

*Nelson*

# **Pediatric Symptom-Based Diagnosis**

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This book is dedicated to the Children's Hospital of Wisconsin residents. Their enthusiasm, thirst for knowledge, and desire to become outstanding pediatricians inspire us.

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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.

# 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)

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 1.2 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

**TABLE 1.4 Distinguishing Features of Parapharyngeal–Upper Respiratory Tract Infections**

	<b>Peritonsillar Abscess</b>	<b>Retropharyngeal Abscess (Cellulitis)</b>	<b>Submandibular Space (Ludwig Angina)*</b>	<b>Lateral Pharyngeal Space</b>	<b>Masticator Space*</b>	<b>Epiglottitis</b>	<b>Laryngotracheobronchitis (Croup)</b>	<b>Bacterial Tracheitis</b>	<b>Postanginal Sepsis (Lemierre Syndrome)</b>
<b>Etiology</b>	Group A streptococci, oral anaerobes <sup>†</sup>	<i>Staphylococcus aureus</i> , oral anaerobes, <sup>†</sup> group A streptococci, “suppurative adenitis”	Oral anaerobes <sup>†</sup>	Oral anaerobes <sup>†</sup>	Oral anaerobes <sup>†</sup>	<i>Haemophilus influenzae</i> type b (rarely), group A streptococci, <i>Streptococcus pneumoniae</i> , <i>Staphylococcus aureus</i> , and non-type b <i>H. influenzae</i>	Parainfluenza virus; influenza, adenovirus, and respiratory syncytial virus less common	<i>Moraxella catarrhalis</i> , <i>S. aureus</i> , <i>H. influenzae</i> type b or nontypable	<i>Fusobacterium necrophorum</i>
<b>Age</b>	Teens	Infancy, preteens, occasionally teens	Teens	Teens	Teens	2-5 yr	3 mo-3 yr	3-10 yr	Teens
<b>Manifestations</b>	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, > 1/3 × 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 “steple 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 thrombophlebitis of internal jugular vein with septic emboli (e.g., lungs, joints), bacteremia

\*Often odontogenic; check for tooth abscess, caries, tender teeth.

<sup>†</sup>*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

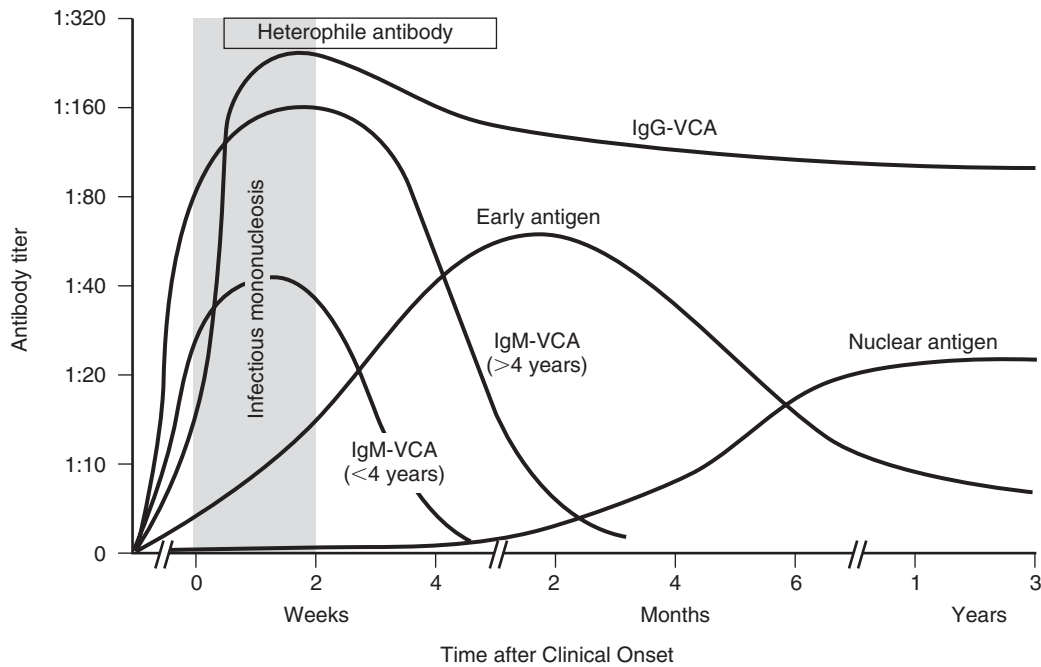
Laboratory studies of diagnostic value include atypical lymphocytosis; these lymphocytes are primarily EBV-specific, cytotoxic T lymphocytes that represent a reactive response to EBV-infected B lymphocytes. A modest elevation of serum transaminase levels, reflecting EBV hepatitis, is common. Tests useful 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**

	<b>Gingivostomatitis</b>	<b>Herpangina</b>	<b>Hand-Foot-Mouth Disease</b>	<b>Systemic Lupus Erythematosus (SLE)</b>	<b>Inflammatory Bowel Disease (IBD)</b>	<b>Aphthous Stomatitis</b>	<b>Behçet Disease</b>	<b>Vincent Stomatitis</b>	<b>Recurrent Scarring Ulcerative Stomatitis (Sutton Disease)</b>
<b>Etiology</b>	Herpes simplex virus (HSV I)	Cocksackievirus A, B; echovirus or HSV (rarely)	Cocksackievirus A, cocksackievirus B (rarely)	Autoimmune	Autoimmune	Unknown	Unknown; vasculitis	Unknown; or anaerobic bacteria	Unknown
<b>Location</b>	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	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
<b>Age</b>	Less than 5 yr	3-10 yr	1 yr-teens	Any age	Any age	Teens and adulthood	Teens, adulthood, occasionally <10 yr	Teens; if younger, consider immunodeficiency and blood dyscrasia	Teens
<b>Manifestations</b>	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	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 Jensen 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

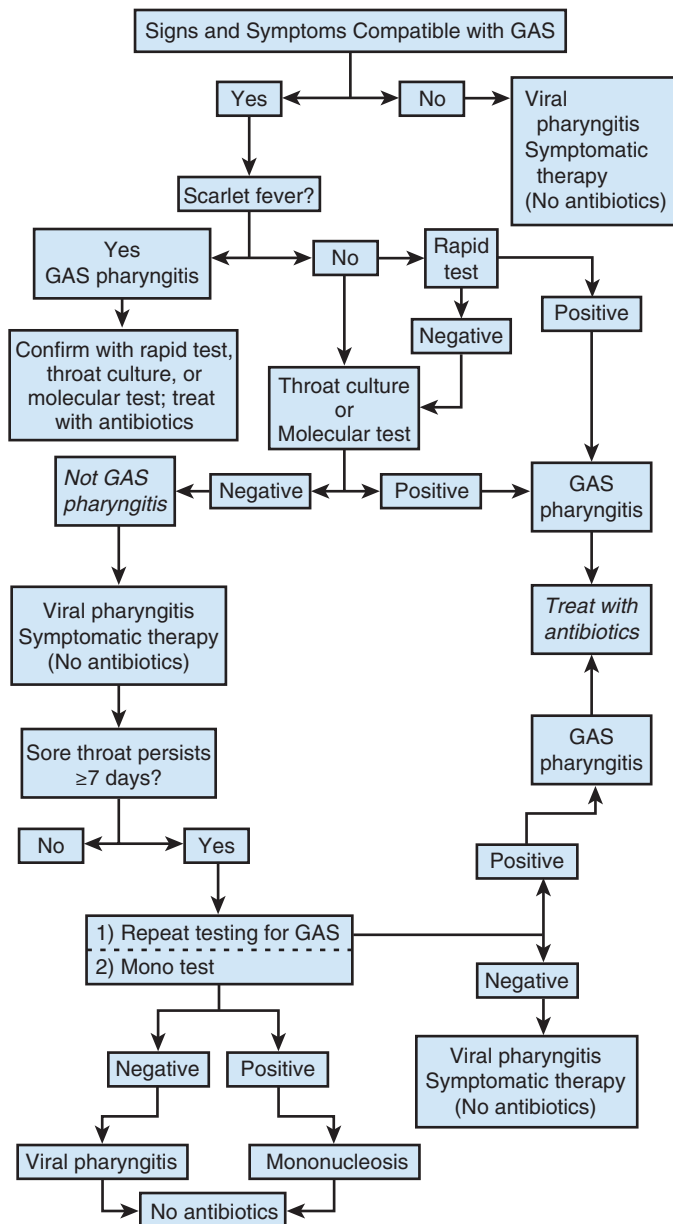
the area around the mouth often appears pale in comparison, giving the appearance of circumoral pallor. Accentuation of erythema occurs in flexor skin creases, especially in the antecubital fossae (Pastia lines). The erythema begins to fade within a few days. Desquamation begins within a week of onset 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  $\beta$ -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	<i>Staphylococcus aureus</i>	<i>S. aureus</i>
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  $\leq 2$  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  $>38^{\circ}\text{C}$ ), 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  $\geq 99\%$  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
<b>Standard Treatment</b>			
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	N/A	Once
	1.2 million U (weight ≥27 kg)/IM	N/A	
<b>Oral Dose</b>			
<b>Treatment for Penicillin-Allergic Patients</b>			
Clarithromycin	15 mg/kg/day up to 500 mg/day	10 days	bid
Azithromycin <sup>†</sup>	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
<b>Cephalosporins<sup>‡</sup></b>			
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.

<sup>†</sup>Maximum dose for children is 500 mg/day. Adult dosage: 500 mg the first day, 250 mg the subsequent 4 days.

<sup>‡</sup>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  $\beta$ -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  $\beta$ -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  $\beta$ -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.

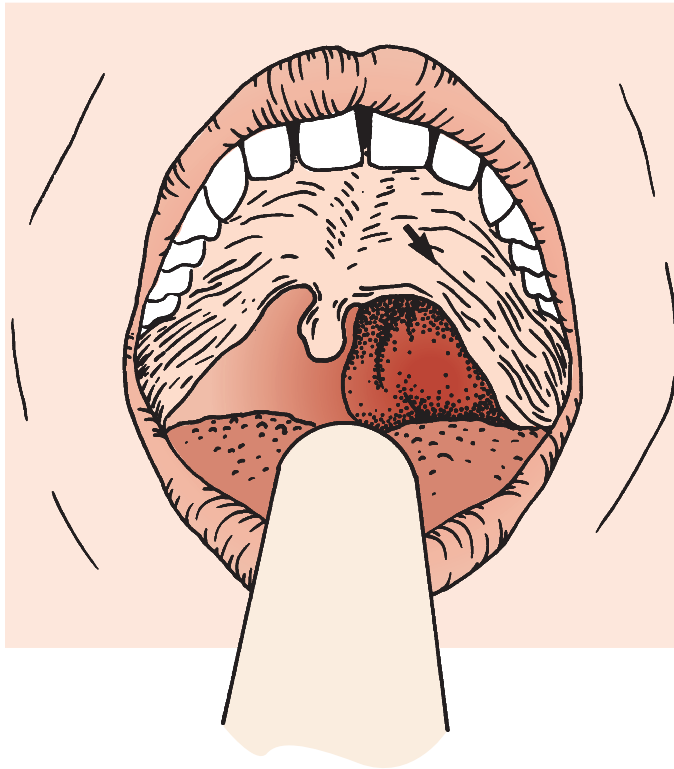
Patients who are allergic to penicillin can receive a cephalosporin if they have not had an immediate hypersensitivity reaction. Erythromycin or another non- $\beta$ -lactam antibiotic, such as clarithromycin, azithromycin, or clindamycin, can be used. Resistance of GAS to macrolides has increased dramatically 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



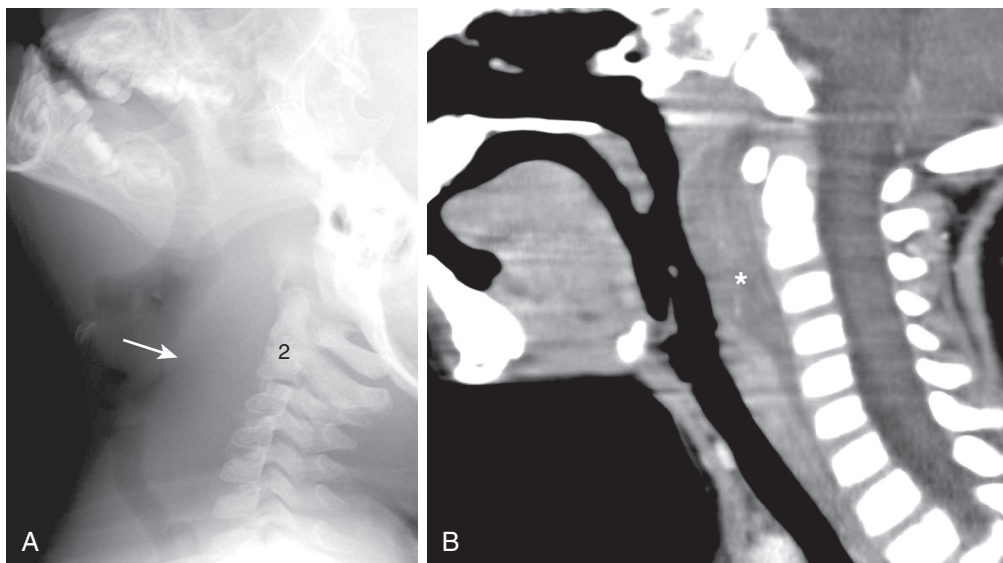
**FIGURE 1.4** Peritonsillar abscess (quinsy, sore throat). The left tonsil is asymmetrically inflamed and swollen; there is displacement of the uvula to the opposite side. The supratonsillar space (*arrow*) is also swollen; this is the usual site of the surgical incision for drainage. Prominent unilateral 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.

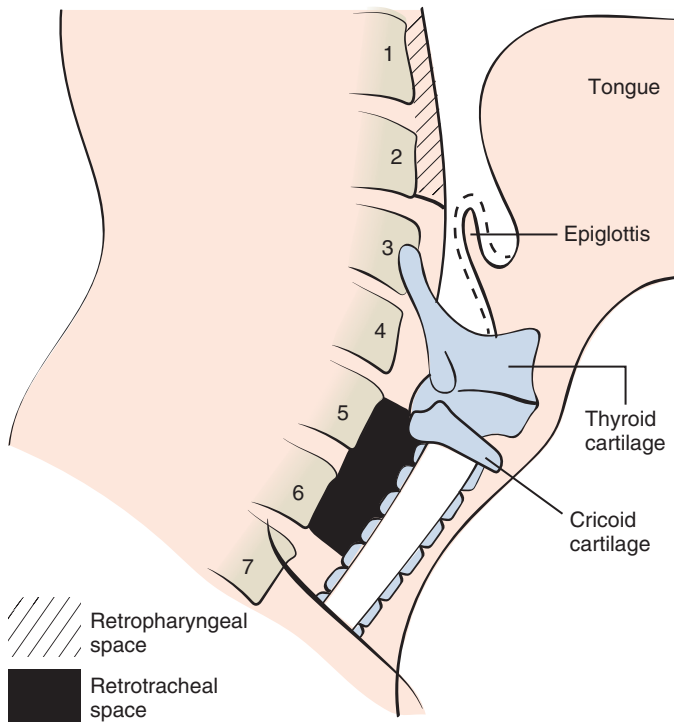
### Nonsuppurative Sequelae

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.)



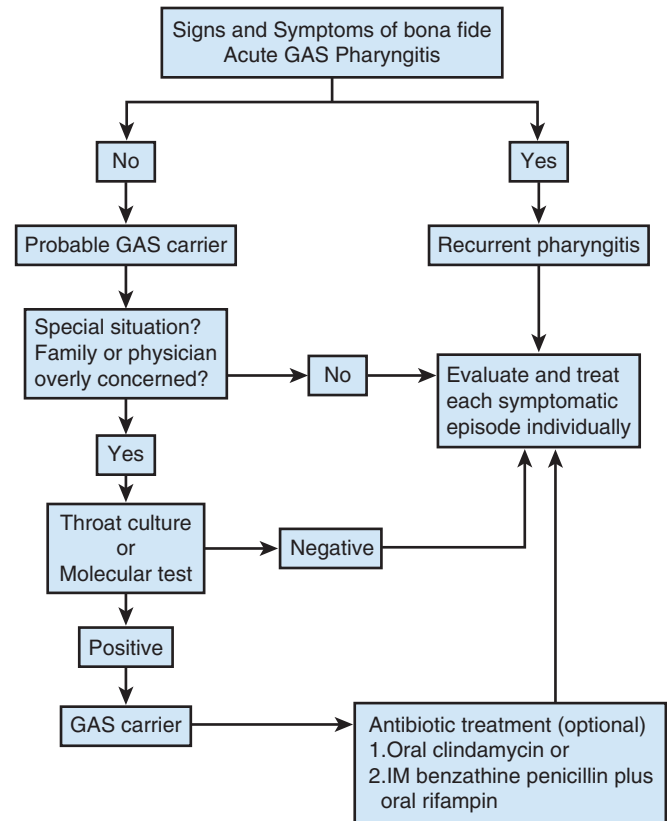
**FIGURE 1.6** In an adolescent, the retropharyngeal space normally does not exceed 7 mm when measured from the anterior aspect of the C2 vertebral body to the posterior pharynx. In infants the retropharyngeal space is usually less than one width of the adjacent vertebral body. However, during crying, 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 Out-patient Medicine*. 2nd ed. Philadelphia: WB Saunders; 1991.)

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 non-adherent 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



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

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  $\beta$ -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  $\beta$ -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  $\beta$ -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 asymptotically 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.

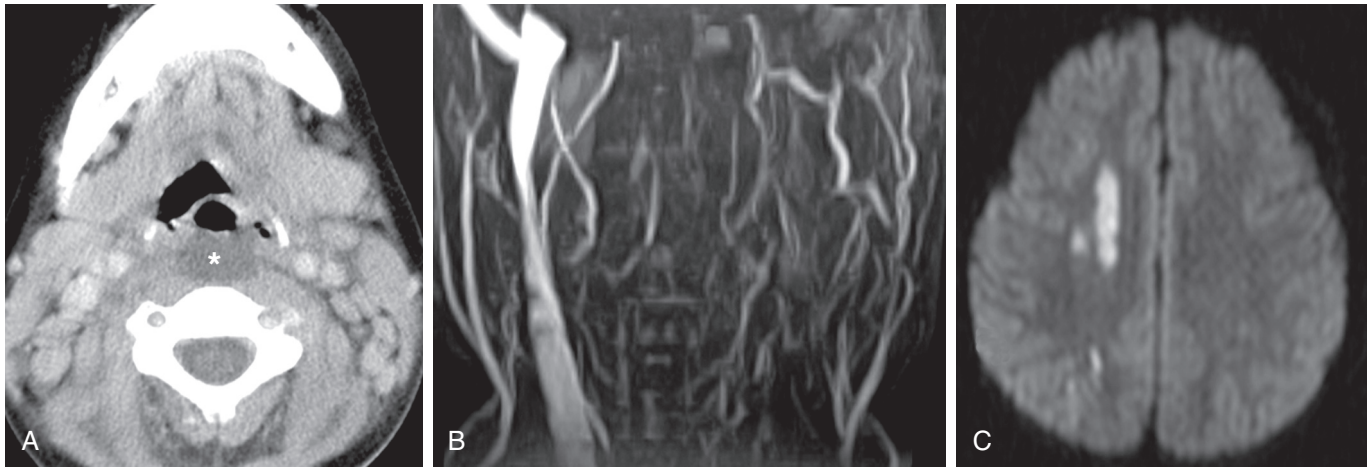
### FUSOBACTERIUM NECROPHORUM

*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  $\beta$ -lactamases, and treatment failure with penicillin has been reported. Many expert clinicians use metronidazole, clindamycin, a  $\beta$ -lactam in combination with a  $\beta$ -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 thrombophlebitis, 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.)

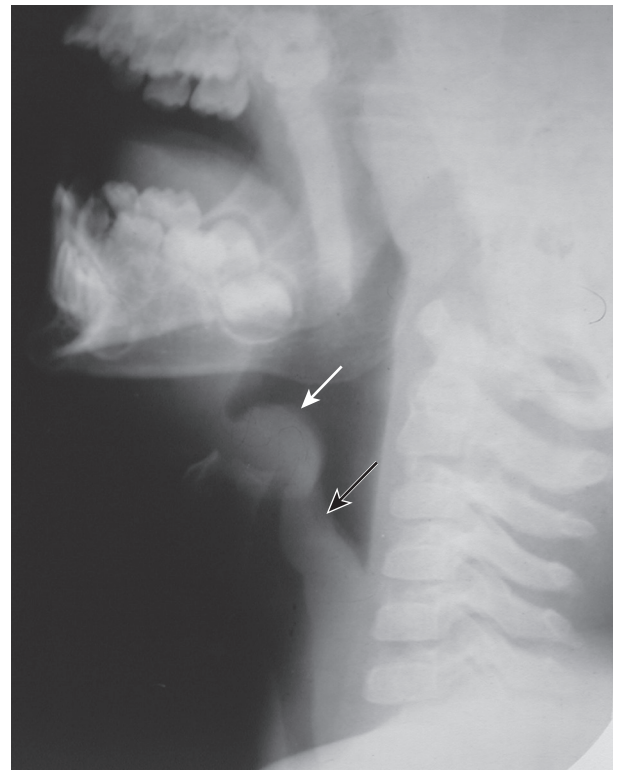
## EPIGLOTTITIS AND BACTERIAL TRACHEITIS

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*, *Staphylococcus 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.

## 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%.



**FIGURE 1.9** Epiglottitis 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.)

(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. Gonorrhoea rarely is transmitted from the pharynx to a sex partner, but pharyngitis can serve as a source for gonococemia. 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](#)).

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A bibliography is available at [ExpertConsult.com](http://ExpertConsult.com)

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

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# 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<sub>2</sub>O). 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

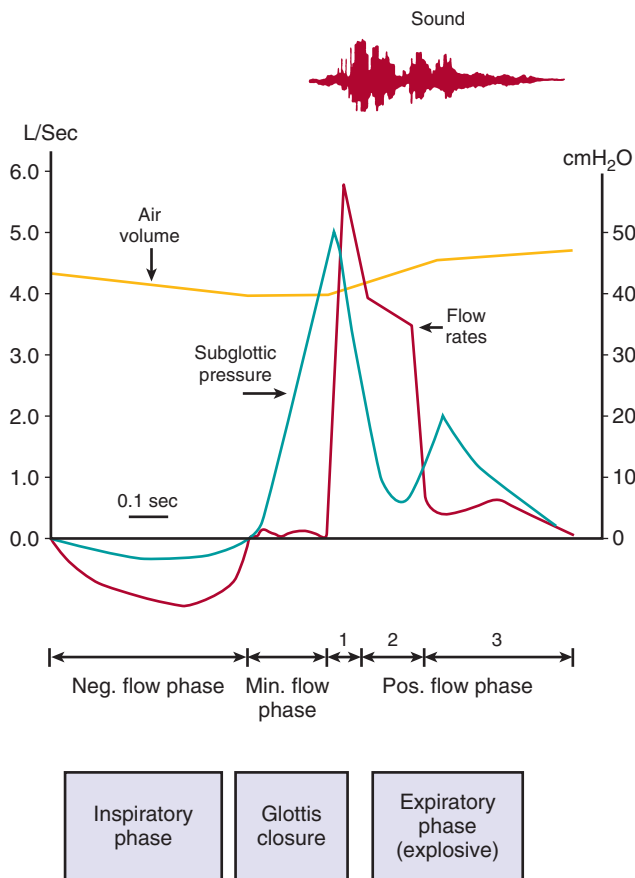
A history of accompanying signs or symptoms, whether localized to the respiratory tract (wheeze, stridor) or elsewhere (failure to thrive, frequent malodorous stools) can give important clues (Table 2.5; see also Tables 2.2 and 2.3). It is essential to remember that the daily language of the physician 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.)

## ◆ 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.

**TABLE 2.1 Causes of Cough**

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

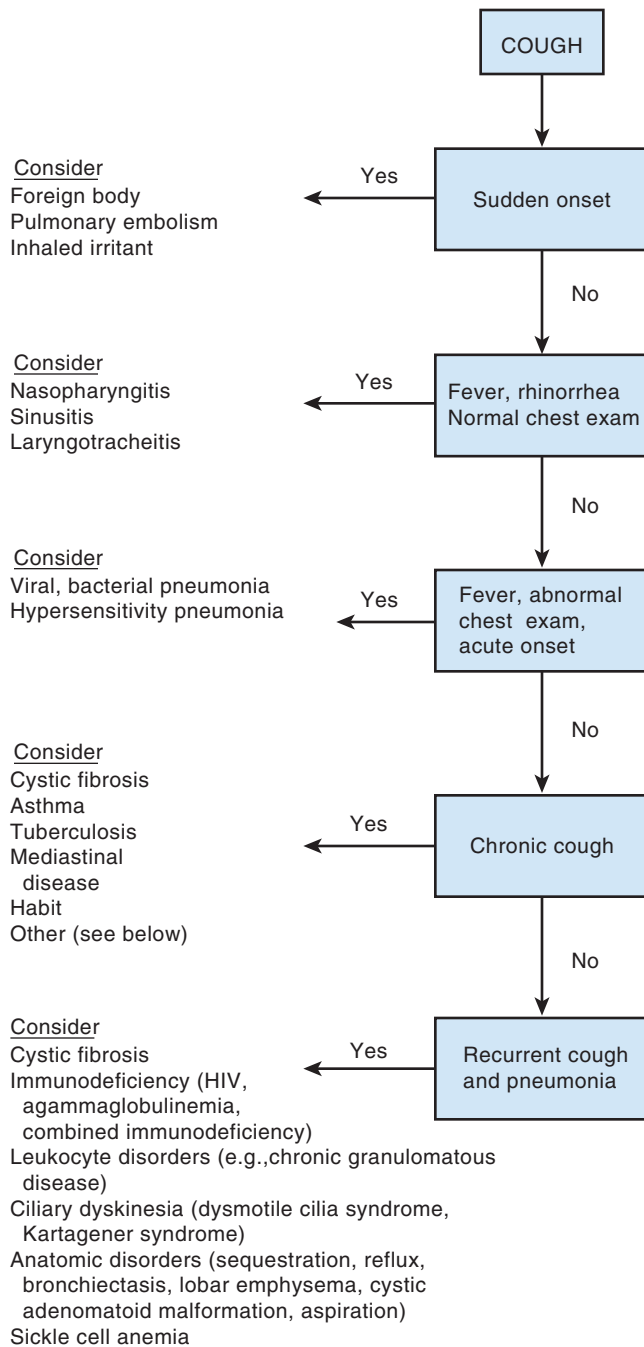
\*Infections include upper (pharyngitis, sinusitis, tracheitis, rhinitis, otitis) and lower (pneumonia, abscess, empyema) respiratory tract disease.

†Anatomic abnormality includes tracheobronchomalacia, tracheoesophageal fistula, vascular ring, abnormal position or take-off of large bronchi.

<sup>1</sup>Common; <sup>2</sup>less common; <sup>3</sup>much less common.

CF, cystic fibrosis; GER, gastroesophageal reflux.

**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.

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.

**TABLE 2.2 Clinical Clues About Cough**

Characteristic	Think of
Staccato, paroxysmal	Pertussis, cystic fibrosis, foreign body, <i>Chlamydia</i> species, <i>Mycoplasma</i> 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, <i>Pneumocystis jiroveci</i> , <i>Mycobacterium tuberculosis</i> , <i>Mycobacterium avium-intracellulare</i> , cytomegalovirus
Dyspnea	Hypoxia, hypercarbia
Animal exposure	<i>Chlamydia psittaci</i> (birds), <i>Yersinia pestis</i> (rodents), <i>Francisella tularensis</i> (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

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
$\beta$ -Adrenergic blockers	Potentiate asthma
ACE inhibitors	(?) Possibly potentiate asthma
Bethanechol	Potentiate 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.

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

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

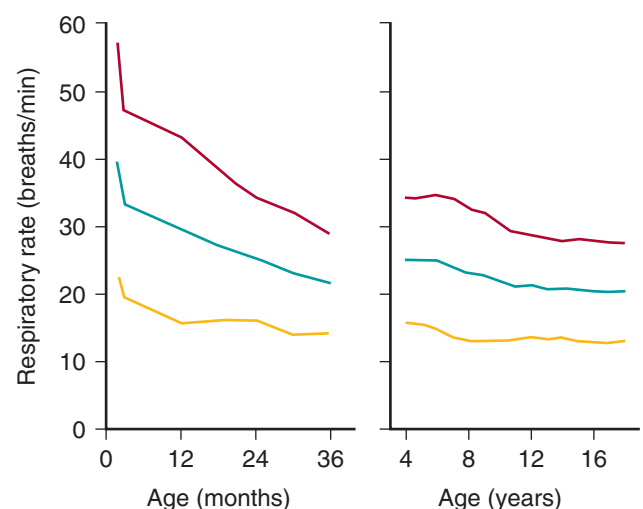
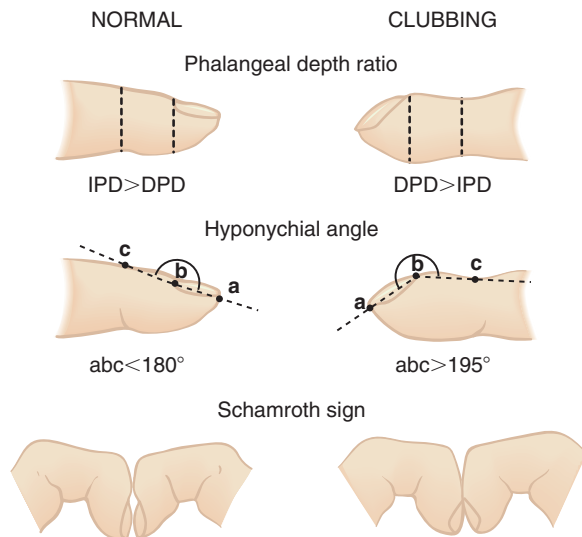


FIGURE 2.3 Mean values (blue line)  $\pm 2$  standard deviations (red and yellow lines) of the normal respiratory rate at rest (during sleep in children younger than 3 years). There is no significant difference between the genders. (Data from Pasterkamp H. The history and physical examination. In: Chernick 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**

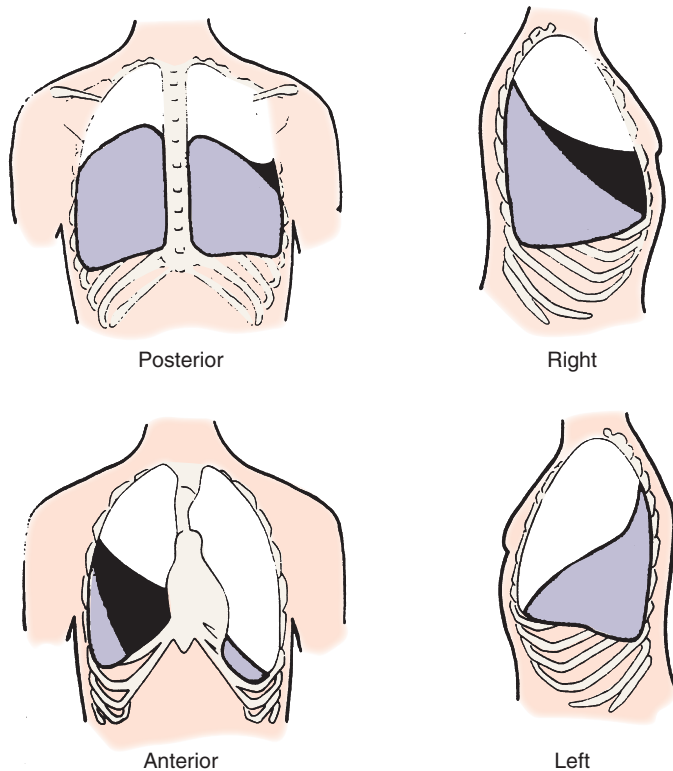
Disease Process	Mediastinal Deviation	Chest Motion	Fremitus	Percussion	Breath Sounds	Adventitious Sounds	Voice Signs
Consolidation (pneumonia)	No	Reduced over area, splinting	Increased	Dull	Bronchial or reduced	Crackles	Egophony,* whispering pectoriloquy increased <sup>†</sup>
Bronchospasm	No	Hyperexpansion 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*.

<sup>†</sup>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.

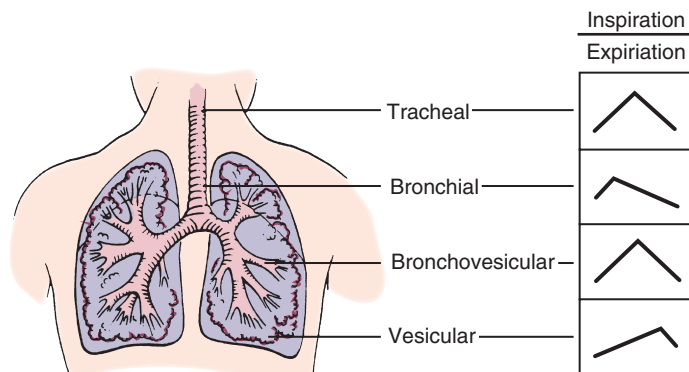
### ◆ Diagnostic Studies

#### 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. *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							Other	
	Normal	Hyper	Lobar Infil	Diff Infil		Other	↑WBC	↑LY	↑EOS	↑PMN	↑IgG	↑IgM		↑IgE
Asthma	+	++	-	-	-	+	+	++	-	+	+	++	+	+bdilator <sup>1</sup>
Cystic fibrosis	+	++	+	+	+++	++	+	+	++	++	+	+	+	See Table 2.8
Other infection														
Croup	++	+	+	+	++ <sup>2</sup>	-	+	+	-	-	-	-	Paraflu +++	
Epi-glottitis	++	+	+	+	++ <sup>3</sup>	-	+	+	+++	+++	++	+	Direct look	
Sinusitis	+++	-	-	-	+++	++	-	+	+++	+++	++	+		
Bronchiolitis	-	+++	+	++	+	+	+	+	+	+	+	+	RSV, metapneumovirus +++	
Pneumonia														
Influenza	-	++	+	++	+	++			+				+++	
Paraflu	-		+	++	+	++			+				+++	
Adenovirus	-	+	+	++	+	++	+	+	++				+++	
Pertussis	++	+	-	+	++	++	+++	+	+	++	+	-	++ <sup>4</sup>	
Chlamydia	-	+++	+	+++	+	+	+	++	+	+++	+++	-	+++	
Mycoplasma	+	+	+	+	++ <sup>5</sup>	+	+	+	+	+	+	-	++	+Cold agglutinin +PPD, Quantiferon
TB	+	-	++	+	++	+	+	+	+	+	+	-	++	+Bid cult <sup>6</sup>
Bacterial	-	+	+++	+	++ <sup>5</sup>	-	+	+	+++	++	+	+	+	Bronch
Foreign body	-	++ <sup>7</sup>	++	-	++ <sup>7</sup>	-	+	+	++	++				Esoph pH <sup>8</sup>
GE reflux	+++	+	-	-	-	+	-	-	-	-	-	+	-	<sup>10</sup>
Aspiration	+	+	+	+	++ <sup>9</sup>	+	-	+	+	-	-	+	-	<sup>12</sup>
Anatomic	+	+	+	-	++ <sup>11</sup>	-	+	-	+	-	-	-	-	
Habit	+++	-	-	-	-	-	-	-	-	-	-	-	-	

<sup>1</sup>Positive response to bronchodilators, either as a home therapeutic trial or in a pulmonary function test in the laboratory.

<sup>2</sup>"Steeple" sign; narrowing of upper tracheal air column.

<sup>3</sup>"Swollen thumb": sign of thickened epiglottis.

<sup>4</sup>Low yield in paroxysmal stage.

<sup>5</sup>Pleural effusion relatively common.

<sup>6</sup>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.

<sup>7</sup>Localized hyperinflation is common; localized atelectasis is common; inspiratory-expiratory radiographs may show ball-valve obstruction.

<sup>8</sup>Esophageal biopsy specimen shows esophagitis.

<sup>9</sup>Multilobar or multisegmental, dependent lobes.

<sup>10</sup>(?) Lipid-laden macrophages from bronchoscopy or gastric washings; barium swallow or radionuclide study showing aspiration.

<sup>11</sup>Right-sided arch, mass effect on airways, mass identified; magnetic resonance imaging (MRI).

<sup>12</sup>Bronchoscopy; computed tomography; MRI.

+++ , almost always—if not present, must question diagnosis; ++ , common; + , less common; - , seldom—if present, must question diagnosis.

+Bid 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 pneumoniae*. 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 epiglottitis 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 <i>Pseudomonas aeruginosa</i>	.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 <i>Staphylococcus aureus</i>	.20	.20		
Positive for <i>Haemophilus influenzae</i>	.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.

**Ureaplasma 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.

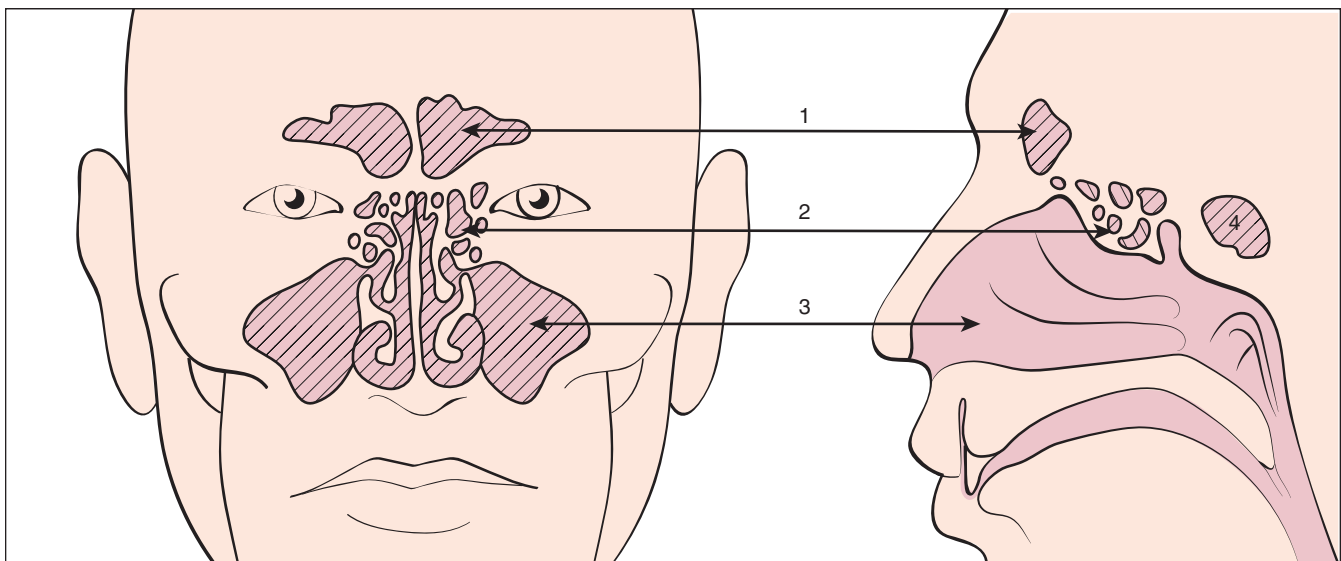
(See *Nelson Textbook of Pediatrics*, p. 2014.)



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 medicamentosa	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, $\beta$ blockers
Hypothyroidism	Uncommon	Chronic	Clear	
Cluster headache	Uncommon	Intermittent	Clear	Associated tearing, headache
Horner syndrome	Uncommon	Chronic	Clear	Ptosis, miosis, anhidrosis

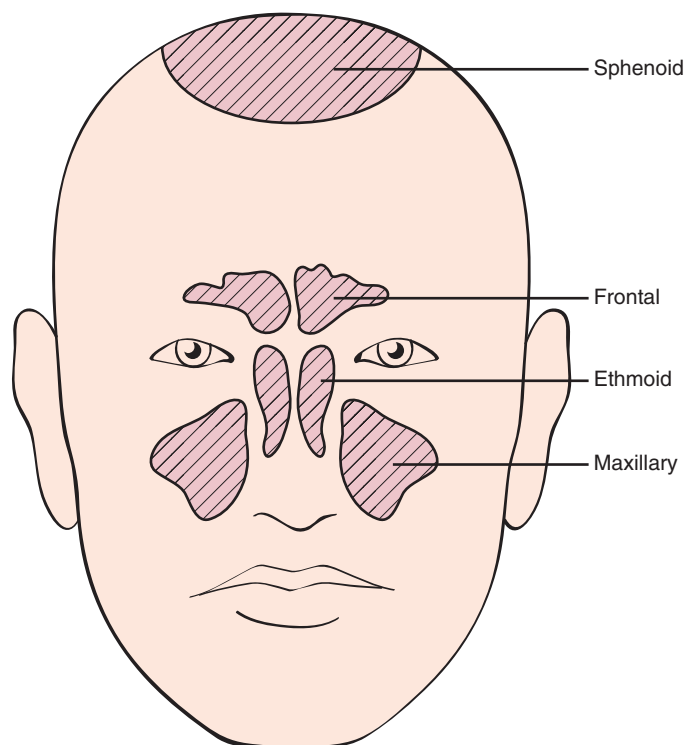
\*Less than 1 week is considered acute.



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

\*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

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 immunosuppressive 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.

to an adult with active tuberculosis. Nonetheless, tuberculosis is an infrequent cause of cough in children, even in those with active disease.

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. Cavitory 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 radio-labeled 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.

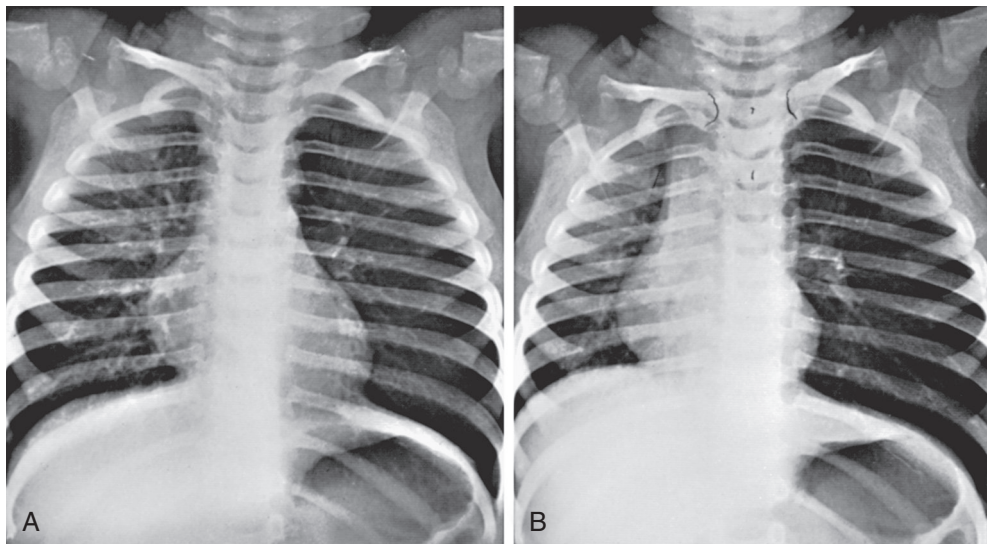
Chest radiographs may be normal in 15% of patients with intrathoracic foreign bodies but should be obtained in both inspiration and expiration because in some cases the only abnormality is unilateral or unilobar air trapping, which is occasionally more clearly identified with an expiratory radiograph. 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.

### 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 ( $\Delta F508$ , indicating a deletion,  $\Delta$ , 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

### 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 $\beta$ -agonists

(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

**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)

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 2.17 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 Kerckmar 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 cyst-adenomatoid 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

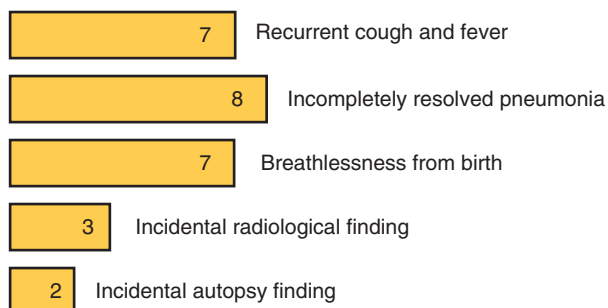
**Gastrointestinal Complications**

- 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 Kerckmar 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.

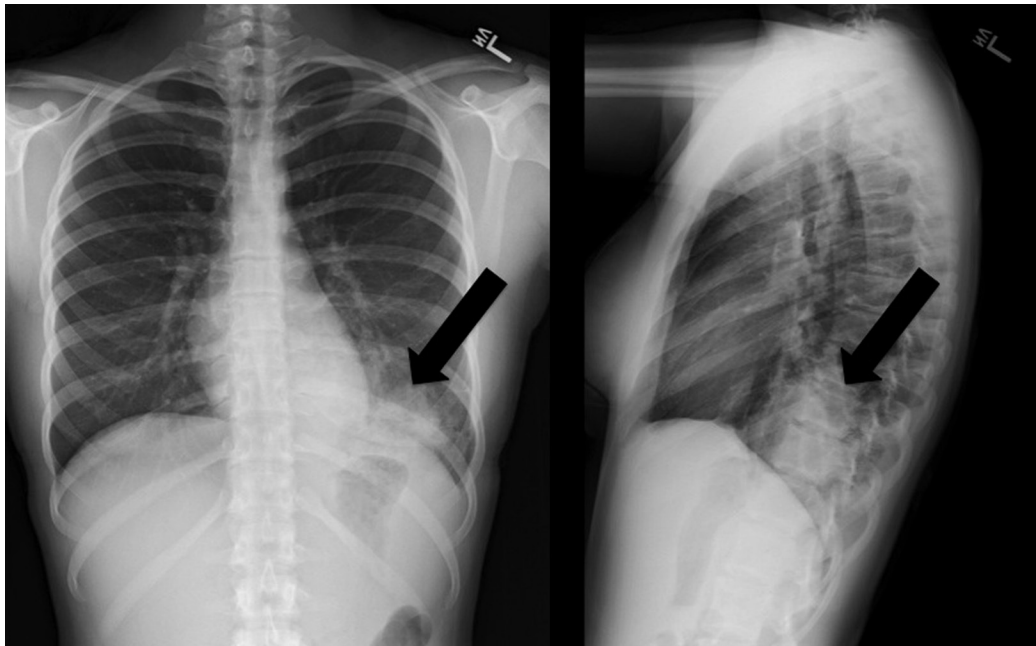
Many airway hemangiomas regress with steroid treatment; however, due to the side effect profile, propranolol is considered the treatment of choice. Asthma is a contraindication for propranolol treatment due to its beta-blocking effect and potential to worsen asthma. Laser ablation may be indicated in 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

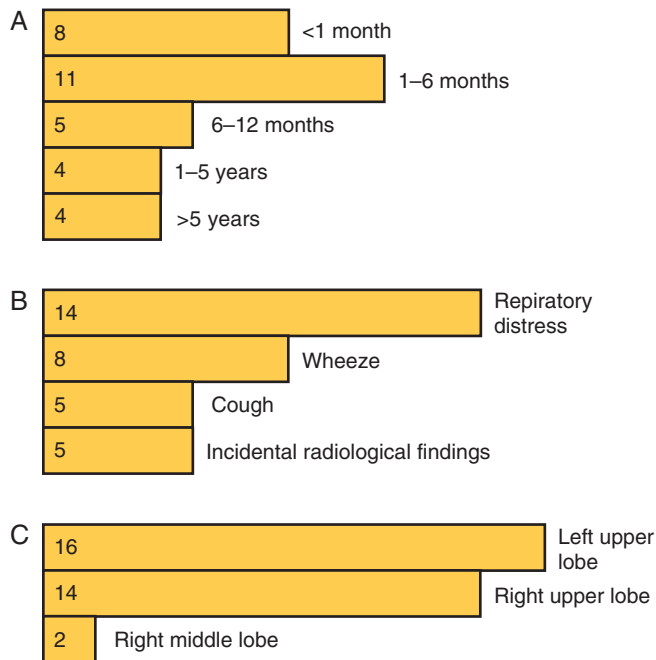
TABLE 2.21 Anatomic Abnormalities Causing Cough

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.

## 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 2.24 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
$\alpha_1$ -Antitrypsin deficiency	(extrinsic allergic alveolitis)
Graft-versus-host disease	Thyroid lesions
Bronchopulmonary dysplasia	Subphrenic abscess
Tumor (bronchial adenoma, carcinoid; mediastinal)	Sarcoidosis
Alveolar proteinosis	Anaphylaxis
Tracheomalacia, bronchomalacia	Pulmonary embolism
Spasmodic croup	Lung contusion

**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.

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.

**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

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](#).