↓↓	Normal	↑	↓↓	↑	↑
Enzyme deficiencies	Severe-constant	Ketonuria +++	+++	↑↑	↑↑	↓↓	↓	↑↑	↑↑	↑↑	0	0-↓↓	0	0
Glucose-6-phosphatase debrancher	Moderate with fasting	++	++	Normal	Normal	↓↓	↓	↑↑	↓↓	Normal	↑	0-↓↓	↑	↑
Phosphorylase	Mild-moderate	Ketonuria ++	+	Normal	Normal	↓	↓	↑↑	↓↓	Normal	0-↑	0-↓↓	↑	↑
Fructose-1, 6-diphosphatase	Severe with fasting	Ketonuria +++	+++	↑↑	↑↑	↓↓	↓	↑↑	↑↑	↑↑	↑	0-↓↓	↓	↓
Galactosemia	After milk or milk products	0 Ketones; (s) +	+++	Normal	Normal	↓	↓	↑	↓	Normal	↑	0-↓↓	↑	↑
Fructose intolerance	After fructose	0 Ketones; (s) +	+++	Normal	Normal	↓	↓	↑	↓	Normal	↑	0-↓↓	↑	↑

Details of each condition are discussed in the text.
0, absence; ↑ or ↓, small increase or decrease, respectively; ↑↑ or ↓↓, large increase or decrease, respectively; +, less likely; ++, likely; +++, definitively.
From Sperling MA. Hypoglycemia. In: Kliegman RM, Stanton BF, St. Geme JW III, et al., eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:780.

Fasting is usually begun at 8 P.M. after bedtime snack or sometimes in the morning, especially in younger patients, to make sure that there is enough supervision and staff available during the time hypoglycemia occurs.

Useful "Casual Specimen" Tests

Only a few tests are informative except at times of hypoglycemia. These include plasma acyl-carnitine profiles and plasma total and free carnitine levels (for suspected fatty acid oxidation defects) and plasma ammonia (for the HI/HA syndrome).

Glucagon Stimulation

If HI is suspected, a glucagon stimulation test at the onset of hypoglycemia (50 mg/dL) may be confirmatory. A glycemic response exceeding 30 mg/dL is consistent with HI, because the normal response would be to have depleted liver glycogen reserves well before reaching hypoglycemia.

Acute Insulin Response Tests for Hyperinsulinism

β-Cell responsiveness to different secretagogues (calcium, leucine, glucose, tolbutamide) can be used to define specific genetic forms of HI and to distinguish focal from diffuse pancreatic disease preoperatively.

Plasma Acyl-Carnitine Profile

Dual tandem mass spectrometry methods have been developed for analyzing plasma acyl-carnitine profiles and other metabolites in small samples, such as filter paper blood spots. These assays are useful for screening for most of the genetic fatty acid oxidation disorders (e.g., MCAD deficiency) and should be performed before patients suspected to have such a defect begin a formal fasting test. Many states incorporate these methods for neonatal screening of up to 30 different inborn errors of metabolism. Some fatty acid oxidation defects do not cause abnormal acyl-carnitine profiles; examples include carnitine palmityl-transferase 1 deficiency, carnitine transporter deficiency, and β-hydroxy-β-methylglutaryl-CoA dehydrogenase deficiency. These disorders must be investigated with additional in vivo and in vitro tests.

Urinary Organic Acid Quantitation

Assays of urinary metabolites by gas chromatography–mass spectrometry are also useful in identifying specific defects in fatty acid oxidation. Abnormalities are most pronounced during activation of lipolysis, such as at the end of a diagnostic fasting test or in the "critical sample" urine collected at the time of an acute illness.

Cultured Cells

For in vitro diagnosis of fatty acid oxidation defects, cultured cells from patients, such as skin fibroblasts or lymphoblasts, may be useful for testing overall pathway activity, for assaying activities of candidate enzymes, or as a source of DNA for mutation analysis. Most enzymes in the pathway are expressed in cultured cells, with the exception of 3-hydroxy-3-methylglutaryl–CoA synthase, which is restricted to liver, intestine, and kidney.

Mutation Analysis

Mutation identification is useful for confirmation of diagnosis and genetic counseling. In a limited number of disorders, common mutations that can be easily screened for as a primary diagnostic test have been identified. These include MCAD deficiency, glucose-6-phosphatase deficiency, and hyperinsulinemia due to ATP-binding cassette transporter 8 *(ABCC8)*, ATP sensitive inward rectifier potassium channel 11 *(KCNJ11A)*, mitochondrial glutamate dehydrogenase 1 *(GLUD1)*, hepatic nuclear factor 4-alpha *(HNF4A)*, glucokinase *(GCK)*, mitochondrial hydroxylacyl-coenzyme A *(HADH)*, and mitochondrial uncoupling protein 2 *(UCP2)*. Easy access to information about disease-associated mutations is available through the Online Mendelian Inheritance in Man (OMIM) web site (http://www.ncbi.nlm.nih.gov/Omim/).

TREATMENT OF HYPOGLYCEMIA

The initial treatment of hypoglycemia is to promptly raise the plasma glucose level to normal and maintain it in the range of 80-100 mg/dL. For long-term management, the minimum goal of therapy is to keep the plasma glucose level above 60 mg/dL at all times.

Whenever treatment begins in a patient with new-onset hypoglycemia, every effort should be made to collect the critical samples for diagnosis. One extra tube of 5 mL of plasma or serum (green-top or red-top tube) is sufficient to measure key chemistry levels, fuels, and hormones. An extra tube of 10 mL or more of urine should also be collected for urinary organic acid quantitation.

For emergency treatment of hypoglycemia, a bolus of dextrose, 200 mg/kg, is given rapidly, and then a continuous infusion is begun to run at a rate equal to at least normal hepatic glucose output (about 4-6 mg/kg/min). With 10% dextrose solutions, this means a bolus of 2 mL/kg followed by continuous infusion at maintenance rates. Infants with HI may require considerably higher rates of dextrose infusion, up to 20-30 mg/kg/min. Infants with fatty acid oxidation disorders should receive sufficient dextrose to ensure that insulin secretion is stimulated enough to suppress lipolysis—that is, 10% dextrose at 8-10 mg/kg/min—and to maintain all plasma glucose levels slightly above 100 mg/dL. Glucagon may be used to treat hypoglycemia on an emergency basis, but only if the hypoglycemia is known to be caused by HI; a dose of 1 mg should be used at all ages to avoid undertreatment.

SUMMARY AND RED FLAGS

Hypoglycemia has many manifestations and must be thought of as a cause of nonspecific signs in newborns. It is a readily treatable cause of lethargy, coma, and seizures. Other affected children have signs of catecholamine excess. Untreated symptomatic hypoglycemia is life-threatening and can produce significant, irreversible central nervous system injury.

Red flags include metabolic acidosis (inborn errors of metabolism, sepsis); a positive family history (inborn errors of metabolism, hyperinsulinism, hypoglycemic agents); hypoketonuria (hyperinsulinemia, fatty acid oxidation defects) and high glucose infusion rates (hyperinsulinism); onset during adolescence (drugs or alcohol); hepatomegaly (glycogen storage disease, other inborn errors of metabolism); feeding intolerance (galactosemia); or recurrent or a family history of emesis, lethargy, coma, or sudden infant death syndrome (medium-chain acyl dehydrogenase deficiency).

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

General

Cornblath M, Hawdon JM, Williams AF, et al. Controversies regarding definition of neonatal hypoglycemia: suggested operational thresholds. *Pediatrics*. 2000;105:1141-1145.

Online Mendelian Inheritance in Man. Available at <http://www.ncbi.nlm.nih.gov/Omim/>; Accessed 04.11.2003.

Scriver CR, Sly WS, Childs B, et al., eds. *The Metabolic and Molecular Basis of Inherited Disease*. 8th ed. New York: McGraw-Hill; 2001.

Stanley CA, Baker L. The causes of neonatal hypoglycemia. *N Engl J Med*. 1999;340:1200-1201.

Stanley CA, Thornton PS, Finegold DN, et al. Hypoglycemia in neonates and infants. In: Sperling MA, ed. *Pediatric Endocrinology*. Philadelphia: WB Saunders; 2002.

Thornton PS, Finegold DN, Stanley CA, et al. Hypoglycemia in the infant and child. In: Sperling MA, ed. *Pediatric Endocrinology*. Philadelphia: WB Saunders; 2002.

Hyperinsulinism

Aynsley-Green A, Hussain K, Hall J, et al. Practical management of hyperinsulinism in infancy. *Arch Dis Child Fetal Neonatal Ed*. 2000;82:F98-F107.

Collins JE, Leonard JV, Teale D, et al. Hyperinsulinaemic hypoglycaemia in small for dates babies. *Arch Dis Child*. 1990;65:1118-1120.

DeVivo DC, Trifiletti RR, Jacobson RI, et al. Defective glucose transport across the blood-brain barrier as a cause of persistent hypoglycorrhachia, seizures, and developmental delay. *N Engl J Med*. 1991;325:703-709.

Ferry RJ Jr, Kelly A, Grimberg A, et al. Calcium-stimulated insulin secretion in diffuse and focal forms of congenital hyperinsulinism. *J Pediatr*. 2000;137:239-246.

Glaser B, Kesavan P, Heyman M, et al. Familial hyperinsulinism caused by an activating glucokinase mutation. *N Engl J Med*. 1998;338:226-230.

Glaser B, Thornton P, Otonkoski T, et al. Genetics of neonatal hyperinsulinism. *Arch Dis Child Fetal Neonatal Ed*. 2000;82:F79-F86.

Grimberg A, Ferry RJ, Kelly A, et al. Dysregulation of insulin secretion in children with congenital hyperinsulinism due to sulfonylurea receptor mutations. *Diabetes*. 2001;50:322-328.

Huopio H, Reimann F, Ashfield R, et al. Dominantly inherited hyperinsulinism caused by a mutation in the sulfonylurea receptor type 1. *J Clin Invest*. 2000;106:897-906.

MacMullen C, Fang J, Hsu BYL, et al. Hyperinsulinism/hyperammonemia syndrome in children with regulatory mutations in the inhibitory GTP binding domain of glutamate dehydrogenase. *J Clin Endocrinol Metab*. 2001;86:1782-1787.

Munns CFJ, Batch JA. Hyperinsulinism and Beckwith-Wiedemann syndrome. *Arch Dis Child Fetal Neonatal Ed*. 2001;84:F67-F69.

Santer R, Schneppenheim R, Dombrowski A, et al. Mutations in GLUT2, the gene for the liver-type glucose transporter, in patients with Fanconi-Bickel syndrome. *Nat Genet*. 1997;17:324-326.

Stanley CA. Hyperinsulinism in infants and children. *Pediatr Clin North Am*. 1997;44:363-374.

Fatty Acid Oxidation Disorders

Stanley CA, Hale DE. Genetic disorders of mitochondrial fatty acid oxidation. *Curr Opin Pediatr*. 1994;6:476.

Treem WR, Shoup ME, Hale DE, et al. Acute fatty liver of pregnancy, hemo lysis, elevated liver enzymes, and low platelets syndrome, and long chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency. *Am J Gastroenterol*. 1996;91:2293-2300.

Ziadeh R, Hoffman EP, Finegold DN, et al. Medium chain acyl-CoA dehydrogenase deficiency in Pennsylvania: neonatal screening shows high incidence and unexpected mutation frequencies. *Pediatr Res*. 1995;37:675.

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Urinary Incontinence and Polyuria

Cynthia G. Pan

Urinary incontinence is a normal developmental stage. When present beyond a certain age defined by parental and societal expectations, it can cause concern and anxiety in the patient and family. Urinary incontinence can also be a symptom of significant pathologic processes. The challenge to the clinician is identifying the child with an organic disorder among the many who are proceeding along a normal developmental track.

VOIDING PHYSIOLOGY

Urinary continence is dependent on normal bladder function and normal urine production. Normal development of bladder function results in the storage and release of urine in a socially and physically acceptable way. During storage, the detrusor muscle is relaxed, and the capacity of the bladder allows urine to be held for several hours. Micturition is then voluntary, with coordinated detrusor contraction and sphincter relaxation, resulting in complete bladder emptying. The bladder capacity in children learning to be toilet trained is variable, being dependent on their own sensation of bladder fullness. The maximum functional bladder capacity may differ greatly among children when measured by home diaries. Cystometry, a method of measuring bladder volume, can be estimated by the following 2 formulas:

In children <2 years of age:

$$\text{Cystometric bladder capacity (ounces)} = (2 \times \text{age [years]}) + 2$$

In children ≥2 years of age:

$$\text{Cystometric bladder capacity (ounces)} = \frac{\text{age (years)}}{2} + 6$$

Although the innervation of the bladder is predominantly autonomic, bladder function is under control of cortical function. Thus, a complex integration of visceral and somatic innervation is necessary for normal voiding, which perhaps explains the wide spectrum in the ages for urinary continence. Parasympathetic neural activity provides the primary input during micturition, leading to relaxation of the urethral smooth muscle and initiating detrusor contractions. Pelvic nerves conducting parasympathetic activity form a reflex arc with the centrally located pontine micturition center. The thoracolumbar sympathetic branch, via hypogastric and pelvic sympathetic nerves, innervates the detrusor to relax and the urinary sphincter to contract during urine storage.

Urinary continence thus relies on the abilities to (1) store urine without leakage, (2) release urine voluntarily and completely, and (3) interrupt micturition voluntarily. The third ability is indicative of fully coordinated cortical-autonomic function.

TOILET TRAINING

The age at which toilet training is achieved is influenced by cultural factors as well as the individual temperament of the child. The achievement of daytime urinary continence follows the attainment of bowel control. There is evidence that the age of daytime and nighttime continence has increased worldwide in the past century. Data suggest a change in parental attitudes toward the toilet training process and their expectations. Temperament of the child and cognitive ability may play a less significant role. Among social factors, children of single parents are successfully toilet trained at an earlier age, whereas enrollment in daycare does not have a significant influence. Consistent findings are the predictive factors of gender and race: Girls are toilet trained earlier than boys, and African-American children are trained earlier than white children. Techniques for toilet training are varied and range from the child-oriented approach to single-day training intensive methods to the use of daytime wet alarms.

URINE VOLUME AND SOLUTE DIURESIS

Polyuria is the overproduction of urine. Polyuria is a symptom that is fixed and therefore occurs during both the daytime and the nighttime. "Nocturnal polyuria," a symptom proposed in a subset of patients with primary nocturnal enuresis, is discussed separately. Overproduction of urine indicates a defect in 1 of several mechanisms regulating water and solute homeostasis. Identification of children with incontinence caused by polyuria is essential for diagnosing a variety of disorders (Table 45.1).

Urine production varies depending on the intake of fluids and solute, activity, caloric expenditure, and the environment. The volume reflects the maintenance of normal fluid and electrolyte balance (1) through the regulation of plasma osmolality by vasopressin and through the thirst mechanism and (2) by the regulation of extracellular volume and solute (mainly sodium) homeostasis by the kidney. The sensation of thirst occurs when plasma osmolality rises above a threshold of 280-290 mOsm/L. Release of vasopressin, a peptide produced by the hypothalamus, parallels the sensation of thirst and then acts on receptors in the collecting ducts of the kidney to diminish water excretion and to concentrate the urine. Hypovolemia is also a stimulant for vasopressin. Once serum osmolality is restored to normal, vasopressin release is inhibited, and renal water excretion increases. Maintenance of extracellular fluid volume depends on sodium homeostasis and directly affects urine volume. It involves the interaction of several systems, including (1) the renin-angiotensin system, (2) atrial natriuretic peptide, and (3) the sympathetic nervous system.

Among patients with primary nocturnal enuresis, there is a subset of patients with "nocturnal polyuria," in which larger volumes of more

(See *Nelson Textbook of Pediatrics,* p. 2584.)

(See *Nelson Textbook of Pediatrics,* p. 2581.)

TABLE 45.1 Causes of Urinary Incontinence

With Polyuria
Osmotic diuresis (urine osmolality > plasma osmolality)
Diabetes mellitus
Central diabetes insipidus
Nephrogenic diabetes insipidus
Primary
- X-linked (most common)
- Autosomal recessive
- Autosomal dominant

Secondary
- Obstructive uropathy: concurrent or postobstructive
- Polyuric phase of acute kidney injury
- Chronic renal failure
- Juvenile nephronophthisis
- Fanconi syndrome (e.g., cystinosis)
- Hypokalemia
- Hypercalcemia
- Bartter syndrome
- Gitelman syndrome
- Sickle cell disease
- Renal tubular acidosis
- Medications (e.g., lithium)
- Interstitial nephritis

Without Polyuria
Primary nocturnal enuresis*
Dysfunctional voiding syndromes
Neuropathic bladder
Anatomic defects of the urinary tract

*Some cases may be characterized by nocturnal polyuria.

TABLE 45.2 Secondary and Acquired Forms of Nephrogenic Diabetes Insipidus-Like Disorders

Acquired
Chronic pyelonephritis
Tubulointerstitial nephritis
Chronic renal failure secondary to obstructive uropathy
Drug-induced tubulopathy

Congenital
Renal tubular acidosis
Nephrocalcinosis
Cystinosis
Sickle cell nephropathy
Juvenile nephronophthisis
Renal dysplasia
Cystic kidney disease
Bartter syndrome
Storage diseases (tyrosinemia, Fabry disease)

dilute urine are produced than in patients who remain dry. Responsiveness to the administration of vasopressin analogs, such as desmopressin acetate (1-deamino[8-D-arginine] vasopressin [DDAVP]), differentiates such patients into responders and nonresponders.

◆ History

The history should begin with careful questioning to determine whether the patient has polyuria. The presence of polyuria suggests a variety of metabolic, systemic, and kidney diseases, whereas the absence of polyuria places the focus on the lower urinary tract (Table 45.2; see also Table 45.1).

Polyuria

Polyuria, the excessive production of urine, can result from the absence of release of antidiuretic hormone (ADH), the failure of the kidney to respond to ADH, or an osmotic diuresis. This can lead to urinary incontinence, especially in young children. Polyuria always results in polydipsia. It is often easier to query parents as to whether the volume of fluid intake by the child is excessive rather than to obtain an estimate of the volume of urine output. The 1st clue to polydipsia in infants is irritability and "hunger" after a successful feeding of formula or breast milk. In young children, favoring water over solids or milk, as well as seeking water in unusual places (e.g., toilets), can be a sign of polydipsia. Waking to seek fluids at night in a consistent pattern is also a sign of polydipsia. Parental stories of bed linens being soaked despite a "double diaper" or training pull-on diaper, are remarkable, especially when recounted by experienced parents who are able to compare the child to other healthy siblings.

An osmotic diuresis leading to polyuria may be an early sign of diabetes mellitus. The previously dry child may develop secondary nocturnal or even daytime enuresis. Associated symptoms include polydipsia and polyphagia with poor weight gain, and fatigue. Children with central diabetes insipidus (CDI) and the genetic forms of nephrogenic diabetes insipidus (NDI) produce very large amounts of hypotonic urine. Along with polyuria and enuresis, these children may have a history of frequent hospitalizations for dehydration, often provoked by relatively minor illnesses. The dehydration is often associated with moderate or severe hypernatremia. Failure to thrive may develop as a result of a preference of low calorie-containing fluids over solid foods. The secondary causes of NDI may include a partial defect in the mechanism for renal concentrating, and urinary incontinence may be the only symptom (see Table 45.2). Conversely, other children may also have growth retardation as a result of associated chronic renal failure or the associated metabolic abnormalities (e.g., metabolic acidosis in renal tubular acidosis [RTA] or rickets in Fanconi syndrome, metabolic alkalosis in Bartter syndrome).

Voiding History

In the presence of enuresis but the absence of polyuria, a voiding history helps to determine whether additional evaluation is warranted. Is the urinary incontinence nocturnal only, or is daytime incontinence also present? Does the patient have stool incontinence? Voiding frequency is sometimes difficult to ascertain in a school-age child, and an assignment to keep a diary of voiding can be given on the 1st visit. This should include information on both bladder and bowel habits, specifically urine volumes and when urinary incontinence occurs. Urine holding patterns with overflow incontinence are most easily identifiable with a diary. Incontinence can be a symptom of a urinary tract infection (UTI) (see Chapter 18). Associated symptoms may include dysuria, frequency, and urgency. Other urinary symptoms such as dysuria, urgency, dampness in the underwear, or other signs of UTI, can all be signs of dysfunctional elimination. Asking parents for specific observations—such as (1) the sudden urge to void followed by incontinence or (2) maneuvers to prevent urine leakage, such as squatting and pressing the heel of the foot into the perineum—elicits clues to a hyperactive detrusor muscle. Incontinence may occur with giggling, with physical stress while jumping, or with activities that require Valsalva maneuvers.

(See *Nelson Textbook of Pediatrics,* p. 2645.)

Secondary enuresis is defined as enuresis occurring after a dry period of at least 6 consecutive months and can be the 1st sign of an acquired renal or metabolic disease. Fecal soiling or constipation may be an accompanying sign of dysfunctional elimination, but it should first raise suspicion for an occult spinal lesion such as spina bifida or a tethered cord. In addition, continuous dribbling, a poor urinary stream, or recurrent infections may be a sign of anatomic or neuropathic lesions (see Table 45.2).

Primary Nocturnal Enuresis

The patient with nocturnal enuresis (bedwetting) is typically without any major daytime symptoms. Enuresis is considered primary when the patient has not had any dry periods for greater than 6 months. Toilet training for daytime control is often achieved easily. The frequency of wet nights should be ascertained to gauge the magnitude of the problem. A family history of nocturnal enuresis increases a patient's risk for nocturnal enuresis. If both parents have a history of enuresis, the rate of recurrence in offspring may be as high as 70-80%. If the father had primary nocturnal enuresis, the child has a fivefold to sevenfold increase in risk.

Behavioral Issues

Social stressors should be ascertained because psychologic factors are important in the occurrence of secondary enuresis. Other psychiatric issues, such as attention-deficit/hyperactivity disorder, have been associated with a higher incidence of daytime and nighttime incontinence. It has been widely accepted, however, that primary nocturnal enuresis is not a psychiatric disorder and that affected children are often emotionally well adjusted. Nonetheless, care should be taken not to underestimate the sequelae of enuresis in the older school-age child, who may feel "abnormal" among peers. Evaluation of the patient should always include inquiring how the patient and other family members are reacting to the problem and how it may be interfering with social or school issues.

Finally, primary nocturnal enuresis may be a sleep disorder or a disorder of arousal. Patients with severe nocturnal enuresis may have defects in arousal to auditory stimuli. Inquiry into symptoms of sleep apnea should also be made, such as snoring or restless sleep, as it may lead to altered arousal states leading to nocturnal enuresis in patients with sleep apnea (see Chapter 5).

◆ Physical Examination

In all affected patients, their growth should be evaluated, because failure to thrive can be seen in many of the metabolic disorders that produce polyuria. The presence of hypertension suggests underlying renal or urologic abnormalities. Careful evaluation of the lower back may reveal cutaneous abnormalities such as hair tufts, pits, dimpling, or vascular malformations, which are possible signs of spina bifida occulta or tethered cord. A significant deviation of the gluteal cleft may also suggest the possibility of spinal dysraphism. The abdominal examination is important for detecting a distended bladder, suprapubic tenderness, or significant stool retention. A neurologic examination should include assessment of lower extremity deep tendon reflexes, observation of the gait, and evaluation of perineal sensation and anal sphincter tone, again screening for the possibility of a neuropathic bladder. Anatomic abnormalities leading to incontinence should be sought by inspection of the genitalia. In girls, the examination includes a search for fused labial folds and dribbling urine from an ectopic ureter. In boys, the phallus should be inspected for the presence of epispadias or undescended testicles.

◆ Diagnosis

The presence or absence of polyuria helps guide the necessary laboratory and radiologic testing (Figs. 45.1 and 45.2). An immediate

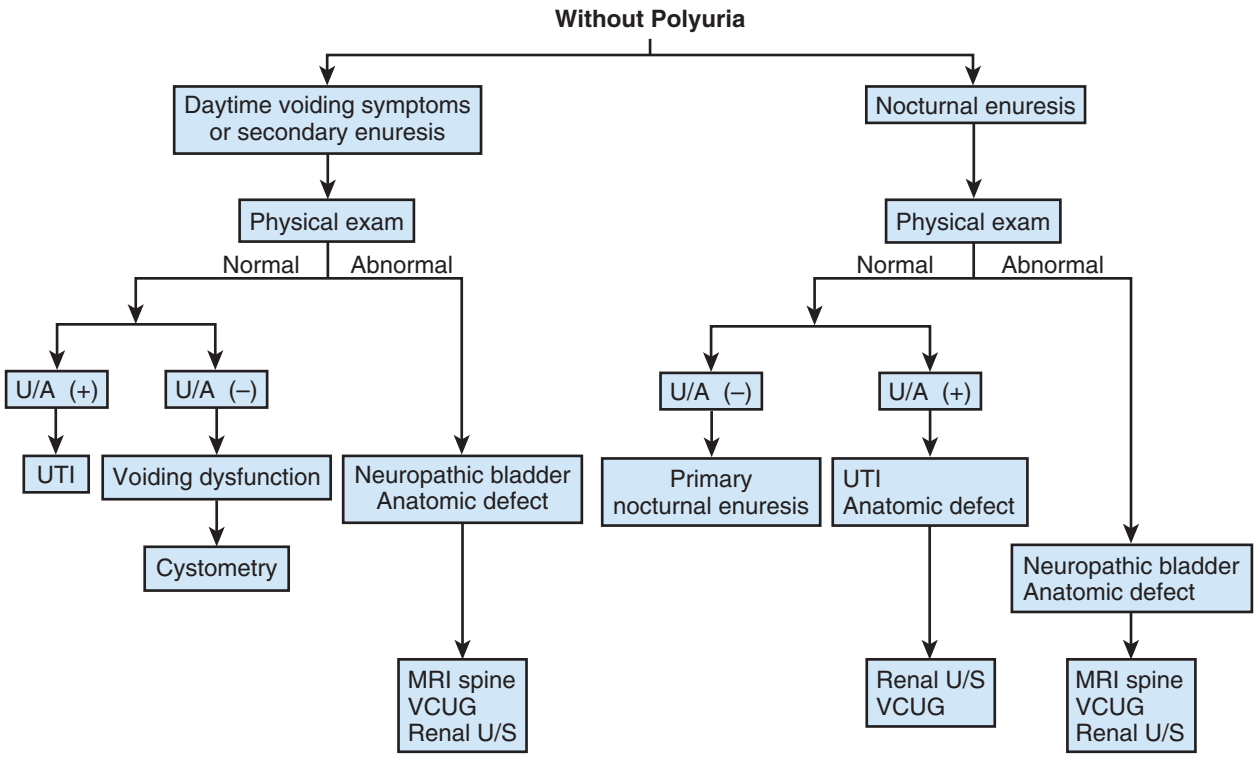

FIGURE 45.1 Diagnosis of enuresis without polyuria. MRI, magnetic resonance imaging; U/A, urinalysis; U/S, ultrasonography; UTI, urinary tract infection; VCUG, voiding cystourethrogram; +, positive; –, negative.

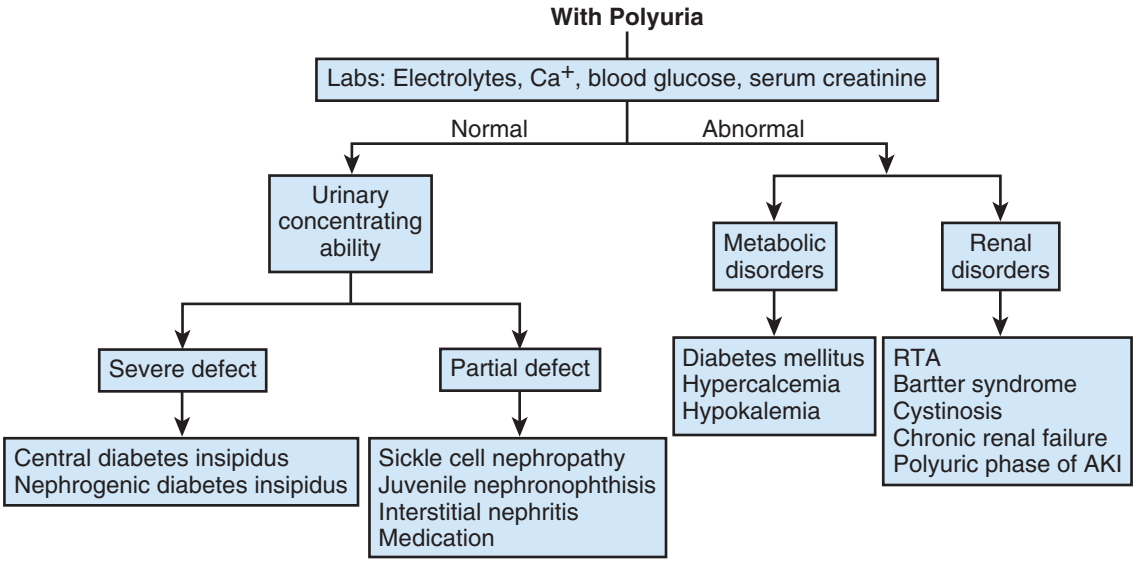

FIGURE 45.2 Diagnosis of enuresis with polyuria. RTA, renal tubular acidosis; AKI, acute kidney injury.

urinalysis is critical for differentiating the glycosuria of diabetes mellitus from the low specific gravity (osmolality) of diabetes insipidus or the proteinuria and/or hematuria of chronic renal disease.

A water deprivation test to examine urine concentrating capacity of patients when diabetes insipidus is suspected should be done in a hospital setting, with close observation of and attention to urine and serum osmolarity, urine output, and weight loss. In patients with significant polyuria, dehydration and hyperosmolarity are easily precipitated with several hours of water deprivation. For patients with a less suspect history of polyuria, a 1st morning void after an overnight fast should be sufficient for checking urine osmolarity or specific gravity.

In some patients, the problem can be better defined with a home voiding diary, which outlines how often and how much they are voiding, and when urinary incontinence, constipation, or encopresis occurs.

◆ Laboratory Assessment

Routine laboratory examination in patients with monosymptomatic nocturnal enuresis includes a urinalysis and then is diagnosed by taking a good history and performing a complete physical examination. In patients with diurnal enuresis or secondary enuresis or when polyuria or polydipsia is present, a screening urinalysis, followed by appropriate blood chemistry studies are important for confirming diabetes mellitus or electrolyte disorders such as metabolic acidosis (RTA), metabolic alkalosis (Bartter syndrome), hypercalcemia, and hypokalemia. Hypernatremia can be seen in the severe forms of diabetes insipidus. UTI should be sought in most patients with incontinence by obtaining a urinalysis and urine culture. A urinalysis also helps screen for occult, chronic glomerular or tubular renal disease. Hematuria or proteinuria can be a sign of renal disease, although its absence does not exclude this possibility. Glycosuria, when associated with normal serum glucose, can indicate tubulointerstitial disease, where proximal tubular injury results in a lowered threshold for glucose reabsorption (see Table 45.2).

◆ Imaging and Cystometry

Radiologic imaging is not necessary in most patients with primary nocturnal enuresis. In select patients with secondary enuresis, daytime symptoms, or a suspect history or urinalysis, renal ultrasonography may provide information regarding acquired or congenital renal diseases. Images of the bladder can reveal urologic abnormalities, including poor bladder emptying or thickened bladder wall. A voiding cystourethrogram is indicated only in patients with a questionable urinary stream, continuous dribbling (aberrant ectopic ureter), or suspected spinal cord lesions with lower extremity neurologic signs. Magnetic resonance imaging of the lower spine should be reserved for patients with cutaneous signs, neurologic or orthopedic symptoms of the lumbar-sacral spine, or complex spinal bone deformities seen on plain radiographs. All patients with central diabetes insipidus must undergo cerebral magnetic resonance imaging with specific focus on the hypothalamic-pituitary region.

Cystometry examination is useful for a select group of patients with a history of dysfunctional voiding symptoms whose response to therapy is poor. Bladder instability is characterized by involuntary contractions at more than 15 cm of water pressure during filling. Small bladder capacity is almost always a functional problem, not anatomic.

◆ Differential Diagnosis

Primary Nocturnal Enuresis

Primary nocturnal enuresis (bedwetting) is considered abnormal in most social contexts after the age of 5 years. The majority of affected patients have no daytime symptoms. It is a common problem, but only a small proportion of patients actually seek medical advice. The prevalence, when the condition is defined as a wet night more than once a month, is estimated at 10% among 6-year-olds, 5% among 10-year-olds, and 0.5-1.0% among teens and young adults. The spontaneous cure rate is approximately 15% per year. The incidence of pure primary nocturnal enuresis without other symptoms is twice as common among boys as among girls. The pathophysiologic mechanism is multifactorial; explanations include defects in osmoregulation, small bladder capacity, and disorders of sleep or arousal states.

Dysfunctional Voiding

This occurs when there is an imbalance or lack of coordination of activity between the detrusor muscle activity (bladder contracture) and the bladder neck or external sphincter activity (bladder outlet control). This poor coordination can, over time, cause a wide spectrum of disorders, including incontinence. The severity depends on the balance of forces among the detrusor activity, bladder neck, and

external sphincter. In the extreme case, high bladder pressures produce acquired urologic abnormalities, including hydronephrosis, vesicoureteral reflux (VUR), and renal damage. Dysfunctional voiding is often classified as mild, moderate, or severe. Early recognition can lead to proper management and avoidance of long-term sequelae.

Mild voiding dysfunction. Daytime urinary frequency is characterized by frequency and urgency every 15-20 minutes. This is usually associated with incontinence or mild pain and occurs in children aged 3-8 years. The condition is also usually self-limiting. A thorough history should be documented, a careful physical examination conducted, and urinalysis performed to rule out other pathologic processes.

Giggle incontinence is most often seen in girls and is characterized by incontinence after laughter. It too is usually self-limiting. Stress incontinence follows athletic activities such as running or jumping and landing; it is common with activities such as gymnastics and cheerleading. Timely bladder emptying before exercise is effective in preventing this problem. Postvoid dribbling can occur in young girls who develop habits of incomplete voiding or can result from urine that is collected in the vagina during voiding. Sitting with the knees slightly apart or sitting on the toilet facing backwards eliminates this problem.

Moderate voiding dysfunction. There are 2 extremes in the spectrum of moderate dysfunctional voiding. Over time, urine holding, as infrequent as once every 8-12 hours, results in incontinence as well as recurrent UTIs. This can be a consequence of behaviors developed when the young child is learning voluntary contraction of the external sphincter muscle while toilet training. It may also develop when a child goes to school or camp and does not want to use an unfamiliar or embarrassing toilet. The child learns additional maneuvers to void infrequently, such as squatting and pressing the heel of the foot in the perineum. Dysfunctional voiding may worsen over time when the child is unable to relax the external sphincter in coordination with detrusor activity during voiding. This results in incomplete and inefficient bladder emptying.

The overactive bladder, or unstable bladder, is the most common abnormality. Low quantity, frequent voiding leading to incontinence is secondary to delayed resolution of uninhibited bladder contractions that normally resolve as the child matures. This asynchronous activity between detrusor muscle and sphincter contraction leads to higher intravesical pressures. Urgency and urge incontinence are the most common symptoms, but recurrent UTIs and VUR may result as well. Complications may include thickening, trabeculations, or diverticula of the bladder. *High bladder pressure can also cause hydroureter and hydronephrosis.*

Severe dysfunctional voiding. This is often referred to as the "nonneurogenic neurogenic bladder," a syndrome representing the extreme end of the spectrum of dysfunctional voiding. Inappropriate voluntary contraction of the external sphincter during voiding produces high intravesical pressure and a functional outlet obstruction, leading to abnormal bladder function, hydronephrosis, and possibly renal failure. With time, the voiding pattern becomes habitual, and the anatomic changes in the bladder impede the ability to void normally. Biofeedback and clean intermittent straight catheterization may restore bladder emptying and function and prevent renal failure.

Neuropathic Bladder

The neuropathic bladder most often occurs in patients with spina bifida, an open or closed congenital spinal cord fusion defect. This results in distortion of normal neural tissues in the spinal cord or nerve roots. The range of anomalies includes meningocele, lipomeningocele, primary tethered cord, dermoid cyst, syrinx, and sacral agenesis. Closed defects can be initially asymptomatic and manifest during toilet training years with incontinence, recurrent UTIs, or orthopedic problems in later childhood. Many children who present with symptoms have a cutaneous finding over the lumbosacral spine noted since birth. The severity of the symptoms does not seem to predict the severity of the bladder dysfunction or renal damage. Despite lesser neurologic deficits in closed spina bifida, affected patients have demonstrated bladder dysfunction as severe as that observed in open spina bifida. Acute spinal injury (trauma), compression (tumor), or infection (transverse myelitis) may produce similar bladder conditions such as acute urinary retention.

Anatomic Defects

Posterior urethral valves and urethral obstruction. This is the most common form of urinary obstruction leading to kidney failure in male infants and children. It is a result of persistence of fetal folds in the posterior urethra, which act as a valve to create urinary obstruction. Poor urinary stream and bladder distention are the most common urinary complaints, but dribbling and incontinence are also observed. UTI can be the presenting problem, and, when it is diagnosed in young boys, especially infants, posterior urethral valves should always be sought.

Prune-belly syndrome is another important cause of urethral obstruction. Early obstruction during embryogenesis leads to hydronephrosis, hydroureter, abdominal distention, abdominal musculature deficiency, and excessive skin folds, thus giving the wrinkly "prune" appearance of the abdomen in severe cases. A spectrum of renal dysplasia can result.

Renal duplication. This is a result of duplication of the ureteric bud during embryogenesis, causing a double collecting system, or 2 ureters. Duplicated ureters can open separately inside the bladder, but in rare cases, an ectopic ureter can end in the vagina, urethra, or vestibule, leading to dribbling and incontinence.

Vesicoureteral reflux. VUR is the retrograde flow of urine from the bladder into the ureters and kidney. Normal insertion of the ureter into the bladder submucosal wall forms a flap-valve mechanism that prevents urine backup during filling and contraction. Congenital VUR is secondary to shorter ureteric segments in the bladder wall. Urine flow mechanics are disrupted by the constant filling of the bladder with urine that has flowed backward and then returns to the emptied bladder. The inability to completely empty the bladder eliminates an important defense against UTIs. Secondary VUR can be associated with dysfunctional voiding. Dyssynergia between detrusor contraction and sphincter relaxation can result in VUR and recurrent UTIs. Urethral obstruction leading to high intravesical pressure also leads to VUR, poor bladder emptying, and thus UTIs and incontinence.

Metabolic Disorders

Hypercalcemia. This is an uncommon electrolyte disorder in children but can be observed in primary hyperparathyroidism, vitamin D intoxication, immobilization, Williams syndrome, malignancy, and idiopathic hypercalcemia of infancy. Polyuria is a symptom of hypercalcemia and is a result of its inhibitory effect on Na^+, K^+-ATPase function in renal tubules. This leads to renal sodium and water losses and thus to polyuria and volume contraction. In chronic hypercalcemia, increased calcium excretion over time can lead to nephrocalcinosis, tubular damage, and poor urinary concentrating ability, thus enhancing polyuria.

Hypokalemia. This is another electrolyte disorder that induces polyuria. In children, it occurs clinically as a result of diuretic use, aldosterone excess states, Cushing syndrome, and intrinsic renal disorders that affect potassium handling. The latter includes disorders such as RTA, Bartter syndrome, or renal injury from nephrotoxic

(See *Nelson Textbook of Pediatrics,* p. 2584.)

medications. Hypokalemia interferes with water reabsorption in the collecting duct of the kidneys.

Diabetes mellitus. Polyuria and urinary incontinence can be the 1st symptoms of diabetes mellitus and are secondary to hyperglycemia and the osmotic diuresis resulting from chronic glycosuria. The renal threshold for reabsorption of glucose is exceeded when the blood glucose level is higher than approximately 180 mg/dL. If oral intake of fluid decreases, as occurs when diabetic ketoacidosis causes anorexia and emesis, significant dehydration and shock frequently develop.

Central Diabetes Insipidus

In CDI, the lack of circulating ADH prevents concentration of the urine, leading to high quantities of dilute urine. The defect can be complete or partial, and thus the degree of polyuria is variable. In complete CDI, the massive polyuria can lead to severe dehydration and hypernatremia. CDI can be secondary to intracranial surgery, head trauma, or tumor involving the nuclei of the hypothalamus (where ADH is produced) or the neurohypophysial axis itself. There is also an idiopathic form and familial forms of CDI. In the idiopathic form, infiltrative diseases such as Langerhans cell histiocytosis (Letterer-Siwe syndrome) should be sought. A significant proportion of young children initially diagnosed with idiopathic CDI have been found to have histiocytosis in subsequent years. Treatment is with ADH or its analogs.

Renal Concentrating Defects

Renal tubular acidosis. In distal (type 1) RTA, the most common form of RTA, there is a defect in the tubular secretion of hydrogen ions and decreased formation of NH_4^+ cations in the urine. In children, the presentation includes failure to thrive, polyuria, and polydipsia. Hypokalemia is a common finding and can be profound, leading to weakness. Hypercalciuria and low urine citrate excretion combine to produce nephrocalcinosis. The autosomal recessive form of the disease is frequently associated with hearing loss. There are also autosomal dominant forms of the disease. Distal RTA may be secondary to medications (e.g., amphotericin) or a variety of conditions, including interstitial nephritis, obstructive uropathy, nephrocalcinosis, renal transplantation, sickle cell disease, and systemic lupus erythematosus.

Proximal RTA is less common and is a primary defect in bicarbonate reabsorption in the proximal tubule. When associated with other proximal tubular defects, such as salt wasting, phosphate wasting, glycosuria, and aminoaciduria, it is referred to as Fanconi syndrome. Manifesting in infancy to early adulthood, cystinosis is the most common cause of proximal RTA in children. This autosomal recessive disorder results from a defect in cystine transport and results in the lysosomal accumulation of cystine throughout the body. The infantile form usually manifests in the 1st year of life. Without intervention, this form results in end-stage renal failure. Acidosis, rickets, polyuria, and severe failure to thrive are hallmarks of the disease. Early intervention with oral cysteamine to bind cysteine has dramatically improved the outcome in affected patients. Proximal RTA is a feature of several other genetic disorders manifesting in childhood (such as galactosemia, tyrosinemia, hereditary fructose intolerance, glycogen storage disease type I, Lowe syndrome, Wilson disease, osteopetrosis) or ingestion of toxins (heavy metals, outdated tetracyclines, carbonic anhydrase inhibitors).

Sickle cell disease. Hemoglobin S is a genetic defect in hemoglobin A that results in red blood cells that deform under low oxygen tension (see Chapter 37). The renal medulla is a site with high osmolality, low oxygen tension, and relative acidosis, all conditions that promote sickling. This results in occlusion of blood vessels and damage to the renal medulla, the primary site where the urine is concentrated. The resultant decreased ability to concentrate leads to a higher incidence of nocturnal enuresis in affected patients.

Nephronophthisis. Juvenile nephronophthisis is an autosomal recessive disorder that leads to end-stage renal failure between preadolescence and early adulthood. Patients have high urine output because of poor renal concentrating ability and renal salt wasting. Patients may have primary or secondary nocturnal enuresis. The salt wasting causes salt craving, and patients have a preference for salty foods or even eat salt directly from the saltshaker. A small percentage of these patients have retinitis pigmentosa, which may cause blindness at birth or later in life. Patients may present with symptoms of chronic renal failure.

Nephrogenic diabetes insipidus. The congenital form of NDI is often diagnosed before toilet training, but it can lead to urinary incontinence in later childhood. Infants may present with poor growth, severe dehydration, seizures, and central nervous system injury or death. In families in which the diagnosis has already been made, early intervention in infants can prevent these symptoms and lead to an excellent outcome. Most patients have the X-linked form of the disease, which is caused by a mutated ADH receptor. Female carriers may be mildly affected. The autosomal recessive and autosomal dominant forms of NDI are caused by mutations in aquaporin, the water channel that allows uptake of water in the collecting duct.

◆ Treatment

Primary Nocturnal Enuresis

Establishing whether the primary nocturnal enuresis is the only symptom or whether there are associated symptoms such as diurnal incontinence, constipation, sleep disorders, or behavioral issues, such as attention-deficit/hyperactivity disorder, is necessary before a treatment strategy is developed.

Many families simply want reassurance that there is not an organic explanation. It is also helpful to let the family and child know that almost all patients "outgrow" primary nocturnal enuresis. Positive reinforcement for dry nights, dispelling any negative attitudes, and avoiding blame enhance the child's self-esteem. If treatment is sought, the enuresis alarm has a high success rate, but patient selection is important. These devices are designed to awaken patients when micturition begins and result in the development of increased bladder capacity. Its effect may not be seen for up to 12 weeks, and therefore the family and patient must be highly motivated. Older patients who are ready to take charge of the problem and who do not have difficulty waking are the best candidates.

Pharmacologic therapy for primary nocturnal enuresis includes the use of DDAVP, an ADH analog. There is probably a subpopulation of patients with enuresis who have "nocturnal polyuria," which led to the drug's popularity, but there is evidence that this is independent of vasopressin secretion. DDAVP is most effective in children with a positive family history of primary nocturnal enuresis, with normal bladder capacity, and who are older than 7 years. Its safety profile has been excellent, but patients should be given careful instruction on restricting fluid intake after the bedtime dose. There are occasional reports of hyponatremic seizures in children who drink excessively while taking DDAVP.

Patients with small bladder capacity and diurnal symptoms tend not to respond to DDAVP; these patients may benefit from anticholinergic therapy, such as oxybutynin. Combination therapy involving a bed alarm plus DDAVP or DDAVP plus anticholinergic therapy may be helpful in select patients.

Imipramine, a tricyclic antidepressant, has been shown to be effective, but its side effects and toxicity have limited its use for this benign condition. Patients with enuresis and other behavioral problems who

(See *Nelson Textbook of Pediatrics,* p. 2646.)

take selective serotonin reuptake inhibitors have reported improvement in the enuresis. This may be an appropriate option in this population.

Dysfunctional Voiding

Treatment of mild voiding dysfunction should begin with nonpharmacologic management. Children should be instructed to void on a regular schedule, typically every 1-2 hours, even if they do not feel the urge to void. This encourages voiding when the patient is relaxed and will lead to fewer contractions of the external sphincter during micturition. Keeping a diary of the voiding schedule involves the child in management and makes him or her more aware of bladder habits. Aggressive management of constipation (see Chapter 16) improves good bladder emptying and decreases bladder instability.

When incontinence continues despite nonpharmacologic methods, anticholinergic therapy should be added in the treatment of a child with an overactive or unstable bladder. Oxybutynin should be started at a low dosage and titrated to its maximum dosage if necessary. The minimum effective dosage should be used to minimize side effects.

Patients with recurrent UTIs who develop urine-holding patterns that lead to overflow incontinence may benefit from a trial of antibiotic prophylaxis. This may keep the child free of infection and may prevent the painful urination that reinforces exaggerated external sphincter contraction and urine holding.

Biofeedback is reserved for patients with moderate to severe dysfunctional voiding. Patients can learn to increase bladder capacity and inhibit detrusor contractions through this method.

Polyuria

The treatment of polyuria depends on the cause. In certain disorders, such as diabetes mellitus, hypokalemia, or hypercalcemia, the underlying disorder can be corrected. The high urine output in central diabetes insipidus decreases markedly with the use of DDAVP. In contrast, there is no effective therapy for reducing urine output in patients with disorders such as juvenile nephronophthisis or obstructive uropathy.

The hereditary forms of NDI cause massive polyuria. A combination of sodium restriction and a thiazide diuretic can decrease this high urine output by producing a subtle volume depletion that results in less water being delivered to the collecting duct. The addition of a nonsteroidal antiinflammatory drug can, by reducing renal blood flow, further decrease urine output in patients with NDI. The use of indomethacin also reduces the high urine output in Bartter syndrome. Despite therapy, patients with Bartter syndrome and NDI continue to have high urine output, and the family should be counseled that a delay in achieving nighttime continence is expected.

TABLE 45.3 Red Flags

Polyuria
Polydipsia
Failure to thrive
Poor urinary stream
Encopresis
Secondary enuresis
Abnormal gait, including toe walking
Recurrent urinary tract infections
Cutaneous lesions over lumbosacral spine
Diminished lower extremity reflexes
Abnormal genitalia
Palpable bladder
Hypertension
Headache
Visual disturbances
Obstructive sleep apneas

Neuropathic Bladder and Anatomic Disorders

The treatment of these disorders depends on the specific defect. In patients with neuropathic bladders resulting from spina bifida, chronic intermittent catheterization of the bladder may be the only way to achieve continence. Uninhibited bladder contractions may necessitate anticholinergic therapy as an adjunct.

Anatomic disorders such as posterior urethral valves or VUR may still necessitate medical therapy or biofeedback after corrective surgery. Urodynamic testing can be very helpful in this population to define the problem leading to incontinence.

SUMMARY AND RED FLAGS

The majority of children with voiding problems do not have an organic problem. The work-up consists of a thorough history and physical examination. Red flags that indicate the need for diagnostic tests are shown in Table 45.3.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Voiding Physiology

Blum NJ, Taubman B, Nemeth N. Relationship between age at initiation of toilet training and duration of training: a prospective study. *Pediatrics*. 2003;111(4 Pt 1):810-814.

Brazelton TB. A child-oriented approach to toilet training. *Pediatrics*. 1962;29:21-128.

Kaefer M, Zurakowski D, Bauer SB, et al. Estimating normal bladder capacity in children. *J Urol*. 1997;158:2261-2264.

Mattsson S, Gladh G, Lindström S. Relative filling of the bladder at daytime voids in healthy school children. *J Urol*. 2003;170(4 Pt 1):1343-1346.

Neveus T, Lackgren G, Tuvemo T, et al. Enuresis—background and treatment. *Scand J Urol Nephrol Suppl*. 2000;20:1-44.

Neveus T, Lackgren G, Tuvemo T, et al. Osmoregulation and desmopressin pharmacokinetics in enuretic children. *Pediatrics*. 1999;103:65-70.

Signs and Symptoms

Combs AJ, Van Batavia JP, Chan J, et al. Dysfunctional elimination syndromes—how closely linked are constipation and encopresis with specific lower urinary tract conditions? *J Urol*. 2013;190:1015-1020.

Fisher R, Frank D. Detrusor instability; day and night time wetting, urinary tract infections. *Arch Dis Child*. 2000;83:135-137.

Herndon CD, Joseph DB. Urinary Incontinence. *Pediatr Clin North Am*. 2006;53(3):363-377.

Issenman RM, Filmer RB, Gorski PA. A review of bowel and bladder control development in children: how gastrointestinal and urologic conditions relate to problems in toilet training. *Pediatrics*. 1999;103:1346-1352.

Schum TR, Kolb TM, McAuliffe TL, et al. Sequential acquisition of toilet-training skills: a descriptive study of gender and age differences in normal children. *Pediatrics*. 2002;109:E48.

Diagnostics

Drzewiecki BA, Bauer SB. Urodynamic testing in children: indications, technique, interpretation and significance. *J Urol*. 2011;186(4):1190-1197.

Patel HP. The abnormal urinalysis. *Pediatr Clin N Am*. 2006;53(3):325-337.

Wraige E, Borzskowski M. Investigation of daytime wetting: when is spinal cord imaging indicated? *Arch Dis Child*. 2002;87(2):151-155.

Specific Disorders

Alexopoulos EI, Malakasioti G, Varlami V, et al. Nocturnal enuresis is associated with moderate-to-severe obstructive sleep apnea in children with snoring. *Pediatr Res*. 2014;76(6):555-559.

Barakat LP, Smith-Whitley K, Schulman S, et al. Nocturnal enuresis in pediatric sickle cell disease. *J Dev Behav Pediatr*. 2001;22:300-305.

Bockenhauer D, Bichet DG. Pathophysiology, diagnosis and management of nephrogenic diabetes insipidus. *Nat Rev Nephrol*. 2015;11:576-588.

Butler RJ, Holland P. The three systems: a conceptual way of understanding nocturnal enuresis. *Scand J Urol Nephrol*. 2000;34:270-277.

Dinneen MD, Duffy PG, Barratt TM, et al. Persistent polyuria after posterior urethral valves. *Br J Urol*. 1995;75:236-240.

Elder JS, Diaz M. Vesicoureteral reflux—the role of bladder and bowel dysfunction. *Nat Rev Urol*. 2013;10(11):640-648.

Johnston LB, Borzyskowski M. Bladder dysfunction and neurological disability at presentation in closed spina bifida. *Arch Dis Child*. 1998;79:33-38.

Readett DR, Morris J, Serjeant GR. Determinants of nocturnal enuresis in homozygous sickle cell disease. *Arch Dis Child*. 1990;65:615-618.

Rodriguez-Soriano J, Vallo A. Renal tubular acidosis. *Pediatr Nephrol*. 1990;4:268-275.

Von Gontard A, Equit M. Comorbidity of ADHD and incontinence in children. *Eur Child Adolesc Psychiatry*. 2015;24:127-140.

Treatment

Feldman AS, Bauer SB. Diagnosis and management of dysfunctional voiding. *Curr Opin Pediatr*. 2006;18(2):139-147.

Glazener CM, Evans JH. Desmopressin for nocturnal enuresis in children. *Cochrane Database Syst Rev*. 2002;(3):CD002112.

Metcalfe PD, Luerssen TG, King SJ, et al. Treatment of occult tethered cord for neuropathic bladder: results of sectioning the filum terminale. *J Urol*. 2006;176(4 Pt 2):1826-1829.

Robson WL. Clinical practice: evaluation and management of enuresis. *N Engl J Med*. 2009;360(14):1429.

Vermandel A, Weyler J, De Wachter S, et al. Toilet training of healthy young toddlers: a randomized trial between a daytime wetting alarm and timed potty training. *J Dev Behav Pediatr*. 2008;29(3):191-196.

Wiener JS, Mischca TS, Hampton J, et al. Long-term efficacy of simple behavioral therapy for daytime wetting in children. *J Urol*. 2000;164:786-790.

Yamanishi T, Yasuda K, Murayama N, et al. Biofeedback training for detrusor overactivity in children. *J Urol*. 2000;164:1686-1690.

Acid–Base and Electrolyte Disturbances

Sarah Vepraskas, Heather Toth, and Michael Weisgerber

The presence of an acid–base or an electrolyte disorder may explain a patient's symptoms or may lead to a specific diagnosis.

ACID–BASE BALANCE

Normal acid–base balance is maintained by the lungs and kidneys. Carbon dioxide, a by-product of normal metabolism, is a weak acid. The lungs are able to prevent an increase in the partial pressure of carbon dioxide (P_{CO_2}) in the blood by excreting the carbon dioxide (CO_2) produced by the body. The pulmonary response to changes in the CO_2 concentration is fast, as it occurs via central sensing of the P_{CO_2}, and there is a subsequent increase or decrease in ventilation to maintain a normal P_{CO_2} (35-45 mm Hg). There is an inverse relationship between P_{CO_2} and ventilation because an increase in ventilation decreases the P_{CO_2}, and a decrease in ventilation increases the P_{CO_2}.

The kidneys are responsible for excreting acid produced by the body. Sources of hydrogen ions include protein metabolism and incomplete metabolism of carbohydrates and fat; urine or stool losses of bicarbonate may contribute to acidemia. The hydrogen ions formed from endogenous acid production are neutralized by bicarbonate from the bicarbonate buffer system. The bicarbonate buffer system, based on the relationship between carbon dioxide and bicarbonate (HCO_3^-), is displayed by the following equation:

$$CO_2 + H_2O \leftrightarrow H^+ + HCO_3^-$$

This equation can help us understand how changes in CO_2 or HCO_3^- affect the acid–base balance.

ACID–BASE DISORDERS

A pH <7.35 is defined as acidosis, and a pH >7.45 is defined as alkalosis. An acid–base disorder is **respiratory** in etiology when it is caused by a primary abnormality in respiratory function (a change in P_{aCO_2}) and is **metabolic** when the primary change is due to a variation in bicarbonate concentration. Acid–base disorders may also be mixed, which occurs when 2 or even 3 primary events act to alter the acid–base state at the same time.

In metabolic disorders, extracellular buffers (bicarbonate) rapidly titrate the presence of strong acids or bases. Intracellular buffers chiefly accomplish the buffering of respiratory disorders. Secondary respiratory compensation for metabolic acid–base disorders begins within minutes by changes in ventilation and is usually complete in 12-24 hours. In contrast, secondary metabolic compensation for respiratory disorders occurs more slowly, beginning within hours but requiring 2-5 days for completion. The kidneys increase net acid excretion in response to a primary respiratory acidosis; renal net acid excretion also increases during a metabolic acidosis if the kidneys themselves are not the cause of the metabolic acidosis. The expected compensation for primary acid–base disorders is shown in Table 46.1. *These compensatory mechanisms never return the pH back to normal until the underlying disease process has subsided or has been effectively treated.*

When only 1 primary acid–base abnormality occurs and its compensatory mechanisms are activated, the disorder is classified as a simple acid–base disorder. When a combination of acid–base disturbances occurs, the disorder is classified as a mixed acid–base disorder. The latter should be suspected if the compensation in a given patient differs from the predicted values (see Table 46.1). Interpretation of data in infants and young children requires caution. Crying results in hyperventilation and can quickly change P_{CO_2} and consequently the pH.

SYMPTOMS OF ACID–BASE DISORDERS

History and clinical evaluation are the 1st steps in assessing a patient with an acid–base disorder. Although the signs and symptoms associated with an acid–base abnormality can be nonspecific, there are certain clues that one can obtain from the signs and symptoms that can assist in the diagnosis of the acid–base disorder. Metabolic acidosis results in increased minute ventilation (manifesting as increased respiratory rate and/or effort) because of respiratory compensation. A patient may have tachypnea present with a metabolic acidosis from a diarrheal illness, metabolic disorder, ingestion, or infection. In more severe acidosis (pH <7.20), the respiratory pattern is characterized by deep and rapid breaths (Kussmaul respiration). Severe acidosis may also lead to hypotension, pulmonary edema, and asystole; its harmful effects are accentuated in the presence of hypoxia. Chronic metabolic acidosis leads to growth retardation and hypercalciuria with subsequent bone disease because bone buffering of acid produces marked mineral losses.

A child with metabolic alkalosis may be asymptomatic. In some cases, careful examination of the child may detect hypoventilation. One should consider metabolic alkalosis in a child who has been vomiting or in a child who has had chronic diuretic use. Severe alkalosis (pH >7.55) can lead to tissue hypoxia, mental confusion, obtundation, muscular irritability, tetany, and an increased risk of seizures and cardiac arrhythmias. Some of these signs and symptoms are related to decreased concentration of serum ionized calcium as a result of its increased binding to protein in the presence of alkalosis. Acid–base disturbances can be assessed through laboratory analysis by obtaining a basic chemistry panel and/or a blood gas analysis.

RENAL REGULATION OF ACID–BASE BALANCE

The kidneys are the principal regulator of bicarbonate homeostasis. The renal regulation of HCO_3^- can be divided into 2 processes:

(See *Nelson Textbook of Pediatrics,* p. 369.)

TABLE 46.1 Changes in P_{CO_2}, HCO_3^-, and pH in Primary Acid–Base Disorders*

Disorder	Primary Event	Degree of Initial Disturbance	Compensation	Degree of Compensation
Metabolic acidosis	↓ $[HCO_3^-]$	For every 10 mEq/L ↓ in HCO_3^-, pH ↓ by 0.15	↓ P_{CO_2}	For 1 mEq/L ↓ $[HCO_3^-]$, P_{CO_2} ↓ 1-1.5 mm Hg
Metabolic alkalosis	↑ $[HCO_3^-]$	For every 10 mEq/L ↑ in HCO_3^-, pH ↑ by 0.15	↑ P_{CO_2}	For 1 mEq/L ↑ $[HCO_3^-]$, P_{CO_2} ↑ 0.5-1 mm Hg
Respiratory acidosis		For every 10 mm Hg ↑ in P_{CO_2}, pH ↓ by 0.08		
Acute (<12-24 hr)	↑ P_{CO_2}		↑ $[HCO_3^-]$	For 10 mm Hg ↑ P_{CO_2}, $[HCO_3^-]$ ↑ 1 mEq/L
Chronic (3-5 days)	↑ P_{CO_2}		↑↑ $[HCO_3^-]$	For 10 mm Hg ↑ P_{CO_2}, $[HCO_3^-]$ ↑ 4 mEq/L
Respiratory alkalosis		For every 10 mm Hg ↓ in P_{CO_2}, pH ↑ by 0.08		
Acute (<12 hr)	↓ P_{CO_2}		↓ $[HCO_3^-]$	For 10 mm Hg ↓ P_{CO_2}, $[HCO_3^-]$ ↓ 1-3 mEq/L
Chronic (1-2 days)	↓ P_{CO_2}		↓↓ $[HCO_3^-]$	For 10 mm Hg ↓ P_{CO_2}, $[HCO_3^-]$ ↓ 1-3 mEq/L

*Normal serum $[HCO_3^-]$ is 24 mEq/L, and normal arterial partial pressure of carbon dioxide (P_{CO_2}) is 40 mm Hg.
↓, decrease; ↓↓, greater decrease; ↑, increase; ↑↑, greater increase.
Modified from Brewer ED. Disorders of acid-base balance. *Pediatr Clin North Am.* 1990;37:429-447.

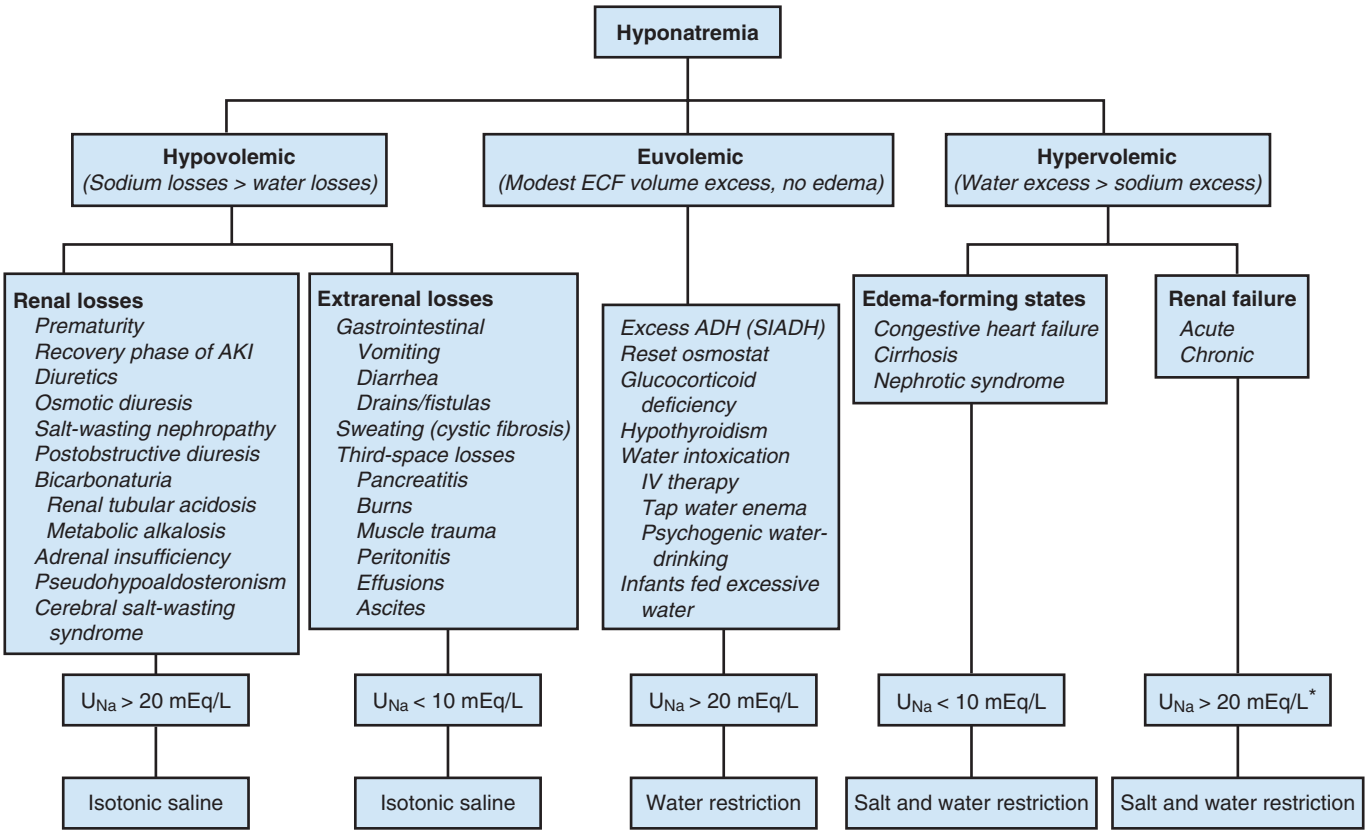

FIGURE 46.1 Classification, Diagnosis and Treatment of Hyponatremic States. *In water intoxication the urine sodium is often <20 mEq/L. †Urinary sodium is <10 mEq/L in acute renal failure secondary to glomerular disease. ADH, antidiuretic hormone; AKI, acute kidney injury; ECF, extracellular fluid; IV, intravenous; SIADH, syndrome of inappropriate antidiuretic hormone secretion. (Modified from Beri T, Schrier RW. Disorders of water metabolism. In: Schrier RW, ed. *Renal and Electrolyte Disorders*. Philadelphia: Lippincott-Raven; 1997.)

reabsorption of HCO_3^- and excretion of H^+. The 1st role of the kidneys is to reabsorb the filtered HCO_3^- so that this important extracellular buffer is not excreted in the urine. The 2nd role of the kidneys is to excrete H^+ that is produced from protein and phospholipid catabolism.

Most (80-90%) of the filtered HCO_3^- is reabsorbed in the proximal tubule (Fig. 46.1). Bicarbonate reabsorption at this site is increased by the contraction of the extracellular fluid (ECF) volume, activation of the renin-angiotensin system (mainly through the effect of angiotensin II), elevated P_{CO_2}, and hypokalemia. Conversely, HCO_3^- reabsorption is decreased when there is expansion of the ECF volume, inhibition of angiotensin II, a fall in P_{CO_2}, and an elevation of the parathyroid hormone level.

The distal tubule and collecting duct regenerate bicarbonate via H^+ ion secretion into the tubular lumen by an H^+-adenosine triphosphatase (H^+-ATPase) pump in the luminal membrane. This active secretion can generate an H^+ ion gradient of 1000:1 between tubular fluid and cells, permitting the urine pH to fall to as low as 4.5. The active H^+ secretion is significantly influenced by the luminal electronegativity caused by active Na^+ reabsorption in the cortical collecting duct. Thus, in the cortical collecting duct, H^+ excretion is influenced by distal Na^+ delivery and reabsorption. In contrast, in the outer medullary portion

of the collecting duct, aldosterone stimulates the H^+ excretion independently of Na^+ delivery or reabsorption. Some of the H^+ secreted is consumed in reclaiming the small amount of HCO_3^- that escaped reabsorption at proximal sites; the rest of the H^+ is excreted in the urine. The ability to excrete large amount of H^+ ions is dependent on the presence of buffers. The H^+ ions are buffered by phosphates and, to a lesser extent, by other nonreabsorbable anions. The other very important urinary buffer is ammonia (NH_3), which combines with a secreted H^+ to generate an ammonium ion (NH_4^+). The proximal tubular cells generate ammonia through the metabolism of the amino acid glutamine. For every H^+ that is finally excreted, an HCO_3^- is added to the ECF compartment. Metabolic acidosis by itself enhances NH_4^+ production and excretion. Ammonia genesis by proximal tubular cells is also stimulated by hypokalemia, whereas hyperkalemia inhibits ammonia genesis. The ability of the kidney to produce ammonia is markedly decreased in conditions such as chronic renal failure as a result of reduced renal mass and in some types of renal tubular acidosis (RTA). The ability to lower urine pH and increase net acid excretion may not be achieved until 4-6 weeks of age.

METABOLIC ACIDOSIS

A metabolic acidosis can result from addition of H^+ to the body, failure to excrete H^+, or loss of HCO_3^-. The differential diagnosis of metabolic acidosis is simplified by classifying the causes into those associated with a normal anion gap (also known as a hyperchloremic metabolic acidosis) and those associated with an increased anion gap (Table 46.2).

The anion gap is easily calculated: $Na^+ - (Cl^- + HCO_3^-)$. The anion gap is normally 8-16 mEq/L. When a strong acid (e.g., lactic acid) is added to or produced in the body, hydrogen ions are neutralized by bicarbonate, HCO_3^- is consumed by the H^+, and the bicarbonate concentration falls. The accompanying anion, such as lactate, is a new unmeasured anion, which increases the anion gap. The increase in the anion gap is usually proportional to the fall in serum (HCO_3^-). In contrast, when HCO_3^- is lost from the body, no new anion is generated. In this situation, there is a reciprocal increase in the serum Cl^- to maintain electroneutrality. The anion gap does not change; the rise in (Cl^-) is proportional to the fall in (HCO_3^-).

Normal Anion Gap (Hyperchloremic) Metabolic Acidosis

Renal Tubular Acidosis

RTA is a group of disorders characterized by impairment of renal HCO_3^- reabsorption and/or H^+ excretion in the presence of a relatively normal glomerular filtration rate (GFR). On the basis of the distinctive pathophysiologic features, 3 types of RTA—type I (distal or classic), type II (proximal or bicarbonate wasting), and type IV (hyperkalemic) are recognized (Table 46.3).

Type I RTA is caused by the inability to secrete H^+ in the distal tubule, resulting in hypokalemic hyperchloremic metabolic acidosis. These patients have a tendency to develop nephrocalcinosis and nephrolithiasis, which results from the excretion of large quantities of calcium, combined with an alkaline urine pH and hypocitraturia. In addition to the deficient H^+ secretion, these patients are unable to increase ammonia genesis. The patient's urine pH remains alkaline (>5.5) despite extreme systemic metabolic acidosis. Type I RTA may occur as an isolated condition or may develop secondary to several diseases, medications, or toxins (Table 46.4).

Type II RTA is caused by an impairment of HCO_3^- reabsorption in the proximal tubule, resulting in hypokalemic hyperchloremic metabolic acidosis. Because the distal acidification mechanisms are intact, these patients can lower the urine pH to less than 5.5 and can excrete adequate amounts of NH_4^+ when the serum HCO_3^- is below the filtration threshold. As a result, their acidosis is usually less profound than that which occurs in distal RTA. In some patients, there may be an increase in urinary calcium excretion, but because citrate excretion is normal, nephrocalcinosis is uncommon. Type II RTA may rarely occur as an isolated defect, but it usually coexists with other defects in proximal tubule function. **Fanconi syndrome** is the combination of multiple defects in proximal tubule reabsorption and, in addition to type II RTA, includes excessive urinary losses of glucose, amino acids, phosphate, and uric acid. The excessive losses of

TABLE 46.2 Causes of Metabolic Acidosis

Normal Anion Gap
Diarrhea
Renal tubular acidosis (RTA):
Distal (type I) RTA (OMIM 179800/602722/267300)*
Proximal (type II) RTA (OMIM 604278)†
Hyperkalemic (type IV) RTA (OMIM 201910/264350/177735/145260)‡
Urinary tract diversions
Posthypocapnia
Ammonium chloride intake
Increased Anion Gap
Lactic Acidosis
Tissue hypoxia
Shock
Hypoxemia
Severe anemia
Liver failure
Malignancy
Intestinal bacterial overgrowth
Inborn errors of metabolism
Medications
Nucleoside reverse transcriptase inhibitors
Metformin
Propofol
Ketoacidosis
Diabetic ketoacidosis
Starvation ketoacidosis
Alcoholic ketoacidosis
Kidney failure
Poisoning
Ethylene glycol
Methanol
Salicylate
Toluene
Paraldehyde

*Along with these genetic disorders, distal RTA may be secondary to renal disease or medications.
†Most cases of proximal RTA are not caused by this primary genetic disorder. Proximal RTA is usually part of Fanconi syndrome, which has multiple etiologies.
‡Hyperkalemic RTA can be secondary to a genetic disorder (some of the more common are listed) or other etiologies.
OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).
From Greenbaum LA. Electrolyte and acid-base disorders. In: Kliegman RM, Stanton BF, St Geme JW, et al., eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:375.

TABLE 46.3 Differentiation of RTA Types

Factor	Type 1	Type 2	Type 4
Serum K^+	Low	Low	High
Renal function	Normal or near normal	Normal or near normal	Stage 3, 4, or 5 chronic kidney disease
Urine pH during acidosis	High	Low	Low or high
Serum HCO_3^- (mmol/L)	10-20	16-18	16-22
Urine P_{CO_2} (mm Hg)	<40	<40	>70
Urine citrate	Low	High	Low
Fanconi syndrome	No	May be present	No

From Palmer BF. Metabolic acidosis. In: Johnson RJ, Feehally J, Floege J, eds. *Comprehensive Clinical Nephrology*. 5th ed. Philadelphia: Saunders; 2015:153.

phosphate often cause hypophosphatemic rickets. There are many causes of type II RTA (see Table 46.4).

Type IV RTA results from low circulating aldosterone concentrations, partial or complete end-organ resistance to aldosterone, or aldosterone antagonism. Because of the lack of aldosterone effect, there is decreased distal acidification and decreased distal sodium reabsorption with hyperkalemic hyperchloremic acidosis. The hyperkalemia seen in type IV RTA is the most characteristic feature and differentiates it from the other 2 types.

The examination of a child with RTA may be normal. Poor skin turgor may be present from dehydration. Muscle weakness and muscle aches from hypokalemia may occur. Low back pain and bone pain may be present in patients with abnormalities of calcium metabolism (type II). All forms of RTA are associated with growth failure. Patients with Fanconi syndrome have severe rickets/osteomalacia and malnutrition.

Laboratory work-up in all patients with RTA shows metabolic acidosis with hyperchloremia and a normal anion gap. The urine pH always exceeds 5.5 in type I RTA but can be less than 5.5 in type II and type IV RTA.

Type I and II RTA are treated with oral sodium bicarbonate titrated to correct the acidosis. Potassium supplementation is needed in hypokalemic patients. Type IV RTA can be treated with furosemide to lower elevated potassium levels, along with sodium bicarbonate to correct significant acidosis. Fludrocortisone can be used to correct mineralocorticoid deficiency. In patients with secondary proximal RTA, treatment should be aimed at the primary disorder.

There needs to be frequent monitoring of potassium levels in type IV RTA. Because of the common occurrence of nephrocalcinosis and nephrolithiasis in type I RTA, renal ultrasound can be used to monitor these patients. A skeletal survey to look for bone disease should also be done, especially in cases of type II RTA. Patients with Fanconi syndrome should be evaluated for cystinosis, the most common cause of Fanconi syndrome in children. Some patients with inherited distal RTA have sensorineural deafness; therefore, infants and children with established distal RTA need routine audiograms.

Additional Causes of Renal Loss of Bicarbonate

Carbonic anhydrase inhibitors such as acetazolamide inhibit the carbonic anhydrase present in the proximal tubule, thus preventing the reabsorption of HCO_3^-. The net effect is similar to that of proximal RTA.

Potassium-sparing diuretics such as spironolactone or amiloride can impair H^+ secretion by the distal nephron by blocking Na^+ absorption in this segment.

Gastrointestinal Loss of Bicarbonate

Diarrhea is the most common cause of non–anion gap hyperchloremic metabolic acidosis in children. The acidosis is secondary to loss of stool bicarbonate. The degree of dehydration should be assessed and appropriate fluid resuscitation should be given, which should help correct the acidosis. If there is persistent acidosis, one should consider additional etiologies such as worsening infection/sepsis, an inborn error of metabolism, or bacteria-associated methemoglobinemia, or production of D-lactate.

Miscellaneous Causes of Hyperchloremic Acidosis

Recovery from ketoacidosis. During recovery from diabetic ketoacidosis (DKA), many patients may eliminate the organic anions (through increased renal clearance and utilization) faster than their acidosis resolves. The clinical picture can resemble normal anion gap acidosis. Excessive fluids with isotonic chloride levels may contribute to this acidemia.

Dilutional acidosis. The rapid expansion of ECF volume with fluids that do not contain HCO_3^- leads to a dilution of HCO_3^- and mild metabolic acidosis. In addition, the expansion of ECF volume by itself promotes urinary HCO_3^- loss, possibly contributing to the dilutional acidosis.

Parenteral alimentation. Amino acid infusions without concomitant administration of alkali (or alkali-generating precursors) may produce a normal anion gap acidosis in a manner similar to that of addition of HCl.

Increased Anion Gap Acidosis

Increased Acid Production

Diabetic ketoacidosis. In DKA, the lack of insulin and excess of glucagon shunts free fatty acids into ketone body formation. The rate of formation of ketone bodies, principally β-hydroxybutyrate and acetoacetate, exceeds the capacity for their peripheral utilization and renal excretion. Accumulation of ketoacids (both of which are relatively strong acids and dissociate rapidly into H^+ and the ketoacid anions) results in metabolic acidosis. Acetone is formed by nonenzymatic conversion of acetoacetate and is responsible for the fruity odor of the patient's breath.

Patients with DKA typically present with polyuria and polydipsia in addition to altered mental status (ranging from confusion and drowsiness, which can progress to obtundation and loss of consciousness), and deep, sighing respirations (Kussmaul respirations). Additional clinical manifestations of DKA can be dehydration, nausea, vomiting, abdominal pain, and tachypnea. Laboratory analysis of a patient with DKA is significant for a severely increased anion gap metabolic acidosis with pH values that may be lower than 7.0. Initially, the increase in the anion gap is in proportion to the decrease in HCO_3^-, but once the patients start recovering with successful management, the kidneys clear the ketoacid anions, and the increase in the anion gap becomes less than the fall in HCO_3^-. The loss of ketoacid anions in urine increases the urinary losses of Na^+ and K^+ as the accompanying cations.

The diagnosis of DKA is made by the combination of increased anion gap metabolic acidosis, hyperglycemia, and demonstration of serum (or urine) ketoacid anions. The therapy for DKA includes careful volume repletion, insulin, and correction of electrolyte disturbances. Severe acidosis is reversible by fluid and insulin replacement. Insulin inhibits ketosis and allows ketoacids to be metabolized, which

TABLE 46.4 Common Causes of Renal Tubular Acidosis

Proximal Renal Tubular Acidosis

Primary

Sporadic (common)

Inherited

- Inherited renal disease (idiopathic Fanconi)
- Autosomal dominant
- Autosomal recessive
- X-linked (Dent disease)
- Inherited syndromes
- Cystinosis
- Tyrosinemia type 1
- Galactosemia
- Oculocerebral dystrophy (Lowe syndrome)
- Wilson disease
- Hereditary fructose intolerance

Secondary

Intrinsic renal disease

- Autoimmune diseases (Sjögren syndrome)
- Hypokalemic nephropathy
- Renal transplant rejection

Hematologic disease

- Myeloma

Drugs

- Gentamicin
- Cisplatin
- Ifosfamide
- Sodium valproate

Heavy metals

- Lead
- Cadmium
- Mercury

Organic compounds

- Toluene

Nutritional

- Kwashiorkor

Hormonal

- Primary hyperparathyroidism

Distal Renal Tubular Acidosis

Primary

Sporadic

Inherited

- Inherited renal diseases
- Autosomal dominant
- Autosomal recessive
- Autosomal recessive with early-onset hearing loss
- Autosomal recessive with later-onset hearing loss
- Inherited syndromes associated with type I renal tubular acidosis
- Marfan syndrome
- Wilson syndrome
- Ehlers–Danlos syndrome
- Familial hypercalciuria

Secondary

Intrinsic renal

- Interstitial nephritis
- Pyelonephritis
- Transplant rejection
- Sickle cell nephropathy
- Lupus nephritis
- Nephrocalcinosis
- Medullary sponge kidney

Urologic

- Obstructive uropathy
- Vesicoureteral reflux
- Hepatic
- Cirrhosis

Toxins or medications

- Amphotericin B
- Lithium
- Toluene
- Cisplatin

Hyperkalemic Renal Tubular Acidosis

Primary

Sporadic

Genetic

- Hypoaldosteronism
- Addison disease
- Congenital adrenal hyperplasia
- Pseudohypoaldosteronism (type I or II)

Secondary

Urologic

- Obstructive uropathy

Intrinsic renal

- Pyelonephritis
- Interstitial nephritis

Systemic

- Diabetes mellitus
- Sickle cell nephropathy

Drugs

- Trimethoprim/sulfamethoxazole
- Angiotensin-converting enzyme inhibitors
- Cyclosporine
- Prolonged heparinization

Addison disease

From Sreedharan S, Avner ED. Renal tubular acidosis. In: Kliegman RM, Stanton BF, St Geme JW, et al., eds. *Nelson Textbook of Pediatrics.* 20th ed. Philadelphia: Elsevier; 2016:2530.

generates bicarbonate. Treatment of hypovolemia improves tissue perfusion and renal function thereby increasing the excretion of organic acids. Most patients with DKA present with considerable total body deficits of potassium, magnesium, and phosphorus, even though serum levels, particularly of potassium, may actually be high on presentation.

Lactic acidosis. Under normal conditions, lactate is formed in relatively small amounts and is further metabolized by the liver. Pathologic conditions associated with either local or systemic hypoxia or ischemia, hypotension (shock), impaired oxidative metabolism, or impaired hepatic clearance can cause significant lactic acidosis.

The diagnosis of lactic acidosis must be considered in all forms of increased anion gap metabolic acidosis. The diagnosis can be confirmed by measuring the serum lactate level. Treatment must be directed at the underlying pathophysiologic process.

Inborn errors of metabolism. Most patients with inborn errors of metabolism that cause a metabolic acidosis present in the neonatal period or shortly thereafter. Organic acidemias, aminoacidopathies, disorders of fatty acid oxidation, mitochondrial disorders, and defects in carbohydrate metabolism are associated with acidosis. Associated presenting signs and symptoms may include vomiting, failure to thrive, lethargy, seizures, developmental abnormalities, hepatomegaly, and elevated blood or urine levels of a particular metabolite. Some of these disorders will be detected by the state newborn screening protocols. In contrast, urea cycle disorders during the 1st few days of life manifest with respiratory alkalosis because of stimulation of the respiratory center by increased ammonia levels.

Poisonings. A variety of toxic agents may be associated with increased anion gap metabolic acidosis; these include salicylate intoxication, ethylene glycol (a component of antifreeze), and methanol. Carbon monoxide, cyanide poisoning, or methemoglobinemia induces hypoxic acidosis.

Classically, **salicylate intoxication** is described as causing respiratory alkalosis (stimulation of the respiratory center), followed by increased anion gap metabolic acidosis (accumulation of salicylic acid itself and lactic acidosis as a result of uncoupling of mitochondrial oxidative phosphorylation). However, children may present with simple increased anion gap metabolic acidosis. Nausea, tinnitus, noncardiogenic pulmonary edema, and prolonged prothrombin time are other associated features. Alkalization of the blood and urine with sodium bicarbonate is beneficial despite the potential problems associated with its use in acute metabolic acidosis. Alkalization of the plasma decreases the diffusion of salicylate into the central nervous system, and alkaline urine improves renal excretion. In severe poisoning, hemodialysis is quite effective at removing salicylate from the body. In cases of poisonings, dialysis serves the dual purposes of removing the poison (if dialyzable) and correcting the acid–base and electrolyte abnormalities.

Failure of Acid Excretion

In both acute and chronic renal failure, the kidneys fail to excrete the acid produced from normal daily metabolism. Both H^+ and anions accumulate in the body, resulting in slow consumption of bicarbonate stores. However, the acidosis is generally not severe unless a markedly catabolic state occurs or other associated conditions coexist. In acute renal failure, there is abrupt and complete inhibition of acid excretion, whereas in chronic renal failure, there initially is enhanced ammonia genesis by the remaining nephrons. As renal failure progresses, excretion of both NH_4^+ and phosphate declines. In addition, the secondary hyperparathyroidism seen with chronic renal failure decreases proximal tubular HCO_3^-reabsorption and adds a component of hyperchloremic acidosis to the increased anion gap acidosis.

◆ Treatment of Metabolic Acidosis

The morbidity and mortality caused by metabolic acidosis are determined not only by the severity of acidosis but also by the amenability of the underlying disorder to medical management. During treatment of metabolic acidosis, the primary effort should focus on the management of the underlying condition. The recommendations and goals of buffer therapy differ for acute acidotic disorders such as DKA and for chronic acidotic states such as RTA.

During the correction of acute metabolic acidosis, particular attention should be paid to ensure an appropriate potassium balance. During an episode of metabolic acidosis, potassium shifts from the intracellular space to the extracellular space in exchange for H^+, and thus the presence of a total body potassium deficit may not be appreciated. Hypokalemia may become evident only as the pH increases and potassium returns to the intracellular space. Chronic metabolic acidosis slows linear growth and interferes with bone mineralization. In chronic metabolic acidosis, there is a need for alkali therapy.

METABOLIC ALKALOSIS

Metabolic alkalosis (pH >7.45) occurs as a result of a primary increase in the serum HCO_3^-, which may occur as a result of (1) net loss of H^+, (2) net gain of HCO_3^- (or its precursors), or (3) loss of fluid with more Cl^- than HCO_3^-. Normally functioning kidneys can excrete large amounts of HCO_3^- and should offset any increase in serum HCO_3^- resulting from these causes. Therefore, factors that prevent the kidneys from excreting HCO_3^- also must be present to maintain the metabolic alkalosis.

Factors Initiating Metabolic Alkalosis

The H^+ can be lost externally, either through the gastrointestinal tract or through the kidneys. For every H^+ lost at these sites, the body gains 1 HCO_3^- ion. This is because H^+ production at both these sites (gastric parietal cell and renal tubular cells) is associated with generation of an equivalent number of HCO_3^- molecules. H^+ can also be "lost" internally, by shifting into the intracellular compartment. This occurs in states of severe potassium depletion (H^+ moves in, whereas K^+ exits the cell, to maintain electroneutrality).

The administration of HCO_3^- or its precursors (such as lactate, citrate, and acetate), at a rate greater than normal metabolic production of acid can lead to net gain of HCO_3^- by the body.

External loss of fluid (gastric fluid) containing more Cl^- than HCO_3^- raises the concentration of HCO_3^- in the body. One of the factors responsible for this type of alkalosis is the associated volume contraction, which leads to increased bicarbonate reabsorption by the proximal tubule of the kidney.

Factors Responsible for Sustaining Alkalosis

Decrease in effective blood volume and kidney perfusion causes increased Na^+ reabsorption, in both the proximal tubule (angiotensin II effect) and the distal renal tubule (mineralocorticoid effect), thereby increasing H^+ excretion.

Increased mineralocorticoid levels directly increase H^+ secretion in the outer medullary collecting duct.

Chloride depletion increases HCO_3^- reabsorption in the proximal tubule. This effect is independent of ECF volume status.

Hypokalemia sustains metabolic alkalosis by decreasing bicarbonate loss. Hypokalemia promotes hydrogen ion secretion in the distal nephron and stimulates ammonia genesis in the proximal tubular cells. When produced, ammonia enhances renal excretion of hydrogen ions.

(See *Nelson Textbook of Pediatrics,* Table 55.11.)

Hypercapnia induces a state of intracellular acidosis, which increases H^+ secretion. Although P_{CO_2} increases as a normal compensatory response to metabolic alkalosis, the elevated P_{CO_2} prevents the renal correction of alkalosis.

◆ Differential Diagnosis of Metabolic Alkalosis

The causes of metabolic alkalosis can be divided into 2 categories on the basis of the urinary chloride level. The alkalosis in patients with low urinary chloride is maintained by volume depletion; volume repletion is needed to correct the alkalosis. In the process of volume depletion, there are losses of sodium, potassium, and chloride, but the loss of chloride is usually greater than the losses of sodium and potassium combined. Since chloride losses are the main cause of the volume depletion, these patients require chloride to correct the volume deficit and metabolic alkalosis; these patients have chloride-responsive metabolic alkalosis. Conversely, patients with alkalosis and an elevated urinary chloride concentration do not respond to volume repletion and have chloride-resistant metabolic alkalosis. Blood pressure can also be useful when considering the etiology of a patient's chloride-resistant metabolic alkalosis (Table 46.5).

Urinary Chloride Level Lower Than 15 mEq/L

Chloride-deficient diet. Although uncommon in developed countries, the ingestion of milk formula with low chloride content has been shown to result in hypochloremic metabolic alkalosis and failure to thrive in infants and to result in later neurodevelopmental abnormalities in childhood.

Upper gastrointestinal losses. The gastric fluid has a high H^+ concentration; loss of gastric fluid by vomiting or by nasogastric drainage leads to a net gain of HCO_3^- in the body. Although this is the initiating factor, the alkalosis is sustained by concomitant Cl^- and K^+ losses. Secondary hyperaldosteronism, resulting from volume contraction, promotes further urinary potassium and H^+ excretion, worsening the hypokalemia and alkalosis; urine is the source of most of the potassium losses caused by emesis. The degree of metabolic alkalosis associated with vomiting is generally mild except in conditions in which gastric secretions are greatly stimulated (e.g., Zollinger-Ellison syndrome) or there is protracted vomiting (e.g., pyloric stenosis).

Metabolic alkalosis can also be seen in newborns of mothers with eating disorders (bulimia). The baby reflects the electrolyte changes of the mother and sustains alkalosis because of the Cl^- deficiency.

Chloride secreting diarrhea. This is a rare congenital syndrome characterized by a defect in small- and large-bowel chloride absorption that leads to a chronic diarrhea with high chloride losses in the stool. The ongoing chloride depletion leads to a sustained metabolic alkalosis.

Diuretic therapy. Chronic use of loop and thiazide diuretics may cause a metabolic alkalosis. The alkalosis is sustained because of hypochloremia, hypokalemia, and volume contraction with resultant secondary hyperaldosteronism. The urinary Cl^- may be high if the diuretics have been ingested recently. The metabolic derangements caused by loop diuretics are identical to those seen in Bartter syndrome.

Hypercapnia. Chronic hypercapnia, as seen in bronchopulmonary dysplasia or cystic fibrosis, leads to an elevated serum bicarbonate concentration from metabolic compensation. The increase in serum bicarbonate is balanced by a decrease in serum chloride. Affected patients have chloride depletion, which may be worsened by concomitant diuretic use. With resolution of the hypercapnia, the bicarbonate concentration remains high until the chloride depletion is corrected.

Urinary Chloride Level Higher Than 20 mEq/L with Hypertension

Pediatric patients with hypertension either have increased levels of aldosterone or act as if they do. Increased aldosterone "effects" cause renal retention of sodium, which results in elevated blood pressure. The disorders of mineralocorticoid excess are characterized by volume expansion and hypertension (see Table 46.5). The mineralocorticoid excess stimulates the renal excretion of H^+ and K^+, resulting in metabolic alkalosis and hypokalemia. The various causes can be differentiated by evaluating the renin-aldosterone axis. Treatment is aimed at removing or correcting the source of the mineralocorticoid excess.

Urinary Chloride Level Higher Than 20 mEq/L with Normal Blood Pressure

Bartter syndrome and Gitelman syndrome. These uncommon autosomal recessive disorders result from defects in various ion transporters within the nephron. Bartter syndrome is a severe disorder that is characterized by urinary chloride wasting, hypokalemia, metabolic alkalosis, and increased serum levels of aldosterone and renin. Hypercalciuria is also common and leads to nephrocalcinosis in some patients. Affected patients present with a history of failure to thrive, polyuria, polydipsia, and a tendency for dehydration. In neonatal Bartter syndrome, there is usually a history of polyhydramnios and premature delivery. Gitelman syndrome, in contrast, is a milder disorder characterized by hypokalemia, metabolic alkalosis, and

TABLE 46.5 Causes of Metabolic Alkalosis

Chloride-Responsive (Urinary Chloride <15 mEq/L)
Gastric losses
Emesis
Nasogastric suction
Diuretics (loop or thiazide)
Chloride-losing diarrhea (OMIM 214700)
Chloride-deficient formula
Cystic fibrosis (OMIM 219700)
Posthypercapnia
Chloride–Resistant (Urinary Chloride >20 mEq/L)
High blood pressure
Adrenal adenoma or hyperplasia
Glucocorticoid-remediable aldosteronism (OMIM 103900)
Renovascular disease
Renin-secreting tumor
17-β-Hydroxylase deficiency (OMIM 202110)
11-β-Hydroxylase deficiency (OMIM 202010)
Cushing syndrome
11-β-Hydroxysteroid dehydrogenase deficiency (OMIM 218030)
Licorice ingestion
Liddle syndrome (OMIM 177200)
Normal blood pressure
Gitelman syndrome (OMIM 263800)
Bartter syndrome (OMIM 607364/602522/241200/601678)
Autosomal dominant hypoparathyroidism (OMIM 146200)
EAST syndrome (OMIM 612780)
Base administration

EAST, epilepsy, ataxia, sensorineural hearing loss, and tubulopathy; OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

From Greenbaum LA. Electrolyte and acid-base disorders. In: Kliegman RM, Stanton BF, St Geme JW, et al., eds. *Nelson Textbook of Pediatrics.* 20th ed. Philadelphia: Elsevier; 2016:378.

TABLE 46.6 Bartter and Gitelman Syndromes

	Type I Bartter Syndrome	Type II Bartter Syndrome	Type III Bartter Syndrome	Type IV Bartter Syndrome	Type V Bartter Syndrome	Gitelman Syndrome
Inheritance	AR	AR	AR	AR	AD	AR
Affected tubular region	TAL	TAL + CCD	TAL + DCT	TAL + DCT	TAL	DCT
Gene	*SLC12A2*	*KCNJ1*	*CLCBRK*	*BSND*	*CASR*	*SLC12A3* Few have *CLCNKB*
Onset	Prenatal, postnatal	Prenatal, postnatal	Variable	Prenatal, postnatal	Variable	Adolescent, adult
Urine PGE_2	Very high	Very high	Slightly elevated	Elevated	Elevated	Normal
Hypokalemic metabolic alkalosis	Present	Present	Present	Present	Present	Present
Features	Polyhydramnios, prematurity, nephrocalcinosis, dehydration, hyposthenuria, polyuria, failure to thrive	Same as type I	Failure to thrive, dehydration, salt craving, low serum magnesium in 20%, mildest form	Same as type I, with sensorineural hearing loss and no nephrocalcinosis	Hypocalcemia, low parathyroid hormone levels, hypercalciuria, uncommon cause of Bartter syndrome	Hypomagnesemia in 100%, mild dehydration, occasional growth retardation, tetany

AD, autosomal dominant; AR, autosomal recessive; CCD, cortisol collecting duct; DCT, descending convoluted tubule; PGE_2, prostaglandin E_2; TAL, thick ascending loop of Henle.
From Sreedharan S, Avner ED. Renal tubular acidosis. In: Kliegman RM, Stanton BF, St Geme JW, et al., eds. *Nelson Textbook of Pediatrics.* 20th ed. Philadelphia: Elsevier; 2016:2534.

hypomagnesemia caused by urinary magnesium wasting; calcium excretion is normal. The growth retardation is not as severe. Children with Gitelman syndrome, however, are more prone to febrile seizures and tetanic episodes (Table 46.6).

◆ Treatment of Metabolic Alkalosis

Treatment focuses on correcting the underlying disorder and depends on the pathophysiologic mechanisms of the alkalosis. Patients with a chloride-responsive metabolic alkalosis (urine Cl^- <15 mEq/L) respond to volume repletion; both sodium and potassium chloride are necessary. In rare cases, if alkalosis persists despite chloride supplementation, the carbonic anhydrase inhibitor acetazolamide can be used to increase urinary bicarbonate losses. In patients undergoing persistent gastric drainage, administration of either an H_2 blocker or H^+ pump inhibitor can be beneficial by decreasing the gastric H^+ secretion.

Treatment of chloride-resistant metabolic alkalosis with hypertension (urinary Cl^- >20 mEq/L) mandates interference with the mineralocorticoid (or mineralocorticoid-like substance) that is maintaining renal H^+ losses. This can sometimes be accomplished pharmacologically (e.g., with spironolactone or with other distal potassium-sparing diuretics such as amiloride).

RESPIRATORY ACIDOSIS

Respiratory acidosis results when there is an inappropriate increase in blood P_{CO_2} that is secondary to impaired pulmonary ventilation. Respiratory acidosis can result from either pulmonary disease, such as in severe bronchiolitis, or nonpulmonary disease, such as a narcotic overdose. In acute compensation, plasma bicarbonate increases by 1 for each 10 mm Hg increase in the P_{CO_2}. In chronic respiratory acidosis, the kidneys increase acid secretion. Renal compensation starts in 12-24 hours and reaches maximum in 3-5 days. In chronic compensation, plasma bicarbonate increases by 3-5 for each 10 mm Hg increase in the P_{CO_2}.

Patients with a respiratory acidosis are often tachypneic as they are trying to correct the inadequate ventilation. The degree of hypercarbia drives the symptoms in a patient with respiratory acidosis. Patients with acute respiratory acidosis have more symptoms than patients with chronic respiratory acidosis. Hypoxia is usually seen in a patient with acute respiratory acidosis who is breathing room air. There may also be central nervous system manifestations of respiratory acidosis, which can include, but are not limited to, anxiety, dizziness, headache, confusion, hallucinations, myoclonic jerks, seizures, psychosis, and coma. The management of respiratory acidosis is directed toward improving alveolar ventilation and treating the underlying disorder.

RESPIRATORY ALKALOSIS

Respiratory alkalosis occurs when there is an inappropriate decrease in P_{CO_2} as a result of pulmonary hyperventilation. In a spontaneously breathing child, this can result from fever, sepsis, mild asthma, panic attack, or central nervous system disorders. In the intensive care unit, the most common cause is mechanical overventilation of an intubated child. A metabolic response to an acute respiratory alkalosis is mediated by hydrogen ion release from nonbicarbonate buffers and occurs within minutes. In this acute compensation, plasma bicarbonate falls by 2 for each 10 mm Hg decrease in P_{CO_2}. In chronic respiratory alkalosis, the kidneys decrease H^+ secretion, which produces a decrease in the serum HCO_3^- concentration. Metabolic compensation for a respiratory alkalosis develops gradually and takes 2-3 days. In chronic compensation, plasma bicarbonate falls by 4 for each 10 mm Hg decrease in the P_{CO_2}. Chronic respiratory alkalosis is the only acid–base disorder in which the pH may be completely normalized by the compensatory mechanisms.

Symptoms of acute respiratory alkalosis may be chest tightness, palpitations, lightheadedness, circumoral numbness, or extremity paresthesias. Less commonly, tetany, seizures, muscle cramps, or syncope can be seen. The lightheadedness and syncope are felt to be a result of

the decrease in cerebral blood flow that is caused by hypocapnia. The parethesias, tetany, and seizures are thought to be related to the decrease in ionized calcium that occurs because alkalemia causes more calcium to bind to albumin. The treatment is management of the underlying process.

MIXED ACID–BASE DISORDERS

Mixed acid–base disorders occur when 2 or 3 primary events act to alter the acid–base state at the same time. The deviations in pH are more marked when 2 primary events block the compensation of each other, such as the combination of a metabolic acidosis and a respiratory acidosis seen in a patient with shock and respiratory failure. In contrast, in the presence of 2 opposing primary events, the pH may be normal or only minimally abnormal, as can be seen with combined vomiting and diarrhea. A mixed acid–base disorder is commonly seen when neonates with respiratory acidosis caused by chronic lung disease also receive diuretics, which can cause a metabolic alkalosis.

The diagnosis of mixed acid–base disorder should be suspected in the following situations:

If the compensation for the primary event is absent or is out of the expected range.

If the deviation in anion gap and/or serum Cl^- is out of proportion to the change in HCO_3^-.

If the anion gap is significantly increased in the presence of a near-normal pH.

POTASSIUM DISORDERS

Potassium is the major intracellular cation with a normal serum concentration of 3.5-5.5 mEq/L. The differential distribution of potassium between the intracellular (150 mEq/L) and extracellular compartments, sustained by the action of the Na^+,K^+-ATPase pump, is the chief determinant of the resting membrane potential. Not surprisingly, both hyperkalemia (serum K^+ >5.5 mEq/L) and hypokalemia (serum K^+ <3.5 mEq/L) have a profound effect on the excitability of the neuromuscular tissue, especially the cardiac tissue. As a result, fatal cardiac arrhythmias are possible sequelae of hypokalemia or hyperkalemia.

Almost all dietary potassium is absorbed. The kidney is the major organ responsible for K^+ excretion, eliminating more than 90% of the daily K^+ intake. However, after an acute ingestion of K^+, the kidneys excrete only half of it over the 1st 4-6 hours; the remainder is transiently redistributed intracellularly before the kidneys eventually excrete it. This intracellular redistribution has a very important role in offsetting acute changes in serum K^+, but it has a limited capacity to do so. Redistribution of a very small fraction (1-2%) of intracellular K^+ into the ECF can easily increase serum K^+ to a dangerous level. A number of factors affect the distribution of K^+ between the intracellular space and the ECF (Table 46.7). The colonic excretion of K^+ is of no significance under normal conditions, but in patients with chronic renal failure, it becomes an important route of K^+ elimination, when colonic excretion increases substantially.

Because the kidney is the major route of potassium elimination from the body, a disturbance in renal potassium handling can be the cause of excessive loss or retention.

In clinical practice, spironolactone, amiloride, and triamterene decrease urinary K^+ excretion. Whereas spironolactone is an aldosterone antagonist, amiloride and triamterene block the Na^+ conductance channels present in the principal cell luminal membrane. The antimicrobial trimethoprim prevents K^+ secretion by the same mechanism as amiloride.

TABLE 46.7 Factors Affecting Potassium Distribution Between Extracellular Fluid and Intracellular Fluid

Insulin	Excess causes hypokalemia Deficiency causes hyperkalemia
Catecholamines	β-agonists cause hypokalemia β-antagonists cause hyperkalemia
Acid–base status	Metabolic alkalosis causes hypokalemia Metabolic acidosis (especially inorganic) causes hyperkalemia
Tissue injury	Causes hyperkalemia

From Chadha V, Alon US. Acid-base and electrolyte disturbances. In: Kliegman RM, Greenbaum LA, Lye PS, eds. *Practical Strategies in Pediatric Diagnosis and Therapy*. 2nd ed. Philadelphia: Elsevier; 2004:455.

HYPOKALEMIA

Hypokalemia (Table 46.8) may result from (1) increased renal losses, (2) increased extrarenal losses, (3) redistribution, or (4) prolonged decreased intake of potassium. When interpreting cases of hypokalemia, the clinician should pay careful attention to blood pressure and obtain laboratory data concerning acid–base status, electrolytes, osmolality of blood and urine, and the renin-aldosterone axis.

Increased Renal Losses with Hypertension

Mineralocorticoid Excess

The presence of excess mineralocorticoid hormone, regardless of its source, results in stimulation of potassium secretion by the distal tubular cells of the nephron. Mineralocorticoid excess can result from primary hyperaldosteronism, rare forms of congenital adrenal hyperplasia (17α-hydroxylase or 11β-hydroxylase deficiency), syndrome of apparent mineralcorticoid excess, glucocorticoid remediable aldosteronism, and Cushing syndrome. The hypokalemia in these conditions is associated with increased sodium chloride retention, causing hypertension. The expansion of the extracellular volume eventually leads to the suppression of Na^+-retaining mechanisms, but the K^+ losses continue unabated. Metabolic alkalosis develops as a result of enhanced proximal ammonium production secondary to potassium depletion.

Liddle Syndrome

Liddle syndrome is characterized by a primary increase in sodium reabsorption in the collecting tubule and associated with increased potassium secretion. The sodium reabsorption is increased through activation of the amiloride-sensitive renal sodium channel. Because serum aldosterone levels are low, spironolactone is ineffective, but amiloride or triamterene, which block the sodium channel, decrease potassium losses and help ameliorate the hypokalemia and the hypertension.

Increased Renal Losses with Normal Blood Pressure

The hypokalemia associated with Bartter syndrome, Gitelman syndrome, RTA, DKA, and vomiting are discussed in the section on acid–base disorders.

Hypomagnesemia of any cause can lead to K^+ depletion, and correction of hypokalemia is not possible until magnesium balance is restored. These effects are believed to be secondary to magnesium's effect on aldosterone secretion and K^+ channels. Magnesium

(See *Nelson Textbook of Pediatrics,* Fig. 55.5.)

TABLE 46.8 Differential Diagnosis of Hypokalemia

Increased Renal Losses (TTKG >6)

With Hypertension

Mineralocorticoid excess
- Primary aldosteronism
- Congenital adrenal hyperplasia
  - 17-α Hydroxylase deficiency
  - 11-β-Hydroxylase deficiency
- Hyperreninemic hyperaldosteronism
- Glucocorticoid-suppressible hyperaldosteronism
- Exogenous mineralocorticoid
- Cushing syndrome
- Liddle syndrome

With Normal Blood Pressure

With Acidosis

Renal tubular acidosis
Diabetic ketoacidosis

With Alkalosis

Vomiting
Diuretics
Congenital chloride diarrhea
Bartter syndrome
Gitelman syndrome
Magnesium depletion
Normotensive hyperaldosteronism

With Normal Acid–Base

Recovery from acute tubular necrosis
Postobstructive diuresis
Drugs (penicillins, amphotericin B)

Extrarenal Losses (TTKG <2)

Diarrhea/GI fistulas
Laxative abuse
Profuse sweating

Redistribution

Alkalosis
β-Adrenergic agonists
Barium intoxication
Familial hypokalemic periodic paralysis

GI, gastrointestinal; TTKG, transtubular potassium gradient.
From Chadha V, Alon US. Acid-base and electrolyte disturbances. In: Kliegman RM, Greenbaum LA, Lye PS, eds. *Practical Strategies in Pediatric Diagnosis and Therapy*. 2nd ed. Philadelphia: Elsevier; 2004:456.

replacement in this situation should be done with magnesium oxide, because the sulfate ion of magnesium sulfate can increase the urinary K^+ losses.

The polyuric recovery phase of acute tubular necrosis and the postobstructive diuresis after relief of urinary tract obstruction are commonly encountered clinical conditions that may be associated with excess urine potassium losses. Penicillins can increase urinary K^+ losses by increased delivery of sodium and nonabsorbable anions to the distal nephron. Amphotericin B enhances urinary K^+ loss by increasing the tubular K^+ permeability and also by causing type I RTA.

Increased Extrarenal Losses

Diarrhea is a very common cause of hypokalemia in pediatric practice. Profuse sweating is a much less frequent cause of hypokalemia.

Redistribution

Alkalosis causes potassium to enter cells in exchange for H^+. β-Adrenergic agonists increase intracellular movement of potassium.

Familial hypokalemic periodic paralysis is a rare disorder characterized by recurring transient episodes of net K^+ transfer from ECF to intracellular fluid (ICF). The autosomal dominant form manifests between the ages of 10 and 19 years. The dominant finding is muscle weakness, which may advance to paralysis. Episodes typically occur after large carbohydrate-rich meals, strenuous exercise, or insulin administration. Hyperthyroid states may also produce hypokalemic paralysis. Therapy is largely symptomatic; empirical treatment with acetazolamide has yielded some results.

Consequences of Hypokalemia

Hypokalemia produces functional alterations in skeletal muscle, smooth muscle, and the heart. The cardiac conduction effects are the most serious consequence of hypokalemia. The characteristic electrocardiographic (ECG) changes include flattening of the T wave with appearance of the U wave. Skeletal muscle weakness usually starts in the limbs before involving the trunk and respiratory muscles. Paralytic ileus and gastric dilatation reflect smooth muscle dysfunction. Rhabdomyolysis is a dramatic and serious complication of hypokalemia. Hypokalemia is particularly dangerous in patients taking digoxin.

In the kidney, potassium deficiency may result in vacuolar changes in the tubular epithelium. The renal concentrating capacity is decreased, causing polyuria. Prolonged and sustained hypokalemia leads to systemic alkalosis.

◆ Treatment of Hypokalemia

The immediate objective of potassium replacement is to prevent life-threatening cardiac conduction and muscle complications. The ultimate goal is to replenish total body potassium stores. There is no method of determining the potassium deficit, because there is no definite correlation between the plasma potassium concentration and body potassium stores. A decrease of 1 mEq/L in serum potassium concentration secondary to potassium loss generally corresponds to a loss of approximately 10-30% of body potassium. In conditions with associated acidosis and/or hyperosmolality (e.g., RTA, DKA), the plasma potassium concentration may underestimate potassium stores, and correction of acidosis with bicarbonate in these conditions may rapidly lower the serum potassium concentration.

The safest route to administer potassium is by mouth, but in states of severe symptomatic hypokalemia or when there are gastrointestinal problems, potassium must be given intravenously. The usual concentration of potassium in intravenous fluid solutions is up to 40 mEq/L. Higher concentrations of up to 60-80 mEq/L can be given in a central vein under continuous ECG monitoring. Dextrose should be avoided in the initial fluids because its administration with secondary increased insulin secretion may result in further lowering of the plasma potassium concentration. The choice of potassium salt depends on the clinical situation. Under most circumstances, when hypovolemia coexists, potassium chloride is appropriate. Potassium bicarbonate (or, more often, other salts such as citrate or acetate, which generate bicarbonate) can be given in the presence of coexistent metabolic acidosis. If there is an associated phosphate deficiency (as in DKA), potassium phosphate can be used. It is important to remember that correction of total body potassium deficits can take days to weeks.

HYPERKALEMIA

Moderate (6.1-7.0 mEq/L) to severe (>7.0 mEq/L) hyperkalemia, especially if it develops acutely, can lead to grave consequences and requires prompt treatment. **Pseudohyperkalemia** can occur as result of release of intracellular potassium (e.g., hemolysis caused by mechanical trauma during venipuncture), and it can also be seen in conditions with marked leukocytosis and thrombocytosis. It can be avoided by minimizing trauma and hand clenching during venipuncture, by rapidly separating red blood cells, and by using plasma rather than serum for potassium measurements. *An unexpected elevated potassium level should be immediately repeated.*

Hyperkalemia can be caused by (1) reduced urinary potassium excretion, (2) increased potassium intake, (3) release of intracellular potassium, and/or (4) impaired cellular potassium uptake (Table 46.9).

Reduced Urinary Potassium Excretion

Renal potassium excretion decreases when the GFR is decreased or when there is a defect in tubular potassium excretion resulting from lack of aldosterone, medications, or a primary defect in tubular potassium excretion.

Renal Failure

Potassium excretion is decreased in both acute and chronic renal failure. Severe hyperkalemia occurs more commonly in acute renal failure. In contrast, in patients with chronic renal failure, hyperkalemia does not occur unless the GFR is lower than 10 mL/min or some other factor predisposing to hyperkalemia is present. In patients with chronic renal failure, potassium balance is maintained by increased K^+ secretion per functioning nephron and also by enhanced excretion of K^+ through the gastrointestinal tract.

Hypoaldosteronism

Low levels or absence of aldosterone (or aldosterone receptor defects) may result from a variety of conditions (Addison disease, congenital adrenal hyperplasia [deficiency of 21-hydroxylase], and hyporeninemic hypoaldosteronism). In addition to hyperkalemia, hyponatremia and hyperchloremic metabolic acidosis are the associated features in these disorders. The diagnosis can be confirmed by measurement of renin activity and aldosterone levels.

Drugs

Several drugs are known to be associated with hyperkalemia; they can either impair renin-aldosterone secretion or action (angiotensin-converting enzyme inhibitors, spironolactone, cyclosporine, or heparin) or impair renal tubular potassium secretion (amiloride, triamterene, trimethoprim, or cyclosporine).

Primary Tubular Defects

In some patients, hyperkalemia occurs as a result of low urinary K^+ excretion despite normal renin and aldosterone levels. The presence of a selective defect in K^+ secretion has been described in subjects with renal transplant rejection and lupus nephritis.

Increased Potassium Intake/Tissue Release

Acute increases in potassium intake, usually through parenteral administration, may result in hyperkalemia. The hyperkalemia is typically transient because normal kidneys have a large capacity for excreting potassium. Sustained hyperkalemia is seen only when renal excretory mechanisms are impaired.

In **tumor lysis syndrome** and rhabdomyolysis, massive amounts of K^+ are released from the intracellular compartment, but hyperkalemia does not usually occur unless acute renal failure supervenes. Similarly, trauma, intravascular hemolysis, transfusion of stored blood, and catabolic states such as infection or high fever are associated with release of K^+ from the cells; however, hyperkalemia is uncommon as long as renal function is normal and normal to high urine output is maintained with fluid therapy.

TABLE 46.9 Differential Diagnosis of Hyperkalemia

Pseudohyperkalemia
Hemolysis
Thrombocytosis
Leukocytosis

Reduced Urinary Potassium Excretion (TTKG <5)
Renal Failure
Acute
Chronic

Hypoaldosteronism
Addison disease
Hereditary adrenal enzyme defects
  21-Hydroxylase deficiency
Hyporeninemic hypoaldosteronism
Pseudohypoaldosteronism (Gordon syndrome)

Drugs
ACE inhibitors
Potassium-sparing diuretics
  Spironolactone
  Amiloride
  Triamterene
Cyclosporine
Trimethoprim
Heparin
Nonsteroidal antiinflammatory agents

Primary Tubular Defects
Post–renal transplantation
Lupus nephritis
AIDS
RTA type IV (chloride shunt)

Increased Intake/Tissue Release (TTKG >10)
Intravenous/oral administration
Hemolysis (endogenous or transfused blood)
Rhabdomyolysis
Tumor lysis

Redistribution
Acidosis
Insulin deficiency (diabetes)
Familial hyperkalemic periodic paralysis
Digitalis toxicity
β-Adrenergic blockade
Succinylcholine

ACE, angiotensin–converting enzyme; AIDS, acquired immunodeficiency syndrome; RTA, renal tubular acidosis; TTKG, transtubular potassium gradient.
From Chadha V, Alon US. Acid-base and electrolyte disturbances. In: Kliegman RM, Greenbaum LA, Lye PS, eds. *Practical Strategies in Pediatric Diagnosis and Therapy*. 2nd ed. Philadelphia: Elsevier; 2004:457.

Redistribution

Acidosis and insulin deficiency result in egress of intracellular potassium. β_2-Receptor blockers, digitalis (by inhibiting the Na^+,K^+-ATPase pump), and succinylcholine (by inhibiting cellular repolarization) cause hyperkalemia by impairing cellular potassium uptake.

Consequences of Hyperkalemia

Overt clinical manifestations are uncommon with hyperkalemia, but cardiac arrhythmias are potentially life-threatening. Generalized muscular weakness and paralysis can occur. The characteristic ECG findings seen with increasing $[K^+]$ are tall, peaked T waves; widening of the QRS complex; decreased amplitude of the P wave; and fusion of the QRS complex with the T wave, forming a sine wave. This can be rapidly followed by atrioventricular dissociation and ventricular tachycardia or fibrillation. Cardiac arrest is more common with hyperkalemia than with hypokalemia.

◆ Treatment of Hyperkalemia

The treatment of hyperkalemia depends on the magnitude of the hyperkalemia, the severity of ECG changes, and the anticipated future rise in $[K^+]$. The specific therapy should always focus on the underlying cause. However, a plasma potassium concentration higher than 7.0 mEq/L or marked ECG changes are potentially life-threatening and necessitate immediate treatment. A normal ECG result should not lead to a more casual approach, because significant ECG changes can appear over a short period of time. All potassium intake (parenteral nutrition, medications with potassium salt) and medications that cause hyperkalemia, such as potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, and trimethoprim, should be discontinued. The treatment modalities usually belong to the following 3 categories: (1) antagonism of membrane excitability, (2) shifting of potassium into the intracellular compartment, and (3) elimination of excess potassium (Table 46.10).

TABLE 46.10 Treatment of Hyperkalemia

Antagonism of Membrane Excitability

Calcium gluconate 10% (elemental calcium, 0.45 mEq/mL), 0.5-1.0 mL/kg body weight (maximum = 10 mL), injected intravenously and slowly over 5-10 min, with continuous monitoring of heart rate)

Shift of Potassium into the Intracellular Compartment

- Sodium bicarbonate, 1-2 mEq/kg body weight intravenously over 10-20 min; usefulness is limited in patients with volume expansion
- Glucose, 1 g/kg body weight, and insulin, 1 unit per every 4 g of glucose, intravenously over 20-30 min
- β_2-Adrenergic agonists, such as albuterol, intravenously or by nebulizer or aerosol

Elimination of Excess Potassium

- Loop/thiazide diuretics
- Fludrocortisone (0.05-0.1 mg/day); should be avoided or given with great caution to hypertensive patients
- Cation exchange resin, sodium polystyrene sulfonate, 1 g/kg body weight (maximum, 15 g/dose), administered orally or rectally in 20-30% sorbitol or 10% glucose, 1 g resin/4 mL (additional 70% sorbitol syrup may be given if constipation occurs)
- Peritoneal dialysis, hemodialysis, or hemodiafiltration

Modified from Hellerstein S, Alon US, Warady BA. Renal impairment. In: Ashcraft KW, Murphy JP, Sharp RJ, et al., eds. *Pediatric Surgery*, 3rd ed. Philadelphia: Saunders; 2000:47-57.

Calcium protects the heart from fatal arrhythmias caused by hyperkalemia by normalizing the difference between the resting and threshold potentials. This protective effect is quite rapid but relatively short-lived; therefore, other measures to reduce the concentration of serum potassium are necessary.

Potassium can be shifted from the extracellular to the intracellular compartment by administration of glucose and insulin, or β_2-adrenergic agonists, as detailed in Table 46.10. Although the intracellular shift of potassium can be accomplished rather quickly, this is only a temporary measure, and further steps should be taken to establish a negative potassium balance.

Loop or thiazide diuretics increase renal potassium excretion. In patients with aldosterone deficiency, fludrocortisone increases renal potassium excretion. Alkalinizing the urine through systemic base administration can further enhance urinary potassium losses.

Cation exchange resins actually remove potassium from the body and are effective in acute situations, particularly when poor renal function is present. Dialysis is needed in patients with severe hyperkalemia, especially in the presence of advanced renal failure or when accompanied by a hypercatabolic state or severe tissue necrosis. For urgent potassium removal, hemodialysis is more effective than continuous hemodiafiltration or peritoneal dialysis.

SODIUM DISORDERS

Sodium is the principal cation of the ECF compartment, and total body sodium content is the major determinant of ECF volume. A normal ECF volume is essential for maintaining an adequate circulating blood volume. The sodium concentration determines cell volume by directing water movement between the ECF compartment and the intracellular compartment. An increase in ECF osmolality causes water to move out of cells, and a decrease in ECF osmolality causes water to move into cells. Sodium homeostasis is coupled with water homeostasis; therefore, disorders of sodium homeostasis usually occur as a result of imbalances of both sodium and water rather than an isolated imbalance of either sodium or water.

The kidneys are pivotal regulators of sodium and water balance. Sodium excretion, which is regulated by the renin-angiotensin-aldosterone system and atrial natruretic peptide, increases in response to an expanded intravascular volume, as may occur with a high sodium intake. In response to a decreased intravascular volume, the urine can be made virtually sodium free.

A detailed history of the underlying disease, food and fluid intake, fluid losses in the form of stool, emesis, and urine should be obtained. The physical examination focuses on an evaluation of the patient's volume status, including the nature and rate of peripheral pulses, blood pressure, fullness of the fontanel, level of consciousness, dryness of mucous membranes, coolness of extremities, and capillary refill time. Urinary sodium concentration can provide valuable information regarding the child's effective blood volume, but it can be misleading if the patient is receiving diuretics or has abnormal renal sodium handling. The clinical features associated with alterations in plasma osmolality are nonspecific. Osmolality is regulated by thirst and vasopressin production, which determines renal water excretion. A low serum osmolality may produce lethargy and confusion, whereas a high serum osmolality may lead to irritability, a high-pitched cry, and a doughy skin texture. The determination of plasma osmolality requires a direct laboratory measurement or can be estimated from the following formula:

$$\text{Serum osmolality}_{(\text{mOsm})} = 2 \times [Na^+]_{\text{mEq/L}} + [\text{glucose}]_{\text{mg/dL}}/18 + [\text{urea}]_{\text{mg/dL}}/2.8$$

HYPONATREMIA

Hyponatremia is defined as a plasma sodium less than 135 mEq/L and is generally characterized as a disproportionate concentration of water to sodium. This may arise from either water retention or sodium losses. Hyponatremia should be differentiated from pseudohyponatremia and factitious hyponatremia. **Pseudohyponatremia** occurs in the presence of excessive amounts of plasma proteins and lipids, which decrease the percentage of plasma water and thus artificially lower the plasma sodium concentration. The measured plasma osmolality of these patients is normal, inasmuch as lipids and proteins do not contribute significantly to osmolality because of their large size. Therefore, a gap between measured and calculated osmolalities can indicate pseudohyponatremia.

Factitious hyponatremia results from high plasma concentrations of impermeable solutes such as glucose or mannitol that cause movement of water from the intracellular to the extracellular space. In contrast to pseudohyponatremia, the low plasma sodium concentration in these situations is a true value, and plasma osmolality is increased as a result of the presence of the extra solutes. The decrease in plasma sodium is approximately 1.6 mEq/L for every 100 mg/dL increase in the plasma glucose concentration.

In true hyponatremia, the plasma osmolality is low (<280 mOsm/kg), and the pathophysiologic processes are caused by (1) loss of both plasma sodium and water (sodium losses exceeding water losses), (2) increase in plasma water (without edema), or (3) increase in both total body water and sodium (increase in water exceeding that of sodium; usually with edema). Estimating the status of the ECF volume (hypovolemia, euvolemia, or hypervolemia) is therefore useful in narrowing the differential diagnosis (see Fig. 46.1).

Hypovolemic Hyponatremia

Hypovolemia hyponatremia occurs when urinary and/or gastrointestinal sodium losses exceed those of water, fluids are sequestered into third spaces such as the peritoneal cavity, subcutaneous tissue, or bowel lumen, or uncommonly, sodium losses in sweat for patients with cystic fibrosis or excessively hot climatic zones. The most common cause of hypovolemic hyponatremia in children is gastroenteritis. Fistulas and various types of gastrointestinal drainage tubes can also lead to a similar clinical picture. The normally functioning kidneys respond by conserving sodium, and the urine sodium concentration is usually less than 20 mEq/L.

The kidneys can be the source of excessive sodium loss in premature infants (tubular immaturity), in patients receiving diuretics, and in those having an osmotic diuresis (DKA). The presence of increased urinary bicarbonate, as seen in certain patients with metabolic alkalosis and RTA, leads to obligatory losses of sodium in the urine. The urinary sodium losses are increased during the recovery phase of acute tubular necrosis, after relief of urinary tract obstruction, and in certain renal diseases (salt-wasting nephropathies) such as medullary cystic disease, polycystic kidney disease, and tubulointerstitial diseases. All of these disorders are usually accompanied by hypokalemia. The presence of hyperkalemia and normal renal function in patients with hypovolemic hyponatremia suggests mineralocorticoid deficiency or type IV RTA.

Some children with acute or chronic central nervous system injury (closed-head trauma, surgery, tumors, or meningitis) present with excessive renal sodium losses and develop hypovolemic hyponatremia. The condition, known as **cerebral (renal) salt-wasting** syndrome, may occur because of secretion of atrial natriuretic hormone or other undetermined factors. Cerebral salt wasting is usually associated with hypovolemia but may be confused with the syndrome of inappropriate antidiuretic hormone secretion (SIADH), which does not demonstrate volume depletion. The 2 syndromes can be differentiated by measuring plasma uric acid concentration, which is increased in cerebral salt-wasting syndrome and decreased in SIADH. Apart from managing the underlying condition, patients with cerebral salt-wasting syndrome require complete replacement of urinary sodium and water losses.

In all patients with renal losses of sodium as a cause of hypovolemic hyponatremia the urinary sodium concentration is usually greater than 20 mEq/L, despite the presence of hypovolemia.

Euvolemic Hyponatremia

The ECF volume status of patients in this group is usually normal; some persons have a slightly increased ECF volume, but they are not edematous. Owing to slight ECF volume expansion, urinary sodium concentration is usually greater than 20 mEq/L.

The **syndrome of inappropriate antidiuretic hormone secretion (SIADH)** is a common cause of euvolemic hyponatremia. Exogenous administration of DDAVP (synthetic analog of vasopressin) can produce a similar clinical picture. SIADH, which has multiple causes (e.g., central nervous system infections, trauma, hypoxia, and various malignancies), results from antidiuretic hormone (ADH) secretion despite the absence of increased plasma osmolality or volume depletion, the normal stimuli for ADH secretion. The diagnostic criteria are as follows:

1. Hypoosmolar hyponatremia
2. Urine osmolality higher than serum osmolality
3. Normal renal function
4. Normal adrenal and thyroid function
5. High urinary sodium concentration (this is not an absolute criterion, inasmuch as urinary sodium concentrations may be low in patients who are severely sodium depleted)
6. Absence of hypovolemia or edema
7. Hypouricemia

In the absence of any obvious clinical signs, the incidental laboratory finding of hyponatremia is usually the 1st clue to the presence of SIADH.

Because SIADH is a problem of water retention and not of sodium depletion, the most appropriate treatment is water restriction. Attempts to correct the hyponatremia with sodium administration cause an increase in urinary sodium excretion and little change in the plasma sodium concentration. Nonetheless, sodium administration is needed if severe hyponatremia leads to neurologic symptoms.

Glucocorticoid and thyroid hormone deficiency can cause hyponatremia similar to that of SIADH. Adrenal insufficiency may also produce volume depletion and an addisonian crisis. The hyponatremia resolves with appropriate hormonal replacement therapy.

Acute water intoxication is an uncommon cause of euvolemic hyponatremia in children receiving hypotonic intravenous fluids; it is likely to happen only if there is an associated impairment of free water excretion capability. Postoperative patients are at particularly increased risk because of high ADH secretion secondary to pain and emotional stress. As the free water excretion ability of infants is limited in comparison with that in older children, they are at increased risk of developing hyponatremia from excessive oral water intake. Infants younger than 1 year fed water without electrolytes may develop hyponatremia and associated symptoms such as lethargy, seizures, and hypothermia. Symptoms correct rapidly with water restriction.

Hypervolemic Hyponatremia

In the absence of renal disease, patients with hypervolemic hyponatremia have decreased effective circulating blood volume with resulting sodium and water retention. Urine sodium concentration is low. The

(See *Nelson Textbook of Pediatrics,* p. 2647.)

edema-forming states such as heart failure, cirrhosis, and nephrosis are characterized by decreased effective blood volume (despite an increased ECF) that leads to stimulation of the renin-angiotensin-aldosterone axis as well as ADH secretion. Although both sodium and water are retained, hyponatremia develops because of proportionately greater water retention. The urinary sodium is usually less than 10 mEq/L because of avid sodium reabsorption as a consequence of decreased effective blood volume and decreased renal perfusion.

◆ Clinical Signs and Symptoms of Hyponatremia

Most patients with mild degrees of hyponatremia (plasma sodium levels, 125-135 mEq/L) are asymptomatic. Once the serum sodium concentration falls below 120 mEq/L, serious sequelae, especially involving the central nervous system, may follow. Cerebral edema develops because the decrease in plasma osmolality causes water to move into the cells. Cerebral overhydration can manifest with varied symptoms, such as headache, vomiting, altered consciousness, seizures, and coma. The severity of symptoms is dependent on both the magnitude and rapidity of the fall in the plasma sodium concentration. Although seizures are common with acute hyponatremia, patients with chronic hyponatremia may manifest focal neurologic deficits and ataxia. The brain is protected during chronic hyponatremia by adaptive changes involving loss of intracellular osmolytes. However, the same protective changes can be responsible for the harmful effects seen when chronic hyponatremia is corrected too rapidly (see later discussion).

Patients with hypovolemic hyponatremia can develop shock at lesser degrees of body water depletion in comparison with patients with normal or increased serum sodium concentration, because of the associated fluid shift from the ECF to the ICF compartment. The decrease in the intravascular volume is a stimulus for ADH secretion, which serves to perpetuate the hyponatremia by limiting renal water excretion.

◆ Treatment of Hyponatremia

The treatment of hyponatremia depends on its severity, its duration, and the ECF volume status. The primary goal should be to treat the underlying condition giving rise to hyponatremia (e.g., management of diarrhea, mineralocorticoid deficiency, nephrosis, or heart failure). However, management of hypovolemia often requires initiation of corrective therapy before the underlying disease is controlled.

Patients with severe hypovolemia should promptly receive parenteral fluids to restore the circulating blood volume and normalize tissue perfusion. Blood and urine specimens should ideally be obtained as soon as possible to assess serum electrolytes, blood urea nitrogen level, creatinine level, and urinary sodium excretion. *Because correction of severe hypovolemia takes precedence over normalization of osmolality, isotonic solutions can be safely administered before the blood chemistry results are available.* Crystalloids are the preferred replacement fluids except if blood transfusion is required in cases of hemorrhagic shock. Isotonic crystalloids such as 0.9% saline (sodium level, 154 mEq/L) or lactated Ringer solution (sodium level, 130 mEq/L) are administered at rate of 10-20 mL/kg over a short period of time. Fluid boluses can be repeated as needed until clinical improvement has occurred. The correction of hypovolemia helps in reversing the pathophysiologic factors causing water retention, thus ameliorating the hyponatremia. In patients with known cardiac, renal, or pulmonary diseases, fluid should be administered with caution, and concomitant measurement of central venous pressure and respiratory function is desirable.

After correction of acute hypovolemia, the remaining fluid deficit should be corrected slowly over 24-48 hours; additional fluid should be given to accommodate ongoing losses.

Patients with significant symptoms attributable to severe hyponatremia should receive hypertonic (3%) saline. Central nervous system symptoms almost always lessen when the serum sodium concentration is increased by 10 mEq/L. It is recommended that the initial serum sodium correction not exceed 125 mEq/L with this treatment.

Patients with SIADH require water restriction. In this group of patients, it is difficult to raise the plasma sodium concentration even with hypertonic saline, unless the ECF volume is simultaneously reduced. Whereas water restriction is enough for patients with mild hyponatremia, patients with symptoms should receive intravenous furosemide followed by intravenous hypertonic saline. In chronic SIADH, demeclocycline is effective because it diminishes the renal response to ADH.

Patients with hypervolemic hyponatremia require salt and water restriction. Any effort to increase the serum sodium concentration by saline administration causes further ECF volume expansion and may worsen the patient's condition. In cases of severe salt and water overload associated with renal failure, dialysis is the most effective therapy.

The management of patients with chronic hyponatremia is controversial. These patients usually have very subtle symptoms because the brain has time to adapt to the disturbance with a decrease in the intracellular osmolytes. Rapid correction of hyponatremia can lead to cellular shrinkage and can cause an osmotically induced **demyelination syndrome**, particularly in the pons. The patients with extensive lesions can have flaccid quadriplegia, dysphagia, and dysarthria.

HYPERNATREMIA

Hypernatremia is a plasma sodium level greater than 145 mEq/L and may occur as result of (1) loss of both body sodium and water (water losses exceeding those of sodium), (2) isolated loss of water, and rarely (3) increase in body sodium. The development of hypernatremia is usually prevented by thirst and renal concentrating mechanisms. Thirst is so effective that even patients with complete diabetes insipidus (DI) avoid hypernatremia by increasing fluid intake. Hypernatremia develops only when hypotonic fluid losses occur in combination with a disturbance in water intake, as a result of inadequate access (as in comatose, developmentally delayed, or very young patients), or as a result of a primary abnormality of thirst mechanism (e.g., hypothalamic adipsic syndrome). Establishing the differential diagnosis of hypernatremia is aided by determining the patient's ECF volume status (hypovolemia, euvolemia, or hypervolemia) (Fig. 46.2).

Hypovolemic Hypernatremia

Disorders associated with losses of both sodium and water but with a relatively greater loss of water lead to hypovolemic hypernatremia. Many of the common causes (e.g., diarrhea, diuretic use) are similar to those that cause hypovolemic hyponatremia. Hypernatremia in these situations develops because of failure to ingest hypotonic fluids. Hypernatremic dehydration and failure to thrive often develop in neonates who nurse poorly, especially if the mother's breast milk has not come in. If the losses are extrarenal (e.g., through diarrhea, vomiting, profuse sweating), the urinary sodium concentration is less than 10 mEq/L. The renal causes are usually associated with a urine sodium concentration higher than 20 mEq/L.

Euvolemic Hypernatremia

Pure water losses do not lead to volume contraction unless the water losses are large; these patients therefore appear euvolemic. In addition, hypernatremia develops only when the hypotonic losses are not accompanied by appropriate water intake. Although water loss can

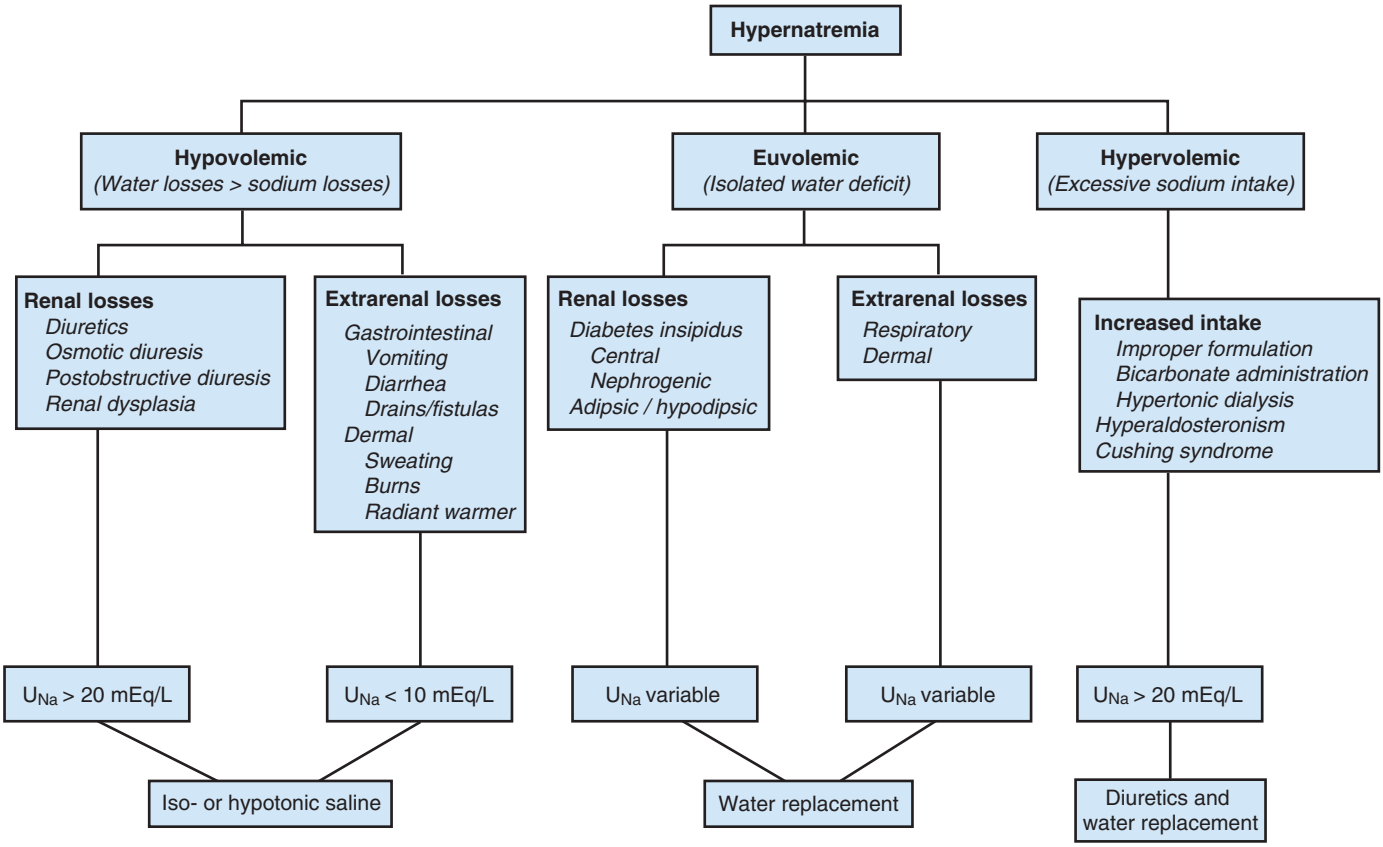

FIGURE 46.2 Classification, Diagnosis, and Treatment of Hypernatremic States. (Modified from Beri T, Schrier RW. Disorders of water metabolism. In: Schrier RW, ed. *Renal and Electrolyte Disorders*. Philadelphia: Lippincott-Raven; 1997.)

occur through the skin or the respiratory tract, the most important disorder in this group is DI.

Patients with DI have a very low urine osmolality. Central DI is caused by a failure to secrete ADH; nephrogenic DI is secondary to a renal resistance to ADH. Acquired forms of central and nephrogenic DI are more common than the hereditary forms.

Hereditary central DI can be either autosomal dominant or, less commonly, autosomal recessive. The autosomal recessive form occurs in association with diabetes mellitus, optic atrophy, and deafness (**Wolfram syndrome**). The acquired causes of central DI include central nervous system trauma, infections, tumors, granulomatous infiltration, and vascular malformations.

Congenital nephrogenic DI is a rare X-linked disorder affecting mainly boys, with variable penetrance in girls. The **acquired form of nephrogenic DI** can be seen in association with chronic renal diseases (e.g., polycystic disease, medullary cystic disease, ureteral obstruction), electrolyte disorders (e.g., hypokalemia, hypercalcemia), drugs (e.g., lithium, demeclocycline, amphotericin, foscarnet), and sickle cell disease/trait.

Older children with DI have polyuria, polydipsia, and nocturia. The urine is hypo-osmolar and remains so even when these children develop dehydration and consequently increased serum osmolality. During infancy, DI can manifest with recurrent episodes of unexplained dehydration and fever. Repeated episodes of hypernatremic dehydration can lead to permanent neurologic sequelae.

Performing a fluid deprivation test and then determining the response to injectable vasopressin can help diagnose DI and differentiate between the central and nephrogenic forms. Primary treatment should focus on the underlying cause. Central DI is managed with hormonal replacement therapy with desmopressin (DDAVP). There is considerable individual variation in the required dosage, and it is important to allow patients to revert to mild polyuria before the next dose is given, to prevent excessive water accumulation. An intravenous form of antidiuretic hormone can be used in sick and comatose patients.

Therapy for nephrogenic DI should ensure a sufficient intake of water to replace the large urinary losses. Because obligatory urinary water losses increase with increasing solute load, restriction of sodium intake reduces the urine output. Administration of diuretics, such as thiazides and amiloride, keeps these patients in a mildly dehydrated state, which leads to increased water reabsorption in the more proximal segments of the nephron, thereby decreasing urine output. Nonsteroidal antiinflammatory drugs such as indomethacin also reduce polyuria and may be used in combination with diuretics. Careful attention should be paid to the fluid balance in these patients when they are sick and have poor oral fluid intake because they require large quantities of water replacement. Frequent monitoring of serum electrolytes is mandatory during these periods.

Adipsic/hypodipsic hypernatremia (essential hypernatremia; reset osmostat) characterizes a group of patients who have persistent hypernatremia, absence or attenuation of thirst, and often partial DI. Many patients are obese as a result of polyphagia. These patients require regimental intake of fluids; they may need supplementation with DDAVP.

Hypervolemic Hypernatremia

This is the least common type of hypernatremia. Most of the causes are iatrogenic (administration of improperly formulated oral rehydration solution, administration of intravenous fluids, excessive bicarbonate administration during resuscitative efforts, inadvertent dialysis against a high sodium concentration dialysate, salt poisoning, and seawater drowning). Other causes include primary hyperaldosteronism and Cushing syndrome.

◆ Clinical Signs and Symptoms of Hypernatremia

Hypernatremia causes intracellular dehydration by movement of water from the intracellular to the extracellular compartment. The consequences of intracellular dehydration are particularly marked in the brain and manifest with irritability, altered sensorium, lethargy, and hyperreflexia and eventually seizures, coma, and death. Brain hemorrhages can result from tearing of small blood vessels when the brain contracts as a result of intracellular dehydration. **Hypernatremia and dehydration may predispose to dural sinus thrombosis**. During chronic hypernatremia, the brain cells adapt to the increased ECF osmolality by accumulating idiogenic osmoles (which are mostly amino acids, particularly taurine). They increase intracellular osmolality, consequently restoring intracellular volume. This protective response has significant implications for therapy and the speed with which hypernatremia should be corrected.

◆ Treatment of Hypernatremia

The treatment of hypernatremia is guided by its severity, its chronicity, and the ECF volume status of the patient.

It is important to realize that patients with hyperosmolality maintain the ECF space at the expense of the ICF compartment, and, therefore, the degree of sodium and fluid losses may be profound before clinical signs of hypovolemia develop. Large volumes of isotonic crystalloid may be necessary to replace the fluid deficit.

Once initial fluid resuscitation has been performed, the serum sodium concentration should be restored slowly over a minimum period of 48 hours. The total water deficit can be estimated as follows (FW, free water; NA, sodium):

$$\text{FW deficit (child)} = 0.6 \times \text{weight (kg)} \times (\text{current NA} / 140 - 1)$$

Hypernatremia is corrected especially slowly when it is more severe and chronic. The rate of fall in plasma sodium concentration should be less than 1 mEq/L/hr. During the correction of hypernatremia, the idiogenic osmoles that brain cells produce to prevent cellular dehydration dissipate slowly. If hypernatremia is corrected too rapidly, the increased intracellular osmolality from the idiogenic osmoles can lead to cerebral edema. In patients with hypervolemic hypernatremia, the 1st line of therapy is restriction of salt intake, followed by administration of diuretics.

CALCIUM DISORDERS

Serum calcium concentration in the extracellular fluid is regulated by parathyroid hormone (PTH), which acts on the kidney and bones, and by 1,25-dihydroxyvitamin D, which acts on the intestines and bones. About 50% of the calcium is in the ionized form, 40% is protein bound (mainly to albumin), and 10% is associated with anions, such as bicarbonate, citrate, sulfate, phosphate, and lactate. It is important to remember that serum albumin levels and pH affect calcium levels. There is a direct relationship between serum albumin concentration and total serum calcium. An alkaline pH will increase protein binding, leading to decreased ionized calcium levels. It is important to obtain an ionized calcium level when evaluating calcium derangements.

Hypocalcemia

There are many causes of hypocalcemia, and measurements of parathyroid hormone can help classify the etiology of hypocalcemia (Fig. 46.3). Hypocalcemia is defined as a total serum calcium level below 8.5 mg/dL and an ionized serum calcium level below 4.65 mg/dL. Patients with mild hypocalcemia are usually asymptomatic. With severe hypocalcemia, patients may present with paresthesias of the extremities, Chvostek sign, Trousseau sign, muscle cramps or spasm, laryngospasm, tetany, and seizures. Cardiac manifestations of hypocalcemia include a prolonged QT interval, which can progress to heart block.

Hypercalcemia

Similar to hypocalcemia, there are also many causes of hypercalcemia (Fig. 46.4). Hypercalcemia usually occurs through 1 of 3 mechanisms: increased bone resorption, increased gastrointestinal absorption of calcium, and decreased renal excretion. Hypercalcemia is defined as total serum calcium above 10.5 mg/dL and an ionized serum calcium of above 5.25 mg/dL. Patients with mild hypercalcemia usually do not have symptoms. Patients with severe hypercalcemia may have neurologic manifestations ranging from drowsiness to coma.

RICKETS

Rickets is a disease caused by deficient mineralization of the osteoid matrix before closure of the epiphyseal plate that results in softening and weakening of bones in infants and children. In patients with rickets, the growth plate cartilage and osteoid continues to expand but mineralization is inadequate, and as a result, the growth plate thickens. The circumference of the growth plate and the metaphysis also increases, which expands bone width at the location of the growth plates and causes some of the classic clinical manifestations, such as widening of the wrists and ankles. There is also softening of the bones that can lead to bone deformities and causes them to bend easily, especially when subject to certain forces.

Rickets is usually caused by vitamin D deficiency. Children at risk are those with limited sun exposure, ages 6-24 months, prematurity, solely breast-fed infants, use of anticonvulsants, and darker skin pigmentation. Rickets is still a significant problem in developing countries, likely due to nutritional vitamin D deficiency and inadequate calcium intake.

◆ Clinical Manifestations

Most clinical features of rickets are due to skeletal changes. Craniotabes is a softening of the cranial bones, which can be appreciated by applying pressure at the occiput or over the parietal bones. Widening of the costochondral junctions produces a rachitic rosary, which can be detected on exam by moving one's fingers along the costochondral junctions from rib to rib, named because it feels like the beads of a rosary. Increased circumference of the wrists and ankles is a result of growth plate widening. Patients with rickets may have an indentation of the lower ribs, known as a Harrison groove, which occurs from the pulling of the softened ribs by the diaphragm during inspiration. Softening of the ribs can impair air movement and predisposes patients to atelectasis and pneumonia. In addition to the skeletal manifestations, rickets can present with hypocalcemia, hypophosphatemia, and tetany (Table 46.11). It is important to note that most children are asymptomatic, and rickets is diagnosed through an incidental finding on physical or radiologic examination.

(See *Nelson Textbook of Pediatrics,* Fig. 571.1.)

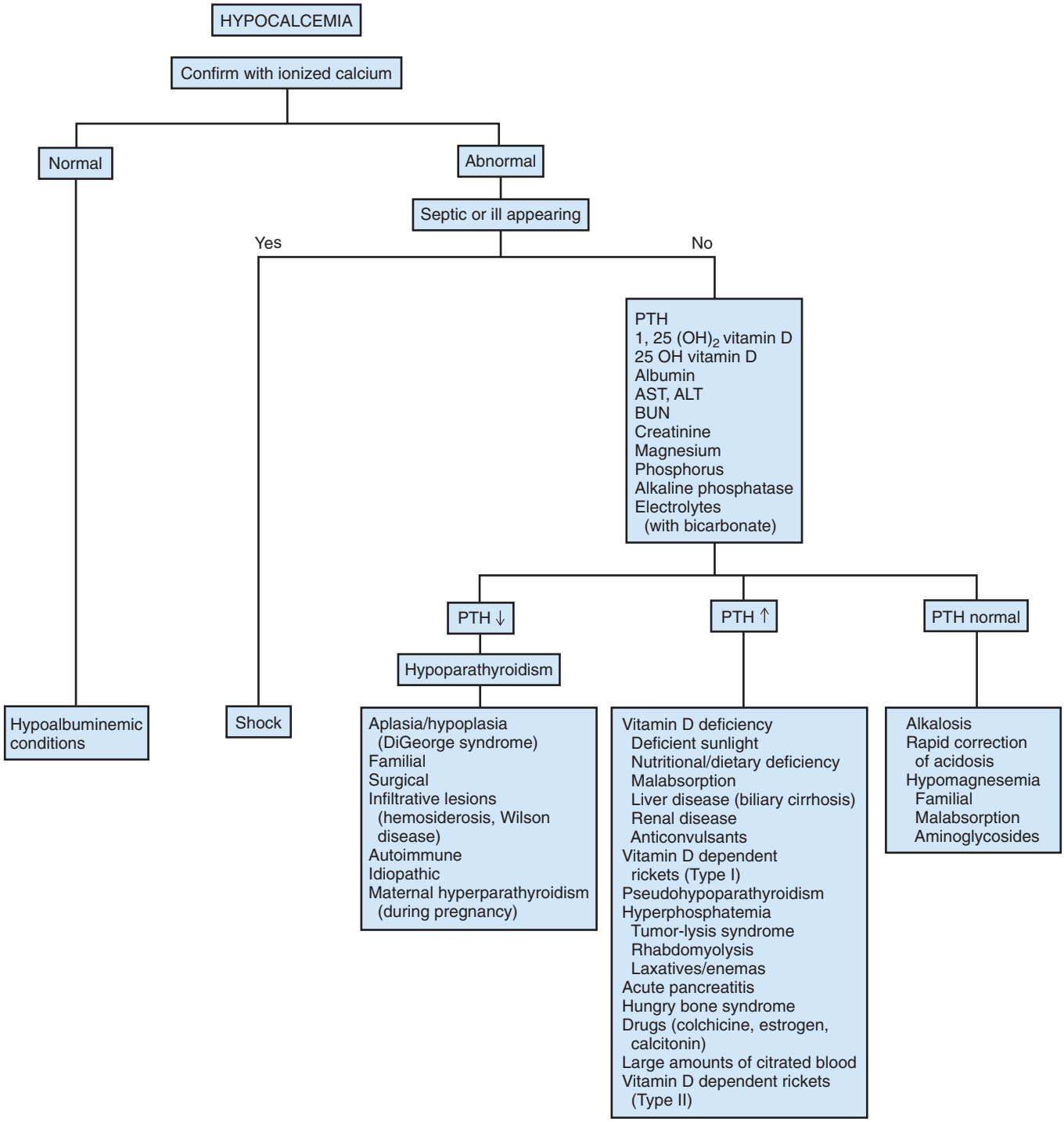

FIGURE 46.3 Causes of Hypocalcemia. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; PTH, parathyroid hormone. (From Pomeranz AJ, Sabnis S, Busey SL, et al. Hypocalcemia. In: Pomeranz AJ, Sabnis S, Busey SL, et al., eds. *Pediatric Decision-Making Strategies*. 2nd ed. Philadelphia: Elsevier; 2016:335.)

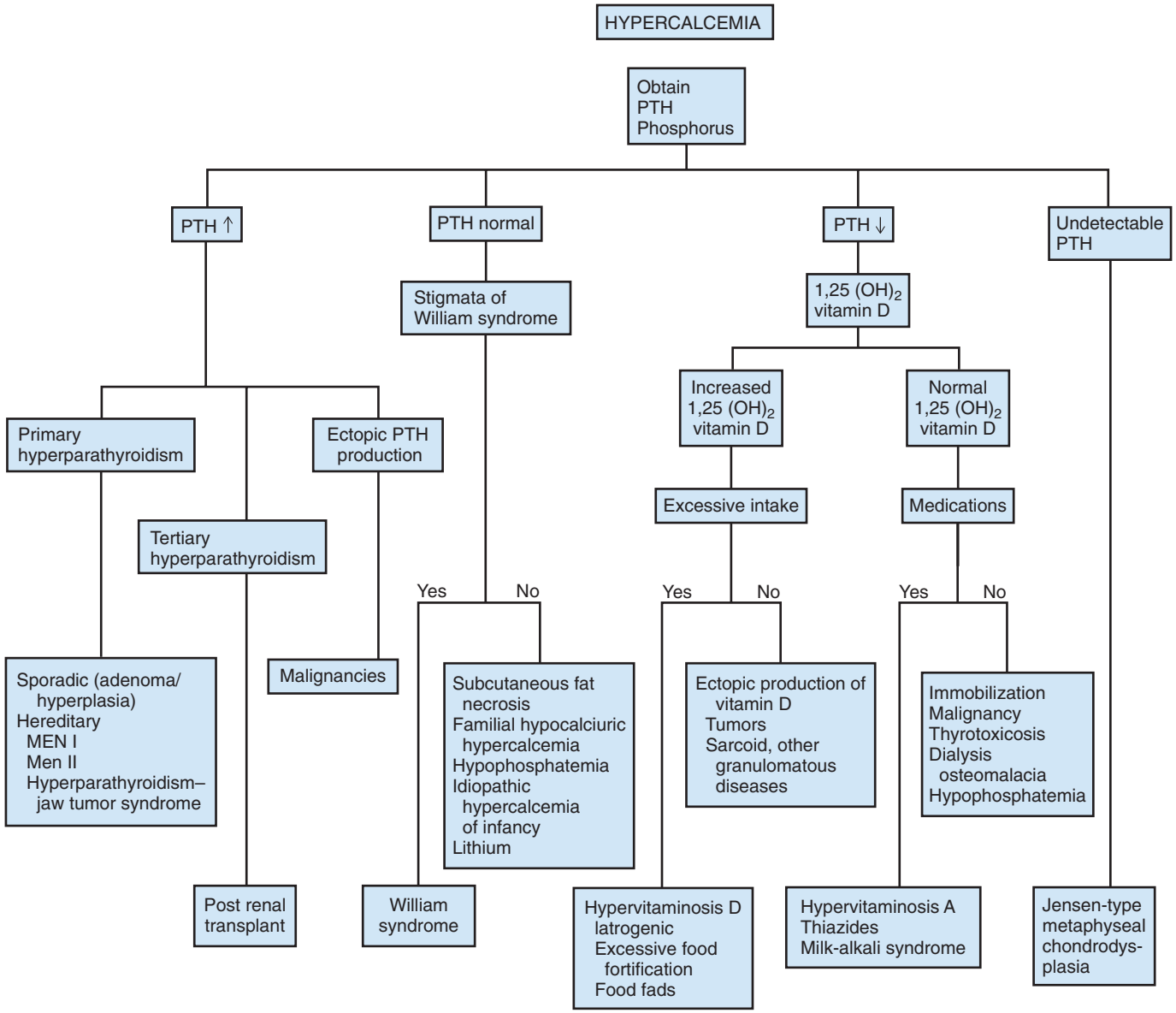

FIGURE 46.4 Causes of Hypercalcemia. MEN, multiple endocrine neoplasia; PTH, parathyroid hormone. (From Pomeranz AJ, Sabnis S, Busey SL, et al. Hypocalcemia. In: Pomeranz AJ, Sabnis S, Busey SL, et al., eds. *Pediatric Decision-Making Strategies*. 2nd ed. Philadelphia: Elsevier; 2016:337.)

There is some variation in the clinical presentation of rickets based on the etiology. Changes in the lower extremities tend to be the dominant feature in X-linked hypophosphatemic rickets. Symptoms secondary to hypocalcemia occur only in those forms of rickets associated with decreased serum calcium (Table 46.12).

Diagnosis of rickets is usually made by radiographic examination of the long bones. Laboratory values can support the diagnosis. Laboratory values may show decreased calcium and phosphorus, increased alkaline phosphatase, decreased 25-(OH) vitamin D_3 levels, increased 1,25-$(OH)_2$ vitamin D levels, and increased parathyroid hormone (PTH) levels. The increased PTH is indicative of the hormonal response that tries to maintain normal calcium (Table 46.13). The appropriate treatment depends on the underlying etiology.

SUMMARY AND RED FLAGS

Acid–base and electrolyte disturbances have many causes that reflect abnormalities of regulation or compensation of these systems. For many acid–base or electrolyte disturbances, the underlying condition needs to be treated before consideration of the electrolyte or acid-base disturbance. This is true in all causes of shock, such as dehydration, adrenal crisis, or systemic hemorrhage. The circulating blood volume must be quickly reestablished; this is usually performed as part of the resuscitation phase of treating dehydration or shock. Thereafter,

TABLE 46.11 Clinical Features of Rickets

General
Failure to thrive
Listlessness
Protruding abdomen
Muscle weakness (especially proximal)
Fractures

Head
Craniotabes
Frontal bossing
Delayed fontanel closure
Delayed dentition; caries
Craniosynostosis

Chest
Rachitic rosary
Harrison groove
Respiratory infections and atelectasis*

Back
Scoliosis
Kyphosis
Lordosis

Extremities
Enlargement of wrists and ankles
Valgus or varus deformities
Windswept deformity (combination of valgus deformity of 1 leg with varus deformity of the other leg)
Anterior bowing of the tibia and femur
Coxa vara
Leg pain

Hypocalcemic Symptoms†
Tetany
Seizures
Stridor due to laryngeal spasm

*These features are most commonly associated with the vitamin D deficiency disorders.
†These symptoms develop only in children with disorders that produce hypocalcemia.
From Greenbaum LA. Rickets and hypervitaminosis D. In: Kliegman RM, Stanton BF, St Geme JW, et al., eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:332.

TABLE 46.12 Causes of Rickets

Vitamin D Disorders
Nutritional vitamin D deficiency
Congenital vitamin D deficiency
Secondary vitamin D deficiency
Malabsorption
Increased degradation
Decreased liver 25-hydroxylase
Vitamin D–dependent rickets type 1A and 1B
Vitamin D–dependent rickets type 2A and 2B
Chronic kidney disease

Calcium Deficiency
Low intake
Diet
Premature infants (rickets of prematurity)
Malabsorption
Primary disease
Dietary inhibitors of calcium absorption

Phosphorus Deficiency
Inadequate intake
Premature infants (rickets of prematurity)
Aluminum-containing antacids

Renal Losses
X-linked hypophosphatemic rickets*
Autosomal dominant hypophosphatemic rickets*
Autosomal recessive hypophosphatemic rickets (1 and 2)*
Hereditary hypophosphatemic rickets with hypercalciuria
Overproduction of fibroblast growth factor-23
Tumor-induced rickets*
McCune–Albright syndrome*
Epidermal nevus syndrome*
Neurofibromatosis*
Fanconi syndrome
Dent disease
Distal renal tubular acidosis

*Disorders secondary to excess fibroblast growth factor-23.
From Greenbaum LA. Rickets and hypervitaminosis D. In: Kliegman RM, Stanton BF, St Geme JW, et al, eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:332.

TABLE 46.13 Laboratory Findings in Various Disorders Causing Rickets

Disorder	Ca	Pi	PTH	25-(OH)D	1,25-$(OH)_2$D	Alk Phos	Urine Ca	Urine Pi
Vitamin D deficiency	N, ↓	↓	↑	↓	↓, N, ↑	↑	↓	↑
Chronic kidney disease	N, ↓	↑	↑	N	↓	↑	N, ↓	↓
Dietary Pi deficiency	N	↓	N, ↓	N	↑	↑	↑	↓
Tumor-induced rickets	N	↓	N	N	RD	↑	↓	↑
Fanconi syndrome	N	↓	N	N	RD or ↑	↑	↓ or ↑	↑
Dietary Ca deficiency	N, ↓	↓	↑	N	↑	↑	↓	↑

↓, decreased; ↑, increased; ↑↑, extremely increased; 1,25-$(OH)_2$D, 1,25–dihydroxyvitamin D; 25-OHD, 25-hydroxyvitamin D; ADHR, autosomal dominant hypophosphatemic rickets; Alk Phos, alkaline phosphatase; ARHR, autosomal recessive hypophosphatemic rickets; Ca, calcium; HHRH, hereditary hypophosphatemic rickets with hypercalciuria; N, normal; Pi, inorganic phosphorus; PTH, parathyroid hormone; RD, relatively decreased (because it should be increased given the concurrent hypophosphatemia); VDDR, vitamin D–dependent rickets; XLH, X-linked hypophosphatemic rickets.
From Greenbaum LA. Rickets and hypervitaminosis D. In: Kliegman RM, Stanton BF, St Geme JW, et al., eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:333.

specific acid–base or, more often, electrolyte abnormalities can be attended to during the replacement phase to correct electrolyte deficits. In general, electrolyte disturbances must be corrected slowly. This is particularly true for sodium abnormalities. The major exceptions are hyperkalemia and acute hypercarbic respiratory acidosis, which must be treated immediately.

Each of the discussed acid–base and electrolyte disturbances are important, and hyperkalemia remains the one of most concern and the most dangerous.

Anuria, hypotension, weight loss, seizures, coma, hypoglycemia or hyperglycemia, apnea, and arrhythmias are additional concerning signs and symptoms. Moreover, the clinician must remain vigilant in identifying the primary reason or reasons for any of these acid–base or electrolyte disturbances.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

Acid–Base Disorders

Adrogue HJ, Madias NE. Management of life-threatening acid-base disorders. *N Engl J Med*. 1998;338:26.

Berend K, de Vries APJ, Gans ROB. Physiological approach to assessment of acid-base disturbances. *N Engl J Med*. 2014;371(15):1434-1445.

Bettinelli A, Bianchetti MG, Girardin E, et al. Use of calcium excretion values to distinguish two forms of primary renal tubular hypokalemic alkalosis: Bartter and Gitelman syndromes. *J Pediatr*. 1992;120:38.

Brewer ED. Disorders of acid-base balance. *Pediatr Clin North Am*. 1990;37:429.

Costanzo LS. Acid-base physiology. In: Costanzo LS, ed. *Physiology*. 5th ed. Philadelphia: Saunders; 2014:303-328.

Fall PJ. A stepwise approach to acid-base disorders. Practical patient evaluation for metabolic acidosis and other conditions. *Postgrad Med*. 2000;107:249.

Ferri FF. Renal tubular acidosis. In: Ferri FF, ed. *Ferri's Clinical Advisor 2016*. Philadelphia: Elsevier; 2016:1071-1072.

Greenbaum LA. Electrolyte and acid-base disorders. In: Kliegman RM, Stanton BF, St Geme JW, et al., eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:346-384.

Palmer BF. Metabolic acidosis. In: Johnson RJ, Feehally J, Floege J, eds. *Comprehensive Clinical Nephrology*. 5th ed. Philadelphia: Saunders; 2015:149-159.

Pereira PC, Miranda DM, Oliveira EA, et al. Molecular pathophysiology of renal tubular acidosis. *Curr Genomics*. 2009;10(1):51-59.

Rodríguez SJ. Renal tubular acidosis: the clinical entity. *J Am Soc Nephrol*. 2002;13:2160-2170.

Shapiro JI, Kaehny WD. Pathogenesis and management of metabolic acidosis and alkalosis. In: Schrier RW, ed. *Renal and Electrolyte Disorders*. Philadelphia: Lippincott-Raven; 1997.

Svoren BM, Jospe N. Diabetes mellitus. In: Kliegman RM, Stanton BF, St Geme JW, et al., eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:2760-2782.

Wolfsdorf J, Allgrove J, Craig ME, et al. Diabetic ketoacidosis. *Pediatr Diabetes*. 2014;15(suppl 20):154-179.

Potassium Disorders

Alon US. Renal tubular acidosis. In: Finberg L, ed. *Saunders Manual of Pediatric Practice*. Philadelphia: WB Saunders; 1998:694.

Carlisle EJF, Donnelly SM, Ethier JH, et al. Modulation of the secretion of potassium by accompanying anions in humans. *Kidney Int*. 1991;39:1206.

Chacko M, Fordtran JS, Emmett M. Effect of mineralocorticoid activity on transtubular potassium gradient, urinary [K]/[Na] ratio, and fractional excretion of potassium. *Am J Kidney Dis*. 1998;32:47.

Halperin ML, Kamel K. Potassium. *Lancet*. 1998;352:135.

Hellerstein S, Alon US, Warady BA. Renal impairment. In: Ashcraft KW, ed. *Pediatric Surgery*. Philadelphia: Saunders; 2000.

Mandal AK. Hypokalemia and hyperkalemia. *Med Clin North Am*. 1997;81:611.

Perazella MA. Drug-induced hyperkalemia: Old culprits and new offenders. *Am J Med*. 2000;109:307.

Peterson LN, Levi M. Disorders of potassium metabolism. In: Schrier RW, ed. *Renal and Electrolyte Disorders*. Philadelphia: Lippincott-Raven; 1997.

Rodriguez-Soriano J, Ubetagoyena M, Vallo A. Transtubular potassium concentration gradient: a useful test to estimate renal aldosterone bio-activity in infants and children. *Pediatr Nephrol*. 1990;4:105.

Wilson FH, Disse-Nicodeme S, Choate KA, et al. Human hypertension caused by mutations in WNK kinases. *Science*. 2001;293:1107.

Sodium Disorders

Abrahm WT, Schrier RW. Renal sodium excretion, edematous disorders, and diuretic use. In: Schrier RW, ed. *Renal and Electrolyte Disorders*. Philadelphia: Lippincott-Raven; 1997.

Ball SG, Vaidja B, Baylis PH. Hypothalamic adipsic syndrome: diagnosis and management. *Clin Endocrinol (Oxf)*. 1997;47:405.

Berl T, Schrier RW. Disorders of water metabolism. In: Schrier RW, ed. *Renal and Electrolyte Disorders*. Philadelphia: Lippincott-Raven; 1997.

Berry PL, Belsha CW. Hyponatremia. *Pediatr Clin North Am*. 1990;37:351.

Cadnapaphornchai MA, Schrier RW. Pathogenesis and management of hyponatremia. *Am J Med*. 2000;109:688.

Conley SB. Hypernatremia. *Pediatr Clin North Am*. 1990;37:365.

Ganong CA, Kappy MS. Cerebral salt wasting in children. The need for recognition and treatment. *Am J Dis Child*. 1993;147:167.

Hall RT, Simon S, Smith MT. Readmission of breastfed infants in the first 2 weeks of life. *J Perinatol*. 2000;20:432.

Harris HW. Diabetes insipidus. In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics*. Philadelphia: Saunders; 2000.

Haycock GB. The syndrome of inappropriate secretion of antidiuretic hormone. *Pediatr Nephrol*. 1995;9:375.

Jakobsson B, Berg U. Effect of hydrochlorothiazide and indomethacin treatment on renal function in nephrogenic diabetes insipidus. *Acta Peadiatr*. 1994;83:522.

Manganaro R, Mami C, Marrone T, et al. Incidence of dehydration and hypernatremia in exclusively breast-fed infants. *J Pediatr*. 2001;139:673.

Trachtman H. Sodium and water homeostasis. *Pediatr Clin North Am*. 1995;6:1343.

Calcium Disorders

Pomeranz AJ, Sabnis S, Busey SL, et al. Hypocalcemia. In: Pomeranz AJ, Sabnis S, Busey SL, et al., eds. *Pediatric Decision-Making Strategies*. 2nd ed. Philadelphia: Saunders; 2016:334-335.

Pomeranz AJ, Sabnis S, Busey SL, et al. Hyercalcemia. In: Pomeranz AJ, Sabnis S, Busey SL, et al., eds. *Pediatric Decision-Making Strategies*. 2nd ed. Philadelphia: Saunders; 2016:336-338.

Thakker RV. The parathydroid glands, hypercalcemia and hypocalcemia. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*. 25th ed. Philadelphia: Saunders; 2016:1649-1661.

Rickets

Ferri FF. Rickets. In: Ferri FF, ed. *Ferri's Clinical Advisor 2016*. Philadelphia: Elsevier; 2016:1086.e2-1086.e3.

Greenbaum LA. Rickets and hypervitaminosis D. In: Kliegman RM, Stanton BF, St Geme JW, et al., eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2016:331-341.

47

Congenital Cutaneous Lesions and Infantile Rashes

Yvonne E. Chiu and Stephen R. Humphrey

Neonates and infants can have a variety of congenital birthmarks and transient rashes, some very common and others more rare. The chapter is organized by the primary cutaneous lesion seen on clinical examinations (Table 47.1).

RASHES

Papules and Pustules—Diffuse or Scattered

Erythema toxicum is a benign condition that occurs in 30-70% of white full-term infants. Erythema toxicum occurs less frequently in premature infants. The eruption is characterized by blotchy, erythematous macules or patches with central papules, pustules, or vesicles that give the infant a "flea-bitten" appearance (Fig. 47.1). The lesions develop most commonly between the 2nd and 4th days after birth; however, they may appear during the 1st 2-3 weeks. They are self-limiting and usually resolve within several days. Typical sites of involvement include the face, trunk, and proximal extremities. There may be very few to hundreds of lesions.

A Giemsa or Wright stain of the intralesional contents reveals sheets of *eosinophils* with a relative absence of neutrophils. Peripheral eosinophilia may be present in up to 20% of affected infants. Erythema toxicum is occasionally confused with transient neonatal pustular melanosis, congenital cutaneous candidiasis, impetigo neonatorum, milia, herpes simplex, or miliaria rubra (prickly heat).

Transient neonatal pustular melanosis, seen in up to 4% of neonates, occurs more often in African-American infants. Typically present at birth, the initial lesions are 2- to 5-mm pustules distributed over the face, neck, and upper chest and, less often, on the sacrum, trunk, thighs, palms, and soles (Fig. 47.2). In contrast to the lesions of erythema toxicum, there is no erythema surrounding each pustule, and Wright stain of pustular contents reveals many neutrophils. In both disorders, the pustules are sterile and should be distinguished from those seen in potentially serious infections caused by herpes simplex virus (HSV), *Staphylococcus aureus*, or *Candida* species.

The superficial pustules of transient neonatal pustular melanosis rupture spontaneously within the 1st few days after birth, leaving hyperpigmented macules that have collarettes of fine scale. It is common to see only the hyperpigmented macules at birth. These brown spots slowly fade over several weeks to months.

Miliaria results from sweat retention and is exacerbated by heat and humidity. Affected newborns are frequently in incubators or receiving phototherapy. Keratinous plugging of the eccrine ducts and subsequent release of eccrine sweat into the surrounding skin produces 2 distinct clinical manifestations with different sites of eccrine duct obstruction. In miliaria crystallina, obstruction occurs just below the stratum corneum, resulting in superficial, noninflammatory 1- to 2-mm vesicles. In miliaria rubra, or "prickly heat," obstruction occurs in the mid-epidermis. This is associated with an inflammatory response exhibited by vesicles, papules, or papulovesicles surrounded by a rim of erythema. The lesions occur in clusters on the trunk, face, scalp, and intertriginous regions. Neither type of miliaria warrants therapy, but improvement occurs with cooling of the skin and avoidance of excessive warmth and moisture.

Eosinophilic pustular folliculitis is another disorder of infancy characterized by recurrent crops of vesicles and pustules, beginning in the 1st year of life. Lesions are often present on the forehead and scalp. The condition tends to occur in a cyclic pattern and is very pruritic. Scraped material from the pustules subjected to Wright stain demonstrates a large number of eosinophils but no evidence of infectious organisms. A complete blood cell count may show peripheral eosinophilia. In rare cases, skin biopsy may be necessary. Histopathologic study demonstrates a perifollicular and dermal infiltrate of eosinophils, as well as lymphocytes and histiocytes. Because the clinical condition is very similar to infantile acropustulosis, some authors contend that eosinophilic pustular folliculitis may be part of the same clinical spectrum. This condition is not associated with systemic disease, and the 1st-line treatment is symptomatic with topical corticosteroids and antihistamines. Oral and topical indomethacin has been effective in recalcitrant cases. Eosinophilic pustular folliculitis usually resolves spontaneously by 2-3 years of age.

Acropustulosis of infancy is a condition that may present at birth or during the 1st few weeks or months afterward. The disorder is characterized by recurrent eruptions of pruritic pustules or vesicles involving the hands and feet (Fig. 47.3). On occasion, involvement includes other sites such as the trunk or abdomen. The lesions frequently begin in crops, which typically last approximately 1 week, and resolve with desquamation, followed by postinflammatory hyperpigmentation.

Acropustulosis is often confused with infantile scabies. Family history and examination of scrapings of the involved area may help differentiate between these 2 diagnoses. However there is some thought that it may occur after a previous scabies infection. Scrapings of lesions in acropustulosis often demonstrate neutrophils. Bacterial infection should also be ruled out by wound cultures. Treatment is symptomatic and consists of control of pruritus with low- to mid-potency topical corticosteroids and antihistamines. Parents should be

TABLE 47.1 Neonatal and Infantile Cutaneous Lesions

Rashes	
Papules and Pustules	
Erythema toxicum	Occurs 1st few days of life. Blotchy red macules with central papule, pustule, or vesicle.
Transient neonatal pustular melanosis	Present at birth. More common in African-American infants. Pustules resolve with hyperpigmented macules.
Miliaria	Associated with overheating. Vesicles and pustules in occluded areas.
Eosinophilic pustular folliculitis	Onset during infancy. Pruritic pustules on the head and neck.
Acropustulosis of infancy	Onset during infancy. Pruritic pustules on the hands and feet.
Neonatal cephalic pustulosis (neonatal acne)	Pink papules, predominately on face.
Langerhans cell histiocytosis	Crusted papules, predominately on the scalp and intertriginous areas.
Herpes simplex virus	Onset from birth to 2 wk. Grouped vesicles and papulopustules favor scalp and trunk.
Varicella	Diffuse vesicles and papules. Associated with sepsis, fever/hypothermia.
Scabies	Pruritic papules, vesicles, and pustules. Can be widespread in infants, but concentrated in intertriginous areas.
Syphilis	Widely scattered scaly red-brown papules and plaques
Patches and Plaques	
Neonatal lupus	Bright red annular patches and plaques distributed on cheeks and periorbital skin. Heart block is most common extracutaneous finding.
Seborrheic dermatitis	Pink patches on the scalp, face, ears, and intertriginous areas. May have yellow, greasy scale. Erosions and fissures can be seen.
Diaper dermatitis	Pink patches with erosions in the groin and buttocks. Can be multifactorial.
Fixed Lesions	
Macules, Papules, and Pustules	
Milia	Pinpoint white-yellow papules without erythema. Typically on face, gingiva, or palate. Resolves with time.
Sebaceous gland hyperplasia	Skin-colored to yellow tiny papules on cheeks and nose. Secondary to maternal androgens. Resolve in 1st few months.
Subcutaneous fat necrosis	Firm, indurated, tender plaques on back, arms, shoulders of newborns. Due to perinatal trauma, hypothermia, or hypoxemia. Monitor for hypercalcemia.
Juvenile xanthogranuloma	Solitary yellow-pink plaques on the face and scalp. May ulcerate and usually resolve spontaneously.
Mastocytoma	Yellow to pink solitary plaques. Can urticate or swell with friction or rubbing. Composed of mast cells. Can be seen in infants but typically more common with toddlers.
Urticaria pigmentosa	Condition with several mastocytomas. Rare in infants. Typically presents with lesions that will urticate. Over time, they become hyperpigmented. Rarely associated with systemic symptoms.
Spider angioma	Rare in infants. Small blanching capillaries with "feeder vessel" on the trunk and face.
Pyogenic granuloma	Solitary, small vascular papules that develop rapidly and bleed profusely. Typically seen in toddlers and occasionally infants.
Patches and Plaques	
Pink (Vascular or Other)	
Hemangioma	Benign vascular tumors, typically present in 1st month of life. Grow rapidly for 1st several months and then involute slowly over a couple of years.
PHACE/PELVIS	Syndromes associated with hemangiomas in particular locations on the face or back.
Capillary malformation	Stable, pink, vascular patches; typically unilateral. In V1 distribution, can be associated with Sturge–Weber syndrome
Nevus simplex	Pink patches on glabella, eyelids, nape of neck, typically. Usually fade over 1st couple of years.
Cutis marmorata telangiectasia congenita	Lacy, reticulated vascular patches. Do not resolve with rewarming of infant. May have atrophic changes or ulcerate.
Kaposiform hemangioendothelioma	Rare vascular tumor. Firm, violaceous, and tends to proliferate. Can lead to consumptive coagulopathy(Kasabach–Merritt syndrome)
Venous/lymphatic malformation	Slow-flow vascular malformations. Typically present at birth. May be associated with atrophy or overgrowth.

TABLE 47.1 Neonatal and Infantile Cutaneous Lesions—cont'd

Hyperpigmented or Darker Pigment	
Congenital melanocytic nevus	Pigmented macules, papules, patches, and plaques. Present in 2–3% of population.
Neurocutaneous melanosis	Defined by a giant melanocytic nevus. Associated with melanocytic infiltration of leptomeninges. Clinically symptomatic lesions have worse prognosis.
Café-au-lait macules	Well-demarcated tan macules or patches. Seen in 10–20% of population. Multiple lesions can be associated with neurofibromatosis.
Dermal melanocytosis	Large, poorly demarcated, slate-gray to blue patches on buttocks and lumbosacral region. Occurs normally in darker skin tones. Typically fades over time.
Hypopigmented or Depigmented	
Nevus depigmentosus	Hypopigmented patch that persists through life.
Ash leaf spots	Hypopigmented macules that present in 1st few months to years of life. Typically seen with tuberous sclerosis.
Piebaldism	Well-circumscribed areas of depigmentation on the skin. Tends to be symmetric and stable in size.
Waardenburg syndrome	White forelock, white patches on skin. Can have heterochromia of irides and hearing loss.
Albinism	Diffuse congenital hypopigmentation of skin. Usually involves eyes and hair. Should be monitored closely by ophthalmologists. Evaluate for hearing loss. Patients need lifelong photoprotection.
Other	
Nevus sebaceus	Sebaceous gland hamartoma, usually present at birth. Yellow-orange and smooth plaque. Thickens during puberty.
Dermoid cyst	Typically found in head/neck region. Potential for intracranial connection.
Aplasia cutis	Congenital absence of skin, typically on scalp. Can resemble scars when child is older.
Hair collar sign	Ring of dense, darker hair encircling a scalp lesion. Can be a sign of spinal dysraphism.
Hypertrichosis of lumbar area	Normal variant in certain ethnicities. Can be indicator of spinal dysraphism.
Sacral dimples	Commonly seen. Large dimples along gluteal crease need to be evaluated for spinal dysraphism. Can be associated with hypertrichosis.
Transient/Changing Lesions	
Patches	
Segmental	
Cutis marmorata	Lacy, reticulated vascular patches, often bilateral. Resolve with warming of infant and disappear over time.
Diffuse	
Harlequin color change	Marked erythema on dependent side. Simultaneous blanching on non-dependent side. Transient.
Distal Extremities	
Acrocyanosis	Bluish-purple discoloration of hands, feet, lips. Occurs with crying and cold stress.

PHACE, posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, and eye abnormalities; PELVIS, perineal hemangioma, external genitalia malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, and skin tag.

FIGURE 47.1 Papules surrounded by erythema are characteristic of erythema toxicum. Typically it is located on the trunk, but can be on the extremities as well.

FIGURE 47.2 Transient neonatal pustular melanosis. Papules and papulopustules that rupture to leave a collarette of fine scales and eventual hyperpigmentation. (From Paller AS, Mancini AJ. Cutaneous disorders of the newborn. In: Paller AS, Mancini AJ, eds. *Hurwitz Clinical Pediatric Dermatology*. 4th ed. Philadelphia: Elsevier; 2011:18.)

FIGURE 47.3 Acropustulosis of infancy. Multiple tense erythematous papules and pustules on the palm of this 4-month-old girl. (From Paller AS, Mancini AJ. Cutaneous disorders of the newborn. In: Paller AS, Mancini AJ, eds. *Hurwitz Clinical Pediatric Dermatology*. 4th ed. Philadelphia: Elsevier; 2011:19.)

FIGURE 47.4 Neonatal acne (cephalic pustulosis) is usually found on the cheeks and scalp in the 1st 2-4 weeks of life; small red papules and pustules without comedones are evident. (Modified from Eichenfield LF, Frieden IJ, Esterly NB. *Textbook of Neonatal Dermatology*. Philadelphia: Saunders; 2001:94.)

advised that lesions tend to occur episodically until approximately 2-3 years of age.

Neonatal cephalic pustulosis (neonatal acne) develops in approximately 20% of newborns. Typically, it is not present at birth, but appears during the 1st few weeks after birth. Characterized by papules and pustules located on the face or trunk, this condition usually resolves within the 1st several months of life (Fig. 47.4). Neonatal acne is a misnomer as neonatal cephalic pustulosis is likely caused by *Malassezia* yeast species. Therapeutic intervention is rarely required, but ketoconazole 2% cream may be of some use.

Langerhans cell histiocytosis (LCH) is a rare disorder, affecting about 5 per 1 million children, which is characterized by a proliferation of clonal dendritic cells, called Langerhans cells. There are 4 main types, 2 of which are most frequently seen in neonates and infants, though there is substantial overlap among the types.

FIGURE 47.5 "Raccoon eyes" eruption of neonatal lupus erythematosus. (From Eichenfield LF, Frieden IJ, Esterly NB. *Textbook of Neonatal Dermatology*. Philadelphia: Saunders; 2001:297.)

Congenital self-healing reticulohistiocytosis (Hashimoto–Pritzker disease) typically presents at birth or within the 1st few days of life and is limited to the skin. There is a diffuse eruption of red to purple-brown papules and nodules that will crust and remit after several weeks. While it is considered a benign, self-limited condition, it can rarely progress to other more aggressive forms of LCH.

Letterer–Siwe disease is the more acute, diffuse form of LCH that has multisystem involvement. It commonly presents before 1 year of age with the majority of patients having skin findings of small 1- to 2-mm papules, pustules, and vesicles, typically on the scalp, intertriginous areas, and trunk. The lesions are often crusted and may have secondary bacterial infections. Fissures and confluence of papules can be seen. It can be confused with seborrheic dermatitis, and other forms of diaper dermatitis (Table 47.1).

Patches and Plaques

Patches are confluent, flat lesions over 1 cm in size, while plaques are slightly raised lesions over 1 cm in size. Many of these conditions have overlapping features but can often be distinguished by their location, distribution, and response to certain treatments (Table 47.1).

Neonatal lupus erythematosus is a unique annular erythematous eruption during the neonatal period. Lesions of neonatal lupus are often scaly, annular plaques that usually occur on the face and scalp and may affect the periorbital and malar areas, creating a "raccoon eyes" appearance (Fig. 47.5). Other manifestations may include transient hypopigmentation with epidermal atrophy or telangiectasia. Cutaneous lesions may be present at birth but often appear within the 1st 2-3 months of life. The lesions are usually exacerbated by sun exposure and are typically photodistributed. The majority of skin findings are transient, lasting up to 6-9 months.

(See *Nelson Textbook of Pediatrics,* p. 1176.)

Cutaneous findings or congenital heart block are each present individually in approximately 50% of affected infants; some studies have shown congenital heart block to be much less common. An overlap of both is present in approximately 10% of affected infants. The major morbidity and mortality of neonatal lupus result from congenital heart block.

The diagnosis of neonatal lupus includes examination of anti-Ro, anti-La, and anti-U1RNP autoantibodies in both the infant and mother. Ninety-five percent of mothers of infants with neonatal lupus have anti-Ro antibodies. Skin biopsy is usually not necessary. Work-up should include an electrocardiogram (ECG), platelet count, and liver function tests because approximately 5-10% of affected infants have liver disease or thrombocytopenia. Rare reports of multisystem involvement, including neurologic and respiratory findings have been reported.

Mothers with high titers of anti-Ro antibodies or with systemic lupus erythematosus have a higher risk of delivering an infant with neonatal lupus and should be counseled appropriately. Despite high antibody titers, fewer than half of mothers of affected infants are symptomatic at the time of delivery. In most of these mothers, evidence of connective tissue disease, usually Sjögren syndrome or subacute cutaneous lupus, develops over time.

Differential diagnosis should include annular erythema of infancy, tinea corporis, and cutis marmorata telangiectatica congenita (CMTC). Treatment consists of photoprotection and topical steroids. Most cutaneous changes resolve spontaneously by 6-9 months of age as a result of a gradual decrease in maternal antibodies.

Seborrheic dermatitis, common during infancy, typically manifests within the 1st several weeks after birth. Characterized by erythema and a yellow, greasy scale, it usually resolves spontaneously within several months. The eruption occurs at sites where sebaceous glands are concentrated, such as the face, chest, posterior auricular scalp, and intertriginous areas. *Malassezia* colonization plays a part in the development of seborrheic dermatitis. "Cradle cap" is seborrhea that is confined to the scalp. Involvement of the diaper area is characterized by salmon-colored patches that arise in skin folds and spread to the genitalia, suprapubic area, and upper medial thighs. Scale may not be as apparent in intertriginous areas. Unlike atopic dermatitis, this eruption is not very pruritic. Secondary candidal or bacterial infection is common, particularly if erosions or fissures are seen.

The diagnosis is established clinically. The presence of greasy yellow scales and salmon-colored patches, involvement of the scalp and intertriginous areas, early onset, and lack of pruritus or atopic history help distinguish seborrheic from atopic dermatitis. However, some infants have an overlap of seborrheic dermatitis and atopic dermatitis. Seborrheic dermatitis should also be differentiated from LCH, in which the lesions are typically purpuric, erosive, or crusted; and from psoriasis (see Chapter 48). Skin biopsy findings, as well as hepatosplenomegaly, purpura, lymphadenopathy, anemia, thrombocytopenia, external otitis, interstitial pneumonia, and osseous lesions, further distinguish LCH from seborrheic dermatitis.

Treatment of the scalp consists of mild keratolytic shampoos, such as those containing selenium sulfide or zinc pyrithione. Ketoconazole 2% shampoo can be efficacious, particularly with controlling overgrowth of the yeast. Mineral oil may be helpful in removing thick, adherent scales. The scalp and diaper dermatitis may be treated with low-potency topical corticosteroids and barrier ointments. Topical antifungal or antibacterial agents should be used for coexisting candidiasis or impetigo.

Diaper dermatitis is 1 of the most common dermatologic disorders of infants and toddlers (Table 47.2). It comprises a group of inflammatory conditions that involve the lower abdomen, genitalia, upper thighs, and buttocks. Clinical manifestations include erythema, edema, erosions, vesicles, and pustules. Secondary changes of postinflammatory hyperpigmentation or hypopigmentation are common.

Diaper dermatitis is often multifactorial, including irritation from feces/urine, skin breakdown from maceration, and bacterial or fungal components. Although urinary ammonia was thought to be the primary factor in the development of diaper dermatitis, feces now appear to play a more important role. Fecal ureases, by converting urea to ammonia, cause the elevation of skin pH, which in turn, increases fecal protease and lipase activity. These proteases and lipases cause the disruption of the epidermal barrier. Skin wetness, friction, maceration, and contact with feces, urine, and microbes further compromise epidermal integrity. This results in increased permeability of the skin to irritants such as soaps, powders, and detergents. Diaper dermatitis may begin as early as 1-2 months of age and may become a chronic or recurrent problem in older infants as well.

Allergic contact dermatitis is another component to consider, although it is more common in toddlers and children than neonates. Offenders can be dispersed dyes from disposable diapers and methylisothiazolinone in wet wipes. The differential diagnosis may also include seborrheic dermatitis, skin or perianal infections (particularly due to group A streptococcus), and psoriasis (see Chapter 48).

FIXED LESIONS

Macules, Papules, and Pustules

Milia are pinpoint white or yellow papules that are commonly present in 40-50% of neonates. Located predominantly on the face, they may also be seen in the oral cavity, where they are referred to as Epstein pearls (palate) or Bohn nodules (gingiva). The lesions represent keratin-filled epidermal inclusion cysts, which usually resolve spontaneously during the 1st few weeks of life. Unusually widespread or persistent lesions may be associated with defects such as hereditary trichodysplasia, oral–facial–digital syndrome, or particular subtypes of epidermolysis bullosa. Milia may be present in several genodermatoses, including Bazex–Christol–Dupre, Rombo, Brook–Spiegler syndromes, atrichia with papular lesions, and pachonychia congenita, type 2.

Sebaceous gland hyperplasia is characterized by the presence of multiple flesh- to yellow-colored tiny papules primarily on the nose and cheeks of full-term infants. The increased sebaceous cell size and number as well as sebaceous gland volume may result from maternal androgen stimulation. Spontaneous resolution occurs within the 1st 4-6 months of life.

Subcutaneous fat necrosis is a condition of otherwise healthy infants that is associated with preceding trauma, cesarean section, cold injury, or hypoxia. This disorder occurs primarily in healthy full-term and postmature infants. Single or multiple erythematous to violaceous, indurated, tender nodules or plaques arise on the buttocks, thighs, back, cheeks, and arms. In rare cases, lesions liquefy, ulcerate, and drain an oily substance (Fig. 47.6). The diagnosis can be confirmed by the histopathologic findings of fat lobules containing pathognomonic needle-shaped clefts surrounded by a mixed inflammatory infiltrate of lymphocytes, histiocytes, and foreign body giant cells. Intact lesions heal spontaneously within several months, whereas ulcerated lesions may heal more slowly and result in scarring. All patients should be screened for hypercalcemia, which may be present in nearly 70% of patients. Fortunately, hypercalcemia tends to be asymptomatic, without evidence of irritability, hypotonia, or weight loss, though life-threatening hypercalcemia may occur. The hypercalcemia may be delayed, with normal serum calcium early in the course of this disorder but elevated levels arising several weeks later.

(See *Nelson Textbook of Pediatrics,* p. 3116.)

TABLE 47.2 Diaper Dermatitis

Disease	Clinical Manifestation	Other Features	Treatment
Friction	Inner surface of thighs, genitalia, buttocks, abdomen.	Course waxes and wanes. Aggravated by talc.	Responds well to diaper changes. Avoidance of diapers.
Irritant	Mild erythema with shiny surface and occasional papules. Confined to convex surfaces. Spares intertriginous areas.	Exacerbated by heat, moisture, and sweat retention.	Gentle cleansing. Regular diaper changes. Barrier creams (zinc oxide, Vaseline). Low-potency topical steroids can help.
Allergic contact	Typically confined to convex surfaces. Skin involved is in direct contact with offending agent. Mild cases: diffuse erythema, papules, vesicles, scaling. Severe cases: papules, plaques, psoriasiform lesions, ulcerations, infiltrative nodules.	Often related to topical antibiotics (neomycin, bacitracin). Certain emulsifiers in topical products. Preservatives in wet wipes can be an offender.	Remove offending agent. Judicious use of low-potency topical steroids. Barrier creams/ointments.
Seborrheic dermatitis	Salmon-colored patches. Often have yellow, greasy scale. Fissures, erosions, maceration, and weeping can be seen.	Axillae, ear creases, and neck are often involved. "Cradle cap" on scalp. Hypopigmentation often seen in patients with darker skin tones.	Low-potency topical steroids. If coexistent infection–antifungal or antibacterial agents.
Candidiasis	Usually involves intertriginous areas and convex surfaces. Bright-red papules and plaques. Satellite lesions on abdomen and thighs.	Oral thrush may be present. Often occurs after treatment with systemic antibiotics or local topical steroid use.	Topical anticandidal agent, including nystatin.
Intertrigo	Well-demarcated, macerated plaques with weeping. Gluteal cleft and fleshy folds of thighs.	May be associated with miliaria.	Avoiding excessive heat. Cool clothing.
Psoriasis	Bright red, scaly, well-demarcated plaques. Can persist for months. Less responsive to topical treatment.	Red, sometimes scaly. Can be present on extremities or trunk. Nail changes seen. Family history.	Low-potency topical steroids. Moisturizers.
Staphylococcal infection	Many thin-walled pustules with pink-red base. Collarette of scale after rupturing.		Antistaphylococcal therapy.
Acrodermatitis enteropathica (zinc deficiency)	Early lesions are vesicular and pustular. Become confluent, pink, dry, scaly, crusty plaques.	Perioral skin typically also involved. Irritability or listlessness. Failure to thrive, alopecia, diarrhea.	Secondary to zinc deficiency or inborn error of zinc transporter. Treat with zinc replacement.
Langerhans cell histiocytosis	May mimic candidiasis or seborrheic dermatitis. Persistent, does not improve with standard treatments. Clusters of infiltrative, crusted, hemorrhagic papules. Ulceration can be seen.	Involvement of groin, axillae, periauricular skin, hairline, and scalp. Anemia, thrombocytopenia, hepatosplenomegaly, and osseous lesions.	Chemotherapy.

Juvenile xanthogranulomas (JXGs) are rare, benign, solitary collections of non-Langerhans cell histiocytes, thought to be reactive in nature. They typically present during the neonatal and infantile period and usually resolve over subsequent months or years. Multiple lesions may exist and should raise suspicion for extracutaneous disease. The incidence of extracutaneous JXG is rare, and the eye is thought to be the most common site, occurring in 0.3-0.5% of patients. Multiple JXGs should trigger a thorough review of symptoms, as neurofibromatosis (NF)-1 is associated with multiple JXGs. Recommendations for ophthalmology examinations are somewhat controversial but should be considered in patients with multiple lesions and those younger than 2 years of age. A skin biopsy is diagnostic and shows collections of histiocytes and multinucleated giant cells called Touton giant cells.

A **mastocytoma** is a solitary skin-colored to light red or tan papule or plaque that is often located on the trunk, extremities, or neck. Some lesions may have a yellow or pink hue. The lesion may appear at birth or within the 1st few months of life. Histopathologic study reveals the dermis densely infiltrated with mast cells. The characteristic finding on physical examination is that stroking the lesion causes histamine release that results in tense edema within the lesion and an erythematous flare, known as the Darier sign. A skin biopsy and special stains for mast cells may confirm the clinical diagnosis. Symptoms such as pruritus or flushing, when present, are usually mild. Treatment is not usually necessary unless the patient has symptoms of excessive histamine release. The condition is self-limited and resolves spontaneously over several years. The lesions do not need to be excised.

FIGURE 47.6 Subcutaneous fat necrosis. Indurated, erythematous plaques on the shoulders and back of this 1-week-old boy. (From Paller AS, Mancini AJ. Cutaneous disorders of the newborn. In: Paller AS, Mancini AJ, eds. *Hurwitz Clinical Pediatric Dermatology*. 4th ed. Philadelphia: Elsevier; 2011:14.)

FIGURE 47.7 Urticaria pigmentosa.

Urticaria pigmentosa is characterized by the development of multiple mastocytomas, usually within the 1st 8-12 months of life (Fig. 47.7). The lesions may vary in size from a few millimeters to several centimeters. Some lesions may not become pigmented until the child is approximately 6 months of age or older. Therefore, early lesions of urticaria pigmentosa may resemble recurrent urticaria until pigmentation is noted. The Darier sign, or urtication of the lesions upon rubbing, is seen in urticaria pigmentosa as well. Rarely, these lesions may produce enough histamine release to cause flushing, diarrhea, vomiting, tachycardia, and hypotension. Parents should be counseled about the avoidance of mast cell–degranulating agents.

Antihistamines should be used in any patient who experiences prominent histamine effects. Patients should be monitored closely for any symptoms that suggest systemic mastocytosis. In rare cases, other organs may be involved, including the intestines, bone, liver, spleen, and bone marrow. Intestinal involvement may be manifested by chronic diarrhea. The liver and spleen should be palpated for hepatosplenomegaly, and the patient should be monitored for any symptoms of bone involvement. Routine bone marrow and hematologic examinations are not required. Systemic manifestations are more common in adults; infants or children with significant systemic symptoms may require further evaluation. In most infants and young children, urticaria pigmentosa remits spontaneously by adulthood. Children who present at an older age tend to have a more persistent condition that is less likely to resolve.

TABLE 47.3 Types of Vascular Tumors and Vascular Malformations

Vascular Tumors	Vascular Malformations
Hemangioma	Capillary malformation
Kaposiform hemangioendothelioma	Venous malformation
Tufted hemangioma	Lymphatic malformation
Non-involuting congenital hemangioma (NICH)	Arteriovenous malformation (AVM)
Rapidly-involuting congenital hemangioma (RICH)	Mixed

TABLE 47.4 Differentiation of Infantile Hemangiomas Versus Vascular Malformations

Infantile Hemangioma	Vascular Malformations
Up to 55% present at birth	90% recognized at birth
Rapid postnatal growth and slow involution	Static malformation of dysplastic vessels that grows proportionally with child
Rapid endothelial cell turnover	Normal endothelial cell turnover and proliferation
Increased incidence in girl-to-boy ratio (3:1–5:1)	Girl-to-boy incidence ratio 1:1

Plaques and Patches

Pink (Vascular or Other)

Vascular birthmarks can be classified into 2 groups: tumors and malformations (Table 47.3). Infantile hemangiomas are the most common of the vascular tumors, and their behavior is characterized by a growth phase (endothelial proliferation), followed by a plateau or stabilization phase and then an involutional phase. Vascular malformations are usually apparent at birth and tend to be relatively stable developmental abnormalities of vessels, including any combination of capillaries, veins, arteries, and lymphatic vessels (Table 47.4).

Infantile hemangiomas are the most common benign tumors occurring in children. These lesions develop in approximately 4% of white infants by 1 year of age. Girls are affected approximately 3 times as often as boys. The incidence is higher in premature infants. Other risk factors for hemangiomas include low birthweight and multiple gestations. The natural course of infantile hemangiomas includes proliferative and involutional phases that end in complete, spontaneous regression in most cases.

There are 3 types of infantile hemangiomas:

1. Superficial hemangiomas, once referred to as strawberry marks, are the most common type (60%). They are bright red with well-demarcated borders (Fig. 47.8). Often, a pale pink stain or bruise-like patch is noted at birth before taking its more characteristic form.

FIGURE 47.8 A superficial hemangioma on the abdomen.

FIGURE 47.9 A mixed hemangioma with prominent deep component on the trunk.

2. Deep hemangiomas, previously known as cavernous hemangiomas, are the least common of the 3 types (15%). They typically have a blue-violaceous to skin-colored surface. These lesions involve the deep reticular dermis and subcutaneous tissue. These may not be noted until the infant is a few months old.
3. Mixed hemangiomas (25%) possess both superficial and deep components (Fig. 47.9).

Most infantile hemangiomas occur on the head and neck, but any area of the body may be involved. Infantile hemangiomas may be indistinguishable from port-wine stains in the early weeks of life. Lesions must be followed closely during the 1st few weeks after birth to determine whether a proliferative phase is present. Although the cause of infantile hemangiomas is not clear, their natural course has been well documented. The initial lesion may be a white macule with central threadlike telangiectases or a red macule resembling a port-wine stain. A peripheral zone of pallor representing vasoconstriction may be noted at this stage. Within the 1st few months of life, the macule becomes raised and enlarges. During the 1st 6 months of life, infantile hemangiomas proliferate at a rapid rate, and after 6 months, the lesions grow at a slower rate. Deep hemangiomas (and to a lesser extent mixed hemangiomas) have a slightly delayed onset of growth, but also have sustained growth when compared to superficial hemangiomas. Involution may begin as early as the 1st year of life and is heralded by a color change from bright cherry red to dull red-violet. Deep hemangiomas start to lose their blue-violet hue. In time, the central portion of the superficial hemangioma develops a grayish-white color that eventually extends to the periphery of the lesion. Lesions on the lips and nose, and deep hemangiomas usually involute more slowly. It is not possible to predict precisely how long an infantile hemangioma will take to involute. Statistically, 50% of lesions are gone by 5 years of age, 70% by 7 years, and more than 90% by 9 years. Once resolved, residual skin changes such as hypopigmentation, atrophy, and telangiectases may be present in up to 10-20% of affected patients. If infantile hemangiomas have grown rapidly during their proliferative phase or were very exophytic, residual fibrofatty tissue may also be seen.

Infantile hemangiomas have many potential complications and associations (Table 47.5). For most, no treatment is needed. Management of infantile hemangiomas is based on a variety of factors. These include the size of the lesion, location of the lesion, age of the patient, rate of growth/involution at the time of presentation, and risk or presence of complications. Steroids used to be the mainstay of treatment, but now β blockers, such as oral propranolol or topical timolol 0.5% solution, are used more frequently, with much improved results. Systematic reviews have shown a response rate in nearly 97% of cases with better efficacy and less toxicity of propranolol compared to steroids. The most common adverse events are sleep changes and cool extremities, but more serious concerns are hypotension, bradycardia, hypoglycemia, and hypoglycemic seizures, though these are rare.

Lesions that may need to be treated include those on the midface, labial, periorbital, genital, or diaper area. These lesions warrant close clinical observation during the rapid growth phase of early infancy. Additional therapeutic modalities that are more rarely used include intralesional steroids, pulsed dye laser therapy, surgery, embolization, and sclerosing agents.

Location of infantile hemangiomas (segmental on face or beard distribution) as well as on the spine and lower back should raise concern for PHACE syndrome or PELVIS/SACRAL syndrome, respectively.

Posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, and eye abnormalities (PHACE) syndrome is a rare syndrome that affects a subgroup of infants with infantile hemangiomas. It is likely the most common vascular neurocutaneous disorder. The cutaneous findings tend to be larger hemangiomas (>5 cm) and also tend to be segmental, rather than arising from 1 point. These hemangiomas can be more confluent, have a telangiectatic appearance, or be composed of grouped papules. They are nearly always located on the head or face. It is important to distinguish them from capillary malformations. Approximately 20% of all infants with segmental facial hemangiomas have extracutaneous anomalies.

Criteria for PHACE syndrome include 1 facial hemangioma (>5 cm in diameter) *plus* 1 major criterion or 2 minor criteria. Major and minor criteria involve a group of cerebrovascular, structural brain, cardiovascular, ocular and ventral/midline defects.

TABLE 47.5 Complications and Syndromes of Infantile Hemangiomas

Location	Complication
Lips/perineal/lumbosacral area	Seen in rapidly growing lesions, especially of oral mucosa and genital area Risk for infection, scarring, hemorrhage; can be very painful
High output, extensive lesions	Congestive heart failure; hypothyroidism Extensive lesions with a large vascular supply may compromise cardiac function
"Beard" distribution	Symptomatic subglottic hemangiomas may occur in 50–60% of patients with extensive "beard" involvement Refer for laryngoscopy to evaluate risk for respiratory or airway compromise Often manifests within 1st 2–3 mo of life
Periorbital distribution	Associated ocular complications in up to 80% of patients Screening by an ophthalmologist to rule out astigmatism or amblyopia
Ear lesions	Location can cause the obstruction of auditory canal or decreased auditory conduction Monitor for otitis media or speech delay
Lumbosacral hemangiomas	High risk for spinal dysraphism; imaging of all midline lumbosacral hemangiomas should be considered Increased risk with other lumbosacral abnormalities (e.g., hypertrichosis, dimple, tags) Associated urogenital/anogenital anomalies may be present
Large, extensive cervicofacial hemangiomas	PHACE syndrome
Benign neonatal hemangiomatosis	Multiple cutaneous hemangiomas without evidence of visceral hemangiomatosis History taking/physical examination should be performed thoroughly to rule out systemic involvement Consider liver ultrasound for infants with ≥5 cutaneous hemangiomas Benign clinical course with involution of hemangiomas within 1st year
Disseminated neonatal hemangiomatosis	Multiple cutaneous hemangiomas with evidence of visceral hemangiomatosis Liver most commonly affected; can affect lungs, gastrointestinal tract, eyes, mouth, and tongue Work-up necessary to determine the extent of systemic involvement; aggressive treatment usually needed

PHACE, posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, and eye abnormalities.

Cerebral vascular anomalies are the most common extracutaneous manifestation. The changes tend to be arterial, unlike Sturge–Weber syndrome, which involves capillaries. Imaging (magnetic resonance imaging [MRI]/magnetic resonance angiography [MRA] of head and neck) greatly aids in the work-up of a patient with a segmental hemangioma on the face/head, looking for arterial changes, as a subset of patients are at increased risk for vasculopathy and ischemic stroke.

Many congenital brain abnormalities have been noted in patients with PHACE syndrome: The most common ones are malformations of the posterior fossa and cerebellum. Most patients with congenital lesions will have normal neurologic examinations during infancy, thus screening should not be based on abnormalities with the neurologic examination.

Cardiovascular anomalies may be seen on echocardiogram in up to 40% of patients and include coarctation of the aorta (most common), aberrant subclavian aneurysm, ventricular septal defect, and arterial aneurysms. Ocular abnormalities are somewhat rare in PHACE syndrome, but include microphthalmia, optic nerve hypoplasia, persistent fetal vasculature, and morning glory disc anomalies. Midline defects include sternal cleft, supraumbilical abdominal raphe, and subtle changes such as sternal pits, dimples, or papules can be seen.

PELVIS, LUMBAR, and SACRAL syndrome are all different acronyms to describe disorders that include a segmental hemangioma of the perineal area or midline lower back with underlying abnormalities. The acronyms PELVIS (perineal hemangioma, external genitalia malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, and skin tag) and SACRAL (spinal dysraphism, anogenital anomalies, cutaneous anomalies, renal and urologic anomalies, associated with angioma of lumbosacral localization) have been used to describe associations with occult spinal dysraphism. The risk of a spinal anomaly was 35% with a solitary lumbosacral hemangioma. MRI is more sensitive than ultrasound in evaluating for underlying spinal abnormalities in lumbosacral lesions, such as tethered cord. There seems to be less of a connection with isolated perineal hemangiomas, however.

Capillary malformations (also known as port-wine stains or nevus flammeus) occur in 0.3% of all newborns. They are present at birth and represent progressive ectasia of the superficial vascular plexus. These lesions do not undergo spontaneous resolution. They are usually unilateral and segmental but can be bilateral (Fig. 47.10). The face and neck are the most commonly affected sites. Capillary malformations are typically pink to red during infancy and darken to reddish-purple hues with advancing age. Affected adults frequently have thickened, nodular port-wine stains that may be associated with soft tissue hypertrophy. Capillary malformations occur as isolated cutaneous lesions or in conjunction with other abnormalities.

Sturge–Weber syndrome includes ipsilateral association of a facial capillary malformation, almost always involving the V1 distribution of the trigeminal nerve, eye abnormalities (primarily glaucoma), and vascular malformations of the ipsilateral leptomeninges and brain. The incidence of Sturge–Weber syndrome is approximately 5-10% in infants with a capillary malformation of the V1 distribution of the trigeminal nerve. Consequences of Sturge–Weber syndrome may include seizures, developmental delay, hemiplegia, and glaucoma. Neuroimaging may be helpful in demonstrating the characteristic calcifications of the leptomeninges and the abnormal cerebral cortex, although these changes may be quite subtle with early studies. Newborns at risk for Sturge–Weber syndrome should have careful clinical follow-ups, including monitoring eye pressure for glaucoma.

Other syndromes associated with capillary malformations include Klippel–Trenaunay syndrome and Parkes–Weber syndrome. **Klippel–Trenaunay syndrome** is characterized by a capillary malformation, venous and/or lymphatic malformation, and soft tissue and/or bone overgrowth of the affected limb. **Parkes–Weber syndrome** is the

(See *Nelson Textbook of Pediatrics,* p. 2879.)

FIGURE 47.10 Capillary malformation of the back and flank, extending down the right arm.

association of arteriovenous malformations, limb overgrowth, and the variable presence of lymphedema and multiple arteriovenous shunts. Klippel–Trenaunay syndrome is a slow-flow capillary-venous malformation, whereas Parkes–Weber syndrome is a fast-flow arterial-venous malformation. Both entities can result in overgrowth and hypertrophy of the affected limb; however, Parkes–Weber syndrome usually results in increased morbidity and clinical consequences.

Treatment of a capillary malformation is best accomplished with the pulsed dye laser. Several treatments are generally required over months to years to achieve desired fading. Depending on the location of the capillary malformation, the response to the pulsed dye laser may be limited. Many experts believe that early initiation of pulsed dye laser therapy results in superior cosmetic results.

Nevus simplex (salmon patch) is the most common vascular lesion in infancy. These lesions consist of ectatic capillaries and are present at birth in about 40% of infants. These pink to red macules can be located on the nape of the neck, glabella, forehead, upper eyelids, and nasolabial regions. More atypical locations include the lateral forehead, nose, upper and lower lip, and back. Unusually persistent or prominent nevus simplex can be associated with Beckwith–Wiedemann syndrome, Nova syndrome, nevus simplex with odontodysplasia, macrocephaly–capillary malformation syndrome, and Roberts-SC syndrome.

No treatment is necessary because most of these fade by 1-2 years of age. Persistent lesions can be treated successfully with the pulsed dye laser if cosmetically disturbing.

Cutis marmorata telangiectasia congenita (CMTC) manifests as an erythematous to dark, bluish-purple, reticulated vascular patch that does not resolve with physiologic warming. This disorder is characteristically more segmental and asymmetric than physiologic cutis marmorata. The clinical findings are most often noted within the 1st few days of life. Associated features may include cutaneous atrophy and ulcerations of the skin. CMTC has also been reported to be associated with additional abnormalities, including body asymmetry (hypotrophy or hypertrophy of affected limb), other vascular malformations, psychomotor or mental retardation, and glaucoma (with lesions in the V1/V2 trigeminal nerve distribution). CMTC may be difficult to differentiate from a reticulated capillary malformation. The clinical course of CMTC is characterized by gradual fading within the 1st 1-2 years of life, and treatment is generally not required.

Kasabach–Merritt phenomenon is the presence of thrombocytopenia, hemolytic anemia, hypofibrinogenemia, and consumptive coagulopathy in association with a vascular tumor. Kasabach–Merritt phenomenon is associated with distinct vascular lesions: namely, kaposiform hemangioendothelioma (KHE) or tufted angioma, but not infantile hemangiomas. KHE and tufted angiomas are rare vascular tumors thought to exist on a spectrum. Clinical examination findings, histologic findings, and the behavior of associated vascular tumors differ from those of conventional infantile hemangiomas. These lesions are often firm and violaceous with a shiny texture and may proliferate for several years. This condition can be life-threatening and may warrant aggressive multimodal therapeutic modalities. Treatment of choice is complete excision, if possible, but may not be feasible given location, size, or tissue infiltration. Vincristine has been considered the 1st-line agent of choice, but complete resolution is rare and is limited by neurotoxicity. Other treatments include sirolimus, high-dose systemic corticosteroids, compression therapy, embolization, irradiation, low-molecular-weight heparin, and interferon-alfa. Unlike infantile hemangiomas, KHE and tufted hemangiomas are not as responsive to propranolol.

Venous and lymphatic malformations are slow-flow vascular malformations that are often present at birth. **Venous malformations** are bluish, poorly demarcated, compressible masses. The characteristic bluish hue is caused by the presence of ectatic venous channels in the dermis. Often there may be associated swelling with changes in position or activity. Venous malformations can be segmental or more generalized, and radiologic imaging may assist in determining the extent of the lesion. Evaluation for central nervous system abnormalities with cranial imaging is recommended for patients with venous malformations of the face, to rule out developmental intracranial venous abnormalities that usually are asymptomatic. Many lesions manifest with pain caused by muscle involvement or with episodes of thrombosis or hematoma. Other associated risks include bone abnormalities (thinning, demineralization, or hypoplasia) and chronic localized intravascular coagulation. Treatment is aimed at correcting disfigurement and functional impairments. Therapy can include sclerotherapy, deep laser surgery, compression, and surgical excision. In many cases, it may be best to not intervene and to treat symptomatically.

Lymphatic malformations, previously referred to as lymphangiomas, are usually skin-colored masses that may have superficial clear or hemorrhagic vesicles that occasionally leak lymphatic fluid. These lesions can be classified as macrocystic, microcystic, or mixed. Macrocystic malformations often occur on the head and neck and are frequently diagnosed by prenatal ultrasonography. When such a large lymphatic malformation occurs on the head and neck region, it is often referred to as cystic hygroma. Microcystic malformations are usually more superficial lesions with a "frog spawn" appearance (hemorrhagic and clear vesicles) that intermittently leak lymphatic fluid. This characteristic lesion was previously referred to as lymphangioma circumscriptum. These lesions usually become more evident in childhood rather than infancy. Large lymphatic malformations may impinge on vital structures and cause severe compromise in the neonatal period. Cellulitis is a potential complication of lymphatic malformations and may require prophylactic antibiotics if recurrent. Treatment includes sclerotherapy and surgery in select lesions, though surgical therapy of these lesions is often difficult and may result in recurrences and complications.

TABLE 47.6 Congenital and Acquired Disorders of Hyperpigmentation

Disorder	Congenital or Acquired	Clinical Features
Freckles (ephelides)	Acquired	Small tan to brown, 1- to 5-mm macules. Increase in number and pigmentation in summer and spring due to sunlight. Seen in fair-skinned individuals in sun-exposed areas.
Lentigines	Acquired	Uniform, dark, brown/black 2- to 5-mm macules. No seasonal variation or change with sun exposure. Can be anywhere on the body, including mucous membranes.
Café-au-lait spots	Congenital or acquired	May be seen at birth or later in life. Tan to brown discrete macules or patches. Round or oval. 6 or more lesions >5 mm in prepubertal persons meets diagnostic criteria for neurofibromatosis (NF). NF lesions are smooth and well demarcated McCune–Albright syndrome spots are larger and more jagged.
Dermal melanocytosis (Mongolian spot)	Congenital	Brown, blue-gray patches often seen on lower trunk. Seen usually in African-Americans, Asians, or Native Americans. Usually fades over time.
Nevus of Ota	Congenital or acquired	50% present at birth; 50% develop in 2nd decade. Unilateral, blue-gray pigmentation in trigeminal nerve distribution. Commonly involves ipsilateral sclera. May darken or enlarge over time.
Nevus of Ito	Congenital or acquired	Patchy blue-gray pigmentation of shoulder, supraclavicular area. May increase in size and color over time.
Congenital melanocytic nevus	Congenital	Tan, brown, dark brown macules, patches, plaques, seen at birth or early infancy. Variable color and texture. Large, giant, or multiple nevi increase risk for neurocutaneous melanosis.
Nevus spilus (speckled lentiginous nevus)	Congenital or acquired	Well-demarcated, hyperpigmented patch with smaller, darker macules and papules within larger patch. May be extensive and segmental in distribution. Small risk for malignant transformation.
Acquired melanocytic nevi	Acquired	May start as hyperpigmented macules (junctional melanocytic nevi). Over time, can become elevated papules (compound melanocytic nevi). Peaks in number during 2nd and 3rd decade of life. Abnormalities in color, borders, size, symmetry may suggest malignancy.
Melanoma	Acquired	Variegation in color, texture, or border of congenital or acquired melanocytic nevi. Rare in childhood or infancy. Risk correlated with family history and sun exposure in childhood.

Hyperpigmented or Darker Pigmented Lesions

Several hyperpigmented or darker pigmented lesions can be seen during the neonatal period and infancy, while others can present later in childhood (Table 47.6).

Congenital melanocytic nevi are pigmented macules, papules, patches, or plaques that are present at birth or early infancy in approximately 2-3% of children. The lesions are often tan at birth and become darker and hairier during infancy and childhood. Congenital nevi can be divided into small (<1.5 cm), medium (1.5-20 cm), large (20-40 cm), and giant (>40 cm) lesions on the basis of their final adult size. In neonates and infants, lesions larger than 9 cm on the head and larger than 6 cm on the body constitute giant congenital melanocytic nevi (Fig. 47.11). Most congenital melanocytic nevi are small to medium in size. The incidence of giant melanocytic nevi is approximately 1/20,000 live births.

The malignant potential of congenital melanocytic nevi remains an area of great controversy. The risk for malignant transformation in the general population for small and medium congenital nevi is thought to be less than 1%, and there are no universal guidelines for their management. For comparison, the overall risk for melanoma in the general population in the United States is 2%. Removal of these nevi can wait until later childhood, when local anesthesia and outpatient surgery are feasible.

The risk for malignant transformation of giant congenital melanocytic nevi is another controversial issue. The incidence of melanoma is approximately 2%. These large lesions warrant close observation and serial photography. Careful annual or semiannual examinations with palpation of the nevi are essential, as melanoma can arise from deep portions of the nevi with little or no apparent surface alterations. Removal of giant congenital nevi is also controversial from a future-melanoma risk standpoint. Removal may require extensive grafting as well as soft tissue expansion procedures.

Neurocutaneous melanosis is defined as the presence of giant (>40 cm) and/or multiple congenital melanocytic nevi, in association with benign or malignant melanocytic infiltration of the leptomeninges. Clinically symptomatic neurocutaneous melanosis substantially worsens the prognosis of large or giant congenital melanocytic nevi and usually presents around or before 2 years of age, but some may

FIGURE 47.11 Giant congenital melanocytic nevus of the lower back. Imaging should be considered to evaluate for tethered cord or spinal dysraphism, as well as melanosis of the spine or brain.

not show symptoms until the 2nd or 3rd decade of life. Most symptomatic patients die within 3 years of the onset of initial neurologic symptoms, typically from central nervous system melanoma or mechanical obstruction. The most frequent clinical manifestations include hydrocephalus, seizures, papilledema, headaches, increase in head circumference, paresis, and developmental delay. Location overlying the axial skeleton and many satellite lesions are predictors of neurocutaneous melanosis.

MRI with contrast of the head *and* spine is suggested in newborns with giant congenital melanocytic nevi, particularly in the posterior axial distribution and especially if satellite nevi are present. MRI abnormalities of the brain have been identified in asymptomatic patients with giant or multiple congenital melanocytic nevi. The most common imaging abnormalities in asymptomatic patients seen were T1 shortening in the cerebellum, temporal lobes, pons, and medulla. Radiologic findings can be very subtle and may be missed by radiologists unfamiliar with this entity. Controversy exists with regard to the need for baseline and follow-up imaging in asymptomatic patients, inasmuch as the implications of these studies are unclear.

Café-au-lait macules are well-circumscribed tan macules that usually measure less than 0.5 cm but may be as large as 15-20 cm in diameter. The lesions are found on any cutaneous site and may be present at birth or appear during early childhood. Although café–au-lait spots are seen in 10-20% of normal individuals, the presence of many macules should raise the clinical suspicion of NF or other genetic disorders (Table 47.6). The presence of 6 or more café-au-lait spots (>0.5 cm in prepubertal children; >1.5 cm in postpubertal children) fulfills 1 of the diagnostic criteria for NF-1. Although the lesions are not pathognomonic, they are present in most patients with NF and tend to be larger and more numerous. Café–au-lait spots have also been associated with tuberous sclerosis, McCune–Albright syndrome, Turner syndrome, Bloom syndrome, ataxia-telangiectasia, Russell–Silver syndrome, Fanconi anemia, epidermal nevus syndrome, Gaucher disease, and Chédiak–Higashi syndrome.

Dermal melanocytosis, also known as **Mongolian spots**, are large, poorly demarcated, slate-gray to blue-black patches usually located over the buttocks or lumbosacral region of normal infants. The condition occurs in approximately 80-90% of black infants, 75% of Asian infants, and 10% of white infants. Mongolian spots may be single or multiple and frequently measure up to 10-20 cm in diameter. This benign disorder is present at birth, usually fades during early childhood, and necessitates no therapeutic intervention. In rare cases, the lesions may persist into adulthood and may benefit from therapy with lasers that treat dermal pigmentation. These lesions should not be confused with bruises.

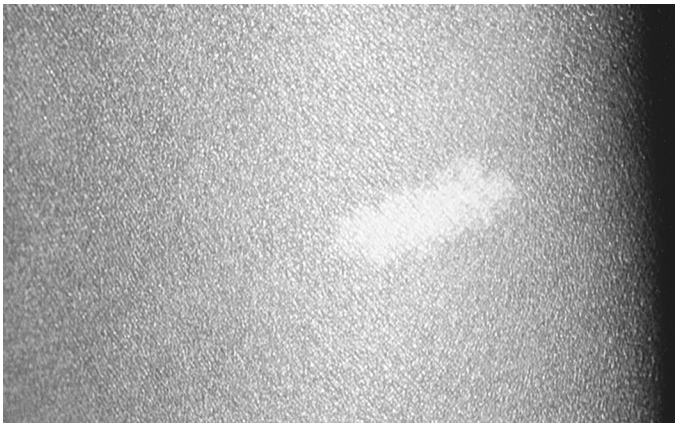

FIGURE 47.12 Ash leaf macule of tuberous sclerosis.

The **nevus of Ota** and **nevus of Ito** are special variants of dermal melanocytosis seen most commonly in Asian and black individuals. In contrast to Mongolian spots, these conditions tend to persist throughout adulthood. The nevus of Ota is a slate-gray to blue-black patch located in the distribution of the trigeminal nerve. The condition is usually unilateral and involves the forehead, temple, periorbital region, nose, and cheek. Pigmentation of the sclera occurs in about 50% of affected individuals. The disorder may be cosmetically disfiguring, and laser treatment may be promising in some cases. The nevus of Ito is a similar lesion occurring in the distribution of the lateral supraclavicular and brachial nerves. The condition is usually unilateral and involves the shoulder, neck, upper arm, scapular, and/or deltoid regions. It may be seen alone or in conjunction with the nevus of Ota.

Hypopigmented and Depigmented Lesions

These conditions are often cosmetically disfiguring and persistent. They can be markers of serious systemic diseases. Pigmentary disorders may be localized or generalized; congenital or acquired; and transient, stable, or progressive (Table 47.7).

Nevus depigmentosus is a benign, solitary, hypopigmented macule or patch that is noted at birth. It is not depigmented as the name suggests. It typically remains stable in size and may grow in proportion to the patient as they grow. It should be differentiated from vitiligo.

Ash leaf spots are hypopigmented macules, sometimes present at birth or within the 1st few months or years of life, that allow early identification of individuals with tuberous sclerosis (Fig. 47.12). Although occasionally observed in normal infants, the characteristic lesions are present in up to 90% of patients with tuberous sclerosis. They are usually 2-3 cm in size and are located on the trunk and extremities. The macules may be lancet-shaped or may have a confetti-like or irregularly shaped appearance. *Wood lamp examination may facilitate identification*. Although tuberous sclerosis is an autosomal dominant disorder, spontaneous mutations are responsible for up to 50% of new cases. Other cutaneous findings include facial angiofibromas (adenoma sebaceum), periungual or subungual fibromas, gingival fibromas, shagreen patches (connective tissue hamartomas), and fibrous plaques (typically on the forehead). Systemic manifestations include seizures, intellectual disability, cardiac rhabdomyomas, renal angiomyolipomas and cysts, retinal nodular hamartomas, and pulmonary cysts. Imaging studies of the brain may demonstrate cortical

TABLE 47.7 Congenital and Acquired Disorders of Hypopigmentation and Depigmentation

Disorder	Congenital or Acquired	Clinical Features
Piebaldism	Congenital	Autosomal dominant inheritance. Leukoderma of frontal scalp. White forelock. Usually involves face, neck, trunk, flank, and extremities. Waardenburg syndrome is a variant, with sensorineural deafness, limb defects, and Hirschsprung disease.
Nevus depigmentosus	Congenital	Well-circumscribed hypopigmented patch (not typically depigmented). May be isolated or segmental. Usually present at birth or infancy. Wood lamp may aid in diagnosis. Often found on trunk or extremities.
Hypomelanosis of Ito	Congenital	Whorls or streaks of hypopigmentation that follow lines of Blaschko. Usually present at birth, but may present in 1st few years of life. Can be associated with CNS, eye, or musculoskeletal abnormalities.
Nevus anemicus	Congenital	Rubbing or temperature change causes erythema of surrounding skin. Often unilateral and on trunk. Not accentuated by Wood lamp. Asymptomatic.
Ash leaf spot	Congenital	Hypopigmented macules/patches often present at birth. Wood lamp may aid in diagnosis. Solitary lesion often of no significance. Multiple lesions are associated with tuberous sclerosis.
Vitiligo	Acquired	Complete loss of pigment in involved areas. May be segmental in distribution. Hyperpigmentation can be seen at the edges of lesions. Infrequently seen with autoimmune disorders, such as hypothyroidism.
Albinism	Congenital	Complete depigmentation or hypopigmentation in skin. Affects eyes and hair. Increased risk for skin cancer.

tubers or subependymal nodules, which are pathognomonic for tuberous sclerosis.

Piebaldism is characterized by circumscribed areas of depigmentation in the newborn. The leukoderma is usually located on the frontal scalp and is associated with a white forelock; however, the depigmented patches characteristically involve the trunk, upper arms, and legs. Hyperpigmented or normally pigmented macules or patches may occur within the depigmented patches. This rare condition is transmitted in an autosomal dominant pattern. The disorder is usually present at birth but may not be recognized until later because of the light color of neonatal skin. A Wood lamp may enhance the contrast between depigmented and normal skin.

Piebaldism is a stable condition throughout life, and most affected individuals are otherwise normal. Sun protection and cosmetic camouflage of the depigmented skin are the mainstays of therapy.

Waardenburg syndrome is a rare genetic disorder characterized by a white forelock, areas of leukoderma, congenital sensorineural deafness, heterochromia of the irides, and lateral displacement of the medial canthi. Other features may include a flattened nasal bridge, confluent eyebrows, hypoplasia of the nasal alae, speech impairment that may or may not be related to presence of a cleft lip or palate, and various skeletal abnormalities. It is most commonly inherited in an autosomal dominant fashion, though autosomal recessive inheritance patterns are sometimes seen.

Albinism is manifested by diffuse congenital hypopigmentation or depigmentation of the skin, hair, and eyes. This heterogeneous group of disorders is composed of approximately 10 types of oculocutaneous albinism and 5 forms of ocular albinism. Most types of oculocutaneous albinism are inherited in an autosomal recessive pattern. The variants of ocular albinism are transmitted in an X-linked or autosomal recessive mode of inheritance.

The various forms of albinism can usually be diagnosed by findings on physical examination. These features include absent or reduced pigmentation of skin and hair and ophthalmologic findings such as foveal hypoplasia, nystagmus, photophobia, transillumination of the irides, fundal depigmentation, and decreased visual acuity. Patients should be monitored closely by ophthalmologists and evaluated for hearing loss. In white persons, the skin is usually milk white and the hair is white, blond, or light brown. The pupils are usually pink, and the irides are blue or gray. In African-Americans, the skin may appear tan or white and is frequently freckled. The hair is usually blond or red, and the eyes are blue or hazel.

Treatment of albinism includes photoprotection and sun avoidance. Individuals are predisposed to severe actinic damage and should be monitored closely for the development of actinic keratoses, basal cell carcinomas, squamous cell carcinomas, and melanomas.

Other

Nevus sebaceus of Jadassohn is a hamartoma of sebaceous gland derivation. Typically present at birth, these lesions are variable in size, usually solitary, and located on the scalp, face, and neck. During infancy, they are well-circumscribed, hairless, yellowish-orange, smooth, velvety, or waxy plaques. These nevi tend to thicken and become verrucous during puberty.

Because up to 15% of these lesions develop secondary benign or malignant neoplasms during adolescence or adulthood, prophylactic surgical excision is recommended before puberty.

Dermoid cysts are nontender, noncompressible, firm, congenital subcutaneous nodules found along sites of closure of embryonic clefts. Dermoids are lined by stratified squamous epithelium that contains mature adnexal structures. Although these lesions can be noted in newborns, they may not be detected until later in infancy or in childhood after the lesion enlarges or becomes inflamed. Lesions are often described as rubbery and may be blue to skin-colored in appearance. A tuft of hair may be seen protruding from an orifice in the dermoid. Dermoid cysts are often found in the head and neck region, often the lateral portion of an eyebrow.

The most important concern with dermoid cysts is the potential for an intracranial connection. Up to 25% of midline or nasal dermoid cysts may have an intracranial connection; all midline head and spinal lesions should be imaged. If a connection is present, the patient is at risk for infection because the dermoid cyst and sinus can serve as a portal of entry for bacteria. These patients should be referred to neurosurgery for removal and repair. Dermoid cysts that are not midline, including those commonly seen at the lateral brow area, should also be excised because of the potential risk for infection and bony erosion. After surgical excision, lesions do not usually recur.

Aplasia cutis congenita is a heterogeneous group of disorders in which there is a congenital absence of skin (Fig. 47.13). This disorder may involve the epidermis, dermis, and subcutaneous tissues. The most common type of aplasia cutis is membranous aplasia cutis. These lesions are well-demarcated, small, oval, 1- to 5-cm defects on the vertex of the scalp. They are easily identified by their classic "punched-out" appearance and may have an atrophic surface with a glistening, membrane-like surface at birth. In older children, these lesions resemble scars. If the lesion is associated with a hair collar or midline in location, the clinician should evaluate for the potential of cranial dysraphism.

The defect is usually solitary; however, in a minority of patients, multiple sites may be affected. Aplasia cutis can also occur on the trunk and limbs, where the defects are often bilateral and symmetric. Aplasia cutis in the midline lumbosacral area is of particular importance because it may be associated with spinal dysraphism.

Lesions of membranous aplasia cutis usually necessitate no further investigation, and gradual epithelialization typically occurs spontaneously. However, large, deep, or widespread lesions with underlying bone defects may necessitate surgical intervention to facilitate healing.

The term **hair collar sign** is a designation for hypertrichosis that usually either partly or completely encircles a congenital scalp lesion (Fig. 47.14). Usually the ring of hair is denser, darker, and coarser in texture than the normal scalp hair. A hair collar sign surrounding a congenital scalp nodule is a marker for cranial dysraphism, including encephaloceles and meningoceles. If a hair collar sign is seen in combination with a capillary malformation or aplasia cutis, the risk for cranial dysraphism is increased substantially. Therefore, all congenital midline lesions with a hair collar sign should be imaged to evaluate for an intracranial connection. MRI is the gold standard, but it occasionally misses a small intracranial connection.

Lumbosacral hypertrichosis may be a normal variant, especially in certain ethnic groups. However, hypertrichosis in this area in association with other stigmata indicative of a neurologic defect is highly suggestive of spinal dysraphism. The area may be poorly circumscribed, and the hair can be light or dark. The hypertrichosis is often present at birth. Complete neurologic examination should be performed. There are no defined parameters to determine further evaluation of isolated hypertrichosis, though suspicion for spinal dysraphism is higher if additional cutaneous markers, such as a vascular stain or a mass, are also present. If a spinal defect is suspected, further evaluation by MRI of the spine is necessary.

Lumbosacral dimples are common findings in neonates. Large, deep dimples that are located in the superior portion of the gluteal crease should be radiologically imaged to rule out dermal sinuses communicating directly with the spinal canal. These dimples should not be probed because of the potential communication with the spinal canal. Sacral dimples seen in association with other cutaneous findings such as hypertrichosis, vascular birthmarks, a mass, or deviated gluteal cleft carry particularly high risk for spinal dysraphism. Imaging should be performed with MRI of the spine as ultrasound has low sensitivity for subtle findings.

Infantile hemangiomas that overlie the midline of the back are strong markers for spinal dysraphism, most often lipomyelomeningocele, intraspinal lipoma, or a tethered cord. Infantile hemangiomas that are larger than 4 cm and overlap the midline appear to carry greater risk for spinal dysraphism, and MRI should be performed. The risk for spinal dysraphism is increased when hemangioma is seen in

FIGURE 47.13 Congenital absence of skin (aplasia cutis congenita) on the scalp of a neonate. As seen here, multiple lesions can be seen.

FIGURE 47.14 A classic hair collar sign (from aplasia cutis).

association with other cutaneous findings such as sacral dimples, hypertrichosis, or a deviated gluteal cleft.

A solitary midline capillary malformation of the back without additional clinical findings may be a marker for spinal dysraphism, but this association is less clear. All affected infants should be evaluated for additional neurocutaneous stigmata. If a lumbosacral capillary malformation is detected with other cutaneous markers of spinal dysraphism, imaging is warranted.

TRANSIENT AND PHYSIOLOGIC CHANGES TO THE SKIN

Many entities unique to newborns are caused by physiologic phenomena in response to the infant's transition to the new environment. Most such entities are benign and self-limited.

Cutis Marmorata

Cutis marmorata is characterized by symmetric reticulated cyanosis involving the trunk and extremities. This marbled appearance usually appears when the skin is cool and resolves upon rewarming of the infant. This benign condition typically improves with age. When this vascular pattern is seen in older infants or children, it may be associated with Down syndrome, Cornelia de Lange syndrome, or hypothyroidism.

Cutis marmorata should be differentiated from Cutis marmorata telangiectasia congenita (CMTC). The persistent cutis marmorata of CMTC is characteristically asymmetric, often segmental, mottled, or marble-like, and more localized than physiologic cutis marmorata. In addition, the reticulated mottling of CMTC is darker in color and does not resolve with rewarming. Although CMTC improves with age, the abnormal vascular pattern is more persistent than that seen in physiologic cutis marmorata. It may be an isolated entity or may have distinct associations, including atrophy or hypertrophy of the affected extremity, ulcerations, or coexistent vascular malformations and tumors, and other extracutaneous anomalies.

Harlequin Color Change

The harlequin color change is a distinctive condition observed in infants lying on their sides. It is characterized by marked erythema on the dependent side of the infant's body with simultaneous blanching of the nondependent side. This phenomenon occurs more often in premature infants but may be observed in full-term newborns. The change may be caused by autonomic immaturity, which results in altered peripheral vascular tone.

Although it typically occurs within the 1st 3 weeks of life, harlequin color change is most often noted at 2-5 days of age. The changes develop abruptly and usually resolve within 20 minutes.

Acrocyanosis

The normal newborn usually displays a bluish-purple discoloration of the hands, feet, and lips. Referred to as acrocyanosis, this typically occurs in association with crying or cold stress and can be seen in greater than 30% of infants. It results from increased peripheral arteriolar tone, which leads to vasospasm and subsequent venous pooling. Acrocyanosis should be differentiated from central cyanosis, which is noted on mucosal surfaces. Physiologic acrocyanosis gradually resolves spontaneously during the neonatal period.

SUMMARY AND RED FLAGS

Neonates and infants can have a variety of congenital birthmarks and transient rashes. It is necessary to identify the primary skin lesion, any secondary skin lesions or changes, and the size, color, distribution, and configurations of the lesions to develop an appropriate differential diagnosis. Many entities unique to neonates are benign and self-limited, and often require only reassurance to the parents.

Red flags are lesions consistent with HSV, *S. aureus*, or LCH (Table 47.2), or those consistent with neurocutaneous diseases, such as ash leaf spots, or a capillary malformation in V1 distribution (Table 47.1). The location of infantile hemangiomas in a beard distribution, or on the spine and lower back should raise concern for PHACE syndrome or PELVIS/SACRAL syndrome (Table 47.5). Lesions found on the midline of the back or head such as hemangiomas or hair collar sign can be associated with spinal dysraphism (Table 47.1 and Fig. 47.14).

REFERENCES

A bibliography is available at ExpertConsult.com.

(See *Nelson Textbook of Pediatrics,* p. 3117.)

REFERENCES

Rashes: Papules and Pustules

Bolognia J, Jorrizo J, Schaffer J. *Dermatology*. Philadelphia: Elsevier Saunders; 2012.

Chia PS, Leung C, Hsu YL, et al. An infant with transient neonatal pustular melanosis presenting as pustules. *Pediatr Neonatol*. 2010;51(6):356-358.

Ehrhardt MJ, Humphrey SR, Kelly ME, et al. The natural history of skin-limited Langerhans cell histiocytosis: a single-institution experience. *J Pediatr Hematol Oncol*. 2014;36(8):613-616.

Eichenfield LF, Krakowski AC, Piggott C, et al. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. *Pediatrics*. 2013;131(suppl 3):S163-S186.

Hashizume S, Ansai S, Kosaka M, et al. Infantile case of eosinophilic pustular folliculitis successfully treated with topical indomethacin. *J Dermatol*. 2014;41(2):196-197.

Good LM, Good TJ, High WA. Infantile acropustulosis in internationally adopted children. *J Am Acad Dermatol*. 2011;65(4):763-771.

Toyonaga E, Abe R, Moriuchi R, et al. Indomethacin for refractory infantile eosinophilic pustular folliculitis. *JAMA Dermatol*. 2013;149(3):367-368.

Rashes: Patches and Plaques

Chang MW, Nakrani R. Six children with allergic contact dermatitis to methylisothiazolinone in wet wipes (baby wipes). *Pediatrics*. 2014;133(2):e434-e438.

Crowley E, Frieden IJ. Neonatal lupus erythematosus: an unusual congenital presentation with cutaneous atrophy, erosions, alopecia, and pancytopenia. *Pediatr Dermatol*. 1998;15(1):38-42.

Gleicher N, Elkayam U. Preventing congenital neonatal heart block in offspring of mothers with anti-SSA/Ro and SSB/La antibodies: a review of published literature and registered clinical trials. *Autoimmun Rev*. 2013;12(11):1039-1045.

Lee LA. The clinical spectrum of neonatal lupus. *Arch Dermatol Res*. 2009;301(1):107-110.

Llanos C, Friedman DM, Saxena A, et al. Anatomical and pathological findings in hearts from fetuses and infants with cardiac manifestations of neonatal lupus. *Rheumatology (Oxford)*. 2012;51(6):1086-1092.

Padilla-Espana L, Diaz Cabrera R, Del Boz J, et al. Congenital lupus with multiorgan involvement: a case report and review of literature. *Pediatr Dermatol*. 2015;32(3):401-404.

Silverman E, Jaeggi E. Non-cardiac manifestations of neonatal lupus erythematosus. *Scand J Immunol*. 2010;72(3):223-225.

Fixed Lesions: Macules, Papules, and Pustules

Berk DR, Bayliss SJ. Milia: a review and classification. *J Am Acad Dermatol*. 2008;59(6):1050-1063.

Chang MW, Frieden IJ, Good W. The risk of intraocular juvenile xanthogranuloma: survey of current practices and assessment of risk. *J Am Acad Dermatol*. 1996;34(3):445-449.

Haveri FT, Inamadar AC. A cross-sectional prospective study of cutaneous lesions in newborn. *ISRN Dermatol*. 2014;2014:360590.

Hernandez-Martin A, Baselga E, Drolet BA, et al. Juvenile xanthogranuloma. *J Am Acad Dermatol*. 1997;36(3 Pt 1):355-367; quiz 368-369.

Mahe E, Girszyn N, Hadj-Rabia S, et al. Subcutaneous fat necrosis of the newborn: a systematic evaluation of risk factors, clinical manifestations, complications and outcome of 16 children. *Br J Dermatol*. 2007;156(4):709-715.

Mitra S, Dove J, Somisetty SK. Subcutaneous fat necrosis in newborn—an unusual case and review of literature. *Eur J Pediatr*. 2011;170(9):1107-1110.

Murphy JT, Soeken T, Megison S, et al. Juvenile xanthogranuloma: diverse presentations of noncutaneous disease. *J Pediatr Hematol Oncol*. 2014;36(8):641-645.

Fixed Lesions: Plaques and Patches

Bayer ML, Frommelt PC, Blei F, et al. Congenital cardiac, aortic arch, and vascular bed anomalies in PHACE syndrome (from the International PHACE Syndrome Registry). *Am J Cardiol*. 2013;112(12):1948-1952.

Chang LC, Haggstrom AN, Drolet BA, et al. Growth characteristics of infantile hemangiomas: implications for management. *Pediatrics*. 2008;122(2):360-367.

Chiu YE, Drolet BA, Blei F, et al. Variable response to propranolol treatment of kaposiform hemangioendothelioma, tufted angioma, and Kasabach-Merritt phenomenon. *Pediatr Blood Cancer*. 2012;59(5):934-938.

Drolet BA, Chamlin SL, Garzon MC, et al. Prospective study of spinal anomalies in children with infantile hemangiomas of the lumbosacral skin. *J Pediatr*. 2010;157(5):789-794.

Drolet BA, Trenor CC 3rd, Brandão LR, et al. Consensus-derived practice standards plan for complicated Kaposiform hemangioendothelioma. *J Pediatr*. 2013;163(1):285-291.

Izadpanah A, Izadpanah A, Kanevsky J, et al. Propranolol versus corticosteroids in the treatment of infantile hemangioma: a systematic review and meta-analysis. *Plast Reconstr Surg*. 2013;131(3):601-613.

Johnson EF, Smidt AC. Not just a diaper rash: LUMBAR syndrome. *J Pediatr*. 2014;164(1):208-209.

Juern AM, Glick ZR, Drolet BA, et al. Nevus simplex: a reconsideration of nomenclature, sites of involvement, and disease associations. *J Am Acad Dermatol*. 2010;63(5):805-814.

Liang MG, Frieden IJ. Infantile and congenital hemangiomas. *Semin Pediatr Surg*. 2014;23(4):162-167.

Luu M, Frieden IJ. Haemangioma: clinical course, complications and management. *Br J Dermatol*. 2013;169(1):20-30.

Marqueling AL, Oza V, Frieden IJ, et al. Propranolol and infantile hemangiomas four years later: a systematic review. *Pediatr Dermatol*. 2013;30(2):182-191.

Metry D, Heyer G, Hess C, et al. Consensus statement on diagnostic criteria for PHACE syndrome. *Pediatrics*. 2009;124(5):1447-1456.

Metry DW, Haggstrom AN, Drolet BA, et al. A prospective study of PHACE syndrome in infantile hemangiomas: demographic features, clinical findings, and complications. *Am J Med Genet A*. 2006;140(9):975-986.

Schumacher WE, Drolet BA, Maheshwari M, et al. Spinal dysraphism associated with the cutaneous lumbosacral infantile hemangioma: a neuroradiological review. *Pediatr Radiol*. 2012;42(3):315-320.

Siegel DH, Tefft KA, Kelly T, et al. Stroke in children with posterior fossa brain malformations, hemangiomas, arterial anomalies, co-arctation of the aorta and cardiac defects and eye abnormalities (PHACE) syndrome: a systematic review of the literature. *Stroke*. 2012;43(6):1672-1674.

Stockman A, Boralevi F, Taieb A, et al. SACRAL syndrome: spinal dysraphism, anogenital, cutaneous, renal and urologic anomalies, associated with an angioma of lumbosacral localization. *Dermatology*. 2007;214(1):40-45.

Wassef M, Blei F, Adams D, et al.; ISSVA board and scientific committee. Vascular anomalies classification: recommendations from the International Society for the Study of Vascular Anomalies. *Pediatrics*. 2015;136(1):e203-e214.

Fixed Lesions: Hyperpigmented or Darker Pigment

Alikhan A, Ibrahimi OA, Eisen DB. Congenital melanocytic nevi: where are we now? Part I. Clinical presentation, epidemiology, pathogenesis, histology, malignant transformation, and neurocutaneous melanosis. *J Am Acad Dermatol*. 2012;67(4):495.e1-e17.

Krengel S, Scope A, Dusza SW, et al. New recommendations for the categorization of cutaneous features of congenital melanocytic nevi. *J Am Acad Dermatol*. 2013;68(3):441-451.

Schaffer JV. Update on melanocytic nevi in children. *Clin Dermatol*. 2015;33(3):368-386.

Sibbald C, Pope E, Randhawa H, et al. Neurocutaneous melanosis and congenital melanocytic nevi: a retrospective review of clinical and radiologic characteristics. *Br J Dermatol*. 2015. [Epub ahead of print].

Surveillance, Epidemiology, and End Results Program (SEER) National Cancer Institute Web site <http://www.seer.cancer.gov/statfacts/html/melan.html>.

Vourc'h-Jourdain M, Martin L, Barbarot S. Large congenital melanocytic nevi: therapeutic management and melanoma risk: a systematic review. *J Am Acad Dermatol*. 2013;68(3):493-498.

Fixed Lesions: Other

Browning JC. Aplasia cutis congenita: approach to evaluation and management. *Dermatol Ther*. 2013;26(6):439-444.

Drolet BA, Clowry L, McTigue K, et al. The hair collar sign: marker for cranial dysraphism. *Pediatrics*. 1995;96:309-313.

Sewell MJ, Chiu YE, Drolet BA. Neural tube dysraphism: review of cutaneous markers and imaging. *Pediatr Dermatol*. 2015;32(2):161-170.

Transient and Physiologic Changes of the Skin

Cizmeci MN, Alagoz D, Avsar MI, et al. Harlequin color change after abdominal paracentesis in a newborn with neonatal hemochromatosis. *Pediatr Dermatol*. 2014;31(6):e114-e115.

Haveri FT, Inamadar AC. A cross-sectional prospective study of cutaneous lesions in newborn. *ISRN Dermatol*. 2014;2014:360590.

Kienast AK, Hoeger PH. Cutis marmorata telangiectatica congenita: a prospective study of 27 cases and review of the literature with proposal of diagnostic criteria. *Clin Exp Dermatol*. 2009;34(3):319-323.

48

Acquired Rashes in the Older Child

Kristen E. Holland and Paula J. Soung

Many skin findings in childhood are benign and self-limited conditions. Other dermatologic complaints may be the 1st manifestation of a systemic disease or associated condition, recognition of which facilitates appropriate evaluation and treatment.

HISTORY, PHYSICAL EXAMINATION, AND DIAGNOSTIC PROCEDURES

◆ History

Obtaining a careful and focused history is necessary to establish diagnoses of pediatric skin disorders. It may be helpful to examine the patient first and then proceed with a relevant line of questioning. Important questions to ask include the following:

1. When did the eruption begin?
2. How did the eruption evolve (distribution, spread, change in the structure of individual lesions)?
3. Are the lesions pruritic or painful?
4. Have there been previous similar episodes?
5. Are there associated systemic symptoms?
6. Are there exacerbating or alleviating factors?
7. Has treatment been rendered? If so, what effect has it had?
8. Are there affected family members or close contacts?
9. Is there a family history of skin disease?

◆ Physical Examination

It is necessary to identify the primary skin lesions, secondary skin lesions, or changes, size, color, distribution, and configuration of the lesions. Several specific signs are pathognomonic for certain diseases. Examination of the hair, nails, and mucosal surfaces should be included. Palpation of cutaneous lesions provides additional information, such as firmness, tenderness, mobility, temperature, and ability to blanch with pressure. Precise morphologic descriptions are critical for establishing a differential diagnosis (Figs. 48.1 and 48.2).

Primary Lesions

Macules and Patches. Macules are flat, circumscribed lesions that are detected because of a change in color. Pink or red macules may be caused by inflammation or vasodilatation. Brown, black, or white lesions may be caused by alterations in melanin synthesis. Purple hues may represent extravasation of blood into the skin. Macules greater than 1 cm in diameter are usually described as patches.

Papules, Nodules, Plaques, and Tumors. Papules are circumscribed, palpable, elevated solid lesions. Typically less than 0.5-1 cm in diameter, these lesions may be epidermal or dermal in origin and may be flat-topped or dome-shaped. Papules that are 0.5-2 cm in diameter are described as nodules. Nodules are epidermal, dermal, or subcutaneous lesions that may, in some cases, evolve from preexisting papules. Plaques are elevated flat-topped lesions, larger than 1 cm in diameter, and often formed by the coalescence of papules. Tumors are larger nodules greater than 2 cm in diameter that are usually solid and well circumscribed.

Vesicles and Bullae. Vesicles are elevated fluid-filled lesions. Bullae are large vesicles, usually greater than 1 cm in diameter. The tenseness or flaccidity of the blister indicates whether the level of separation is intraepidermal or subepidermal (Fig. 48.3 and Table 48.1).

Pustules. Pustules are white or yellow well-circumscribed lesions that contain purulent material. Pustules do not always signify an infectious cause.

Wheals. Wheals are edematous, elevated lesions that are transient in nature and variable in shape and size. They may be white or erythematous and often have central pallor.

Telangiectases. These are ectatic, dilated superficial blood vessels of the skin that typically blanch when pressure is applied.

Secondary Lesions

Secondary lesions may represent the natural evolution of primary lesions or changes that result from external manipulation, such as scratching.

Crusts. Crusts represent serum, pus, blood, or exudate that has dried on the skin surface.

Scales. Scales appear as yellow, white, or brownish flakes on the skin surface that represent desquamation of stratum corneum.

Erosions. Erosions are moist, erythematous, circumscribed lesions that result from partial or complete loss of the epidermis. They often result from rupture of a blister. Erosions do not involve the dermis or subcutaneous tissue; therefore, they heal without scarring.

Ulcers. Ulcers are deeper than erosions and penetrate the dermis or fat and usually heal with scarring.

Lichenification. Lichenification, or thickening of the skin, usually results from chronic scratching or rubbing. Accentuation of skin markings or hyperpigmentation is observed.

Fissures. A fissure is a linear crack in the epidermis extending to the dermis.

Atrophy. Atrophy represents loss of substance of the skin. Epidermal atrophy is characterized by loss of skin markings, increased wrinkling, and transparency with visibility of underlying vasculature. Dermal or subcutaneous atrophy results in depression of the skin with minimal, if any, epidermal changes.

Excoriations. Excoriations are linear erosions on the skin caused by scratching.

◆ Diagnostic Techniques

Potassium Hydroxide Test

This simple and rapid test can confirm the diagnosis of dermatophyte or candidal infections. Scale is scraped with a curved blade onto a microscope slide. Hair or nail fragments can also be examined. A glass

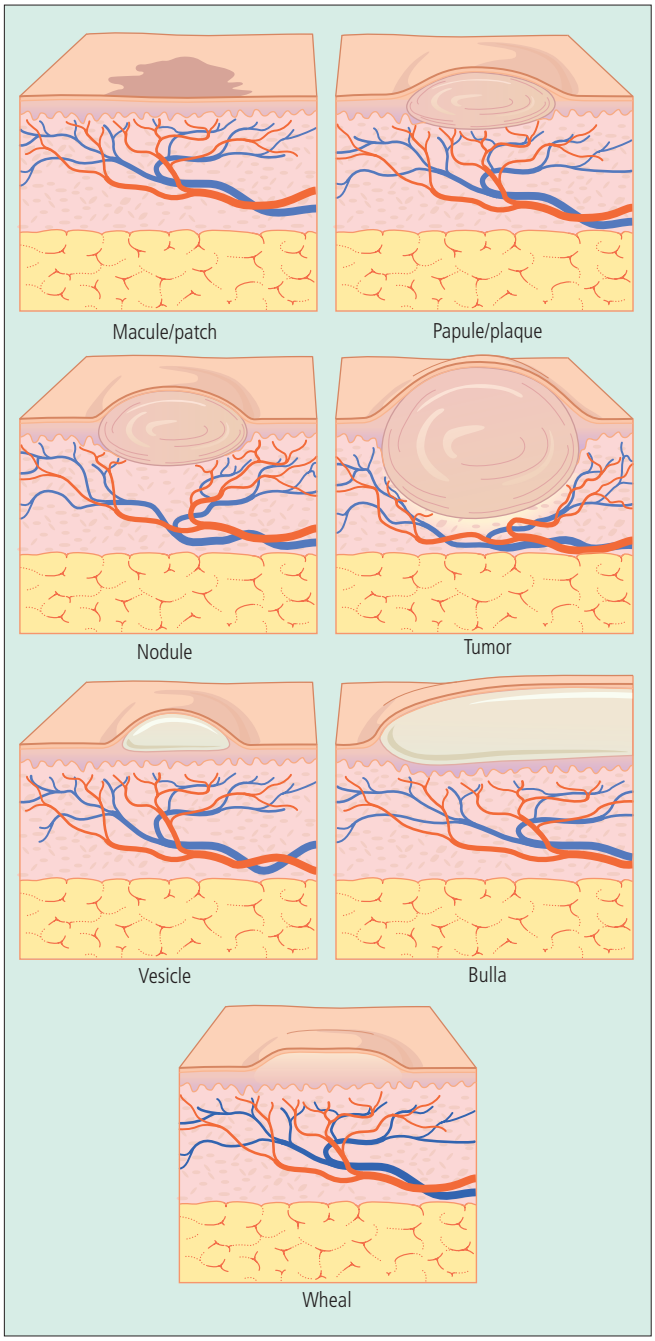

FIGURE 48.1 Primary skin lesions. (From Cohen BA. Introduction to pediatric dermatology. In: Cohen BA, ed. *Pediatric Dermatology*. Philadelphia: Saunders; 2013.)

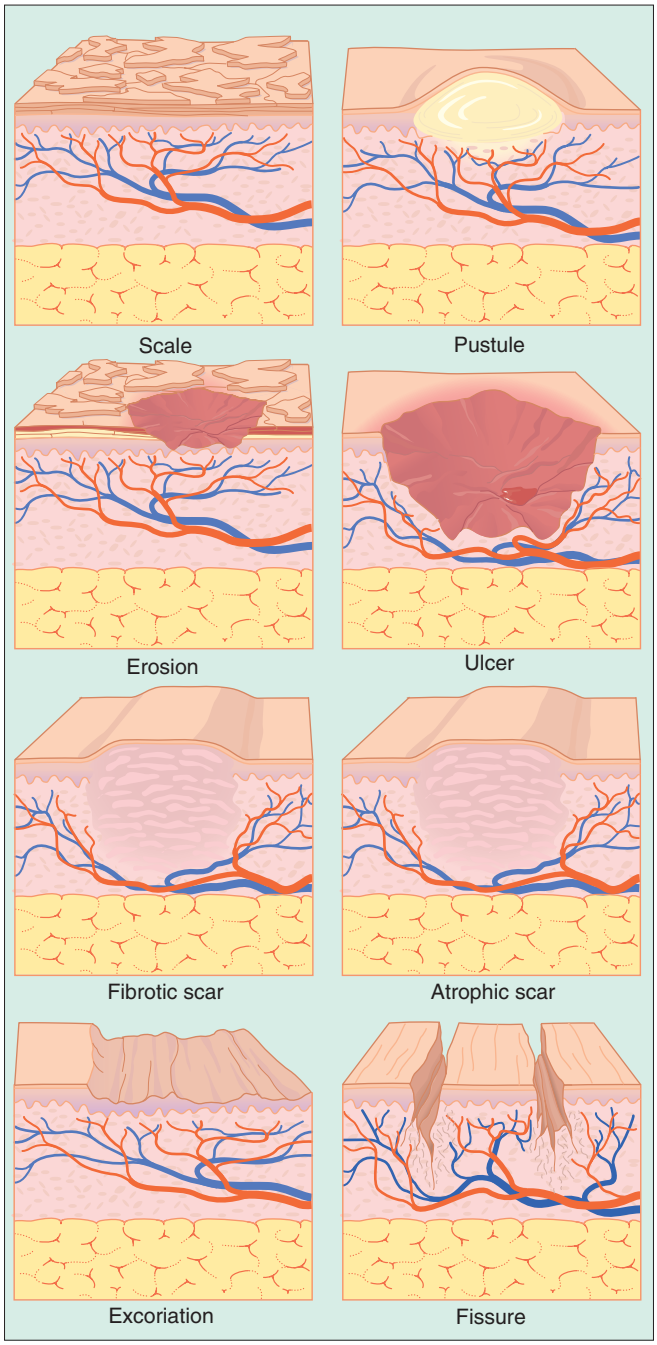

FIGURE 48.2 Secondary skin lesions. (From Cohen BA. Introduction to pediatric dermatology. In: Cohen BA, ed. *Pediatric Dermatology*. Philadelphia: Saunders; 2013:1-13.)

coverslip is then placed on the slide after 1-2 drops of 10-20% KOH are added. The slide is heated gently but not boiled, which can result in KOH crystallization and subsequent difficulty in interpretation. Dermatophyte infections are confirmed by identifying **fungal hyphae**, which appear as long, branching septate filaments. **Pseudohyphae** or **budding spores** are characteristic of candidiasis. Short, broad hyphae and clusters of budding cells resembling "spaghetti and meatballs" are diagnostic of tinea versicolor.

Tzanck Smear

A Tzanck smear is useful for the diagnosis of varicella-zoster virus and herpes simplex virus (HSV) infections. The smear is prepared by unroofing a blister with a curved blade and gently scraping the blister base and underside of the roof. The material is spread in a thin layer onto a glass slide. The slide is air-dried and stained with Giemsa or Wright stain. Identification of **multinucleated giant cells**, a syncytium of epidermal cells with multiple overlapping nuclei, establishes the

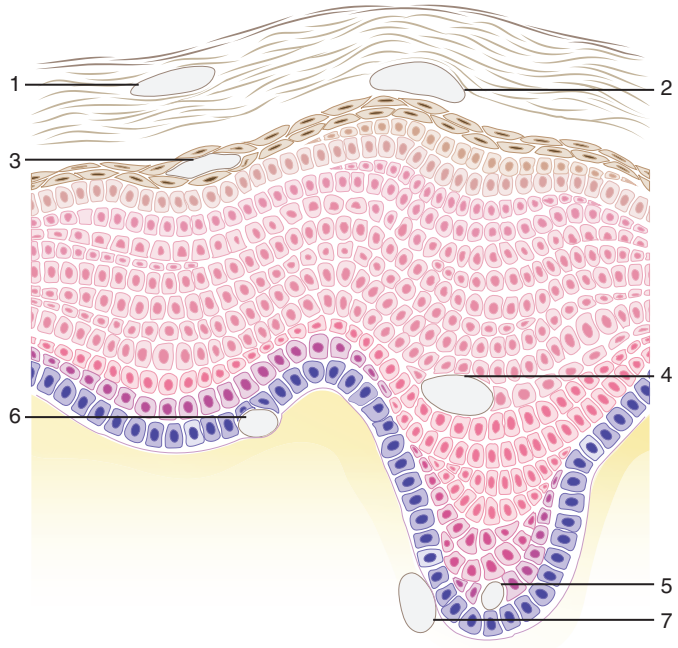

FIGURE 48.3 Blister cleavage sites in the skin. *1,* Intracorneal. *2,* Subcorneal. *3,* Granular layer. *4,* Intraepidermal. *5,* Suprabasal. *6,* Junctional (between the basal cell membrane and basement membrane). *7,* Subepidermal. (From Esterly NB. The skin. In: Behrman RE, ed. *Nelson Textbook of Pediatrics*. 14th ed. Philadelphia: WB Saunders; 1992:1640.)

TABLE 48.1 Sites of Blister Formation of Selected Vesiculobullous Diseases

Site of Cleavage	Clinical Example
Intracorneal	Miliaria crystallina
Granular layer	Bullous impetigo Staphylococcal scalded skin syndrome Pemphigus foliaceus
Intraepidermal	Dermatophytosis Insect bites Incontinentia pigmenti Scabies Viral blisters
Suprabasal	Pemphigus vulgaris
Basal cell layer	Epidermolysis simplex
Junctional	Junctional epidermolysis bullosa
Subepidermal	Toxic epidermal necrolysis Dermatitis herpetiformis Recessive dystrophic epidermolysis bullosa Dominant dystrophic epidermolysis bullosa Linear IgA disease of childhood

IgA, immunoglobulin A.

diagnosis. These cells may have 2-15 nuclei and are much larger than other inflammatory cells. Although a positive result of Tzanck preparation is confirmatory, a negative test result does not rule out herpes viral infection. Viral specimens should be obtained for culture or polymerase chain reaction (PCR) to differentiate HSV from varicella-zoster virus infections.

Scabies Test

A scabies preparation exhibiting the mite, egg, or feces (scybala) confirms the diagnosis of scabies infestation with *Sarcoptes scabiei*. The mite is most often found within burrows (serpiginous or elongated papules), which may have a vesicle or pustule at one end. A drop of mineral oil should be applied to the lesion so that the scraped material adheres to the blade. The site is then scraped firmly with a curved blade, which occasionally induces minimal bleeding. The material is applied to a microscope slide, another drop of mineral oil is added, and a glass coverslip is placed. Mites are 8-legged arachnids that are easily identified under low magnification. Eggs are frequently observed as smooth ovals approximately half the size of the mite. Feces are smaller than ova and appear as red-brown pellets, often in clusters.

Gram Stain

A Gram stain can be useful in the diagnosis and treatment of suspected bacterial infections. After the site is disinfected, the pustule or blister roof is carefully removed with a needle or straight blade. The contents of the pustule are removed in a sterile manner and spread thinly onto a glass slide. The specimen is air-dried or heat-fixed, stained, and examined microscopically. Results help determine which antibiotic, if any, is indicated. Bacterial cultures are typically obtained simultaneously.

Wood Lamp Examination

A Wood lamp emits low-intensity ultraviolet light at 365 nm and is useful for accentuating pigmentary alterations such as those of piebaldism or ash leaf macules in the newborn and detecting several fungal or bacterial infections. The examination is performed in a darkened room, and the lamp is held 4-6 inches from the patient's skin. Characteristic color changes of infectious etiologies are outlined in Table 48.2.

Skin Biopsy

A skin biopsy can be performed when a clinical diagnosis is unclear. Histologic evaluation of a small skin specimen may reveal changes in the epidermis, dermis, or subcutaneous tissue that confirm or rule out specific disorders. Direct immunofluorescence testing can be extremely helpful in the diagnosis of collagen vascular and autoimmune bullous diseases (Table 48.3).

DERMATOLOGIC DISORDERS IN OLDER INFANTS AND CHILDREN

Many forms of skin lesions are acquired during childhood and adolescence with a range from benign asymptomatic dermatoses to infectious or chronic skin disorders. A thorough history to understand the symptomatology and time course, as well as a detailed skin examination to evaluate the morphology of the lesions, can help distinguish between childhood dermatoses.

Scaling Disorders

The term *papulosquamous* refers to conditions in which the primary lesions are papules or plaques associated with scale. These disorders are typically benign but can be chronic and therapeutically challenging.

Pityriasis Rosea

Pityriasis rosea is an acute, common, self-limited eruption that has no gender predilection. Although the precise cause is unknown, a viral origin is suspected because there have been reports of epidemics, clusters of cases among closely related individuals, and low recurrence

TABLE 48.2 Wood Lamp Examination Findings

Fluorescence	Clinical Appearance	Organisms/Disease
Coral, red, pink	Brown or red thin plaques on the groin, axillae, or toe webs	Erythrasma (*Corynebacterium minutissimum*)
Pale green or yellow	Hypopigmented or hyperpigmented macules and plaques on the trunk	Tinea versicolor (*Pityrosporum orbiculare, P. ovale, Malassezia furfur*)
Bright yellow-green	Infection of the toe web space; often in burn patients	*Pseudomonas aeruginosa*
Yellow-green	Scaling of the scalp with patchy hair loss	Tinea capitis (*Microsporum canis, M. audouinii*) Not *Trichophyton tonsurans*

TABLE 48.3 Immunofluorescent Findings in Immune-Mediated Cutaneous Diseases

Disease	Involved Skin	Uninvolved Skin	Direct IF Findings	Indirect IF Findings	Circulating Antibodies
Dermatitis herpetiformis	Negative	Positive	Granular IgA ± C in papillary dermis	None	IgA antiendomysial and transglutaminase antibodies
Bullous pemphigoid	Positive	Positive	Linear IgG and C band in BMZ, occasionally IgM, IgA, IgE	IgG to BMZ	IgG anti-BP180 and anti-BP230
Pemphigus (all variants)	Positive	Positive	IgG in intercellular spaces of the epidermis between keratinocytes	IgG in intercellular spaces of the epidermis between keratinocytes	IgG antidesmoglein 1 and 3 (pemphigus vulgaris and foliaceus). IgA antidesmocollin 1 (IgA pemphigus)
Linear IgA bullous dermatosis (chronic bullous dermatosis of childhood)	Positive	Positive	Linear IgA at BMZ, occasionally C	Low titer, rare IgA, anti-BP180	None
Discoid lupus erythematosus	Positive	Negative	Linear IgG, IgM, IgA, and C3 at BMZ (lupus band)	None	Usually ANA-negative
Systemic lupus erythematosus	Positive	Variable; exposed to sun, 30–50%; nonexposed, 10–30%	Linear IgG, IgM, IgA, and C3 at BMZ (lupus band)	None	ANA Anti-Ro (SSA), anti-La (SSB) Anti-RNP Anti-dsDNA Anti-Sm
Henoch–Schönlein purpura	Positive	Positive	IgA around vessel walls	None	None

ANA, antinuclear antibody; BMZ, basement membrane zone at the dermal–epidermal junction; BP, bullous pemphigoid; C, complement; dsDNA, double-stranded deoxyribonucleic acid; IF, immunofluorescence; Ig, immunoglobulin; Sm, Smith; SSA/SSB, Sjögren syndrome A/B; RNP, ribonucleoprotein.

rates. Pityriasis rosea has been associated with systemic reactivation of human herpesvirus 6 (HHV-6) and HHV-7. Furthermore, a prodrome of malaise, headache, and respiratory symptoms is occasionally observed.

The eruption usually begins with a solitary oval, pink scaly plaque approximately 3-5 cm in diameter, typically located on the trunk or proximal extremities (Fig. 48.4). Referred to as the **herald patch**, this finding is observed in 50-70% of cases. When the herald patch has an elevated red border and central clearing, it resembles tinea corporis. Performing a KOH preparation can differentiate these two conditions. Within 1-2 weeks after appearance of the herald patch, numerous small, pink scaly papules or plaques arise over the trunk and proximal extremities, sparing the face and distal extremities. The lesions classically have a fine cigarette paper–like peripheral collarette of scale. These oval 0.5- to 2-cm lesions have their long axis oriented along skin lines, and when present on the trunk, result in a "Christmas tree" pattern on the back (Fig. 48.4). Young children, particularly African-Americans, may have an "inverse" type of pityriasis rosea, with most lesions distributed on the distal extremities, face, neck, and intertriginous regions. Other variants seen in children demonstrate lesions that are papular, vesicular, pustular, purpuric, or lichenoid.

The duration of the eruption varies from 2-12 weeks. Therapy is unnecessary; emollients, topical corticosteroids, or oral antihistamines help relieve pruritus. In addition, pityriasis rosea improves significantly with exposure to ultraviolet light. Postinflammatory hypopigmentation or hyperpigmentation may persist for weeks to months, especially in dark-skinned patients. There are many other dermatoses that can resemble pityriasis rosea (Table 48.4). In sexually active adolescents, a rapid plasma reagin (RPR) test should be obtained to rule out the possibility of secondary syphilis, especially if the palms and soles are involved. Persistence of the eruption after 3-4 months necessitates an evaluation for another diagnosis.

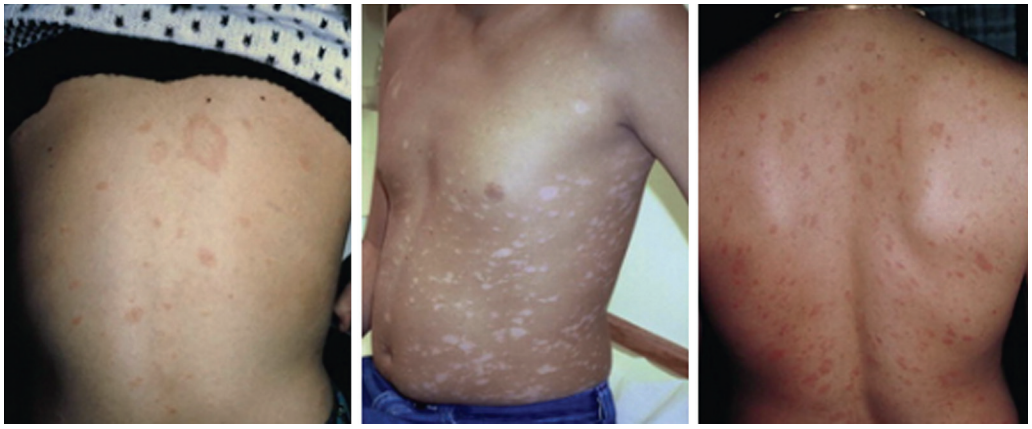

FIGURE 48.4 Pityriasis rosea. *A,* The herald patch. *B,* Oval lesions oriented along the lines of skin cleavage on the trunk. *C,* Christmas tree distribution on the back. (From Cohen BA, Davis HW, Gehris RP. Dermatology. In: Zitelli BJ, et al, eds. *Atlas of Pediatric Physical Diagnosis*. Philadelphia: Saunders; 2012:299-368.)

TABLE 48.4 Differential Diagnosis of Papulosquamous Disorders (Primary Skin Lesions Are Papules or Plaques Associated with Scale)

Lichen planus
Lupus erythematosus
Lichen striatus
Lichen nitidus
Psoriasis
Guttate psoriasis
Pityriasis rosea
Pityriasis lichenoides (parapsoriasis)
Pityriasis rubra
Dermatophyte infections
Dermatomyositis
Drug eruption
Nummular eczema
Atopic dermatitis
Seborrheic dermatitis
Secondary syphilis
Cutaneous T-cell lymphoma

Psoriasis

Psoriasis is an immune-mediated inflammatory skin condition characterized by well-demarcated, erythematous scaly papules and plaques located most often on the scalp, elbows, knees, genitalia, and lumbosacral regions. The course is more chronic and unpredictable than that of pityriasis rosea. Psoriasis occurs in approximately 1-3% of the population and is estimated to manifest before the age of 20 years in about 30% of patients. It affects both genders equally in adulthood, but childhood psoriasis has a slight female predominance. The cause is multifactorial, but there is a genetic predisposition in many affected individuals and about 50% have a positive family history when onset occurs during childhood. The association between psoriasis, obesity, and metabolic syndrome has been described in both adult and pediatric patients with psoriasis, and screening for individuals with moderate-to-severe involvement should be considered.

Psoriasis encompasses a broad spectrum of clinical manifestations, ranging from mild, asymptomatic, virtually undetectable disease to extensive, chronic, debilitating disease. The course is usually marked by recurrent flares and remissions and is often exacerbated by stress, trauma, infection, climate, hormonal factors, and particular medications.

FIGURE 48.5 Well-demarcated erythematous, scaly plaques of psoriasis. (From Kliegman RM, et al. Diseases of the epidermis. In: Kliegman RM, et al, eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2015:3160-3162.)

Although morphologic variations exist, the classic lesions of **plaque psoriasis** are well-demarcated erythematous papules or plaques with a silvery-white scale (Fig. 48.5). The lesions usually begin as small erythematous papules that gradually enlarge and coalesce to form plaques up to several centimeters in diameter. The micaceous (mica-like) scale of the psoriatic plaque is more adherent centrally than peripherally. Removal of this scale results in multiple small bleeding points. This is referred to as the *Auspitz sign* and is secondary to disruption of the dilated blood vessels that are located high in the papillary dermis. Although this finding is seen in psoriasis, it is not pathognomonic.

The **Koebner phenomenon**, another characteristic feature of psoriasis, although observed in a number of dermatologic conditions, is an isomorphic response (development of new or larger lesions) occurring at sites of injury or trauma such as scratching, sunburn, or surgery (Fig. 48.6). Psoriatic lesions tend to be distributed symmetrically. Although extensor surfaces are typically involved, a variant of psoriasis known as inverse psoriasis affects flexural surfaces, such as the axillae and groin.

FIGURE 48.6 Koebner phenomenon in psoriasis with linear plaques formed in the pattern of excoriations. (From Papulosquamous eruptions. In: Cohen BA, ed. *Pediatric Dermatology*. Philadelphia: Saunders; 2013:68-103.)

FIGURE 48.7 Small droplike plaques of guttate psoriasis. (From Cohen BA, Davis HW, Gehris RP. Dermatology. In: Zitelli BJ, et al, eds. *Atlas of Pediatric Physical Diagnosis*. Philadelphia: Saunders; 2012: 299-368.)

Scalp lesions are present in most children with psoriasis. Diffuse, thick white scale may be accompanied by erythema. In contrast to seborrhea, psoriasis often extends beyond the hairline, affecting the forehead, ears, and neck. The lesions are variably pruritic and are generally not associated with hair loss. Scalp psoriasis tends to be more resistant to therapy than seborrheic dermatitis.

Nail abnormalities are seen in 25-50% of patients with psoriasis. Nail pits are the most common finding, identified by multiple pinpoint depressions that are irregularly distributed over the nail plate. Although nail pitting is characteristic of psoriasis, it is not a pathognomonic sign; it is also associated with atopic dermatitis, alopecia areata, and trauma. Other nail changes include separation of the nail plate from the nail bed (onycholysis), subungual hyperkeratosis, discoloration, crumbling, and yellowish-brown "oil spots" on the nail plate.

Guttate psoriasis, characterized by numerous droplike lesions, is a variant commonly seen in children and young adults (Fig. 48.7). The round-to-oval, pinkish-red, somewhat scaly papules arise in crops and are widely distributed, particularly on the trunk. Two-thirds of affected patients have a history of an upper respiratory tract infection, usually streptococcal in origin, which was present 1-3 weeks before the onset of lesions. Clinical improvement is often seen after appropriate antibiotic therapy; however, the clinical course may range from spontaneous resolution to chronic disease.

Psoriasis is usually diagnosed from the clinical appearance of skin lesions. However, when the diagnosis is unclear, a skin biopsy may be helpful. Differential diagnosis of psoriasis includes seborrheic dermatitis, dermatophytosis, pityriasis rosea, lichen planus, atopic dermatitis, and subacute cutaneous lupus erythematosus (Table 48.4).

The course of psoriasis is marked by recurrent flares and remissions. Although it is unpredictable, there appears to be a subset of individuals whose disease gradually improves over time. Management of psoriasis varies depending on a number of factors including age of the child, extent of involvement, functional limitations, and psychosocial impact. For limited disease, topical therapy (emollients, corticosteroids, vitamin D derivatives, retinoids, tar, keratolytics) alone may afford control. For more extensive or debilitating disease, the addition of phototherapy or a systemic agent (immunosuppressants, retinoids, "biologic" therapy) may be necessary.

Pityriasis Lichenoides

Pityriasis lichenoides can manifest in two forms: pityriasis lichenoides et varioliformis acuta (PLEVA) or pityriasis lichenoides chronica. These diseases most commonly affect children between ages 5 and 15 years. Both diseases are believed to be part of the same clinical spectrum. **PLEVA** is characterized by an abrupt eruption of multiple, 2- to 4-mm, nonpruritic, variably scaly erythematous macules and papules that may progress to vesicular, necrotic, or crusted lesions. The lesions often occur in crops, and are thus present in different stages most commonly on the trunk, but may spread to the extremities. The condition may resolve spontaneously within several months, or recurrences and relapses may occur episodically for several years.

Pityriasis lichenoides chronica manifests more gradually and is characterized by pink-to-brown 2- to 5-mm papules with central adherent scale, found primarily on the trunk and proximal extremities. The clinical course is variable, and the lesions may last from months to years. After the papules recede, postinflammatory hypopigmentation or hyperpigmentation commonly occurs. Sequelae are uncommon, and the lesions usually heal without a scar. Pityriasis lichenoides chronica may initially resemble pityriasis rosea and other papulosquamous eruptions (Table 48.4). Reports of cutaneous T-cell lymphoma (**mycosis fungoides**) in the setting of pityriasis lichenoides chronica exist, and the patient with a persistent or atypical eruption should be evaluated with consideration of a skin biopsy (Fig. 48.8).

Treatment may be limited to lubricants in an asymptomatic patient. If treatment is required, first-line agents include oral antibiotics with antiinflammatory properties (erythromycin, doxycycline) for several weeks, which have shown benefit in some children.

Lichen Planus

Lichen planus occurs in patients of all ages but is less commonly seen in children than in adults. It is characterized by the "**5 Ps**": purple, polygonal, planar, pruritic papules. The primary lesion is a shiny, violaceous, flat-topped papule, often with angulated borders, measuring from 2 mm to more than 1 cm in diameter. The lesions are very pruritic and demonstrate the Koebner phenomenon, which results in the development of new lesions (often in a linear configuration) at sites of scratching. The distribution may be localized or generalized, and lesions may number from few to numerous. Sites of predilection include the volar wrists, forearms, legs, genitalia, and mucous membranes. A reticulated pattern of delicate white lines or streaks (**Wickham striae**) seen on the buccal mucosa or skin aids in confirming the diagnosis.

Nail changes are seen in approximately 10% of patients. These include longitudinal ridging, generalized nail destruction, red or brown discoloration, subungual hyperkeratosis, and thinning of the

nail plate. Pterygium formation results from the overgrowth of fibrous tissue, which extends from the proximal nail fold to the tip of the nail, obliterating the nail plate.

Common **medications** that can produce a lichenoid eruption that is indistinguishable from lichen planus include antihypertensives (β blockers, angiotensin-converting enzyme inhibitors), diuretics (hydrochlorothiazide), antimalarials, penicillamine, and gold salts. Rarely, tetracycline, griseofulvin, nonsteroidal antiinflammatory medications, phenytoin, and carbamazepine can be causes. Unlike other cutaneous medication reactions, the lichenoid reaction may not occur for months or years after medication initiation.

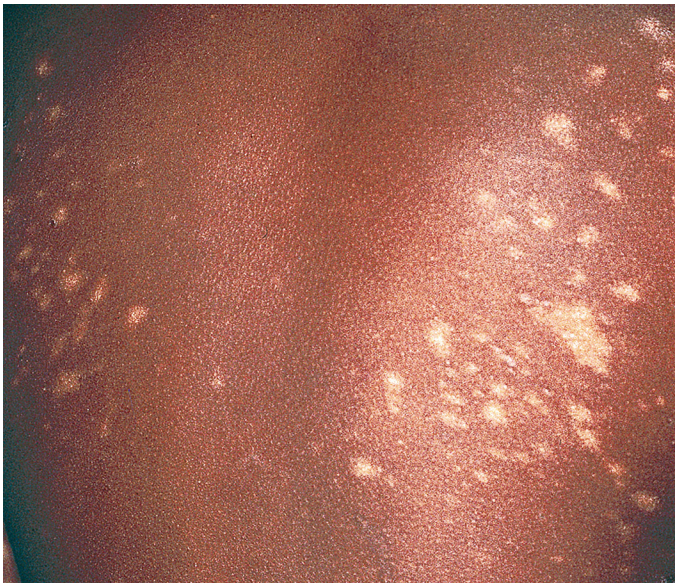

FIGURE 48.8 Asymptomatic, hypopigmented, minimally scaly patches on the trunk of a child, which were present for several years and found to be cutaneous T-cell lymphoma. (From Papulosquamous eruptions. In: Cohen BA, ed. *Pediatric Dermatology*. Philadelphia: Saunders; 2013:68-103.)

It is often possible for the experienced clinician to diagnose lichen planus strictly on clinical grounds. If necessary, a skin biopsy specimen can reveal specific findings. The clinical differential diagnosis most often includes psoriasis and drug eruptions (Table 48.4). If oral lesions are present, the clinician must consider the possibility of aphthous stomatitis, erythema multiforme (EM), herpes simplex, or leukoplakia.

Topical corticosteroids are the treatment of choice in most cases. Lichen planus often resolves spontaneously over 1-2 years, but some cases may persist for many years. Generalized eruptions may respond to a short course of systemic corticosteroids. Oral antihistamines provide symptomatic relief.

Seborrheic Dermatitis

Seborrheic dermatitis is characterized by an erythematous, scaly, symmetric eruption that occurs most often in hair-bearing and intertriginous regions. Seborrhea of infancy is discussed in Chapter 47. In adolescents, yellowish, greasy scale of the scalp, eyebrows, nasolabial folds, nasal bridge, posterior auricular regions, and midchest may be accompanied by mild erythema (Fig. 48.9). Immunodeficiency disorders and neurologic dysfunction may be associated with severe, recalcitrant seborrheic dermatitis. Although patients usually respond well to therapy, it is a chronic condition characterized by recurrences. It is often responsive to low-potency topical corticosteroids or topical antifungals (azoles, ciclopirox, selenium sulfide). These preparations may be available in a number of vehicles, including solutions or shampoos for the scalp. Keratolytics may be added when thicker scale is present.

Atopic Dermatitis

Atopic dermatitis (**eczema**) is a chronic condition characterized by pruritus, a personal or family history of atopy, and an age-dependent distribution. It is common during infancy and childhood. Up to 95% of affected individuals have signs before the age of 5 years.

Typical lesions are pink-to-red crusted or scaly plaques or papules. Some individuals have follicular accentuation, particularly on the trunk, manifested by a goosebump-like texture. **Lichenification** (thickened skin with exaggerated skin markings) is a feature of chronic atopic dermatitis and results from repeated rubbing and scratching.

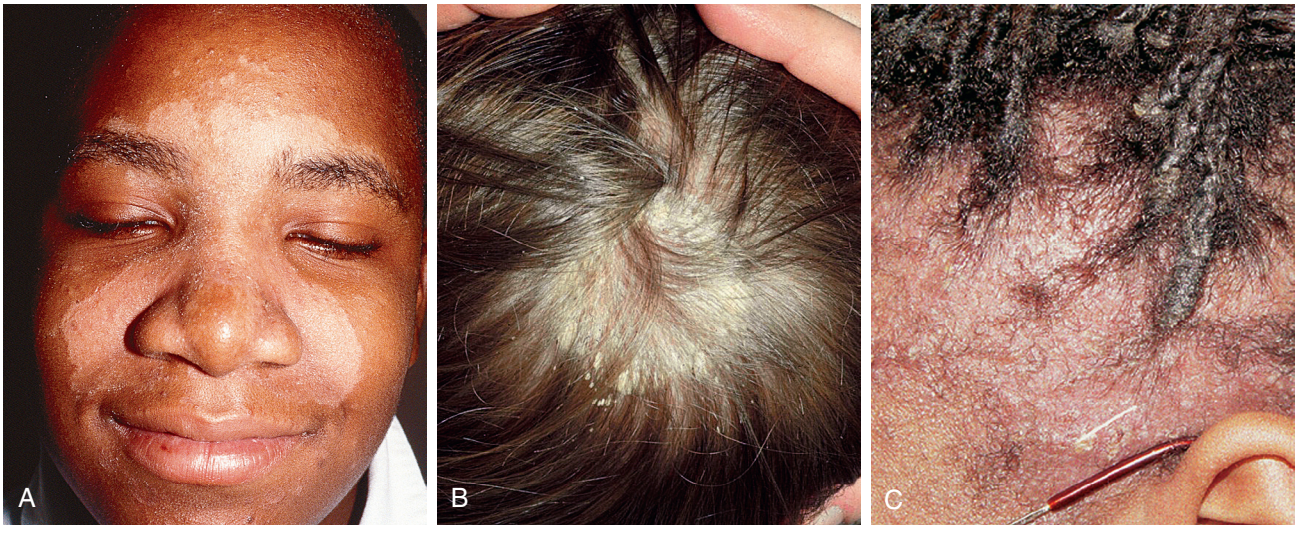

FIGURE 48.9 Seborrheic dermatitis in the older child or adolescent. *A,* Scaly, hypopigmented lesions on the face involving eyebrows, nasolabial folds, and nasal bridge. *B,* Thick, yellow, adherent scale in the scalp. *C,* Confluent, scaly patches on the scalp with mild erythema. (From Papulosquamous eruptions. In: Cohen BA, ed. *Pediatric Dermatology*. Philadelphia: Saunders; 2013:68-103.)

Excoriations are secondary lesions caused by scratching. Postinflammatory pigmentary changes are frequently noted, especially in dark-skinned individuals (Fig. 48.10). Associated findings are noted in Table 48.5.

The distribution of the lesions tends to be age dependent. The cheeks, face, scalp, trunk, and extensor surfaces of the arms and legs are characteristically involved in the infant form. Between the ages of 2 and 10 years (childhood atopic dermatitis), the distribution predominately involves the neck, wrists, ankles, and flexural surfaces of the extremities (Fig. 48.11). After puberty, atopic dermatitis has a predilection for the face, neck, hands, and feet. The clinical features of the skin lesions are not specific to this condition, as other eczematous eruptions (contact dermatitis, seborrheic dermatitis) have a similar appearance. Laboratory tests are of limited value, and histologic findings reveal nonspecific spongiotic dermatitis. The distribution of lesions, age at onset, and history are most important for establishing the diagnosis. Obtaining a complete personal and family history of atopic diatheses is necessary.

Secondary infections are the most common complication. Individuals with atopic dermatitis have increased colonization with *Staphylococcus aureus*. Most affected children need occasional treatment with antibiotics to eradicate secondary infection, and dilute sodium hypochlorite bleach baths can help reduce infection with *S. aureus*. The presence of pustules, extensive excoriations, or weeping and crusted lesions suggests the need for antibiotic therapy. Topical therapy with mupirocin may be sufficient for limited areas; however, widespread involvement may necessitate the use of oral antimicrobial agents. The increase in methicillin-resistant *S. aureus* (MRSA) infections has limited therapeutic options in some patients. Secondary infection with HSV is referred to as **eczema herpeticum** or **Kaposi varicelliform eruption** (Fig. 48.12). Transmission may occur during routine child care from a caretaker with a herpetic fever blister, whereby the eczematous skin becomes inoculated with HSV. The hallmark of this condition is the rapid development of numerous umbilicated vesicles and pustules. Later in the course, multiple erosions are seen, and identification of an intact vesicle may be difficult. The infection may be associated with fever and other constitutional symptoms, and expedient treatment with acyclovir is required. Hospitalization may be necessary in young infants or severely affected individuals. Recurrences of eczema herpeticum can be problematic.

Other dermatologic conditions to consider in the differential diagnosis of a rash that looks like atopic dermatitis are presented in Table 48.6.

An overview of the management of atopic dermatitis is presented in Table 48.7.

FIGURE 48.10 Postinflammatory pigment changes of the ankles *(A)* and hands *(B)*. (From Papulosquamous eruptions. In: Cohen BA, ed. *Pediatric Dermatology*. Philadelphia: Saunders; 2013:68-103.)

LUMPS AND BUMPS

The presence of cutaneous or subcutaneous **nodules** and **tumors** can present a diagnostic challenge. They are also a source of great concern to parents, who fear the possibility of malignancy. Fortunately, most

TABLE 48.5 Atopic Dermatitis: Associated Findings

Ichthyosis vulgaris	Affects 20% of patients with atopic dermatitis Primarily involves the legs and trunk
Keratosis pilaris	Asymptomatic hyperkeratotic follicular papules found mainly on the extensor surfaces of the upper arms and anterior thighs, also on the face in children
Pityriasis alba	Hypopigmented patches on the cheeks and occasionally upper body
Hyperlinear palms/soles	Common physical finding
Dennie–Morgan fold	A double line found under the lower eyelids Not pathognomonic
Lichen spinulosus	More commonly seen in darker skin Pruritic grouped hyperkeratotic follicular spires
Eye findings	Keratoconjunctivitis, cataracts, keratoconus (abnormally shaped cornea), retinal detachment (rare)
Dyshidrotic eczema	Firm vesicles found on the palms and soles and lateral aspects of digits Frequently associated with hyperhidrosis
Nummular eczema	Well-demarcated, scaly, coin-shaped lesions usually on the lower extremities Associated with xerosis
Juvenile plantar dermatosis	Occasionally exudative lesions Painful erythema, scaling, cracking, and fissuring of weight-bearing surfaces of the feet Often associated with hyperhidrosis Improvement after puberty

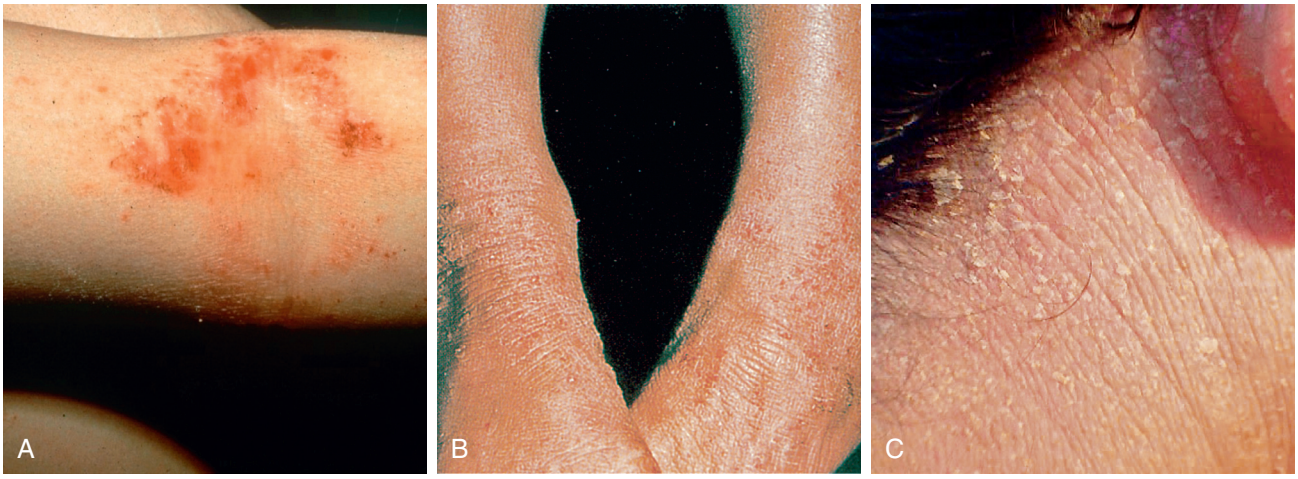

FIGURE 48.11 Atopic dermatitis in childhood with lesions of the arm *(A)*, ankles *(B)*, and neck *(C)*. (From Papulosquamous eruptions. In: Cohen BA, ed. *Pediatric Dermatology*. Philadelphia: Saunders; 2013: 68-103.)

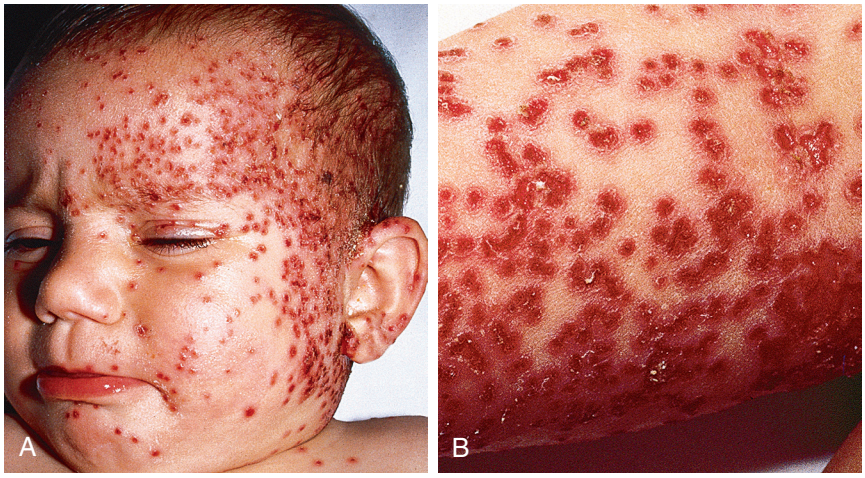

FIGURE 48.12 Eczema herpeticum infection in a patient with atopic dermatitis. Numerous punched out vesicles and erosions involving the face *(A)* and extremities *(B)*. (From Papulosquamous eruptions. In: Cohen BA, ed. *Pediatric Dermatology*. Philadelphia: Saunders; 2013:68-103.)

nodules and tumors in children are benign, and cutaneous malignancies are rare (Table 48.8).

Granuloma Annulare

Granuloma annulare is characterized by skin-colored to mildly erythematous dermal papules and nodules that may expand and coalesce into rings. These asymptomatic annular plaques measure 1-4 cm in diameter and appear most commonly on the dorsal hands and feet or extensor surfaces of the extremities (Fig. 48.13). The centers of these lesions usually appear normal but are occasionally hyperpigmented or violaceous in color. The overlying epidermis is unaffected. Multiple lesions are common, particularly in children. Granuloma annulare may be seen in all age groups, but at least 40% of cases occur before 15 years of age. The etiology remains unknown. Some cases have been associated with preceding trauma, such as insect bites. Histologically, there is dermal infiltration of lymphocytes and histiocytes surrounding degenerated collagen. Some authorities postulate that the condition may result from a cell-mediated immune response. In children, this condition is less commonly associated with systemic diseases such as diabetes, as has been reported in adults. The eruption is most

FIGURE 48.13 Ring of confluent dermal papules with a depressed center typical of granuloma annulare. (From Kliegman RM, et al. Diseases of the dermis. In: Kliegman RM, et al, eds. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2015:3176.)

TABLE 48.6 Differential Diagnosis of Atopic Dermatitis

Condition	Similarities	Differences
Seborrheic dermatitis	Scaly plaques Erythroderma may be seen when severe	Earlier onset is typical, can be seen in older children Increased severity associated with immunodeficiency disorders and neurologic dysfunction Pruritus minimal or absent Well-demarcated lesions Characteristic yellowish-salmon greasy lesions with intertriginous distribution
Contact dermatitis		
Primary irritant	Common in infants, young children May have similar distributions depending on the irritant (i.e., cheeks, chin, neck)	Usually less pruritic and less eczematoid Diaper area distribution uncommon in atopic dermatitis
Allergic	Pruritic Erythematous, papulovesicular eruption	Well circumscribed Uncommon in 1st few months of life Involutes spontaneously after the removal of the offending agent
Psoriasis	Scaly, red lesions	Deeper red-violaceous hue Thick micaceous scale Characteristic nail changes Sharply demarcated lesions Distinct distribution Pruritus may be less intense
Scabies	Frequent eczematous changes secondary to scratching, rubbing, or irritating therapy Can be very difficult to distinguish in infancy	Presence of hyperpigmented nodules Presence of burrows Isolation of a mite from skin scrapings Acute onset Affected household members
Langerhans cell histiocytosis	Scaly, erythematous eruption Usually begins during 1st yr of life	Primarily children <3 yr of age Presence of purpuric papules Associated hematologic abnormalities, hepatosplenomegaly
Acrodermatitis enteropathica	Vesiculobullous eczematoid lesions Onset during infancy	Acral, periorificial distribution Associated features: failure to thrive, diarrhea, alopecia, nail dystrophy, low serum zinc levels
Wiskott–Aldrich syndrome	Severe eczematous dermatitis	X-linked recessive disorder Associated features of thrombocytopenia, defects in cellular and humoral immunity, bloody diarrhea
Phenylketonuria	Eczematous eruption	Hereditary Intellectual disabilty, seizures Diffuse hypopigmentation, blond hair, photosensitivity Elevated blood phenylalanine levels
Hyper-IgE syndrome	Symptoms begin in 1st 3 mo of life Eczematous dermatitis involving the face and extensor surfaces Personal or family history of atopy	Coarse facial features, irregularly proportioned jaw and cheeks, broad nasal bridge, prominent nose, severe oral mucositis Lifelong history of severe streptococcal or staphylococcal infections of the skin, limbs, joints Exceptionally high serum IgE levels Diminished neutrophil chemotaxis

IgE, immunoglobulin E.

commonly confused with that of tinea corporis, but tinea has epidermal changes such as scaling, vesiculation, or pustules.

There are several variants of granuloma annulare. Generalized granuloma annulare is characterized by many asymptomatic papules symmetrically distributed. The ringlike lesions may coalesce into reticulated or circinate forms. The features of subcutaneous granuloma annulare are single or multiple deep hard nodules on the extremities, buttocks, and scalp. This entity is most frequently mistaken for rheumatoid nodules; however, the latter are usually larger.

Granuloma annulare resolves spontaneously over several months to years. Although more than 50% of cases clear within 2 years, recurrences are common. Treatment is generally unnecessary, but the use of topical or intralesional corticosteroids may hasten resolution.

Juvenile Xanthogranuloma

Juvenile xanthogranulomas (JXGs) are papules, nodules, or plaques within the skin that are solitary or multiple; well demarcated; rubbery to firm; and yellow, orange, brown, or red in color. One of the most

TABLE 48.7 Atopic Dermatitis Management

Therapeutic Modality	Indications and Recommendations
Bathing	Recommended daily for 10–15 min with warm, not hot, water. May use fragrance-free bath oils. Hydrates the skin.
Soaps	Mild, fragrance-free cleansers, such as Dove, Basis, Aveenobar, Olay, Cetaphil, or Aquanil, are essential.
Emollients	Best applied immediately after bathing/showering. Should be used as often as possible. Petroleum jelly is an ideal emollient: contains no water, additives, or preservatives and prevents evaporative water loss from the skin. Thick creams such as Eucerin, Nivea, Aquaphor, Vanicream, and Cetaphil are some alternatives.
Bleach (sodium hypochlorite)	Depending on the size of the bathtub/amount of water used, 0.25–0.5 U.S. cup (60–120 mL) of common bleach solution (6% sodium hypochlorite) is added to a full bath (40 gallon tub). Performed 2–3 times/wk to reduce *S. aureus* colonization.
Compresses	Indicated for acute weeping lesions. Helps cool and dry the skin, reduces inflammation. Use cool tap water or aluminum acetate solutions for 20 min, 2–4 times daily. Follow with topical corticosteroid application.
Topical corticosteroids	Indicated to reduce pruritus and inflammation. The potency of the topical corticosteroid is determined by the age of patient, site of involvement, severity of dermatitis, and duration of therapy. Facial and intertriginous skin should be treated with low-potency preparations. Apply before emollient. Use the lowest potency that is effective. Monitor closely for potential side effects, such as striae and cushingoid features.
Topical Immunomodulators	Tacrolimus and pimecrolimus may be effective steroid-sparing agents for more severe involvement.
Antihistamines	Controversial whether effective in this condition. Topical formulations should be avoided. May help some patients sleep. Hydroxyzine often more effective than diphenhydramine. May induce drowsiness. Nonsedating antihistamines include cetirizine, loratadine and fexofenadine.
Antibiotics	Patients have increased colonization with *S. aureus*. Use if multiple weeping excoriations, crusts, or pustules suggest secondary infection or if severe or resistant eczema is present. Treat with antistaphylococcal antibiotics; specific antibiotic is based on local sensitivities.
Ultraviolet light	Useful for severe, uncontrollable atopic dermatitis. May administer narrowband ultraviolet B light (NBUVB).
Tars	Useful for chronic, dry, lichenified lesions, not for acute dermatitis.
Environmental conditions	Environmental factors may influence the severity of the dermatitis. Some helpful measures: • Avoid fragrances in all topicals and laundry products. • Avoid wool, feathers, dust exposure. • Reduce house dust mites. • Eliminate animal dander. • Use plastic mattress covers. • Reduce stress/anxiety. • Increase environmental humidity to reduce skin evaporative losses. • Avoid smoking.
Systemic immunosuppressants	Oral corticosteroids should be avoided. Cyclosporine, methotrexate, mycophenolate mofetil, and azathioprine have shown some benefit in the management of atopic dermatitis, but given the side effect profile, should be prescribed under the direction of a dermatologist.

S. aureus, Staphylococcus aureus

distinct clinical features of a JXG is its characteristic yellow color. On examination, an overlying telangiectasia may be visualized. Lesions are of variable size, usually 0.5-2 cm, and are most commonly located on the head and neck region. The differential diagnosis should include Spitz nevus, solitary mastocytoma, and occasionally nevus sebaceous. Biopsy demonstrates the characteristic histopathologic features of lipid-laden histiocytes and Touton giant cells. Most JXGs are asymptomatic, but occasionally they cause pruritus or pain. The lesions may be present at birth or within the 1st years of life. JXGs are usually benign, and treatment of cutaneous lesions is generally not required. After a brief period of growth, the lesion often stabilizes and involutes spontaneously in months to years.

Multiple lesions should prompt a search for the rare possibility of extracutaneous involvement. The eye is the most common extracutaneous site. Lesions may be found in the iris, and JXG is the most common cause of anterior chamber hemorrhage in children. The incidence of ocular disease in JXGs is approximately 0.3-0.4%. Ophthalmologic examination is recommended if a JXG is present near the eye or with multiple lesions. Involvement has also been described in other organs including the testes, lungs, liver, spleen, heart, and central nervous system. An increased risk of juvenile myelomonocytic leukemia has been reported in the setting of patients with both neurofibromatosis type 1 and JXGs.

Vascular Lesions

Spider Angioma (Nevus Araneus)

Telangiectases are dilated capillaries that appear as red linear stellate or punctate lesions. There are many causes of *primary* telangiectasia (spider angiomas, hereditary hemorrhagic telangiectasia syndrome) and *secondary* telangiectasia, such as collagen vascular diseases. Spider

TABLE 48.8 Lumps and Bumps: Distinguishing Features

Diagnosed Lesion	Usual Onset	Color	Size	Site	Comments	Therapy
Epidermal cyst	Birth, childhood, adolescence	Skin-colored	1–3 cm	Face, scalp, neck, trunk	Potential for inflammation and infection	Elective excision vs observation
Dermoid cyst	Birth	Skin-colored	1–4 cm	Face, scalp, lateral eyebrow	When midline, may have sinus tract	Elective excision
Pilomatricoma	Any age, 50% before adolescence	Skin-colored, reddish-blue, bluish-gray	0.5–3 cm	Head, neck	Malignant transformation possible but rare	Elective excision vs observation
Dermatofibroma	Adulthood, 20% before age 20 yr	Skin-colored, tan brown, black	0.3–1 cm	Extremities	May follow trauma	Elective excision vs observation
Neurofibroma	Occasionally at birth Usually childhood or adolescence	Usually skin colored Also pink, blue	2 mm to several centimeters	Any body site	May be associated with neurofibromatosis May see café-au-lait spots	Elective excision vs observation
Juvenile xanthogranuloma	Birth Childhood	Yellow to reddish-brown	0.5–4 cm	Head, neck, trunk, proximal extremities	Extracutaneous lesions involving eye, other organs	Ophthalmology consult; resolves spontaneously
Keloids	Peak between puberty and age 30	Pink to violaceous	Variable	Any site of injury Commonly earlobes after piercing	Often tender or pruritic Familial tendency	Difficult; intralesional steroids, excision
Granuloma annulare	Childhood Adolescence	Skin colored to red	1–4 cm	Distal extremities	May be generalized in approximately 15% of cases	Observe, self-limited Topical steroids if needed
Lipoma	Puberty, adulthood	Skin colored	Variable May be >10 cm	Any, but usually neck, shoulders, back; abdomen	Malignant change Very rare	Observe, excision
Solitary mastocytoma	Birth Early infancy	Skin colored to light brown or tan Occasionally pink or yellowish hue	1–5 cm	Any site; but most often on arms, neck, trunk	Positive Darier sign Urticaria with stroking	Usually resolves spontaneously; antihistamines may be helpful
Erythema nodosum	Usually >10 yr of age Peak in the 3rd decade	Begins bright to deep red, then develops a brownish-red to violaceous bruiselike appearance	1–5 cm	Symmetric distribution over pretibial region, legs Occasionally arms	Tender Association with many infectious agents (group A streptococci, tuberculosis, mycoplasma), inflammatory diseases (sarcoidosis, inflammatory bowel disease), medications (birth control pills)	Thorough evaluation and treatment of underlying cause, antiinflammatory agents Bed rest/elevation of legs

FIGURE 48.14 Pyogenic granuloma. Hemorrhagic nodule with a central crust. (From Nodules and tumors. In: Cohen BA, ed. *Pediatric Dermatology*. Philadelphia: Saunders; 2013:126-147.)

angiomas are the most common of the telangiectasias. In the pediatric age group, these lesions are typically not associated with systemic disease. Spider angiomas are seen most often on the face and tops of hands. They usually develop after 2 years of age. Small vessels radiate from a central punctum (arteriole), giving the appearance of a "spider." When pressure is applied to the central punctum, the lesion blanches. Treatment, if desired, consists of gentle electrodesiccation or pulsed dye laser therapy. In some cases, spider angiomas clear without treatment.

Pyogenic Granuloma

Pyogenic granulomas are acquired vascular lesions that arise from the connective tissue of the skin or mucous membranes. These vascular nodules may be associated with antecedent trauma and represent a reactive, proliferative process. They are usually solitary, but multiple lesions occur in rare cases (Fig. 48.14). Arising as small red papules, pyogenic granulomas grow rapidly and can ulcerate, leading to profuse bleeding. Histologically, these lesions resemble infantile hemangiomas (IH). Unlike IH, onset after the 1st year of life is typical and spontaneous regression is rare and recurrences may be seen. Treatment involves destruction by pulsed dye laser therapy, electrodesiccation, surgical removal, or cryotherapy.

DISORDERS OF PIGMENTATION

These conditions are often cosmetically disfiguring and persistent. They can be markers of serious systemic diseases. Pigmentary disorders may be localized or generalized; congenital or acquired; and transient, stable, or progressive (see Chapter 47).

Acquired Disorders of Hypopigmentation or Depigmentation

Postinflammatory Hypopigmentation

Postinflammatory hypopigmentation is a common form of acquired hypopigmentation and may follow any inflammatory skin condition, including bullous disorders, infections, eczema, psoriasis, pityriasis rosea, secondary syphilis, insect bites, acne, pityriasis lichenoides chronica, and burns. More frequently detected in dark-skinned individuals, the clinical findings consist of irregularly shaped hypopigmented patches of variable size, often ill-defined, located at sites of preceding inflammation. Postinflammatory hypopigmentation usually resolves gradually over several months, and no treatment is necessary other than photoprotection.

FIGURE 48.15 Poorly demarcated areas of hypopigmentation in pityriasis alba. (From Papulosquamous eruptions. In: Cohen BA, ed. *Pediatric Dermatology*. Philadelphia: Saunders; 2013:66-103.)

Pityriasis Alba

Pityriasis alba is characterized by oval but poorly demarcated, slightly scaly, hypopigmented macules or patches located on the face (typically the cheeks), upper trunk, or extensor surfaces of the arms (Fig. 48.15). The lesions generally vary from 0.5-2 cm in diameter, are often multiple, and are usually asymptomatic. Sun exposure may increase the contrast with normal skin, prompting patients to seek treatment. An association with atopic dermatitis may be seen, and differentiating this from postinflammatory hypopigmentation associated with patches of atopic dermatitis may be difficult. In contrast to postinflammatory hypopigmentation, the histology of pityriasis alba demonstrates low-grade inflammation. Pityriasis alba may resemble tinea versicolor or tinea corporis but can be differentiated by negative KOH results. The hypopigmentation typically persists for several months to years. Although no therapeutic intervention is required, the use of emollients and low-potency topical corticosteroids may be effective.

Vitiligo

Vitiligo is an acquired disorder characterized by complete loss of the pigment of the involved skin. The condition often manifests during childhood and is believed to be linked to specific genetic mutations. Many authorities believe that vitiligo is an autoimmune process with circulating antibodies that destroy melanocytes. There is an increased incidence of autoimmune diseases in affected individuals and their families. The incidence of vitiligo in persons with diabetes mellitus is also higher than that in the general population.

The onset of vitiligo may be precipitated by sunburn or other trauma. Physical findings are usually sufficient for establishing the diagnosis. Well-demarcated depigmented macules and patches that are often bilateral and symmetric are distributed on the extremities, on the periorificial areas, and within skin folds. In some cases, depigmentation may have a segmental distribution. This variant is seen more commonly in children than in adults. The clinical course is unpredictable. Spontaneous complete repigmentation is unusual; however,

partial repigmentation may be seen, especially within lesions of less than 2 years' duration. Repigmentation proceeds gradually and is more likely to occur in children than in adults.

Treatment response often takes months. For limited involvement, topical corticosteroids are most frequently used, but calcineurin inhibitors provide an option in places where corticosteroids may be preferable to avoid. For more widespread involvement in motivated, compliant patients, phototherapy may provide the best chance of repigmentation. Other interventions may consist of camouflage with cosmetics to reduce the contrast between affected and unaffected sites and careful photoprotection to prevent the development of cutaneous malignancy. Bleaching agents are another option in individuals with depigmentation of greater than 50% of their cutaneous surface.

Disorders of Hyperpigmentation

Lentigines

Lentigines are 1- to 5-mm macules that are darker than freckles and may occur on any cutaneous site, including the mucous membranes. Lentigines have no seasonal variance, and those that manifest during early childhood often disappear during adulthood. A lentigo may be clinically indistinguishable from a junctional nevus (mole); however, these lesions are histologically distinct.

Several syndromes are associated with multiple lentigines. *Lentiginosis profusa* is an entity characterized by multiple deeply pigmented macules that are usually present at birth or in early infancy. These individuals have no associated systemic or developmental abnormalities, unlike children with **LEOPARD syndrome** (multiple lentigines, electrocardiograph abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, growth retardation, and neural deafness), which also manifests during infancy. Multiple lentigines located on the mucous membranes, especially the vermilion border of the lips and buccal mucosa, should alert the clinician to the possibility of **Peutz–Jeghers syndrome**, which is characteristically associated with intestinal polyposis and subsequent risk of malignant transformation and intussusception. **Solar lentigines** occur in sun-exposed areas in older children.

Café-Au-Lait Macules

Café-au-lait macules are well-circumscribed tan macules that usually measure less than 0.5 cm and may be as large as 15-20 cm in diameter. The lesions are found on any cutaneous site and may be present at birth or appear during early childhood. Although café-au-lait spots are seen in 10-20% of normal individuals, the presence of many macules should raise the clinical suspicion of **neurofibromatosis** (Table 48.9). The presence of 6 or more café-au-lait spots (>0.5 cm in prepubertal children; >1.5 cm in postpubertal children) fulfills 1 of the diagnostic criteria for neurofibromatosis type 1. Although the lesions are not pathognomonic, they are present in most patients

TABLE 48.9 Neurocutaneous Syndromes

Syndrome	Mode of Inheritance	Cutaneous Findings	Systemic Findings
Tuberous sclerosis	Autosomal dominant	Ash leaf macules Angiofibromas (adenoma sebaceum) Shagreen patches Periungual/subungual fibromas Gingival fibromas	CNS involvement (seizures, intellectual disabilty, cortical tubers) Cardiac rhabdomyomas Retinal gliomas Renal carcinoma or hamartoma Renal or pulmonary cysts Skeletal abnormalities
Neurofibromatosis (NF) (NF1 >85% of cases)	Autosomal dominant	Café-au-lait macules (>6 measuring ≥1.5 cm) in adults and >0.5 cm in children Axillary, inguinal freckling (Crowe sign) Neurofibromas Blue-red macules and pseudoatrophic macules (involuted neurofibromas) Lisch nodules (melanocytic hamartomas of the iris)	Acoustic neuroma in NF2 Optic glioma may result in exophthalmos, decreased visual acuity Intellectual disability (rarely) Seizure disorders (rarely) Tumors (astrocytomas) Hyperactivity, macrocephaly Learning disabilities, speech delay Osseous defects (up to 50%) Intestinal neurofibromas Endocrine disorders
Incontinentia pigmenti	X-linked dominant	Phase 1: inflammatory vesicles/bullae in crops over trunk and extremities, may persist weeks to months Phase 2: irregular linear verrucous lesions on ≥1 extremity, resolves spontaneously within several months Phase 3: brown to blue-gray hyperpigmentation, swirl-like formations on extremities and trunk; increases in intensity through 2nd yr of life, then remains stable or fades over many years Phase 4: streaked hypopigmented lesions	Eosinophilia CNS involvement (seizures, spasticity, ↓IQ) in 30% Spasticity Ophthalmic changes (strabismus, cataracts, optic atrophy, retinal damage) Alopecia Skeletal abnormalities Dental abnormalities

CNS, central nervous system; IQ, intelligence quotient.

with neurofibromatosis and tend to be larger and more numerous. Café-au-lait spots have also been associated with tuberous sclerosis, McCune–Albright syndrome, Turner syndrome, Bloom syndrome, ataxia-telangiectasia, Russell–Silver syndrome, Fanconi anemia, Gaucher disease, and Chédiak–Higashi syndrome.

Postinflammatory Hyperpigmentation

Postinflammatory hyperpigmentation is the most common cause of acquired hyperpigmentation in children. This pigmentary alteration can follow any inflammatory insult and is seen commonly after insect bites, acne, drug reactions, or other skin trauma. The clinical features are usually more striking in darkly pigmented individuals and often may be more pronounced than the original inflammatory lesions. The increased pigmentation usually resolves gradually over several months to years.

Acquired Melanocytic Nevi

Acquired melanocytic nevi arise during early childhood as 1- to 2-mm brown macules occurring most often on sun-exposed skin. These early flat nevi usually represent junctional nevi, in which nests of nevus cells are located along the dermoepidermal junction. Over time, some nevus cells may spread into the dermis, forming compound melanocytic nevi, which clinically appear somewhat larger and more papular than junctional nevi. In some nevi, the nevus cells may become restricted to the dermis. These intradermal nevi are usually fleshy or even pedunculated in appearance. Located usually on the head, neck, or upper trunk, these nevi may clinically resemble skin tags.

There is a gradual increase in the number of nevi during childhood and adolescence. The average individual acquires approximately 20-40 melanocytic nevi. This number peaks at 25 years of age. In general, fair-skinned persons have a greater number of nevi than do darkly pigmented persons.

Melanoma

Although melanomas are very rare in childhood, their incidence is increasing and can present with atypical features compared to the classic criteria of adult cases. The overall lifetime risk of melanoma in white persons in the United States is currently approximately 1 in 50 individuals. Melanoma can arise de novo or from preexisting congenital or acquired melanocytic nevi. Nevi should be observed for specific changes that may be indicative of malignancy. These alterations include:

1. Rapid growth of the nevi
2. Changes in texture, including nodularity, crusting, ulceration, bleeding, or loss of normal skin lines
3. Changes in pigmentation, especially the development of red, white, or blue hues
4. Border irregularity, especially notched or scalloped edges
5. Symptoms of itching, tenderness, or pain

In general, melanomas occur more frequently in light-pigmented individuals, in individuals with a high nevus count, and in those with a family history of melanoma. Melanomas usually appear as darkly pigmented nodular masses, often with color variegation, larger than 6 mm in diameter. They are often asymmetric and tend to have irregular borders and surface characteristics. Melanomas must be differentiated from other benign pigmented lesions, including congenital and acquired melanocytic nevi, blue nevi, Spitz nevi, vascular lesions such as hemangiomas and pyogenic granulomas, and pigmented lesions caused by trauma. Suspect lesions should be referred to a dermatologist.

The mortality rate of melanoma is estimated to be between 10% and 20%. The prognosis depends on the thickness of the lesion. For lesions less than 0.75 mm in depth, the prognosis is excellent. Surgical excision is the treatment of choice. Patients should be educated on the importance of photoprotection with broad-spectrum (ultraviolet A and B) sunscreens.

REACTIVE ERYTHEMAS

Morbilliform Drug Eruption

Morbilliform (measles-like) eruptions are the most common cutaneous manifestations of drug-induced eruptions in children. In this eruption, fine erythematous macules and papules are distributed over the trunk. The rash often spreads centripetally from the trunk to the extremities. Lesions may coalesce into large plaques and are usually pruritic. Morbilliform drug eruptions are often difficult to differentiate from viral exanthems. It is believed that concomitant viral infections may predispose susceptible individuals to develop an allergic morbilliform drug eruption.

Many agents, including common antibiotics, can trigger a morbilliform drug eruption. These medications include penicillins, sulfonamides, thiazides, sulfonylureas, nonsteroidal antiinflammatory drugs (NSAIDs), aromatic anticonvulsants, and gold. Treatment includes prompt diagnosis with discontinuation of the offending medication and symptomatic care with antihistamines and emollients. The rash may last an average of 1-2 weeks and sometimes progresses despite discontinuation of the offending medication. In rare cases for which discontinuation of the offending medication is not possible, continuation of the medication with close monitoring for the development of a more severe reaction may be considered as tolerance may develop with subsequent resolution of the eruption.

Although this eruption is usually self-limited, it may be an early manifestation of a more severe reaction such as **Stevens–Johnson syndrome (SJS)**, **toxic epidermal necrolysis (TEN)**, or **DRESS** (drug reaction with eosinophilia and systemic symptoms). Worrisome signs and symptoms of these life-threatening entities may include high fever, mucous membrane involvement, lymphadenopathy, and other systemic involvement. Signs of visceral involvement may include elevated hepatic transaminases, hematologic changes, or renal manifestations.

Fixed Drug Eruption

A fixed drug eruption is characterized by the sudden development of solitary or multiple well-demarcated, annular, erythematous, or hyperpigmented plaques. One of the distinguishing features is persistent postinflammatory hyperpigmentation, which may last weeks to months after the eruption subsides. The size of the lesion may vary, and the sites of predilection include the lips, trunk, legs, arms, and genitals. In some cases, the lesion may have a central bulla. Systemic symptoms are rare, although the patient may complain of local pruritus or a burning sensation.

Discontinuation of the offending medication causes a decrease in the intensity of the erythema and edema; repeated challenge with the same agent causes a reappearance of the lesion in the same location and may produce new lesions. Future outbreaks may be progressively more severe. The most common agents inducing fixed drug eruption include barbiturates, sulfonamides, tetracyclines, phenolphthalein, paracetamol, salicylates, NSAIDs, and even certain foods that contain yellow dye No. 5. Treatment is aimed at discontinuation and avoidance of the offending agent.

When numerous lesions occur, the condition may resemble erythema multiforma (EM), and the clinical history becomes paramount in establishing the diagnosis, particularly as there is significant histologic overlap.

HYPERSENSITIVITY REACTIONS

Urticaria

Urticaria is characterized by transient, edematous, erythematous, often annular wheals (Fig. 48.16). Central clearing may be seen but is not always present. The eruption is often sudden and pruritic, and each lesion rarely lasts longer than a few hours. Although the lesions are transient, they may continue to appear in new locations, and the entire urticarial episode may last hours to years.

Giant annular urticarial lesions are usually large, up to 20-30 cm, and polycyclic. A centrally bruised appearance is common within these lesions. Lesions may be of different sizes with bizarre shapes and patterns. Affected patients are often irritable and may have edema of the hands, eyelids, or feet. **Angioedema** is a form of urticaria that manifests with marked edema affecting deeper tissue planes and frequently involves the lips, dorsum of the hands or feet, scalp, scrotum, or periorbital tissue.

Giant annular lesions are often confused with the target lesions of EM. However, there are key features by which to differentiate the 2 disorders. Urticarial lesions, by definition, are transient and individual lesions last less than 24 hours, whereas lesions in EM are fixed and usually last 1-2 weeks in the same anatomic location. Outlining the lesions with a marker may help determine whether the lesions are fixed or transient. Another differentiating feature is that the lesions in EM usually have a dusky, necrotic center or blister. A skin biopsy may also aid in differentiating between the 2 disorders (Table 48.10).

Urticaria may be defined as either acute or chronic. **Acute** urticaria lasts less than 6 weeks. When hives continue to develop for more than 6 weeks, urticaria is considered to be chronic. Acute urticaria has numerous etiologies but is often caused by medications (particularly antibiotics), foods, infections, or environmental stimuli such as stinging insects (Table 48.11). The cause of **chronic** urticaria is typically difficult to determine and there is a broad list of etiologies (Table 48.11). A thorough history and a careful physical examination are the most helpful tools for determining the cause. There is no routine battery of laboratory tests that should be obtained for the evaluation of urticaria. However, evaluation for infection and other causes as suggested by the history and physical examination findings should be pursued.

Urticaria is usually self-limited. Treatment of pruritus consists of elimination of identifiable causes and administration of antihistamines. Hydroxyzine and diphenhydramine are often used but produce drowsiness. Nonsedating antihistamines are popular, but prescribers must be aware of potential interactions with concurrent medications. H_1- and H_2-blockers may be combined as needed. Systemic steroids are usually not indicated unless there is airway involvement or anaphylaxis.

FIGURE 48.16 Acute urticaria. Giant annular urticaria with large, bizarre shapes. (From Lee AD, Jorizzo JL. Acute urticaria. In: *Dermatologic Signs of Internal Disease*. 2009:53-62.)

Erythema Multiforme

Erythema multiforme (EM) is a distinct hypersensitivity eruption that has numerous implicated etiologies but is most often associated with HSV infection. Additional etiologies include other infections, and less commonly medications (Table 48.12). This self-limited condition lacks internal organ involvement and has minimal complications. EM may not be preceded by a clinically recognizable herpetic lesion, but PCR and in situ hybridization techniques have demonstrated HSV DNA and antigens in the lesions of EM.

The clinical picture in EM may be variable. The typical lesion in EM is an erythematous papule with a dusky, purpuric, or necrotic center (Fig. 48.17). The lesions are described as targetoid with concentric zones of color change: a dusky center or blister, a peripheral ring of pale edema, and an erythematous halo. Some lesions may not demonstrate the characteristic concentric changes, and the appearance of the lesions may be variable depending on the stage at which the lesion is visualized. Lesions start as red macules or urticaria and expand to form the target appearance. The Koebner phenomenon may be seen with lesions occurring in areas of injury. The lesions present abruptly and symmetrically. They are commonly distributed on the upper extremities and may appear on the dorsa of the hands, feet, palms, and soles (Table 48.10).

Erythema multiforme minor is often differentiated from *erythema multiforme major*. EM minor consists of mainly cutaneous lesions with 0-1 areas of mucosal involvement, typically orolabial. EM major has a similar cutaneous eruption with 2 or more sites of mucosal involvement with more extensive oral involvement. The mucous membranes most commonly involved are the conjunctiva and oral mucosa. Patients with EM major associated with *Mycoplasma* infection usually have

TABLE 48.10 Urticaria Versus Erythema Multiforme

Urticaria	Erythema Multiforme
Transient lesions: usually last for hours	Fixed lesions: lasting several days in the same location
Asymmetric, variable, and bizarre shapes	Usually round or oval
No epidermal change: may have central clearing	Epidermal change: usually central necrosis, duskiness, blistering or crusting
Continued appearance of new lesions	All lesions present within 1st few days
Associated edema of hands/feet, eyelids	No edema
Generalized	Acral distribution

TABLE 48.11 Etiology of Acute and Chronic Urticaria

Etiology of Acute Urticaria	
Foods	Eggs, milk, wheat, peanuts, tree nuts, soy, shellfish, fish, strawberries, food additives (direct mast cell degranulation)
Medications	Suspect all medications, even topical, nonprescription or homeopathic (examples include penicillin, aspirin, sulfonamides, codeine)
Insect stings	Hymenoptera (honeybee, yellow jacket, hornets, wasp, fire ants), biting insects (papular urticaria)
Infections	Bacterial (streptococcal pharyngitis, *Mycoplasma*, sinusitis); viral (hepatitis, mononucleosis [Epstein–Barr virus], coxsackieviruses A and B); fungal (dermatophytes, *Candida*); parasitic (*Ascaris, Ancylostoma, Echinococcus, Fasciola, Filaria, Schistosoma, Strongyloides, Toxocara, Trichinella*)
Contact allergy	Latex, pollen, animal saliva, nettle plants, caterpillars
Transfusion reactions	Blood, blood products, or IVIG administration
Etiology of Chronic Urticaria	
Idiopathic/ autoimmune	Approximately 30% of chronic urticaria cases are physical urticaria and 60–70% are idiopathic. Of the idiopathic cases approximately 35–40% have anti-IgE or anti-FcεRI (high-affinity IgE receptor α chain) autoantibodies (autoimmune chronic urticaria)
Physical	Dermatographism Cholinergic urticaria Cold urticaria Delayed pressure urticaria Solar urticaria Vibratory urticaria Aquagenic urticaria
Autoimmune diseases	Systemic lupus erythematosus Juvenile idiopathic arthritis Thyroid (Graves, Hashimoto) Celiac disease Inflammatory bowel disease Leukocytoclastic vasculitis
Autoinflammatory/ periodic fever syndromes	NOMID (neonatal-onset multisystem inflammatory disease) Muckle-Wells syndrome Familial cold autoinflammatory syndrome Cold urticaria, immunodeficiency, autoimmunity as a result of *PLCG2* deficiency
Neoplastic	Lymphoma Mastocytosis Leukemia
Angioedema	Hereditary angioedema (autosomal dominant inherited deficiency of C1-esterase inhibitor) Acquired angioedema Angiotensin-converting enzyme inhibitors

IVIG, intravenous immunoglobulin.
From Lasley MV, Kennedy MS, Altman LC. Urticaria and angioedema. In: Altman LC, Becker JW, Williams PV, eds. *Allergy in Primary Care*. Philadelphia: Saunders; 2000:232-234.

TABLE 48.12 Precipitating Factors in Erythema Multiforme-Like Reaction*

Infection (90% of cases)	Viral	**Herpes simplex virus (HSV-1, HSV-2)** Parapoxvirus Vaccinia (smallpox vaccine) Varicella-zoster virus Adenovirus Epstein–Barr virus Cytomegalovirus Hepatitis virus Coxsackievirus Parvovirus B19 Human immunodeficiency virus
	Bacterial	***Mycoplasma pneumoniae*** *Chlamydophila (formerly Chlamydia) psittaci* *Salmonella* *Mycobacterium tuberculosis*
	Fungal	*Histoplasma capsulatum* Dermatophytes
Medications		Nonsteroidal antiinflammatory drugs Sulfonamides Anticonvulsants Other antibiotics Allopurinol
Exposures (unusual)		Poison ivy
Systemic disease (rare)		Inflammatory bowel disease Lupus erythematosus Behçet disease

*Most common causes are bolded.

lesions in a predominantly acral distribution, and the eruption tends not to be as generalized as in SJS.

Histopathologic study of the lesions usually demonstrates a perivascular lymphocytic infiltrate with individual keratinocyte necrosis. There may be vacuolar degeneration of the basal layer, spongiosis, papillary dermal edema, and junctional or subepidermal cleft formation. In general, patients with EM major tend to have increased inflammation and decreased epidermal necrosis in comparison with patients with SJS.

The disease is usually self-limited and necessitates supportive treatment with analgesics, topical steroids, and antihistamines for symptomatic relief. Systemic steroids are not indicated. Lesions often heal within 1-3 weeks and may leave residual hyperpigmentation. In children with recurrent HSV-associated EM, antivirals may prove helpful. Antimicrobial treatment is warranted if *M. pneumoniae* is diagnosed.

Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis Complex

Most authorities consider SJS and TEN to be part of a continuum of disease. They are severe reactions most often elicited by medications with frequent internal organ involvement and an increased incidence of complications and sequelae. SJS and TEN differ in the severity of body surface involvement. In SJS, there is less than 10% body surface involvement; with 10-30% body surface involvement, the condition is labeled *SJS/TEN overlap*; and TEN refers to cases with more than 30% body surface involvement.

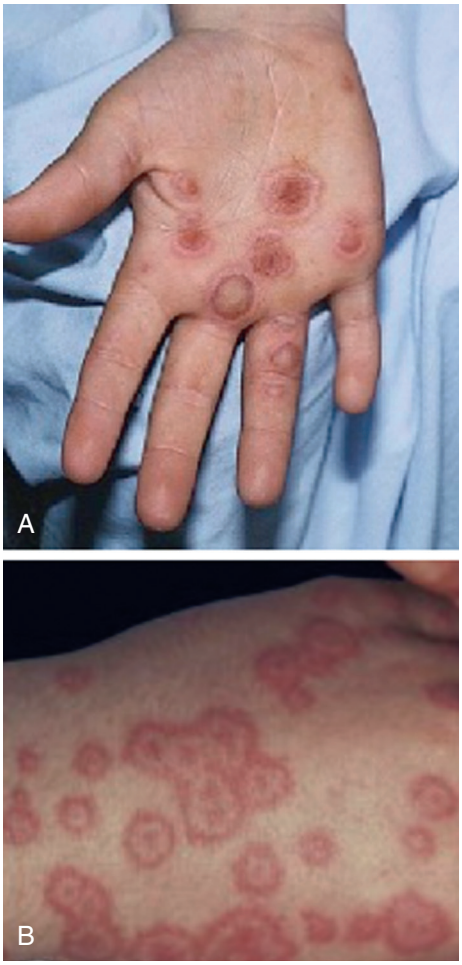

FIGURE 48.17 Target lesions of erythema multiforme with characteristic dusky centers on the palms *(A)* and dorsum of the hand *(B)*. (*A,* From Kliegman RM, et al. *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2015:3142; *B,* From Bolognia JL, et al. Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. In: Bolognia JL, et al. *Dermatology Essentials*. Elsevier; 2014: 140-150).

SJS is a unique hypersensitivity reaction. Although many factors have been implicated in the origin of SJS/TEN, medications are the most common causes in children. In particular, sulfonamides, anticonvulsants (phenytoin, carbamazepine, lamotrigine, phenobarbital), and NSAIDs are cited as some of the most common triggers. The nature of the reaction is not clearly understood, but it is believed to be a cytotoxic immune reaction aimed at the destruction of keratinocytes expressing drug-related antigens. In children, infections are also associated with SJS. Classifications such as ***Mycoplasma pneumoniae*-associated mucositis** have been used when children have documented *M. pneumoniae* infection with predominant mucosal involvement and limited SJS/TEN cutaneous involvement.

SJS usually begins with a nonspecific prodrome followed by generalized blisters, erosions, erythema, and hemorrhagic crusting of mucous membranes of the mouth, nose, eyes, and/or genitalia as well as the trunk and extremities (Fig. 48.18). At least 2 mucous membranes must be involved to establish this diagnosis. Lesions are usually roundish, irregularly shaped, and less targetoid with numerous erythematous to violaceous macules and papules with dusky centers. The macules may then quickly progress to bullae with skin necrosis. Involvement usually begins more proximally, with a predilection for the face, chest, and neck. There is a striking tendency for coalescence, reminiscent of a diffuse erythema. The eruption in SJS is more generalized and tends to be more truncally distributed than that of EM major.

Histopathologic findings in SJS are characterized by prominent epidermal necrosis with minimal inflammation. Epidermal injury and subepidermal separation may be observed. Spongiosis and dermal edema are usually absent.

TEN is the most severe hypersensitivity reaction, with an estimated mortality rate of 5-20%. Patients experience tender erythema of the skin that progresses rapidly to blistering and subsequent denudation. Malaise and prolonged fever often accompany these skin changes. Sheets of necrotic epidermis may slough off and leave denuded patches in areas of pressure, such as the back and shoulders. Mucous membranes are typically involved, and lesions are similar to those seen in SJS with flaccid, hemorrhagic blisters. In severe cases of TEN, sheets of necrotic epidermis may include skin appendages such as fingernails and toenails.

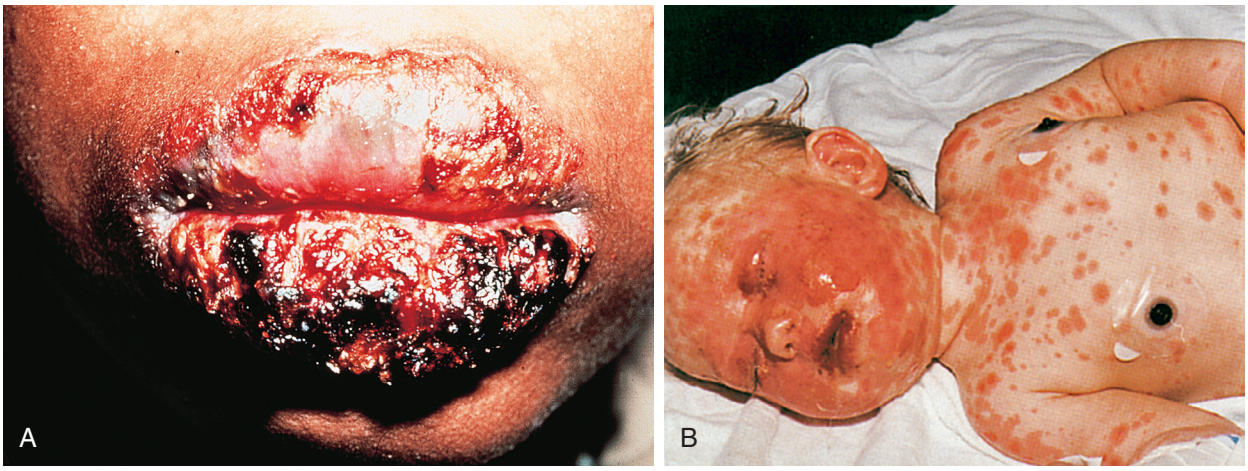

FIGURE 48.18 *A,* Erosions and crusting of the lips in Stevens–Johnson syndrome. *B,* Widespread blistering and erosions of the skin and mucous membranes. (From Vesicopustular eruptions. In: Cohen BA, ed. *Pediatric Dermatology*. Philadelphia: Saunders; 2013.)

Systemic signs such as fever, weakness, and arthralgia occur commonly. SJS/TEN may be complicated by dehydration, electrolyte imbalance, and bacterial infection or sepsis. TEN is often accompanied by a systemic toxic state with increased morbidity and mortality. Generalized lymphadenopathy and hepatosplenomegaly may be present. Internal organ involvement, manifesting as tracheal and bronchial symptoms, pneumonitis, hepatitis, acute kidney injury, myocarditis, confusion, and coma, can be prominent in TEN.

Supportive therapy is the mainstay of treatment. Some physicians believe that systemic corticosteroids are helpful in SJS/TEN, although this remains a topic of controversy as studies have not shown it to be efficacious with reports of increased morbidity and mortality. Removal of the offending medication or triggering factor is of utmost importance. Careful *ophthalmologic* monitoring is necessary because corneal scarring may lead to blindness. Affected patients are cared for as if they sustained a severe burn; fluid and electrolyte balance, temperature control, protein loss, and prevention of infection are serious concerns. Affected children usually require initial management in a pediatric intensive care unit or burn center. Intravenous immunoglobulin (IVIG) may be considered because its use has shown some improved outcomes.

With meticulous supportive care, most children survive; however, there is a high morbidity. Poor prognostic factors include neutropenia, impaired renal function, and extensive skin lesions. Recovery is slow; skin lesions require several weeks to heal, depending on the extent of involvement. Scarring and stricture formation may occur at mucosal sites, as well as postinflammatory hypo- or hyperpigmentation.

Allergic Contact Dermatitis

Allergic contact dermatitis is an example of a type IV delayed hypersensitivity reaction. This T cell–mediated immune response occurs after contact of the responsible antigen with the skin. The reaction becomes apparent 7-14 days after the 1st antigenic exposure. Future contact with the same antigen provokes an inflammatory response within hours to 1-3 days.

Acute contact dermatitis is usually characterized by the sudden onset of erythema, vesiculation, edema, and intense pruritus. Chronic contact dermatitis results in the development of lichenification, scaling, and hyperpigmentation and can be complicated by secondary bacterial infection. **Poison ivy** is the most common cause of allergic contact dermatitis (*Rhus* dermatitis) in the United States. Direct contact of the skin with the sap of poison ivy, oak, or sumac may result in dermatitis. Contact with clothing or pets that have been exposed to the plant resin or smoke from the fire of such plants being burned are other forms of exposure. The eruption is usually seen as linear vesicles and papules or plaques. The spread to body sites is caused by exposure to the plant resin, not by the blister fluid. Therefore, scratching affected skin or contact with affected individuals should not result in spreading of the eruption. Other common forms of allergic contact dermatitis result from exposure to cosmetics, fragrances, hair dyes, and nickel.

Nickel dermatitis often results from prolonged contact with the nickel in jewelry or belt buckles (Fig. 48.19). The eczematous changes are usually localized to the sites of contact, including the earlobes, neckline, wrists, and waistline, although generalized lichenoid papular id reactions have been described. The diagnosis of contact dermatitis can usually be determined from history and clinical examination findings. The distribution of linear or well-demarcated areas may be helpful in confirming the diagnosis. When allergic contact dermatitis is suspected but the responsible agent is unclear, patch testing with a selected group of antigens may provide useful information. Prevention of future exposure to inciting antigens is necessary.

FIGURE 48.19 Nickel contact dermatitis. Wrist lesions in the distribution of the nickel bracelet clasp. (From Cohen BA, Davis HW, Gehris RP. Dermatology. In: Zitelli BJ, et al, eds. *Atlas of Pediatric Physical Diagnosis*. Philadelphia: Saunders; 2012:299-368.)

Usually, treatment with topical corticosteroids, emollients, and antihistamines is sufficient to control the eruption. However, widespread dermatitis or severe involvement of the face may necessitate administration of systemic corticosteroids. Wet compresses with aluminum acetate aid in the drying of weeping, vesicular lesions and provide symptomatic relief.

BULLOUS LESIONS

Staphylococcal Scalded Skin Syndrome

Staphylococcal scalded skin syndrome (SSSS) (Table 48.13) is an exfoliative dermatitis produced by staphylococcal epidermolytic toxins associated with *S. aureus* phage group II. The condition is most common in children younger than 5 years. The condition may be localized, as in the case of bullous impetigo, or become more generalized as the result of hematogenous spread of the epidermolytic toxin from localized sites of infection. The diagnosis of SSSS should be considered in children with generalized tender erythema. The onset of the erythema may be preceded by fever, skin tenderness, malaise, and irritability. The initial sites of involvement are the flexural (neck, groin, and axillae) and periorificial skin. Circumoral erythema with radial crusting and fissuring around the mouth, eyes, and nose is characteristic (Fig. 48.20). A positive **Nikolsky sign**, the ability to laterally spread a blister or slough the skin with the application of light tangential pressure, is seen in most cases. Flaccid bullae, sheets of desquamating skin, or moist red erosions may be present, with the desquamation phase typically beginning 2-5 days after the onset of erythema. Healing without residual scarring occurs within 1-2 weeks. Patients may have conjunctivitis and superficial lip erosions, but in contrast to SJS or TEN, the mucosal surfaces are usually unaffected. The diagnosis is usually established from the clinical presentation. *S. aureus* may be isolated from a minority of blood cultures. The organism is more likely to be isolated from distant sites, such as the nares, throat, and conjunctivae, than from the bullae themselves. In some children, the toxin may be produced by an underlying infection, such as pneumonia, osteomyelitis, or septic arthritis.

Oral antibiotics may be indicated in localized SSSS. Children with widespread involvement usually require hospitalization and treatment with intravenous antistaphylococcal antibiotics with antibiotic choice

TABLE 48.13 Childhood Skin Eruptions Categorized by Etiology

Entity	Clinical Clues
I. Hereditary	
A. Epidermolysis bullosa (AR, AD)	Bullae at birth in more severe forms Localized or widespread Dystrophic nails in some forms Bullae induced by trauma, friction; may occur spontaneously Mucosal involvement in severe forms
B. Incontinentia pigmenti (X-linked recessive)	Crops of blisters at birth or early infancy Often linear May have coexistent streaky hyperpigmentation Eosinophilia Associated CNS, dental, ocular, cardiac, skeletal abnormalities Girls affected; boys may have Klinefelter syndrome
C. Porphyria cutanea tarda (AD or acquired)	On dorsal hands, other sun-exposed skin Heal with milia formation Increased fragility of skin Hypertrichosis
D. Epidermolytic hyperkeratosis (bullous congenital ichthyosiform erythroderma) (AD)	Bullae within the 1st wk after birth Verruciform scales on flexural surfaces Hyperkeratosis after the 3rd mo Collodion membrane at birth in some cases
II. Autoimmune	
A. Linear IgA disease (chronic bullous disease of childhood)	Onset usually before the age of 6 yr Sites of predilection: perioral, periocular, lower abdomen, buttocks, anogenital region Annular or rosette configuration of tense blisters: "cluster of jewels" Mucous membranes commonly involved Spontaneous remission DIF shows linear deposits of IgA at DEJ
B. Bullous pemphigoid	Large, tense subepidermal bullae Lower abdomen, thighs, face, flexural areas Oral lesions common; rare in children DIF shows linear deposits of C3 and IgG at DEJ
C. Pemphigus vulgaris	Flaccid bullae, persistent erosions Seborrheic distribution Mucosal involvement very common, usually the initial manifestation Positive Nikolsky sign DIF with intercellular (desmosomal) deposits of IgG, C3
D. Pemphigus foliaceus	Small flaccid bullae or shallow erosions with scaling, crusting Back, scalp, face, upper chest, abdomen; photodistribution Oral lesions uncommon May resemble a generalized exfoliative dermatitis DIF shows intercellular deposition of IgG, C3 in superficial epidermis
E. Dermatitis herpetiformis	Intensely pruritic Associated with Celiac disease Extensor surfaces of elbows, knees, buttocks, shoulders, neck Hemorrhagic lesions on palms and soles DIF shows granular deposition of IgA in dermal papillae
III. Infectious	
A. Bacterial	
1. Staphylococcal scalded skin syndrome (SSSS)	Generalized, tender erythema Positive Nikolsky sign Occasionally associated with underlying infection such as osteomyelitis, septic arthritis, pneumonia Desquamation, moist erosions observed More common in children <5 yr of age
2. Bullous impetigo	Localized SSSS Transparent flaccid bullae initially, then moist erythematous shallow erosions once bullae disrupted Covered sites of trunk and perineum likely, can occur on face and extremities
B. Viral	
1. Herpes simplex virus	Grouped vesicles on erythematous base May be recurrent at the same site: lips, eyes, cheeks, hands Reactivated by fever, sunlight, trauma, stress Positive Tzanck smear, herpes PCR
2. Varicella	Crops of vesicles on erythematous base: "dewdrops on rose petal" Highly contagious Multiple stages of lesions may be present simultaneously Associated with fever Positive Tzanck smear, varicella-zoster PCR
3. Herpes zoster	Grouped vesicles on erythematous base, limited to 1 or several adjacent dermatomes Usually unilateral Burning, pruritus Positive Tzanck smear, varicella-zoster PCR Thoracic dermatomes most commonly involved in children
4. Hand-foot-mouth syndrome (coxsackievirus)	Prodrome of fever, anorexia, sore throat Oval blisters in acral distribution, usually few in number classically, but more generalized eruptions or concentration in the diaper area may be seen Shallow oval oral lesions on erythematous base Highly infectious Peak incidence: late summer, fall

Continued

TABLE 48.13 Childhood Skin Eruptions Categorized by Etiology—cont'd

Entity	Clinical Clues
C. Fungal	
1. Tinea corporis	Annular scaly plaques, usually with central clearing Pustule formation common Positive KOH, fungal culture Vesicles and erosions on instep
2. Tinea pedis	Interdigital fissuring Positive KOH, fungal culture Burrow formation
D. Scabies	Interdigital web spaces, genitalia, ankles, lower abdomen, wrist Intensely pruritic; vesicles on palms and soles Very contagious Positive scabies preparation
IV. Hypersensitivity	
A. Erythema multiforme (EM) major (Stevens–Johnson syndrome [SJS])	Prodrome of fever, headache, malaise, sore throat, cough, vomiting, diarrhea EM major with involvement of 2 mucosal surfaces; hemorrhagic crusts on lips usually present Target lesions progress from central vesiculation to extensive epidermal necrosis; sheets of denuded skin may be present SJS has <10% body surface involvement Associated with infection (e.g. HSV, *Mycoplasma*), medications
B. Toxic epidermal necrolysis	Possible extension of SJS involving >30% of body surface Severe exfoliative dermatitis Affects older children, adults Frequently related to medications (e.g., sulfonamides, anticonvulsants) Positive Nikolsky sign
V. Extrinsic	
A. Contact dermatitis	Irritant or allergic Distribution dependent on the irritant/allergen Distribution helpful in establishing diagnosis
B. Insect bites	Occur occasionally after flea or mosquito bites May be hemorrhagic bullae Often in linear or irregular clusters Very pruritic
C. Burns	Irregular shapes and configurations May be suggestive of abuse Vary from 1st–3rd degree; bullae with 2nd and 3rd degree
D. Friction	Usually on acral surfaces May be related to footwear Often activity related
VI. Miscellaneous	
A. Urticaria pigmentosa	Positive Darier sign Coexistent pigmented lesions Usually manifests during infancy Dermatographism commonly seen
B. Miliaria crystallina	Seen in the setting of fever or overheating Clear, 1–2-mm superficial vesicles occurring in crops, rupturing spontaneously Intertriginous areas, especially the neck and axillae

AD, autosomal dominant; AR, autosomal recessive; C, complement; CNS, central nervous system; DEJ, dermoepidermal junction; DIF, direct immunofluorescence; HSV, herpes simplex virus; IgA and IgG, immunoglobulins A and G; KOH, potassium hydroxide; PCR, polymerase chain reaction.

to be based on local resistance patterns given the emergence of MRSA. Clindamycin may be added to inhibit bacterial protein (toxin) synthesis. Supportive management should be undertaken with close monitoring for fluid and electrolyte imbalances, signs of sepsis, or underlying focal infections. The skin should be handled very carefully. Aluminum acetate wraps may be used with skin care and adhesive bandages should be avoided. Application of an emollient in the desquamation phase may help lubricate the skin and reduce discomfort. Pain control is frequently necessary. The prognosis is good in immunocompetent children.

Epidermolysis Bullosa

Epidermolysis bullosa is a heterogeneous group of inherited blistering disorders characterized by spontaneous and posttraumatic bulla formation. It is estimated to occur in approximately 1 in 50,000 births; the severe variants are seen less frequently. There are several distinct variants that are distinguished by the inheritance pattern, cutaneous manifestations, histologic findings, and ultrastructural abnormalities.

In **epidermolysis bullosa simplex (EBS)**, the level of blister cleavage is intraepidermal (see Fig. 48.3). This form results from a defect in the basal cell keratins 5 and 14, which have been localized to chromosomes 12 and 17, respectively, and are necessary for epidermal integrity. Most of the simplex forms are relatively mild and are autosomal dominant conditions. Bullae formation may be localized or generalized, but it is usually worst in areas of frequent trauma, such as the hands, feet, and joints.

In the **localized form of EBS** (formerly *Weber–Cockayne*), blisters are usually confined to the hands and feet and develop after significant friction or trauma. This form may not become apparent until adolescence or adulthood and may manifest after strenuous activities such as hiking, military training, or golf. There are also generalized forms of EBS in which the bullae are much more extensive and usually apparent at birth and during early infancy. In general, the various EBS subtypes are characterized by bullae that heal without scarring, mild or no nail changes, and minimal mucosal involvement. There are usually no associated extracutaneous manifestations.

In **junctional epidermolysis bullosa (JEB)**, the cleavage plane occurs at the level of the lamina lucida of the dermoepidermal junction. The junctional form is transmitted in an autosomal recessive mode of inheritance. There is a wide spectrum of subtypes, including

FIGURE 48.20 Staphylococcal scalded skin syndrome. Perioral crusting and generalized tender erythematous skin with areas of desquamation. (From Vesicopustular eruptions. In: Cohen BA, ed. *Pediatric Dermatology*. Philadelphia: Saunders; 2013:104-125.)

Herlitz and non-Herlitz types, ranging from moderate involvement to a more severe, potentially fatal variant. The majority of JEB subtypes results from defects in the protein laminin 5, which is localized to the anchoring filaments, fibrillar structures within the lamina lucida. Other JEB variants occur as the result of mutations in collagen XVII, an important component of the hemidesmosome. There are subsets of epidermolysis bullosa associated with pyloric atresia classified under both EBS and JEB resulting from altered expression of plectin and $\alpha_6\beta_4$ integrin, respectively. Ureterovesical obstruction may produce recurrent urinary tract infections. Most forms are clinically apparent at birth.

In general, there are widespread bullae that heal with atrophy, not scarring. Dysplastic nails, severe oral lesions, and enamel dysplasia are usually seen. The most severe variant has been referred to as JEB, **generalized severe** (formerly junctional epidermolysis bullosa, Herlitz type). Often fatal by 2 years of age, this variant is characterized by exuberant granulation tissue on the face and around the mouth. Extracutaneous manifestations include pyloric atresia, chronic anemia, and laryngeal involvement that often necessitate tracheostomy.

In **dystrophic epidermolysis bullosa (DEB)**, tissue separation occurs below the dermoepidermal junction at the level of the lamina densa. The lamina densa is made up of anchoring fibrils composed of type VII collagen. Individuals with the dystrophic form have qualitative or quantitative abnormalities caused by mutations in the gene for type VII collagen. DEB is further separated into variants that may be inherited in either an autosomal dominant or recessive pattern. They are usually apparent at birth; there is a wide array of clinical manifestations, but the condition is generally characterized by nail dystrophy and generalized blisters that heal with scarring and milia formation. In the more severe recessive dystrophic form, affected individuals usually have severe interdigital scarring, which results in syndactyly between fingers and eventual encasement of fingers and thumbs known as the mitten deformity. Severe mucosal involvement is a constant feature of recessive DEB, and esophageal stenosis and obstruction are significant causes of morbidity and mortality. Chronic malnutrition, growth failure, and increased susceptibility to infection may lead to sepsis and death in children with this epidermolysis bullosa subset. Affected patients have multiple extracutaneous manifestations, as well as a very high frequency of aggressive and recurrent squamous cell carcinomas. The dominant dystrophic forms are usually more localized and have a better prognosis than does recessive DEB.

It is usually impossible to distinguish the variants of epidermolysis bullosa on the basis of clinical manifestations alone; skin biopsies are generally necessary. Immunofluorescence antigen mapping (IFM) and/or transmission electron microscopy on newly induced blisters are used to begin to classify epidermolysis bullosa subtypes. Monoclonal antibodies directed toward the skin basement membrane zone and epidermal antigens may provide further data. Mutational analysis directed by the results of IFM is recommended for the most precise subclassification.

Treatment modalities are dependent on the severity of the particular variant. In general, the emphasis is on wound care, prevention of infection, and prevention of mechanical factors likely to induce blister formation. Topical antibiotics and nonadhesive semipermeable dressings may be necessary for recalcitrant wounds. All adhesives should be avoided. In patients with the severe variants of epidermolysis bullosa, a multidisciplinary approach is imperative and should focus on preventive care. All affected patients should undergo genetic counseling.

PURPURA AND PETECHIAE

Purpura results from leakage of blood from vessels into the skin or mucous membranes associated with diverse causes (Table 48.14). Purpuric lesions do not blanch when pressure is applied. Small lesions that are pinpoint-sized or a few millimeters in diameter are called **petechiae**. Large lesions may be referred to as *ecchymoses*. Raised or palpable purpura is diagnostic of vasculitis and can be seen in conditions such as Henoch–Schönlein purpura (HSP), lupus erythematosus, and Rocky Mountain spotted fever. Inflammation and destruction of blood vessel walls are responsible for the raised quality of these lesions. Nonpalpable purpura can be seen with platelet abnormalities, leukemia, and other thrombocytopenic conditions (see Chapter 38), capillaritis (pigmented purpuras), scurvy, viral exanthems, and physical exertion. Petechiae on the upper body (above the nipple line) can result from crying, vomiting, or coughing. Careful clinical examination is important for detecting these lesions and establishing a proper diagnosis.

Henoch–Schönlein Purpura

HSP is a small-vessel vasculitis that usually occurs in children and young adults with most cases occurring between 3 and 10 years (Table 48.15). HSP is the most common vasculitis of childhood. It is a leukocytoclastic vasculitis and is characterized by perivascular immunoglobulin A deposition in affected tissues. The skin, joints, kidneys, and gastrointestinal tract can be involved. Given the seasonality and frequency of preceding upper respiratory infections, bacterial (such as streptococcal infections) and viral etiologies are suspected, although the precise nature of the pathogenesis is unclear.

The classic presentation is that of **nonthrombocytopenic palpable purpura** predominately on the lower extremities and buttocks (Fig. 48.21). However, urticarial and ecchymotic lesions may appear as well. Hemorrhagic bullae and ulcerations can also be present. Edema of the hands, feet, genitalia, and face is common. Systemic involvement is present in approximately two-thirds of affected patients with abdominal pain from bowel angina and arthritis or arthralgias occurring as the most common extracutaneous symptoms. Arthritis most frequently affects the lower extremities; joint effusions are rare.

TABLE 48.14 Causes of Purpura

Infections
Rocky Mountain spotted fever
Sepsis
Bacterial endocarditis
Streptococcal infection
Gonococcemia
Meningococcemia
Hepatitis
Atypical measles
Varicella
Parvovirus 19
Epstein–Barr virus

Collagen Vascular Diseases*
Lupus erythematosus
Dermatomyositis
Rheumatoid arthritis
Ehlers–Danlos syndrome

Hematologic Disorders
Idiopathic thrombocytopenic purpura
Acute lymphocytic leukemia
Aplastic anemia
DIC
Thrombotic thrombocytopenic purpura
Clotting factor deficiencies
Warfarin or heparin use
Malignancy

Medications
Aspirin
Corticosteroids
Penicillins
Sulfonamides
Thiazides
Antiepileptics (phenytoin, valproic acid)

Vasculitis
Henoch–Schönlein purpura
Polyarteritis nodosa
Polyangiitis with granulomatosis
Cryoglobulinemia

Other
Scurvy
Trauma

*Usually livedo pattern.
DIC, disseminated intravascular coagulation.

Gastrointestinal features may include vomiting, colicky abdominal pain, nausea, diarrhea, bleeding, and, in rare cases, intussusception or bowel perforation (see Chapter 10). Renal involvement is the most serious complication and can be manifested by hematuria and/or hypertension (see Chapter 20). Patients with HSP require close monitoring for nephritis as renal manifestations can develop several months after diagnosis.

The diagnosis of HSP is usually made on clinical grounds, but a skin biopsy confirms the presence of leukocytoclastic vasculitis in atypical or severe cases. Direct immunofluorescence staining of the skin biopsy specimen reveals immunoglobulin A deposition around the blood vessels in the superficial dermis (Table 48.3).

Treatment includes supportive care and analgesics for joint pains. Systemic corticosteroids may be indicated when there is significant gastrointestinal or joint pain as well as renal involvement, but this treatment remains controversial as it does not alter the renal prognosis. Systemic corticosteroids are generally not indicated for skin involvement alone. The clinical course is characterized by acute onset of cutaneous lesions, often associated with fever and malaise. Systemic symptoms usually last for several weeks. Recurrences are common, but spontaneous resolution almost always occurs. The prognosis is excellent, with the primary factor being the extent of renal involvement. Mortality is rare and is usually caused by chronic renal disease.

HAIR LOSS

Alopecia (hair loss) is the most common hair abnormality seen in children. Hair loss can have a number of presentations ranging from focal patches to diffuse thinning. An accurate history alone can often lead to a presumptive diagnosis. Information regarding duration of loss, rate of shedding, medications, trauma, family history of hair disorders, symptoms such as pruritus or burning, breakage, and hair care is particularly important. The scalp should be examined for the pattern and distribution of hair loss, erythema, scaling, scarring, pustules, and crusts. Abnormal or broken hairs, as well as texture, length, and color should be noted. Associated abnormalities of the teeth, nails, and sweat glands may occur. Hair pulls (gentle pulling on small tufts of hair) and microscopic examination of removed hairs should be performed. Appropriate tests (KOH, fungal culture, scalp biopsy) may be necessary to confirm the clinical suspicions.

Classification of alopecia is somewhat arbitrary, but it is helpful to determine whether hair loss is acquired or congenital and localized or diffuse. Congenital alopecia usually results from aplasia cutis, intrauterine injury, or nevus sebaceous. Five common disorders responsible for most cases of childhood hair loss are (1) alopecia areata, (2) tinea capitis, (3) traction alopecia, (4) trichotillomania, and (5) telogen effluvium.

Alopecia Areata

Alopecia areata is a common disorder that affects all ages, particularly children. Although several hypotheses have been proposed, it is generally thought to be an autoimmune condition linked to specific genetic mutations. There is a family history of alopecia areata for approximately 20% of affected individuals. Clinically, there is acute onset of hair loss that is occasionally preceded by burning or itching of the scalp. In most cases, well-demarcated, localized areas of alopecia result, and the scalp is usually normal without epidermal changes. The **exclamation point hairs** are pathognomonic and are caused by breakage of abnormally growing hairs. Exclamation point hairs, when pulled out, appear as a tapered or attenuated bulb secondary to atrophy of that portion. When the disease is active, dystrophic anagen hairs can be easily pulled from the periphery of lesions. Nail pitting, often seen in rows, is seen in some cases. Factors that portend a poor prognosis for regrowth include extensive loss, early onset, nail involvement, atopic background, and an ophiasis pattern (involvement of the temporal and occipital hairline).

Treatment consists of topical, intralesional corticosteroids; topical minoxidil; anthralin; and sensitization to contact allergens. Other supportive measures include camouflage, hairpieces, and support groups. In some cases, hair regrows without medical intervention. Although the course is unpredictable, about half of affected patients have a recurrence.

TABLE 48.15 Types of Vasculitis and Associated Skin Lesions

Type of Vasculitis	Blood Vessels Involved	Type of Skin Lesion
Leukocytoclastic or hypersensitivity angiitis: Henoch–Schönlein purpura, cryoglobulinemia, hypocomplementemic vasculitis	Dermal capillaries, venules, and occasional small muscular arteries in internal organs	*Purpuric papules*, hemorrhagic bullae, cutaneous infarctions
Rheumatic vasculitis: systemic lupus erythematosus, rheumatoid vasculitis	Dermal capillaries, venules, and small muscular arteries in internal organs	*Purpuric papules*: ulcerative nodules; splinter hemorrhages; periungual telangiectasia and infarctions
Granulomatous vasculitis Churg–Strauss allergic granulomatous angiitis	Dermal small and larger muscular arteries and medium muscular arteries in subcutaneous tissue and other organs	Erythematous, *purpuric*, and ulcerated nodules, plaques, and *purpura*
Granulomatosis with polyangiitis (Wegener)	Small venules, arterioles of dermis, and small muscular arteries	Ulcerative nodules, peripheral gangrene
Periarteritis: classic type limited to skin and muscle	Small and medium muscular arteries in deep dermis, subcutaneous tissue, and muscle	Deep subcutaneous nodules with ulceration; livedo reticularis; *ecchymoses*
Giant cell arteritis: temporal arteritis, polymyalgia rheumatica, Takayasu disease	Medium muscular arteries and larger arteries	Skin necrosis over scalp

From Wyngaarden JB, Smith LH, eds. *Cecil Textbook of Medicine*. 18th ed. Philadelphia: WB Saunders; 1988.

FIGURE 48.21 Henoch–Schönlein purpura. Palpable purpura in the lower extremities. (From Kliegman RM, et al. Vasculitis syndromes. In: Kliegman RM, *Nelson Textbook of Pediatrics*. 20th ed. Philadelphia: Elsevier; 2015:1217.)

Tinea Capitis

Tinea capitis (**ringworm**) is another common cause of alopecia in children, although it may not always be associated with hair loss or breakage. The "seborrheic" type of tinea capitis is manifested by diffuse scaling without scalp inflammation. Alopecia is often not noted, but broken hairs are occasionally present. This type of alopecia is frequently misdiagnosed as dandruff. Tinea capitis can also manifest as localized scaly patches, kerions, and "black-dot" patches. This latter type features hairs that have broken at the surface of the scalp, resulting in a black-dot appearance. **Kerions** are boggy, inflammatory plaques on the scalp that are caused by hypersensitivity to the offending dermatophyte (Fig. 48.22). Pustules and drainage are common, but the

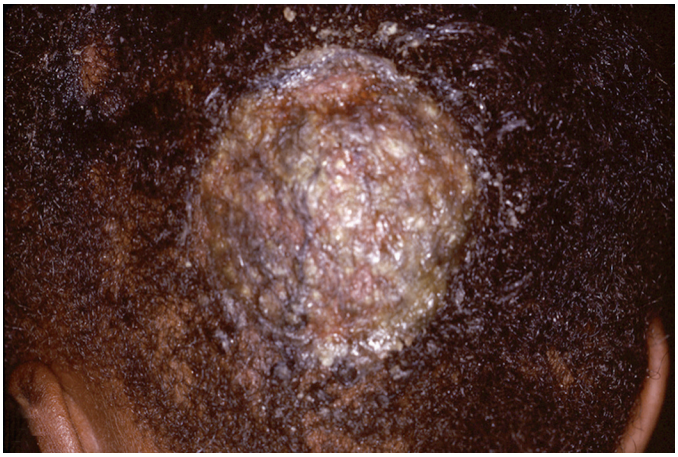

FIGURE 48.22 Boggy, purulent mass of the scalp typical of kerions. (From Kliegman RM, et al. Cutaneous fungal infections. In: Kliegman RM, *Nelson textbook of pediatrics*. 20th ed. Philadelphia: Elsevier; 2015:3215.)

purulent material is often sterile. Cervical lymphadenopathy, fever, and elevated white blood cell counts may accompany kerions. The differential diagnosis of tinea capitis includes psoriasis, alopecia areata, trichotillomania, folliculitis, and seborrheic dermatitis.

The most common etiologic agent of tinea capitis is *Trichophyton tonsurans*, a dermatophyte that produces endothrix infections. Because spores are not present on the surfaces of the hair shafts, Wood lamp examination is not useful. If, the infection is caused by *Microsporum canis* or another dermatophyte that produces an ectothrix infection, Wood lamp examination results in positive fluorescence (Table 48.2). Fungal cultures should be performed in all suspected cases of tinea capitis. Fungal culture can be performed with a standard toothbrush and Petri dish. KOH preparations can be useful if positive, but false-negative results are common. Some children may be asymptomatic carriers.

Traditional therapy consists of oral griseofulvin for 6-8 weeks. Selenium sulfide 2.5% shampoo or 2% ketoconazole shampoo should be used to decrease surface spores and reduce spread to other individuals. On occasion, there is a secondary bacterial infection that necessitates antibiotic therapy. Kerions typically respond to griseofulvin; but in

severe cases, systemic corticosteroids may be added to decrease inflammation and reduce the risk of scarring. Antifungal agents that may be useful include oral fluconazole, itraconazole, and terbinafine. Incision and drainage are not indicated. A follow-up fungal culture may be obtained to confirm adequacy of treatment.

Traction Alopecia

Traction alopecia is seen in individuals whose hair is tightly braided or pulled into ponytails or cornrows for long periods of time. Chronic tension on the hair shafts leads to breakage and gradual hair loss. Damaging hairstyle procedures such as straightening and waving may also result in hair breakage if performed improperly. On clinical examination, the clinician sees linear areas of hair loss at the part line or throughout the scalp. The alopecia is reversible in most cases. However, if the traction is maintained for years, the alopecia may become permanent secondary to scarring. Treatment is aimed at avoiding all tension-producing trauma. The patient should be advised to stop all hair chemical procedures, wear loose styles with no braids, avoid wearing heavy objects in the hair or ponytails, and handle hair as gently as possible.

Trichotillomania

In trichotillomania, individuals pull, break, or twist hair from the scalp, eyebrows, eyelashes, and/or pubic hair. In younger children, this form of hair pulling is usually a harmless habit that is outgrown. Trichotillomania in older children and adolescents may represent a more serious psychologic problem with a less favorable prognosis. Psychiatric assistance may be required, and the disorder may be refractory to treatment. On physical examination, there are hairs of varying length in bizarre, often geometric, patterns. The occiput is often spared. Hairs have blunt tips because of mechanical breakage. Scalp biopsy may be necessary if the diagnosis is unclear. Treatment is aimed at identifying underlying psychologic stressors. Supportive therapy and psychologic and/or psychiatric evaluation are usually needed.

Telogen Effluvium

Telogen effluvium is characterized by excessive shedding of telogen (resting) hairs. This may result from medications, febrile illness, crash diets, parturition, surgical procedures or anesthesia, endocrine disorders, or severe emotional stress. A large number of growing hairs enters the resting phase, resulting in a 3-fold to 5-fold increase in the number of resting hairs. Gradually, these numerous telogen hairs are shed over 6-24 weeks. Affected individuals notice increased hair loss and sparser scalp hair 2-4 months after exposure to the inciting factor. The prognosis for this type of diffuse alopecia is excellent. Patient education is important, as is reassurance that regrowth can be expected within approximately 6 months. No treatment is indicated.

INFECTIONS AND INFESTATIONS

Impetigo

Impetigo is the most frequently diagnosed bacterial skin infection. It is a contagious superficial skin infection, occurring most often in infancy and early childhood. The 2 major pathogens, *S. aureus* and group A β-hemolytic streptococcus *(Streptococcus pyogenes)*, can cause lesions at any body site.

Nonbullous Impetigo

Nonbullous impetigo accounts for the majority of cases and is secondary to infection with either of the aforementioned pathogens. The lesions of nonbullous impetigo caused by either organism are indistinguishable. The lesions typically arise on the face or extremities after trauma such as insect bites, cuts, and abrasions, or after varicella infection. The primary lesion is usually a vesicle or a pustule that develops secondary changes of honey-colored crusting, the clinical hallmark of this condition. In general, the lesions are smaller than 2 cm and may be single or multiple (Fig. 48.23). Although the lesions are generally asymptomatic with little surrounding erythema, regional lymphadenopathy may be present.

The differential diagnosis includes HSV infections, nummular eczema, varicella, kerions, and scabies, which all may become secondarily infected. Nonbullous impetigo usually resolves spontaneously within 2 weeks. It is highly contagious to other parts of the body and to close contacts, however, and should therefore be treated with appropriate antimicrobial agents.

Bullous Impetigo

Bullous impetigo develops on intact skin and is a localized form of SSSS. The initially transparent flaccid bullae are more likely to occur on covered body sites such as the trunk and perineum than are the lesions of nonbullous impetigo. They can, however, occur on the face and extremities as well. Intact vesicles or bullae may be observed, or moist, erythematous shallow erosions may be the sole clinical finding after disruption of the bullae (Fig. 48.24). Bullous impetigo should be differentiated from early SSSS, herpetic infection, allergic contact dermatitis, burns, EM, and inflammatory bullous diseases.

Impetigo may be treated with topical or oral antibiotics depending on the number and locations of the lesions. Topical antibiotics may be acceptable for localized disease.

Systemic therapy is indicated for streptococcal infections or staphylococcal infections with an extensive number of lesions or more severe soft tissue involvement. One of the more cost-effective 1st-line choices includes cephalexin. However, the incidence of MRSA has increased dramatically and local resistance patterns should be taken into account. If MRSA is suspected, initial medication choices including clindamycin, doxycycline (over age 8 years), or sulfamethoxazole-trimethoprim are recommended. A culture should be obtained and antibiotic choice should be based on sensitivity patterns when available. Recurrent impetigo is often secondary to carriage of *S. aureus*. Although intranasal carriage is common, colonization can also involve the axillae and perineum. Intranasal application of mupirocin may eradicate the

FIGURE 48.23 Multiple honey-colored crusted lesions of impetigo. (From Kliegman RM, et al. Cutaneous bacterial infections. In: Kliegman RM. *Nelson textbook of pediatrics.* 20th ed. Philadelphia: Elsevier; 2015:3203.)

FIGURE 48.24 Thin-walled vesicles and shallow erosions with surrounding erythema seen with bullous impetigo. (From Paller AS, Mancini AJ, eds. *Hurwitz Clinical Pediatric Dermatology*. Philadelphia: Elsevier; 2015:334-359.)

organism; however, recolonization occurs over time. Of note, there are reports of increasing resistance with prolonged use of mupirocin. Dilute bleach baths (sodium hypochlorite) may help reduce recurrent skin infections by decreasing bacterial carriage.

Potential but rare complications of impetigo include pneumonia, cellulitis, osteomyelitis, septic arthritis, and septicemia. More specifically, streptococcal infections can result in scarlet fever, guttate psoriasis, lymphadenitis, and lymphangitis. Furthermore, nephritogenic strains of group A β-hemolytic streptococcus can result in poststreptococcal glomerulonephritis (see Chapter 20). The latency period after impetigo is approximately 3 weeks. Treatment does not prevent poststreptococcal glomerulonephritis but does prevent the spread of the organism to other people.

Molluscum Contagiosum

Molluscum contagiosum, caused by a large DNA poxvirus, is most often seen in children and adolescents. The characteristic well-circumscribed, skin-colored to pearly papules usually arise in crops on the face, trunk, and extremities but have a predilection for the axillary, antecubital, and crural regions (Fig. 48.25). Generally ranging in size from 1-5 mm, these asymptomatic papules have a central umbilication, often with a central core. In some individuals, eczematous changes develop at sites of the molluscum lesions, probably representative of a delayed hypersensitivity response. This so-called "molluscum dermatitis" may be localized or more extensive, is not an uncommon finding, and in fact may be more prominent on examination than the molluscum papules, which are occasionally missed. The associated eczematous dermatitis may resemble nummular eczema or tinea corporis. Molluscum lesions often become inflamed or appear infected shortly before spontaneous involution. The diagnosis is made by the clinical appearance of the lesions. However, skin biopsies or microscopic examination of the cores of the lesions can confirm the diagnosis by revealing molluscum bodies, which are masses of virus-infected epidermal cells. The condition should be differentiated from warts, closed comedones, and milia.

Molluscum contagiosum is both contagious and autoinoculable. The incubation period ranges from 2 weeks to 6 months, and multiple family members are often affected. Immunosuppressed persons are at risk for more aggressive disease, especially patients infected with

FIGURE 48.25 The characteristic umbilicated lesions of molluscum contagiosum. (From Nodules and tumors. In: Cohen BA, ed. *Pediatric Dermatology*. Philadelphia: Saunders; 2013.)

human immunodeficiency virus. Patients with preexisting atopic dermatitis are also at greater risk for widespread molluscum.

Treatment options include curettage, topical cantharidin, liquid nitrogen, immunotherapy with *Candida* or *Trichophyton* antigen, topical retinoids, and imiquimod cream. Most pediatric dermatologists avoid application of cantharidin to facial or genital lesions because of concerns of a possible aberrant reaction. As with other poxvirus infections, these lesions occasionally result in scarring or pits as the lesions resolve.

Warts

Warts are intraepidermal tumors caused by human papillomavirus (HPV), a small DNA virus. They may be present in up to 10% of the general population. There are more than 200 types of human papillomavirus. The virus produces 4 major types of warts: common, flat, plantar, and genital (condyloma acuminatum). The incubation period generally varies from 1-6 months, depending on HPV type, the size of the inoculum, the site of infection, and the host's immune status. The duration of the wart is variable as well; approximately 65% of the lesions resolve spontaneously within 2 years. Warts can be spread between persons and between body sites by direct or indirect contact. Most warts are located on the fingers, hands, and elbows because trauma to these sites promotes inoculation of the virus. Warts also display the Koebner phenomenon, which results in linear configurations of lesions at sites of shaving or scratching.

Common Warts

Verruca vulgaris, or the common wart, is found most commonly on the dorsal surface of the hands or fingers, although it may be located at any body site. The lesions may be solitary or multiple and measure from several millimeters to more than 1 cm. Varying in color from yellowish-tan to grayish-black, the common wart has a distinct rough, papillated surface. Punctate thrombosed capillaries, clinically manifested as black dots, may be seen on the surface.

Flat Warts

Verrucae plana, or flat warts, are 2- to 5-mm flat-topped papules that are typically skin-colored, tan, or brown. They are distributed on the face, neck, and extremities. They often appear grouped, especially when the Koebner phenomenon has occurred secondary to shaving or other trauma. These lesions are most often confused with lichen planus or lichen nitidus because these disorders also feature flat-topped papules.

Plantar Warts

Verrucae plantaris, or plantar warts, develop on the weight-bearing areas of the toes, heels, and the midmetatarsal region. The lesions are pushed into the skin in such a manner that the verrucous surface is even with the surrounding skin. These warts are often very tender and may produce significant discomfort with ambulation. Plantar warts may be difficult to distinguish from corns and calluses.

Genital Warts

Condylomata acuminata, or genital warts, are fleshy papillomatous growths found on the genitalia. In early or mild cases, the only physical finding may be subtle skin-colored, flat-topped papules. Their growth can be exuberant in some patients when untreated, resulting in cauliflower-like masses. These genital warts should be differentiated from moist papular or nodular lesions of secondary syphilis (condylomata lata). Although nonvenereal transmission may occur, such as spread from cutaneous warts, the presence of genital warts in young children is usually associated with sexual abuse.

Treatment of Warts

Treatment of warts is designed to be cytodestructive and varies depending on the type of wart, site of the lesion, age and immune status of the patient, and extent of involvement. Topical treatments include keratolytic preparations, such as salicylic acid, ammonium lactate, and 5-fluorouracil. In-office treatments include topical cantharidin, cryotherapy with liquid nitrogen, or immunotherapy with *Candida* or *Trichophyton* antigen. In children with numerous warts, cryotherapy may be limited by discomfort and immunotherapy may be preferable. Podophyllin is reserved for the treatment of genital warts because it is most effective on mucosal surfaces. Imiquimod (Aldara) has been approved for the treatment of genital warts, although it is not approved by the US Food and Drug Administration for use in children. Cimetidine has been used in children with multiple lesions that have failed other treatment options. Extremely recalcitrant warts may necessitate surgical or laser (pulsed dye or carbon dioxide) treatment. Multiple or serial treatments may be necessary, and recurrences are common. A conservative approach is often best for this self-limited infection because the treatment may be worse than the condition. Prolonged periods of applying duct tape to the wart (plantar, finger) have also resulted in resolution.

Herpes Simplex Virus

HSV is a large DNA virus that is divided into two major antigenic subtypes. Type 1 (HSV-1) has been traditionally associated with oral and skin nongenital herpes infections; type 2 (HSV-2) is generally responsible for genital and neonatal infections. The clinical lesions are indistinguishable but can be differentiated by serologic tests. HSV infections are categorized as either primary or recurrent. Primary manifestations usually follow an incubation period of approximately 1 week. They range from subclinical infections to localized or generalized vesicular eruptions to life-threatening systemic infections. Primary herpetic infections can involve any cutaneous or mucosal surface.

The classic clinical manifestation consists of grouped thin-walled vesicles on an erythematous base (Fig. 48.26). The lesions usually begin as papules, which evolve into vesicles or, sometimes, pustules within approximately 48 hours. The vesicles rupture and form a crust over the next 5-7 days and generally heal within 2 weeks. The cutaneous eruption is often accompanied by fever, regional lymphadenopathy, or flulike symptoms (Table 48.13).

FIGURE 48.26 A cluster of vesicopustular lesions on an erythematous base in herpes simplex virus. (From Vesicopustular eruptions. In: Cohen BA, ed. *Pediatric Dermatology*. Philadelphia: Saunders; 2013:104-125.)

After the primary infection, the virus remains dormant until reactivated. Recurrent infections are characterized by localized vesicular eruptions and symptoms such as itching or burning at the same site. Recurrent HSV infections are usually less severe than primary herpes. Reactivation of the virus may be triggered by sunburn, cutaneous trauma, febrile illnesses, menstruation, or emotional stress. Oral antivirals, if administered during the prodromal period before the onset of lesions, may abort or shorten recurrent episodes.

Herpetic gingivostomatitis is typically seen in infants and toddlers. Multiple vesicles and subsequent erosions develop on the lips, gingivae, anterior portion of the tongue, or hard palate. The condition is very painful and is often accompanied by inability to eat and drink. Fever, irritability, and cervical lymphadenopathy are frequently observed. The fever typically resolves within 3-5 days, whereas the oral lesions may persist for up to 2 weeks. The lesions may resemble aphthae, which are usually more localized and are not accompanied by systemic symptoms. Enteroviruses may produce similar oral manifestations; however, they tend to spare the gingivae and often affect the posterior pharynx.

The test of choice to confirm the diagnosis of HSV infection is PCR for HSV. Tzanck smear can suggest HSV, but is not specific. Treatment is supportive, with an emphasis on pain control and fluid replacement. Systemic antivirals may hasten resolution of the lesions and shorten the course of the illness.

Neonatal herpes is a potentially fatal infection, often with severe central nervous system involvement. Vigilant evaluation to determine extent of infection, intravenous acyclovir, and supportive care are required. Immunocompromised children who develop a herpetic infection should receive intravenous acyclovir and be monitored carefully for evidence of pulmonary, hepatic, and central nervous system involvement.

Another high-risk group consists of children with underlying atopic dermatitis who, if exposed to HSV, are susceptible to rapid spread of herpetic blisters. This condition, referred to as **eczema herpeticum** or **Kaposi varicelliform eruption**, may be accompanied by fever and malaise (see Atopic Dermatitis). Oral or intravenous antivirals and supportive care are indicated.

Varicella

Varicella (**chickenpox**) is a very contagious, but usually self-limited infection caused by the varicella-zoster virus. Since the introduction

of the varicella vaccine, mild and atypical variants of this disease have been common.

Transmitted by close contact and respiratory droplets, varicella has an incubation period of 10-21 days. The cutaneous manifestation in healthy children is characterized by crops of lesions (usually 2 or 3 crops of 50-100 lesions each) that initially appear as 2- to 3-mm red macules and then evolve through papular, vesicular, and finally pustular stages within approximately 24 hours. The vesicular stage has traditionally been described as resembling "dewdrops on a rose petal" (Fig. 48.27). The presence of lesions in various stages is characteristic of varicella. Varicella lesions often appear first on the scalp, face, or trunk, and then progress to the extremities. All vesicles become crusted and resolve over several days. Chickenpox usually heals without scarring, except for lesions that have been excoriated or secondarily infected. The eruption is usually accompanied by fever, intense pruritus, and malaise (Table 48.13). The exanthem may be more extensive in children with skin disorders.

When the diagnosis is unclear, confirmatory tests include PCR, immunofluorescent staining, and viral culture. A positive Tzanck smear supports the diagnosis but is not specific for varicella. Symptomatic treatment consists of oral antihistamines, aluminum acetate soaks, oatmeal baths, calamine lotion, and cool compresses. Lesions should be observed for signs of secondary bacterial infection. Antiviral therapy is not routinely recommended in otherwise healthy children. Oral antivirals, if given, should be administered within 24 hours of the onset of the eruption. Immunosuppressed individuals usually require intravenous acyclovir.

High-risk individuals (immunosuppressed, immunocompromised, those with malignancies) who have been exposed to varicella should receive gamma globulin prophylaxis as soon as possible. If varicella develops in a pregnant woman within 5 days before delivery or in a mother 48 hours after delivery, the infant should also be treated with gamma globulin prophylaxis. Complications may include visceral organ involvement, coagulopathy, hemorrhage, pneumonia, or encephalitis.

Herpes Zoster

Similar to HSV, the varicella-zoster virus remains dormant in the dorsal root ganglia after initial infection. Reactivation of the virus results in the clinical manifestations of herpes zoster, or shingles. The infection usually manifests as a linear or bandlike papulovesicular eruption affecting 1 or several dermatomes (Fig. 48.28; see also Table 48.13). Commonly, there is a prodrome of burning, pruritus, or pain of the affected skin that may last several days before the appearance of cutaneous lesions. Vesicles become crusted, and all lesions resolve within a few weeks. The most common dermatomes involved are within the thoracic regions. Up to 10 **satellite lesions** may be encountered outside the primary dermatomes in uncomplicated zoster. An increased number of satellite lesions is observed in **generalized zoster**, which carries a greater risk of systemic involvement. Widespread vesicles should raise the suspicion of an underlying immunodeficiency disorder.

Immunocompromised patients, especially children with lymphoreticular malignancies, are at increased risk for zoster and should be treated with either oral or intravenous acyclovir. As with HSV infection, lesions around the eyes, nose, and forehead require careful ophthalmologic examination. Ocular complications occur in approximately 50% of the patients with ophthalmic zoster. The potential for deep keratitis, uveitis, secondary glaucoma, and loss of vision warrants prompt ophthalmologic evaluation. Patients with zoster should avoid contact with high-risk individuals who are susceptible to development of varicella.

Scabies

Scabies is an extremely common eruption. It occurs in persons of all ages and results from infestation of the superficial layers of skin by the human mite *Sarcoptes scabiei*. The infestation is highly contagious and is therefore seen frequently among individuals living in crowded conditions. Humans are the only source of the mite, which can be passed from 1 person to another. Fomites can also play an important role in transmission. In previously unexposed individuals, the incubation period varies from 2-6 weeks. The incubation period is significantly shortened in individuals who have been previously exposed to the mite.

Although the morphologic appearance of scabies can vary dramatically, the hallmark lesion is the burrow. A burrow is a serpiginous or linear papule caused by movement of the mite through the epidermis. Although considered to be characteristic of scabies, the burrow is

FIGURE 48.27 Lesions in various stages of development including the dewdrop on a rose petal appearance characteristic of varicella. (From Vesicopustular eruptions. In: Cohen BA, ed. *Pediatric Dermatology*. Philadelphia: Saunders; 2013:104-125.)

FIGURE 48.28 A dermatomal distribution of umbilicated vesicles is characteristic of herpes zoster. (From Vesicopustular eruptions. In: Cohen BA, ed. *Pediatric Dermatology*. Philadelphia: Saunders; 2013: 104-125.)

apparent in only a minority of patients. Other typical lesions include papules, vesicles, and pustules, the distribution of which is age dependent. Nodules may appear during active infection and may persist for several weeks to months after treatment; these are common in infantile scabies and on the penis and scrotum of affected males. These persistent nodules are referred to as postscabetic nodules and may be a manifestation of an ongoing hypersensitivity response. In infants, the distribution is generalized and involves the trunk, scalp, face, neck, axillae, palms, and soles. Because the eruption is extremely pruritic, secondary infection and eczematization are common, leading to misdiagnoses of impetigo and atopic dermatitis. In affected older children, adolescents, and adults, the lesions characteristically involve the volar aspects of the wrists, ankles, interdigital web spaces, buttocks, genitalia, groin, abdomen, and axillae (Fig. 48.29). Unlike infantile scabies, the lesions always spare the head.

The diagnosis can be confirmed by scraping the newer lesions, ideally a burrow, with a blade after the application of mineral oil. The scraping may be viewed microscopically, and the presence of mites, ova, or feces is considered diagnostic. Although the yield may be low, suspect lesions should be scraped and an attempt to identify evidence of the mite should be made. In prolonged cases of scabies, which have been appropriately treated, the diagnosis of acropustulosis of infancy needs to be considered.

Topical 5% permethrin cream (Elimite) is the treatment of choice for infants over 2 months and children. Permethrin cream is applied to the entire body from the neck down and thoroughly washed off after 8-12 hours. Scalp and neck treatment is often necessary for infants. This treatment should be repeated 1 week later. Lindane is not recommended as 1st-line treatment for scabies because of its potential for neurotoxicity. Six percent sulfur ointment should be used as an alternative therapy in infants younger than 2 months and in pregnant women. Topical and oral ivermectin are options for resistant infestations. Because scabietic lesions are the result of a hypersensitivity reaction, itching may persist for several weeks despite treatment, which can be relieved with emollients, topical corticosteroids, and antihistamines.

It is critical that all household members as well as close contacts be treated simultaneously to prevent reinfestation. All linens and clothes should be washed and dried in an electric dryer because heat kills the mite. Bulkier linens and stuffed toys can be placed in plastic bags for several days. Mites do not survive without a human host for more than 2-3 days.

FIGURE 48.29 Papulopustular eruption of scabies with burrows visible on the palms and wrist of a child. (From Papulosquamous eruptions. In: Cohen BA, ed. *Pediatric Dermatology*. Philadelphia: Saunders; 2013:68-103.)

Pediculosis

Lice are ectoparasitic insects. *Pediculus humanus capitis*, the head louse, causes the most common form of louse infestation. This occurs more often in whites; girls are more susceptible than boys. Because the head louse can survive for more than 2 days off the host's scalp, the condition can be transmitted via shared hats, combs, brushes, towels, or bedding. On physical examination, the nits (ova) can be found close to the scalp on the proximal hair shafts. They appear as small, oval, whitish bodies approximately 0.5 mm in length. They adhere tightly to the hair shaft and are not easily removed. The nits can be more readily identified by their fluorescence under a Wood lamp. Microscopic examination of the proximal hair shaft may further aid in recognition of the nits. The infestation is characterized by intense pruritus, especially at night.

Some sources start treatment of pediculosis capitis with over-the-counter topical application of 1% permethrin shampoo or pyrethrin combined with piperonyl butoxide products, both of which have good safety profiles. However, resistance to these products has been documented. In treatment failures or known resistance, additional topical agents such as malathion 0.5%, benzyl alcohol, spinosad, and ivermectin lotions are options. Oral ivermectin may be used when lice are resistant to all topical agents. However, each agent's recommended age, weight, and safety profile need to be considered.

It is extremely important to wash and dry (on a hot cycle) all exposed bedding and clothing. All combs and brushes should be soaked in the pediculicide for 15 minutes, and all items that cannot be machine-washed with hot water or dry-cleaned should be placed in plastic bags for 2 weeks. All household members should be treated at the same time. Nits must be removed with a fine-toothed comb after application of a damp towel to the scalp.

Candidiasis

Candidal species, particularly *Candida albicans*, may be considered part of the normal cutaneous flora in most individuals. However, predisposing factors such as endocrinologic disorders, genetic disorders, immunosuppressive conditions, and the administration of systemic corticosteroids or antibiotics may allow for overgrowth of this organism and subsequent infection. Candidiasis refers to an acute or chronic infection of the skin, mucous membranes, or internal organs caused by this pathogenic yeast. Other conditions, such as warmth, moisture, and disruption of the epidermal barrier, further promote invasion and overgrowth. Cutaneous candidiasis can have a variety of clinical manifestations, depending on the site of infection. Some of the most common manifestations include (1) oral candidiasis (thrush), (2) candidal diaper dermatitis, (3) vulvovaginitis, and (4) paronychia.

Oral candidiasis is a common condition of infancy and in immunosuppressed individuals. It is characterized by painful inflammation of the oral cavity with multiple, often confluent, white plaques on an intensely erythematous base. The disorder usually responds to treatment with oral nystatin suspension, which is applied to the oral mucosa 4 times daily until 2 days after the lesions have completely resolved. Oral fluconazole is another therapeutic option for more extensive or resistant cases. Extensive involvement or failure to respond to treatment may suggest an underlying immunodeficiency disease. Cutaneous lesions in the intertriginous and diaper areas are frequently coexistent with thrush.

Candidal paronychia manifests with erythema and edema of the proximal and lateral nail folds, which is usually not associated with tenderness, in contrast to acute bacterial paronychia. The nail is often dystrophic, crumbly, and thick. The condition is seen commonly in thumb suckers. Treatment with topical antifungal creams with yeast

coverage, applied nightly under occlusion for several weeks, usually results in clinical resolution.

Dermatophytoses

The dermatophytes are a group of fungi that infect the hair, skin, and nails and result in a collection of clinical syndromes referred to as dermatophytoses. The clinical conditions are referred to as tinea (or ringworm), and the affected body site determines the name of the entity. This group of infections is caused by species of *Trichophyton*, *Microsporum*, and *Epidermophyton*. Dermatophyte infections are usually confined to the epidermis.

Tinea Capitis

Tinea capitis is discussed in the section on alopecia.

Tinea Corporis

Tinea corporis is characterized by 1 or multiple annular erythematous patches that can occur anywhere on the body. The lesions typically have a papular scaly border and demonstrate central clearing (Fig. 48.30). Vesiculation and pustulation, especially peripherally, are commonly observed. The borders are usually sharply demarcated. Identification of fungal hyphae by KOH examination of scrapings of the lesion's scaly border confirms the diagnosis. Psoriasis, nummular eczema, secondary syphilis, the herald patch of pityriasis rosea, and the annular plaques of granuloma annulare may resemble tinea corporis.

Tinea Pedis

Tinea pedis is diagnosed most often in postpubertal adolescents. The clinical manifestation is variable, but multiple vesicles or erosions on the insteps are characteristic. Other findings include fissures and maceration of the web spaces and "moccasin foot" tinea pedis, in which there is generalized scaling of 1 or both soles with extension onto the lateral aspect of the foot. The differential diagnosis includes atopic or contact dermatitis, juvenile plantar dermatosis, psoriasis, and scabies. The clinician should have increased suspicion for tinea pedis if unilateral involvement is present. A positive KOH scraping or fungal culture rules out these other entities.

Tinea Faciei

Tinea faciei, a dermatophyte infection of the face, is commonly seen in children. Erythematous, scaly, and often in a malar distribution, the condition may resemble lupus erythematosus but is less symmetric. Atopic, contact, and seborrheic dermatitis may have similar cutaneous manifestations. Again, the diagnosis can be confirmed by a positive KOH scraping or fungal culture.

Tinea Cruris

Tinea cruris, uncommon before adolescence, is an erythematous, scaly eruption involving the inguinal creases and medial thighs. The eruption is usually symmetric, and sometimes the margins are papular. This infection may resemble candidiasis, in which there is also scrotal erythema. *Erythrasma*, an uncommon superficial bacterial infection caused by *Corynebacterium minutissimum*, may also mimic tinea cruris. The coral red fluorescence seen on Wood lamp examination is diagnostic of erythrasma, which can be further differentiated from tinea cruris by a negative KOH preparation and fungal culture.

Dermatophyte infections of the skin can usually be successfully managed with topical antifungal agents such as clotrimazole, econazole, ciclopirox, tolnaftate, or terbinafine creams or lotions. These medications are applied twice daily for approximately 2-4 weeks. They should be continued for several days after clinical resolution is apparent. Widespread eruptions or treatment failures may necessitate systemic antifungal therapy, such as griseofulvin, fluconazole, itraconazole, or terbinafine.

Tinea Versicolor

Occurring more frequently in adolescents and adults, tinea versicolor is a superficial fungal infection characterized by multiple slightly scaly macules and patches located on the upper trunk, neck, proximal extremities, and, on occasion, the face. The macular lesions vary in hue (pink, tan, brown, white), hence the name "versicolor." In darkly pigmented or tanned individuals, the macules appear hypopigmented; in fair-skinned persons or during winter months, the lesions usually appear tan-brown. Tinea versicolor is caused by *Pityrosporum orbiculare*, also called *Malassezia furfur*, a dimorphic fungus that is a skin saprophyte. It is generally present in its yeast form, which does not produce a rash. When proliferation of the filamentous form occurs, the organism produces the characteristic lesions of tinea versicolor. Usually asymptomatic or only slightly pruritic, tinea versicolor is primarily a cosmetic disturbance that occurs most commonly in warm and humid environments.

Although the diagnosis is established by the distinctive clinical presentation, a KOH scraping of the fine scale reveals multiple round spores and short, curved hyphae, giving the characteristic "spaghetti and meatballs" appearance typical of this disorder. Wood lamp examination may demonstrate yellow to yellow-green fluorescence, further

FIGURE 48.30 Annular erythematous, scaly plaques with central clearing as seen in tinea corporis. (From Cohen BA, Davis HW, Gehris RP. Dermatology. In: Zitelli BJ, et al, eds. *Atlas of Pediatric Physical Diagnosis*. Philadelphia: Saunders; 2012:299–368.)

supporting the diagnosis (Table 48.2). The differential diagnosis includes postinflammatory pigment alteration, pityriasis alba, vitiligo, contact dermatitis, seborrheic dermatitis, and pityriasis rosea. Tinea versicolor is a chronic condition.

Although usually responsive to therapy, recurrences are common. Application of 2.5% selenium sulfide shampoo to the affected skin can be very effective. Other topical treatments include broad-spectrum antifungal creams or lotions. In extremely widespread or recalcitrant cases, or in immunosuppressed individuals, oral treatment with fluconazole, itraconazole, or terbinafine may be indicated. After successful treatment, the lesions remain temporarily hypopigmented or hyperpigmented.

ACNE VULGARIS

Acne is a very common condition in adolescents, but all age groups can be affected. Open and closed comedones, inflammatory papules, pustules, and nodules are characteristic primary lesions. Scarring and sinus tracts are present in moderate-to-severe forms. Androgens stimulate the hair follicle unit leading to hyperkeratosis of the follicular epithelium and increased sebum production resulting in follicular plugging. The microscopically plugged follicle is clinically apparent as a comedo. With further accumulation of keratin and sebum, the follicle wall may rupture and elicit an inflammatory reaction as contents are released into the surrounding dermis. Clinically, this corresponds to inflammatory lesions ranging from inflammatory papules and pustules to nodules or cysts. *Propionibacterium acnes*, an anaerobic follicular diphtheroid, contributes to the inflammatory process.

The diagnosis of acne is a clinical one; skin biopsies and other diagnostic studies are not necessary. In some cases of midchildhood acne (1-7 years of age), or associated signs or symptoms of androgen excess (e.g., hirsutism, irregular menses), endocrinologic evaluation may be needed to further elucidate the hormonal factors contributing to formation of acne lesions. Medication-induced acne can be seen in all age groups; the offending medications include glucocorticoids, androgens, hydantoin, and isoniazid.

Treatment of acne varies depending on the types of lesions present and individual tolerance to acne medication. Patients should be instructed to use mild cleansers and oil-free, noncomedogenic moisturizers, sunscreen, and makeup. Antibacterial soaps and cleansers may help reduce surface bacteria. Topical medications include benzoyl peroxide, retinoids, antibiotics and combination products. Retinoids are most effective in decreasing new comedo formation and promoting expulsion of existing comedones by reducing and preventing abnormal keratinization of the follicular canal. Benzoyl peroxide has mostly anti-inflammatory activity as the result of its antibacterial activity with mild comedolytic effects, and can be used as an adjunct to retinoid therapy.

Inflammatory acne, particularly with evidence of scarring, often requires the use of antibiotics, either topically or systemically. Oral contraceptives may also provide a significant benefit for the treatment of acne in women, particularly in those with a perimenstrual flare. **Nodulocystic acne** or recalcitrant severe inflammatory acne is best treated with isotretinoin, a synthetic vitamin A derivative. Given the restrictions surrounding its prescription and side effects, referral to a dermatologist is typically needed to pursue this therapy.

SUMMARY AND RED FLAGS

While the time course of dermatosis often is variable, one should be vigilant to reevaluate skin lesions not following the typical course, to identify skin findings that represent manifestations of underlying chronic disorders or life-threatening disease processes. An ill-appearing child with acute skin findings and systemic symptoms should narrow the focus to specific subsets of disease processes. A careful history and physical examination can help differentiate between disease processes of hypersensitivity such as SJS and TEN, DRESS, and infections (SSSS, HSV, meningococcemia) to determine appropriate acute evaluation and management of these life-threatening entities.

REFERENCES

A bibliography is available at ExpertConsult.com.

REFERENCES

General Overview

Cohen BA. Introduction to pediatric dermatology. In Cohen BA, ed. *Pediatric Dermatology*. Elsevier Limited; 2013:1-13.

Harper J, Oranje A, Prose N. *Textbook of Pediatric Dermatology*. London: Blackwell Sciences; 2000:629-636, 1743-1752.

Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology*. Philadelphia: Elsevier; 2016.

Weston WL, Lane AT, Morelli JG. *Color Textbook of Pediatric Dermatology*. St. Louis: Mosby; 2002.

Scaling Disorders

Drago F, Ciccarese G, Broccolo F, et al. Pityriasis rosea in children: clinical features and laboratory investigations. *Dermatology*. 2015;231:9-14.

Eichenfield LF, Lucky AW, Boguniewicz M, et al. Safety and efficacy of pimecrolimus cream (ASM 981) 1% in the treatment of mild to moderate atopic dermatitis in children and adolescents. *J Am Acad Dermatol*. 2002;46:495-504.

Ersoy-Evans S, Greco MF, Mancini AJ, et al. Pityriasis lichenoides in childhood: a retrospective review of 124 patients. *J Am Acad Dermatol*. 2007;56(2):205-210.

Goldminz AM, Buzney CD, Kim N, et al. Prevalence of the metabolic syndrome in children with psoriatic disease. *Pediatr Dermatol*. 2013;30:700-705.

Huang JT, Rademaker A, Paller AS. Dilute bleach baths for *Staphylococcus aureus* colonization in atopic dermatitis to decrease disease severity. *Arch Dermatol*. 2011;147:246-247.

Magna M, Napolitano M, Balato A, et al. Psoriasis in children: a review. *Curr Pediatr Rev*. 2015;11(1):10-26.

McCollum AD, Paik A, Eichenfield LF. The safety and efficacy of tacrolimus ointment in pediatric patients with atopic dermatitis. *Pediatr Dermatol*. 2010;27:425-436.

Patel D, Jahnke MN. Serious complications from *Staphylococcal aureus* in atopic dermatitis. *Pediatr Dermatol*. 2015;32:792-796.

Lumps and Bumps

Chang MW, Frieden IJ, Good W. The risk of intraocular juvenile xanthogranuloma: survey of current practices and assessment of risk. *J Am Acad Dermatol*. 1996;34:445-449.

Keirnig EL. Granuloma annulare. *Dermatol Clin*. 2015;33(3):315-329.

Marion F, Jean-François S, Barbarot S. Juvenile xanthogranulomas are highly prevalent but transient in young children with neurofibromatosis type 1. *J Am Acad Dermatol*. 2014;71(2):389-390.

Thornsberry LA, English JC III. Etiology, diagnosis, therapeutic management of granuloma annulare: an update. *Am J Clin Dermatol*. 2013;14(4):279-290.

Zvulunov A, Barak Y, Metzker A. Juvenile xanthogranuloma, neurofibromatosis, and juvenile chronic myelogenous leukemia. *Arch Dermatol*. 1995;131:904-908.

Disorders of Pigmentation

Iannella G, Greco A, Didona D, et al. Vitiligo: pathogenesis, clinical variants and treatment approaches. *Autoimmun Rev*. 2016;15:335-343.

Pinto FJ, Bolognia JL. Disorders of hypopigmentation in children. *Pediatr Clin North Am*. 1991;38:991-1017.

Shpall S, Frieden I, Chesney M, et al. Risk of malignant transformation of congenital melanocytic nevi in blacks. *Pediatr Dermatol*. 1994;11:204-208.

Sreeraman Kumar R, Messina JL, Reed D, et al. Pediatric melanoma and atypical melanocytic neoplasms. *Cancer Treat Res*. 2016;167:331-369.

Reactive Erythemas and Hypersensitivity Reactions

Bruce F. Could it be a drug eruption? *Aust Fam Physician*. 1997;26:689-695.

Canavan RN, Mathes EF, Frieden IF, et al. *Mycoplasma pneumonia*-induced rash and mucositis as a syndrome distinct from Stevens-Johnson syndrome and erythema multiforme: a systematic review. *J Am Acad Dermatol*. 2015;72(2):239-245.

Gianetti A, Malmusi M, Girolomoni G. Vesiculobullous drug eruptions in children. *Clin Dermatol*. 1993;11:551-555.

Huang YC, Li YC, Chen TJ. The efficacy of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis: a systematic review and meta-analysis. *Br J Dermatol*. 2012;167:424-432.

Manders SM. Serious and life-threatening drug eruptions. *Am Fam Physician*. 1995;51:865-871.

Schopf E, Stuhmer A, Rzany B, et al. Toxic epidermal necrolysis and Stevens-Johnson syndrome. An epidemiological study from West Germany. *Arch Dermatol*. 1991;127:839.

Sharma V, Beyer D, Paruthi S, et al. Prominent pruritic periumbilical papules: allergic contact dermatitis to nickel. *Pediatr Dermatol*. 2002;9:106-109.

Sharma VK, Dhar S. Clinical pattern of cutaneous drug eruptions among children and adolescents in North India. *Pediatr Dermatol*. 1995;12:178-183.

Straussberg R, Harel L, Ben-Amitai D, et al. Carbamazepine-induced Stevens-Johnson syndrome treated with IV steroids and IVIG. *Pediatr Neurol*. 2000;22:231-233.

Viard I, Wehrli P, Bullani R, et al. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. *Science*. 1998;282:490-493.

Bullous Lesions

Braunstein I, Wanat KA, Abuabara K, et al. Antibiotic sensitivity and resistance patterns in pediatric staphylococcal scalded skin syndrome. *Pediatr Dermatol*. 2014;31(3):305-308.

Feldman SR. Bullous dermatoses associated with systemic disease. *Dermatol Clin*. 1993;11:597-608.

Fine JD, Bauer EA, Briggaman RA, et al. Revised clinical and laboratory criteria for subtypes of inherited epidermolysis bullosa. *J Am Acad Dermatol*. 1991;24:119-135.

Hetem DJ, Bonten MJ. Clinical relevance of mupirocin resistance in *Staphylococcal aureus*. *J Hosp Infect*. 2013;85(4):249-256.

Niar R, Penencevich EN, Blevins AE, et al. Clinical effectiveness of mupirocin for preventing *Staphylococcal aureus* infections in nonsurgical settings: a meta-analysis. *Clin Infect Dis*. 2016;62:618-630.

Rabinowitz LG, Esterly NB. Inflammatory bullous diseases in children. *Dermatol Clin*. 1993;11:565-581.

Tolar J, Wagner JE. Allogeneic blood and bone marrow cells for the treatment of severe epidermolysis bullosa: repair of the extracellular matrix. *Lancet*. 2013;382(9899):1214-1223.

Purpura

Yang YH, Yu HH, Chiang BL. The diagnosis and classification of Henoch–Schönlein purpura: an updated review. *Autoimmun Rev*. 2014;13(4):355-358.

Hair Loss

Atton A, Tunnessen W. Alopecia in children: the most common causes. *Pediatr Rev*. 1990;12:25-30.

Castello-Soccio L. Diagnosis and management of alopecia in children. *Pediatr Clin North Am*. 2014;61(2):427-442.

Muller SA. Trichotillomania. *Dermatol Clin*. 1987;5:595-601.

Stroud JD. Hair loss in children. Symposium on pediatric dermatology. *Pediatr Clin North Am*. 1983;30:641-657.

Infections and Infestations

Ahmad HM, Abel-Azim ES, Abel-Aziz RT. Clinical efficacy and safety of topical versus oral ivermectin in treatment of uncomplicated scabies. *Dermatol Ther*. 2016;29:58-63.

Bangert S, Levy M, Hebert AA. Bacterial resistance and impetigo treatment trends: a review. *Pediatr Dermatol*. 2012;29:243-248.

Chen SF. *Staphylococcus aureus* decolonization. *Pediatr Infect Dis J*. 2005;24:79-80.

Darmstadt GL, Lane AT. Impetigo: an overview. *Pediatr Dermatol*. 1994;11:293-303.

Kahn RM, Goldstein EJ. Common bacterial skin infections. *Postgrad Med*. 1993;93:175-182.

Kimberlin DW, Brady MT, Jackson MA, et al., eds. *Red Book: 2015 Report of the Committee of Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015.

Meinking TL, Entzel P, Villar ME, et al. Comparative efficacy of treatments of pediculosis capitis infestations: update 2001. *Arch Dermatol*. 2001;137:287-292.

Nolan K, Kamrath J, Levitt J. Lindane toxicity: a comprehensive review of the medical literature. *Pediatr Dermatol*. 2012;29:141-146.

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