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21 Respiratory Tract Symptom Complexes

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MUCOPURULENT RHINORRHEA

Mucopurulent rhinorrhea (i.e., purulent nasal discharge) denotes nasal discharge that is thick, opaque, and colored.[1] It occurs at any age and usually is a manifestation of a self-limited and uncomplicated viral upper respiratory tract infection (URI). Mucopurulent rhinorrhea is most problematic in children younger than 3 years because of a protracted course and frequent recurrence, especially in those in out-of-home childcare[2]; parental concern and misperception about the cause; and overprescription of antibiotics by healthcare providers.[3–5] Occasionally, this symptom is a clue to the diagnosis of a treatable bacterial infection or underlying condition.

Acute, sporadic mucopurulent rhinorrhea has an infectious cause and almost always is the manifestation of a viral upper respiratory tract infection or the uncomplicated common cold due to rhinoviruses, coronaviruses, human metapneumovirus (MPV), influenza, enteroviruses, parainfluenza, respiratory syncytial virus (RSV), or other circulating viruses.[6,7] When the problem is chronic or recurrent or persistent and unilateral, broader underlying anatomic, obstructive, immunologic, and allergic disorders are considered (Table 21.1).[8–10] Onset in an infant younger than 3 months heightens suspicion of an anatomic anomaly, ciliary dyskinesia, or cystic fibrosis. Accompanying sinusitis, otitis media, or pneumonia at this young age prompts consideration of an immunologic deficiency, especially humoral immunodeficiency (e.g., hypogammaglobulinemia, agammaglobulinemia, human immunodeficiency virus [HIV] infection); neutrophil defect; cystic fibrosis; or ciliary dyskinesia. URIs are conspicuously severe in such instances, with recrudescence occurring almost immediately after discontinuation of antibiotic therapy. Unilateral nasal discharge and obstruction should prompt investigation for a foreign body, mass lesion, or unilateral posterior choanal atresia.

Table 21.2 shows differentiating features of important or common causes of acute mucopurulent rhinorrhea. Allergic rhinitis is included because of its place in the differential diagnosis for older children and adolescents.

TABLE 21.1 Causes of Mucopurulent Rhinorrhea

	Chronic or Recurrent	
Acute	**Underlying Conditions**	**Obstructing Lesions**
Viral nasopharyngitis	Allergy[a]	Polyps
Bacterial sinusitis	Medications or rhinitis medicamentosa[a] (antihypertensive drugs, oral estrogens, α_1-adrenergic agonists, aspirin and nonsteroidal anti-inflammatory drugs)	Congenital nasal anomalies (choanal atresia or stenosis, Tornwaldt cyst, deviated septum)
Acute otitis media		
Streptococcal nasopharyngitis		
Anaerobic bacterial nasopharyngitis (nasal foreign body)		Neuroembryonal mass (dermoid, encephalocele, glioma, teratoma)
Adenoiditis	Cocaine use[a]	Tumor (hemangioma, angiofibroma, neurofibroma, lipoma, craniopharyngioma)
Syphilis	Pregnancy[a]	
Pertussis	Hypothyroidism[a]	
Cerebrospinal fluid rhinorrhea[b]	Immunoglobulin deficiency	Neoplasm (lymphoma, rhabdomyosarcoma, nasopharyngeal carcinoma)
	Human immunodeficiency virus (HIV) infection	
	Cystic fibrosis	
	Ciliary dyskinesia	

[a]Rhinorrhea is characteristically clear, but an opaque, white discharge is not unusual.
[b]Rhinorrhea is characteristically clear.

Causes

Viral Nasopharyngitis

In uncomplicated viral nasopharyngitis or rhinitis, the nasal discharge initially is clear but can become white, yellow, or green due to mucous secretions, dryness, blood, exfoliation of damaged epithelial cells and cilia, and a leukocytic inflammatory response. High fever and persistence of discharge can be seen, depending on the specific viral agent, but they are more common in uncomplicated infection than generally perceived.

In a study of hospitalized children, more than 50% with uncomplicated adenovirus, influenza, parainfluenza, or RSV infection had temperatures greater than 39°C, and 12% had temperatures greater than 40°C; the height of fever in these children was not different from that in children with serious bacterial infection.[11] Fever persisted for 5 or more days in 37% of the children in the study; 20% to 30% of those with adenovirus or influenza A infection had fever for ≥7 days. In another study, nasal discharge or congestion associated with uncomplicated URI persisted for 6.6 days in 1- to 2-year-old children who were in home care and for 8.9 days in children younger than 1 year in out-of-home childcare.[1] In a systematic review of studies on the common cold and nonspecific URIs in children, symptoms resolved in 50% by day 10 and 7, respectively, and in 90% by days 15 and 16.[12,13]

The bacteriology of nasopharyngeal flora in children with uncomplicated viral respiratory illnesses, mucopurulent rhinorrhea, acute otitis media, and sinusitis has been evaluated and compared with that in healthy children.[6,14–21] Viral infection is associated with acquisition of new serotypes of *Streptococcus pneumoniae* and with temporally increased risk of acute otitis media.[20] Quantitative and some qualitative differences in nasopharyngeal flora have been found in children with purulent nasopharyngitis during uncomplicated viral URIs, with excessive isolation rates reported for *S. pneumoniae* and *Haemophilus influenz*ae, *Peptostreptococcus* spp., *Fusobacterium* spp., and *Prevotella melaninogenica*.[14,18,19] Differences may reflect new bacterial acquisition or exuberant proliferation in virus-induced inflammatory mucus or availability of a more robust specimen than in healthy subjects. A high rate (25%–46%) of isolation of *S. pneumoniae* does not exceed that in healthy young children when fastidious technique is used.[21]

In a prospective study, there was no difference in the duration of illness or complications in children with clear or purulent nasal discharge.[15] A large Cochrane meta-analysis concluded no benefit of antibiotic therapy in children with URI or cough.[5,22] In a placebo-controlled, blinded study of 142 children 3 months to 3 years old with mucopurulent rhinorrhea of any duration, antibiotic therapy (e.g., cephalexin) or systemic use of an antihistamine-decongestant, or both, had no effect on the course or complications of mucopurulent rhinorrhea.[14] In a meta-analysis of randomized, controlled trials assessing the effect of probiotics on URIs in children and adults, significantly fewer days of illness and absences from childcare, school, or work occurred in those receiving a probiotic (i.e., *Lactobacillus* or *Bifidobacterium* strains) compared with placebo.[16]

Acute bacterial adenoiditis has been postulated as a cause of purulent nasal discharge when tympanic membranes are normal, *S. pyogenes* is not found in culture specimens, and radiographs show an enlarged adenoid shadow but no sinus abnormality.[23] No study has been performed to validate this entity. Mucopurulent rhinorrhea plus additional clinical features, such as prolonged or new fever, cough or ill appearance; stridor or auscultatory abnormalities can indicate another diagnosis.

TABLE 21.2 Differentiating Among Causes of Nasal Discharge

Characteristic	Viral Nasopharyngitis	Acute Bacterial Sinusitis	Streptococcal Nasopharyngitis	Foreign Body–Related Bacterial Rhinitis	Allergic Rhinitis
HISTORY					
Peak age	Peak in first 2 yr after enrollment in childcare or school	Any	<3 yr	<3 yr	>2 yr
Onset	Acute; dryness, burning in nose or nasopharynx	Insidious with cough day and night or with secondary fever or worsening upper respiratory tract infection symptoms; occasionally, acute, febrile, toxic	Insidious; occasionally acute, febrile, toxic	Insidious	Can be seasonal or perennial; precipitants often identified
Associated symptoms	Nasal congestion, sneezing, malaise	Malodorous breath; head or facial pain, edema		Malodorous breath ± hyponasal voice	Sneezing; nasal congestion, nasal itching; postnasal drip/cough, allergic conjunctivitis with itching and tearing
Fever	Yes/no	No/yes	Low/high	No	No
Duration of discharge	3–15 days	≥10 days	>5 days	Chronic	Seasonal or perennial
PHYSICAL EXAMINATION					
Associated findings	Red, excoriated nares; sometimes acute otitis media	Periorbital swelling, facial tenderness; mucopurulent postnasal discharge	Anterior cervical lymphadenitis; impetiginous lesions below nose	Mouth-breathing	Transverse nasal or lower eyelid creases; infraorbital edema and darkening, conjunctivitis, cobblestoning of conjunctivae or posterior pharynx
Character of discharge	Clear or colored, watery or thick	Thick, colored	Thick, colored	Unilateral, purulent, putrid bloodstained	Watery, clear
Rhinoscopy	Hyperemic mucosa; dry or glazed early, edematous later; crusted discharge	Normal mucosa; discharge from middle meatus	Normal, hyperemic, or excoriated mucosa	Identifiable object (button, pit, nut), boggy mass (vegetable), or rhinolith	Pale or blue, edematous turbinates
DIAGNOSIS					
Diagnostic tests	None; nasal smear shows neutrophils and mononuclear cells ± inclusion bodies, pyknotic epithelial cells	None unless suppurative complications suspected	Nasopharyngeal culture for *Streptococcus* only	Rhinoscopy	Positive allergen skin tests or serum IgE levels, rhinoscopy or nasal smear in rare cases
ETIOLOGY					
Causes	Multiple agents, depending on age and season	*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*	*Streptococcus pyogenes*	Normal nasopharyngeal facultative and anaerobic bacteria	Allergens
TREATMENT					
Therapies	Saline nasal drops, humidification; antibiotic only for secondary bacterial infection (acute otitis media or sinusitis)	Amoxicillin; amoxicillin-clavulanate (14:1 formulation), 90 mg/kg/day of amoxicillin component	Penicillin V	Removal of obstruction; amoxicillin-clavulanate for tissue or sinus complication	Allergen avoidance; glucocorticoid nasal spray, oral antihistamines, antihistamine nasal sprays, leukotriene receptor antagonists, nasal saline irrigation, allergen immunotherapy

Bacterial Sinusitis

Bacterial sinusitis reportedly complicates 5% to 10% of viral upper respiratory tract infections in children.[24] In a prospective study of 236 children 4 to 7 years of age, 8.8% of symptomatic URIs were complicated by sinusitis using the definitions that follow; all episodes met one of the first two definitions.[13] Mucopurulent rhinorrhea or daytime cough (which frequently is worse at night), or both, of 10 or more days' duration without improvement, worsening symptoms (i.e., recrudescence after improvement or new onset of fever), or severe onset of symptoms with fever of 39°C or higher and purulent nasal discharge for at least 3 consecutive days strongly suggests paranasal bacterial sinusitis and response to antibiotic therapy.[25–27]

Guidelines on the diagnosis and management of acute bacterial rhinosinusitis have been published.[24,26,27] Sinus radiographs show significant abnormalities in almost 90% of children 2 to 6 years old and many older children with uncomplicated upper respiratory tract illness, supporting a clinical approach to diagnosis without imaging.

Streptococcal Nasopharyngitis

In children younger than 3 years of age, *S. pyogenes* can be associated with high fever, toxicity, and rhinorrhea or indolent infection with irregular fever and purulent nasal discharge, sometimes with associated excoriation of nares or tender anterior cervical lymphadenitis.[13,18,25] In a streptococcal outbreak studied in a childcare facility for school-aged and young children, 26% of children younger than 3 years of age were affected, but pharyngitis was predominant, with no case of nasal streptococcosis.[28]

Other Infectious Causes

Bacterial nasopharyngitis associated with a nasal foreign body is typified by the young age of the patient and putrid, commonly bloodstained, unilateral nasal discharge. Fever is unusual unless infection has spread to contiguous sinuses or distant sites. *Prevotella, Fusobacterium,* and *Peptostreptococcus* spp., as well as facultative flora, are responsible. Nasal discharge can be the first manifestation of congenital syphilis and a later finding in nasal diphtheria, in which discharge is putrid and sanguineous with pieces of pseudomembrane.

Allergic Rhinitis

Allergic rhinitis is uncommon before 2 years of age. Diagnosis can be suspected because of the season, environmental precipitants, personal and family history of allergy or atopy, other associated symptoms, physical findings, and the response to specific interventions, such as avoidance or pharmacotherapy (see Table 21.2). Nasal secretions typically are clear.

Management

For most children with purulent nasal discharge (even if thick and green) of up to 1 week's duration, the history and setting of illness, associated symptoms, and physical findings suggest an uncomplicated viral URI. Antimicrobial therapy is inappropriate unless acute otitis media or sinusitis is diagnosed from additional findings.[5] Symptomatic therapy with saline nose drops or lavage facilitates expulsion of secretions and provides humidification. Its effectiveness reduces parental pressure to prescribe an antibiotic.[29] Over-the-counter medications should be avoided for children, especially those younger than 6 years of age. Antipyretic or analgesic medication is appropriate for the treatment of fever and discomfort.

If mucopurulent rhinorrhea persists for more than 5 days, especially if the epidemiology or certain findings (e.g., anterior cervical lymphadenopathy, scarlatiniform rash, excoriation around nostrils) heighten the likelihood of streptococcal disease, nasopharyngeal specimens should be obtained for the culture of *S. pyogenes* only. If the culture is positive, penicillin V is given for 10 days. Routine culture for or recovery of *S. pneumoniae, H. influenzae, Moraxella catarrhalis,* or *Staphylococcus aureus* has no meaning and can result in misinterpretation.

If mucopurulent rhinorrhea persists for 10 or more days without diminution, especially if other symptoms are present, paranasal sinusitis is likely. Nasal mucosa is examined after use of a single or second (i.e., 5 minutes after the first) application of a topical vasoconstrictor such as oxymetazoline. If purulent secretions flow from the middle meatus, the diagnosis of acute sinusitis is confirmed. Signs of allergic rhinitis can also be confirmed. An imaging study such as contrast-enhanced computed tomography is performed if suppurative complication of sinusitis is suspected.[26,27]

Patients fulfilling a definition of sinusitis are treated with a high-dose (90 mg/kg/day) of amoxicillin with or without clavulanate as first-line therapy, which has been shown to decrease the duration of symptoms.[30] When antimicrobial therapy is effective, substantial improvement of symptoms is expected within 48 to 72 hours. Therapy is continued for 10 to 14 days in children and at least 1 week after resolution of symptoms.[26]

STRIDOR

Characteristics

Stridor is a rough, high-pitched, monophonic sound caused by passage of air through a narrowed upper airway, which includes the extrathoracic trachea, larynx, and hypopharynx. Because the extrathoracic airway normally narrows during the inspiratory phase of respiration, stridor due to upper-airway disease occurs during inspiration or is more pronounced during inspiration if severe narrowing causes obstruction during inspiration and expiration. Because the intrathoracic trachea normally narrows during expiration, obstruction of the intrathoracic trachea, as occurs with extrinsic compression from a vascular ring or sling or intraluminal obstruction from a foreign body, inflammation, or tracheomalacia, causes a loud noise that is acoustically like stridor and heard during both phases of respiration, but it is more pronounced on expiration. Extrathoracic obstruction (i.e., inspiratory stridor) is associated with prolonged inspiration and underaeration of the chest, whereas intrathoracic obstruction (i.e., expiratory stridor or wheezing) is associated with prolonged expiration and an overinflated chest.

Stridor can be associated with mild tachypnea, but a respiratory rate higher than 50 breaths/min should not be ascribed to upper airway obstruction alone. The degree of obstruction associated with stridor can range from minimal to life-threatening.[31]

The timbre of the stridulous sound provides a clue to the cause. For example, a high-pitched, fixed, dry sound is associated with congenital subglottic stenosis; a wet, rhonchal changing sound with inflammatory laryngotracheitis; and a low-pitched, vibratory, positionally variable sound with laryngomalacia. Associated voice changes also are useful in specifying disease. Vocal cord paralysis causes a weak, dysphonic cry, supraglottic obstruction causes a muffled voice, and laryngotracheitis causes hoarseness or aphonia, frequently with a barking cough.

Etiology

Categorization of the setting and duration of stridor as acute, persistent, or recurrent/episodic provides a framework for considering likely causes (Table 21.3).[31–34] Infections cause most acute upper airway obstruction by means of intraluminal, epithelial inflammation or by encroachment on the airway by reactive or infected lymphoid tissue in parapharyngeal or paratracheal spaces. Viral laryngotracheitis is the most common cause of abrupt-onset stridor in young children.[31] Fungal or viral tracheobronchitis must be considered when stridor occurs in

TABLE 21.3 Causes of Upper-Airway Obstruction and Stridor

Acute	Persistent
INFECTIOUS	**CONGENITAL**
Viral laryngotracheitis (croup)	Laryngotracheal web, cleft, cyst, hemangioma
Bacterial tracheitis	Tracheal stenosis
Epiglottitis, supraglottitis	Vascular ring or sling
Peritonsillar, retropharyngeal, or parapharyngeal abscess	Laryngotracheal malacia
Tracheobronchitis associated with immunodeficiency	Neuromuscular disorder
	Cystic hygroma
NONINFECTIOUS	**ACQUIRED**
Angioedema	Posttraumatic tracheal stenosis
Anaphylaxis	Subglottic stenosis
Foreign body	Foreign-body aspiration
Necrotizing tracheobronchitis in neonates	Mediastinal mass (tumor, lymphatic, vascular)
Recurrent/episodic spasmodic croup	Papilloma (perinatally acquired)
Caustic burns	Posttraumatic spinal cord, vagal or glossopharyngeal nerve, or vocal cord damage
Gastroesophageal reflux	Vocal cord dysfunction or paralysis
	Bulbar neuropathy (infectious, postinfectious, malignant)
	Eosinophilic esophagitis

an immunocompromised child; odynophagia and dysphagia also are common.[32]

Congenital anatomic abnormalities should be considered, especially for infants whose persistent stridor began neonatally. Acquired obstruction can have an abrupt onset and an obvious cause (e.g., foreign body aspiration, necrotizing tracheobronchitis in ventilated neonates) or more insidious onset and an inapparent cause (e.g., expanding laryngotracheal papillomas or hemangioma, an extrinsic compressing mass). The younger the infant, the more likely that sudden obstruction, apnea, or feeding difficulties overshadow a singular complaint of stridor.

Clinical Features of Acute Infectious Causes

Recognition, avoidance of precipitating sudden airway occlusion, and urgent, expert intervention to establish an airway when indicated are paramount to avert disastrous outcomes of acute upper airway obstruction. Table 21.4 shows characteristic features of infectious causes of stridor and acute airway obstruction.[35–42] Viral laryngotracheitis (i.e., infectious croup) or laryngotracheobronchitis due to parainfluenza viruses, especially type 1, is by far the most common.[35,36] Influenza viruses, RSV, adenoviruses, measles, MPV, and other viruses typically cause symptomatic disease elsewhere in the respiratory tract, but during epidemic seasons, stridor is the predominant feature in a minority of infected children.

Bacterial tracheitis usually is a complication of viral laryngotracheitis (with concordant peak age and season) but can occur at any age or as a complication of oropharyngeal surgery.[43] *S. aureus* is the most common cause, followed by *S. pyogenes;* the role of anaerobic bacteria is less clear.[41,43] With the universal use of *H. influenzae* b vaccine, epiglottitis is a rare cause of stridor; current cases of supraglottitis are more likely to affect the aryepiglottic region and to be caused by streptococci and staphylococci. Other agents, including *Fusobacterium* spp. and other anaerobes that can cause parapharyngeal and retropharyngeal infections in children, must be considered because the incidence is increasing[42,44,45] (see Chapter 28).

The history surrounding the onset of stridor and the patient's age and examination findings are the most helpful clues to the likely site and cause of infection. The child with viral laryngotracheitis usually has had 2 to 3 days of a typical URI when cough worsens and stridor begins. The child with bacterial tracheitis usually has had a similar background illness

TABLE 21.4 Differentiating Infectious Causes of Upper Airway Obstruction

Characteristic	Viral Laryngotracheitis	Epiglottitis or Supraglottitis	Bacterial Tracheitis	Retropharyngeal Abscess
HISTORY				
Peak age	6–36 mo	<6 yr, any	2–4 yr, any	2–4 yr
Peak season	Late fall, late spring	Any	Fall, winter; any	Any
Prodrome	Viral illness	Uncommon	Viral illness	Uncommon
Onset of stridor	Gradual	Abrupt	Abrupt	Abrupt
PHYSICAL EXAMINATION				
Peak temperature (°C)	38–39	>39	>39	>39
Predominant findings	Brassy or barking cough, stridor	Toxicity, stridor	Toxicity, stridor	Toxicity, stridor
Associated findings	Bark, rhinorrhea	Sore throat, odynophagia, dysphagia, anxiety, drooling	Brassy cough, anxiety	Lethargy, dysphagia, drooling, trismus
Voice	Hoarse, raspy	Normal, muffled, mute	Hoarse, raspy	Muffled, mute
Position	Any; thrashing	Tripod or sniffing position; stillness; refusing to lie flat	Any; thrashing	Sniffing position; stillness; reluctance to move neck
Airway occlusion	Predictable from degree of stridor	Sudden	Sudden	Sudden
Response to racemic epinephrine	Yes, with rebound	No	No or partial	No
LABORATORY TESTS				
Peripheral neutrophils	Normal or low	High	Immature	Immature
RADIOGRAPHY				
Hypopharynx	Distended	Distended	Distended	Anteriorly displaced
Airway	Subglottic narrowing steeple sign; edema cords	Enlarged epiglottis (thumb sign) and aryepiglottic folds	Subglottic narrowing; irregular trachea ± intraluminal membranes	Prevertebral soft tissue mass with anterior displacement of airway (not valid sign for expiratory film, flexed neck)
ENDOSCOPY				
Examination findings	Red, edematous subglottis and lateral tracheal walls; crusting pseudomembrane	Red, edematous supraglottic structures	Red, edematous, eroded trachea and bronchi; thick purulence, pseudomembrane	Bulging mass in posterior pharyngeal wall; purulence
ETIOLOGY				
Agents	Parainfluenza viruses, especially type 1 (epidemic); other viruses (sporadic)	*Streptococcus pyogenes, Streptococcus pneumoniae, Haemophilus influenzae* b and other *Haemophilus* spp., *Staphylococcus aureus*	*Staphylococcus aureus, Streptococcus pyogenes, Streptococcus pneumoniae*	*Streptococcus pyogenes; Staphylococcus aureus;* rare *Streptococcus pneumoniae*; other oral flora

TABLE 21.5 Expected Course and Sequelae of Acute Infectious Upper Airway Obstruction

Characteristic	Viral Laryngotracheitis	Supraglottitis, Epiglottitis	Bacterial Tracheitis	Retropharyngeal Abscess
Artificial airway (% of cases)	<1	>90	>75	<50 to >75[a]
Median intubation period	4 days	2 days	6 days	2 days
Airway occlusion after intubation	Rare	No	Yes	No
Death during hospitalization	No	No	Yes	No
Airway sequelae (% of cases)	<3	Rare	<3	No

[a]Varies according to age and site (e.g., higher retropharyngeal; lower in older, parapharyngeal and surgical drainage)

and then has sudden onset of high fever, toxicity, and rapid progression to airway obstruction. The young child with retropharyngeal abscess or adolescent with peritonsillar abscess has less stridor but refuses to swallow and has a muffled voice, reluctance to move the neck, and a guarded posture to maximize oropharyngeal airway patency. Trismus is an expected and useful finding in patients with peritonsillar abscess and some lateral pharyngeal space infections of odontogenic origin.[38] Epiglottitis and supraglottitis cause the patient to guard anxiously in a sitting posture with arms back, jaw forward, and chin raised (i.e., sniffing position) to maximize lift of the epiglottis away from the airway. In contrast, subglottic, tracheal obstruction cannot be lessened by position; patients with laryngotracheitis or bacterial tracheitis thrash about with the anxiety of suffocation.

The expected course[36,46,47] and sequelae of acute infectious airway obstruction are shown in Table 21.5. Children with viral laryngotracheitis are less prone to sudden complete obstruction; the hourly course is predictable by degree of stridor and adequacy of aeration. The response to racemic epinephrine and dexamethasone therapy usually averts intubation.[48] In a systematic review of children with croup, symptoms resolved in 2 days for 90%.[12] Establishment of an artificial airway is urgently required for almost all patients with stridor due to acute supraglottitis and bacterial tracheitis and for many with retropharyngeal infection. The course of disease in children with bacterial tracheitis can be further complicated because infection (and obstructive consequences) commonly extends the length of the trachea and below.

COUGH

Characteristics

Cough is a critical protective mechanism to expel particulate matter from the larynx and trachea and is a cardinal sign of infectious and noninfectious respiratory tract and nonrespiratory tract disorders. Occasional acute, life-threatening infectious and noninfectious causes may be overlooked unless the clinician adopts a disciplined diagnostic approach. Careful assessment of a pathologic cough—its onset, duration, clinical context, association with other findings, specific timbre, pattern, and productivity—frequently predicts the site of pathophysiology and narrows the differential diagnosis to a limited number of entities.

Cough usually is defined as acute (<3 weeks), subacute (3–8 weeks), or chronic (>8 weeks). A wet or moist cough in children, frequently referred to as *productive*, is associated with detectable secretions by bronchoscopy and can be reported accurately by parents and clinicians.[47]

Etiology

A dry cough is expected in allergic rhinitis/sinusitis and asthma, and a wet cough is typical in infectious sinusitis, bronchiolitis, bronchiectasis, and pneumonia. In a systematic review of self-limited URIs, acute cough symptoms resolved by day 10 after onset in 50% and by day 25 after onset in 90% of children.[12] Isolated subacute cough (in absence of other symptoms), which usually is dry and follows a viral infection, frequently is related to increased cough receptor sensitivity.[49] Chronic cough (≥8 weeks) is pathologic. If the durations of 4 to 8 weeks are included, many coughs are postinfectious and resolve spontaneously.[50–52]

The differential diagnosis can be focused by age, history, and clinical findings. The algorithms for sequential evaluation and management sometimes are complex[50,51,53,54] and best performed by a pediatric pulmonologist. Most common causes of chronic cough in older children are allergic or nonallergic rhinitis and sinusitis, asthma, protracted bacterial bronchitis, and gastroesophageal reflux disease.[50–56] An important minority of children have cystic fibrosis, non– cystic fibrosis bronchiectasis, immunodeficiency disorders, or ciliary dyskinesia. These diagnoses are considered especially in the preschool-age child with chronic cough.[53]

Management focuses on determining the cause. No evidence supports the use of medications aimed at symptomatic relief of acute or chronic cough, and some data suggest harmful effects are possible.

Cough should not be accepted as a sign of a self-limited URI in infants younger than 3 months of age. The mnemonic CRADLE, which is used to recall the differential diagnoses for cough in infants,[57] refers to cystic fibrosis (C); respiratory tract infections (R), especially pneumonia and pertussis; aspiration (A) due to swallowing dysfunction, gastroesophageal reflux, or tracheoesophageal fistula; ciliary dyskinesia (D); lung, vascular, or airway malformations (L); and edema (E) due to heart failure or pulmonary lymphangiectasia.

Table 21.6 provides a framework for consideration of cough illnesses. There is considerable overlap in symptoms of cough caused by certain infectious agents, such as *Bordetella pertussis* or *Mycoplasma pneumoniae* in adolescents[58] because of a common tracheobronchial site of pathophysiology and frequent dual infections.[59] *B. pertussis* causes a dramatic, debilitating, paroxysmal cough without airway or lower tract abnormalities (unless secondary pneumonia occurs, leading to fever and toxicity), whereas *Chlamydia trachomatis* causes pneumonia with prominent tachypnea: the cough is important only because it brings the child to medical attention (see Chapters 162 and 167). Diagnosis of pneumonia is based on signs of lower respiratory tract involvement, such as tachypnea and retractions, in addition to cough, and the likely causative agent is determined from the constellation of clinical findings (Tables 21.7 and 21.8).

Protracted bacterial bronchitis is inadequately studied, but it may be an underdiagnosed cause of chronic wet cough for which antibiotic therapy may be appropriate.[60] Confirmation rests on bronchoscopic findings of dense bacteria and an acute neutrophilic inflammatory response.[61] Because isolated bacteria are those found commonly in oropharyngeal flora, acute otitis media, and sinusitis, some pulmonologists prescribe a diagnostic or therapeutic trial of amoxicillin-clavulanate for 2 weeks for patients with a typical isolated episode of chronic cough.

TACHYPNEA AND OTHER SIGNS OF LOWER RESPIRATORY TRACT DISORDERS

Tachypnea can be a voluntary or involuntary response to anxiety, fright, or pain; an abnormal breathing pattern related to central nervous system dysfunction; or the physiologic response to increased temperature or metabolic state. Most commonly, tachypnea is the response to respiratory acidosis or hypoxemia of acute infection or the attempt to restore pH balance during metabolic acidosis (e.g., diabetes, salicylate poisoning, dehydration). Metabolic causes should not be forgotten while the clinician pursues the much more likely primary pulmonary causes. Tachypnea can result from primary cardiac abnormalities (e.g., congestive heart failure, cyanotic congenital heart disease), pulmonary vascular abnormalities (e.g., cardiac shunts, capillary dilatation, hemorrhage, obstructed return to the heart, infarction), impaired lymphatic flow (e.g., congenital

TABLE 21.6 Differentiating Among Causes of Cough

Cause	Peak Age	Nature of Cough	Cough as Dominant Feature	Anticipated or Associated Findings
INFECTIONS OF THE RESPIRATORY TRACT				
Viral laryngotracheitis	<5 yr	Brassy, painful	Yes	Hoarse, raspy voice; viral URI complex[a]
Viral laryngotracheitis or laryngotracheobronchitis	6–36 mo	Barking, brassy	Codominant with stridor	Stridor, hoarseness, viral URI complex[a]
Mycoplasma pneumoniae	Adolescent	Hacking, paroxysmal, painful	Yes	Prodromal, fever, headache, myalgia; then gradual worsening cough; crackles
Pertussis	Infancy, adolescence	Sudden paroxysm of explosive, machine-gun bursts (15–30 per breath) when beyond neonatal age	Yes	Bulging, watering eyes during paroxysm, posttussive emesis; skin and conjunctival hemorrhages; afebrile, without lower respiratory tract symptoms or symptoms between paroxysms
Chlamydia trachomatis pneumonia	1–3 mo	Staccato, dry (single cough per breath)	Yes	History can include prior/concurrent conjunctivitis; afebrile, tachypnea, crackles
Bronchiolitis	4 mo–2 yr	High-pitched or grunt	No	Wheezing, rhinorrhea, respiratory distress; ± fever
Pneumonia (bacterial or viral)	Any	Wet, productive or nonproductive	Codominant with respiratory distress	Tachypnea, rales, respiratory distress; fever
Pleurodynia	Any	Inspiratory hitch; expiratory grunt	Codominant with chest pain	Chest pain; costochondral tenderness
Sinusitis	Any	Irritative; occurs during day and worsens at night	Sometimes	Mucopurulent rhinorrhea, postnasal discharge; facial pain, swelling, or tenderness; headache; ± fever
Tracheoesophagitis (fungal or viral)	Any	Irritative	No	Odynophagia or dysphagia; immune-compromised host; hoarseness; oropharyngeal lesions
Cystic fibrosis	<2 yr; any	Wet, productive; paroxysmal, hacking	Sometimes	Poor growth; persistent and recurrent sinusitis, pneumonia; digital clubbing
Protracted bronchitis	Any; mean, 8–9 yr	Wet, productive; >8 wk	Yes	Bronchoscopy; neutrophils, bacteria, cytokines; response to antibiotic
OTHER CONDITIONS				
Purulent pericarditis	Any	Grunt	Sometimes	Fever, toxicity, respiratory distress or dyspnea; displaced point of maximum impulse; muffled heart sounds
Myocarditis	Any	Grunt	Sometimes	Fatigue, dyspnea, tachypnea; ± fever
Congestive heart failure	Any	Grunt, wet, or brassy	Sometimes	Fatigue, dyspnea, sweating, tachycardia, tachypnea; ± fever; distended neck veins, liver
NONINFECTIOUS AIRWAY ABNORMALITIES				
Gastroesophageal reflux	6 wk–6 mo	High-pitched, dry	Codominant with other symptoms	Stridor, choking, gagging, irritability, arching (Sandifer syndrome) ± regurgitation, pneumonia
Reactive airway, asthma	6 mo–adolescence	Irritative dry, repetitive (not paroxysmal); night especially	Sometimes	Atopic, precipitants, seasonal; ± wheezing; response to β-agonist
Congenital vascular rings, pulmonary sling	Infancy	Brassy	No	Stridor; onset of symptoms in first month of life
Compression on airway or glossopharyngeal or phrenic nerve	Any	Irritative, dry	Sometimes initially	Can be positional (tumors, other masses), associated with other neuropathies, stridor, changes in phonation
Habit cough	Adolescence	Vibratory, low-pitched, honking; disappears with sleep	Yes, sole feature	"La belle indifference"; family dynamics and other somatization

[a]Viral upper respiratory tract infection (URI) complex consists of fever, rhinorrhea, sore throat, conjunctivitis, exanthem, and enanthem.

lymphangiectasia, tumor), or pleural fluid collections (e.g., hemorrhagic, purulent, transudative or lymphatic fluid, an infusion from a misplaced vascular catheter).

Clinical practice guidelines for management of community-associated pneumonia in infants and children by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America include an excellent literature review of clinical findings.[62] Table 21.7 shows symptoms and signs of pneumonia in infants and children. Tachypnea is thought to be the best clinical predictor of lower respiratory tract infection in children. The World Health Organization (WHO) defines pneumonia primarily as cough or difficult breathing and tachypnea. The definition of tachypnea is related to age, with a respiratory rate of >60 breaths/min in infants aged 0 to 2 months, >50 in infants 2 to 12 months, >40 in children 1 to 5 years, and >20 in children older than 5 years of age.[63,64]

Tachypnea has a sensitivity of 50% to 85% for the diagnosis of lower respiratory tract infection and a specificity of 70% to 97%.[65,66] At less than 24 months of age, the younger the patient, the less likely that pneumonia is the diagnosis if tachypnea is absent. In one study, for infants younger than 2 months of age, a respiratory rate of 60 breaths/min, retractions, or nasal flaring had sensitivity for the diagnosis of pneumonia of 91%.[66] In a study from a U.S. emergency department of children younger than 5 years who were undergoing chest radiography for possible pneumonia, respiratory rates in those with or without documented pneumonia did not differ significantly. However, 20% of those with WHO-defined tachypnea had pneumonia confirmed compared with 12% of those who did not.[67]

Obtaining chest radiographs for febrile infants without an apparent focus of infection to exclude pneumonia missed by physical examination has a low yield in the absence of tachypnea.[68,69] Cough is a more sensitive but nonspecific symptom of pneumonia. Other symptoms and signs associated with pneumonia, such as nasal flaring, intercostal retractions, and cyanosis, have lower sensitivity (25%, 9%, and 9%, respectively) but high specificity (87%, 93%, and 94%, respectively).[65] Although fever, cough, and tachypnea are cardinal features, they can be overshadowed or overlooked in patients who come to medical attention for pneumonia-associated stiff neck, abdominal pain, or chest pain or for nonspecific symptoms of illness, such as feeding difficulty in infants. Although a chest radiograph is not routinely needed for children with any of these complaints, it should be considered if the patient has fever and cough or tachypnea.[70,71] Classic symptoms of pneumonia reported in adolescents and adults are fever, chills, pleuritic chest pain, and cough that produces purulent sputum, with less noticeable tachypnea.

Grunting is an expiratory sound produced in the larynx when vocal cords are adducted to generate positive end-expiratory pressure (i.e., self-induced PEEP) and increased resting volume of the lung. Its causes are myriad but never trivial. Grunting can be a sign of surfactant deficiency in the neonate or of pulmonary edema, foreign body aspiration, severe pneumonia, mediastinal mass or severe mediastinal shift from any cause, pleuritic or musculoskeletal chest pain, or myopericarditis or other cardiac abnormalities at any age.[72] Retractions (i.e., intercostal, subcostal, or suprasternal) and grunting have been associated with severe pneumonia, and nasal flaring and head bobbing with hypoxemia.

TABLE 21.7 Symptoms and Signs of Pneumonia

Symptoms	Signs	Physical Examination Findings
Fever	Fever	Crackles (rales)
Cough	Cough	Wheezes (depending on cause)
Rapid breathing	Tachypnea	Diminished breath sounds
Difficulty breathing	Dyspnea	Bronchial (tubular) breath sounds
Vomiting	Retractions	Dullness to percussion
Poor feeding	Nasal flaring	Decreased tactile and vocal fremitus
Irritability	Grunting	Meningismus (upper lobe, bacterial)
Lethargy	Splinting	Ileus (lower lobe, bacterial)
Chest pain	Apnea	Pleural friction rub (pleural fluid)
Abdominal pain		
Shoulder pain		

TABLE 21.8 Clinical Features of Pneumonia in Infants Younger Than 3 Months

Characteristic	Respiratory Syncytial Virus	Other Respiratory Viruses	*Chlamydia trachomatis*	Pertussis[a]
HISTORY				
Season	Winter	Unique to each	Any	Any; peak July–October
Onset	Acute, days	Acute, days	Insidious	Progressive, days
Illness in others	URI	URI, flu, croup	No	Cough
Fever	Half of cases	Most cases	No	No
Cough	Yes	Yes	Yes/staccato	Yes/paroxysmal
Associated features	Apnea, URI	URI, croup, conjunctivitis	Conjunctivitis (prior or current)	Apnea, cyanosis, posttussive emesis
PHYSICAL EXAMINATION				
Predominant feature	Respiratory distress	Respiratory distress	Cough	Cough
General appearance	Ill, not toxic	Ill, not toxic	Well, tachypneic	Well between paroxysms
Degree of illness: respiratory findings	Degree of illness = findings	Degree of illness = findings	Findings > degree of illness	Ill only during cough
Auscultation	Wheezes, coarse crackles	Crackles, wheezes	Diffuse crackles	Clear
LABORATORY STUDIES				
Chest radiograph	Hyperaeration, subsegmental atelectasis, peribronchial cuffing	Hyperaeration, ± peribronchial thickening, ± diffuse interstitial infiltrates	Hyperaeration, diffuse alveolar and interstitial infiltrates	Normal or perihilar infiltrate
White blood cell count	Normal or lymphocytosis	Normal, lymphocytosis, neutropenia	Eosinophilia	Lymphocytosis; no eosinophilia
Other findings	Hypoxemia	—	Increases in IgG, IgA, IgM	—
Diagnostic tests	Nasal wash EIA, DFA, PCR	Nasal wash EIA, DFA, PCR	Conjunctival, NP DFA, EIA	NP, PCR, culture

[a]Pertussis is included in this table because it should be considered in young infants with cough and respiratory distress, although pneumonia is characteristically absent.
DFA, direct fluorescent antibody (test); EIA, enzyme immunoassay; Ig, immunoglobulin; NP, nasopharyngeal specimen; PCR, polymerase chain reaction; URI, upper respiratory tract infection.

Adventitial respiratory sounds usually indicate lower respiratory tract disease, pulmonary edema, or hemorrhage. *Wheezes* are continuous musical sounds made predominantly on expiration and are a sign of airway obstruction. Widespread bronchiolar narrowing, as most commonly occurs with the inflammation of virus-associated lower respiratory tract infection, produces heterophonous, high-pitched, sibilant wheezes of variable pitch and presence in different lung fields.[73] Fixed obstruction in a larger airway, as from a foreign body or anomaly, produces a homophonous, monotonous wheeze. The rate of radiographically confirmed pneumonia among children with wheezing is low (<5% overall and 2% in the absence of fever).[70]

Rhonchi, sometimes also called low-pitched wheezes or coarse crackles, are nonrepetitive, nonmusical, low-pitched sounds frequently produced during early inspiration and expiration that usually are a sign of turbulent airflow through secretions in large airways. *Fine crackles,* the term preferred by pulmonologists over *rales* (which has a variety of meanings in different languages) are high-pitched, low-amplitude, end-inspiratory, discontinuous popping sounds indicative of the opening of peripheral air-fluid interfaces. Fine crackle is the auscultatory finding suggesting the diagnosis of pneumonia.

Auscultatory abnormalities of crackles and wheezing have disparate diagnostic usefulness in various studies, depending on the categorization of bronchiolitis. Tachypnea is a more sensitive finding than crackles for bacterial pneumonia; wheezing is more sensitive than tachypnea for bronchiolitis.

Diminished or distant breath sounds, dullness to percussion, and decreased vocal fremitus indicate parenchymal pulmonary consolidation, pleural mass, or fluid collection. *Bronchial* (*tubular*) *breath sounds* have a low-pitched sound of similar intensity throughout inspiration and expiration, as is heard normally in the intrascapular area. Bronchial breath sounds, dullness to percussion, and increased vocal fremitus over an anatomically (tubular) confined lung field indicate parenchymal consolidation, atelectasis, or another continuous tissue or fluid density juxtaposed between a bronchus and the chest wall.

Radiographic infiltrates have been reported in 5% to 19% of children with fever in the absence of symptoms or signs of lower respiratory tract infection.[74,75] Rate of pneumonia deemed occult fell from 15% to 9% after universal vaccination with 7-valent pneumococcal conjugate vaccine (PCV7) in one study.[70] Clinical features associated with occult pneumonia in another study included cough, fever of more than 5 days' duration, fever greater than 39°C, and leukocytosis greater than 20,000 cells/mm^3; only 5% of children without cough had radiographically confirmed pneumonia.[74]

DIFFERENTIATING FEATURES OF PNEUMONIA

Pneumonia in Young Infants

In young infants, acute infection with bacterial and nonbacterial respiratory tract pathogens frequently leads to lower respiratory tract infection. Except in the first few days of life, when pneumonia predominantly is caused by bacteria acquired from the mother's genital tract or organisms acquired transplacentally, nonbacterial pathogens are overwhelmingly predominant.[72] As perinatally acquired agents persist, community exposures increase, and maternally derived antibody protection wanes, the infant between 3 weeks and 3 months of age is vulnerable to a unique array of lower respiratory tract pathogens.[76]

The clinical setting, specific symptom complex, and severity of illness in proportion to findings on physical examination aid identification of likely causes and guide the diagnostic and therapeutic approach (see Table 21.8). Although the pathogens listed in Table 21.8 frequently are referred to as causing afebrile pneumonia, this is a misnomer because *B. pertussis* infrequently causes lower respiratory tract abnormalities, and RSV and especially other respiratory viruses frequently cause fever.[11,72,77,78] A causal role for *Ureaplasma urealyticum* is not completely defined because the situation is confounded by the asymptomatic presence of this organism in women and young infants. Pneumonia due to *Pneumocystis jirovecii* probably is confined to infants with severe debilitation or immune defects.

Pneumonia in Older Infants, Children, and Adolescents

Table 21.9 categorizes the features of acute pneumonia in older infants, children, and adolescents by cause. No single fact in the medical history or examination finding is unique for any agent, but when taken together, a working diagnosis emerges and guides intervention or further diagnostic testing. Chest radiography and laboratory tests usually are reserved for patients who are ill and hospitalized or whose clinical picture is not compelling for a category of etiologic agents.

TABLE 21.9 Clinical Features of Acute Pneumonia in Children and Adolescents

Characteristic	Bacteria	Virus	Mycoplasma	Tuberculosis
HISTORY				
Age	Any; infants especially	Any	School age	Any; <4 yr and 15–19 yr especially
Temperature (°C)	Most ≥39	Most <39	Most <39	Most <39 (unless empyema)
Onset	Abrupt	Gradual	Worsening cough	Insidious cough
Others in home ill	No	Yes, concurrent; upper respiratory tract infection, rash, conjunctivitis	Yes, weeks apart; pharyngitis, flulike illness, cough	Yes, persistent cough
Associated signs, symptoms	Toxicity, rigors	Myalgia, rash, mucous membrane involvement	Headache, sore throat, chills, myalgia, rash, pharyngitis, myringitis, chest pain	Weight loss, night sweats (late)
Cough	Wet, productive	Nonproductive	Hacking, paroxysmal, usually nonproductive	Irritative or productive
PHYSICAL EXAMINATION				
Predominant feature	Toxicity, respiratory distress	Respiratory distress	Cough	Persistent cough
Degree of illness: respiratory finding	Degree of illness > findings	Degree of illness ≥ findings	Degree of illness < findings	Well: no findings (+ cough); ill with findings
Pleuritic chest pain	No/yes	No	No	No/occasional
Auscultation	Unilateral, anatomically confined crackles or none; dullness, diminished or bronchial/tubular sounds	Diffuse, bilateral crackles, wheezes, rhonchi	Unilateral, anatomically confined crackles; ± wheezes	Most normal; or unilateral crackles ± dullness

Continued

TABLE 21.9 Clinical Features of Acute Pneumonia in Children and Adolescents—cont'd

Characteristic	Bacteria	Virus	Mycoplasma	Tuberculosis
LABORATORY STUDIES				
Chest radiograph	Hyperaeration, patchy alveolar infiltrate or consolidation in lobe, segment, subsegment	Hyperaeration, interstitial infiltrate in diffuse or perihilar distribution; "wandering" atelectasis	Patchy alveolar and/or interstitial infiltrate in single or contiguous, usually unilateral lower lobe or lobes; perihilar adenopathy	Patchy alveolar infiltrate in single or contiguous lobes with disproportionate hilar adenopathy; miliary or lobar consolidation
Pleural fluid	No/yes (large)	No/yes (small)	No/yes (small to moderate)	No/yes (small, large)
Peripheral white blood cell count (cells/mm^3)	Most cases >15,000; neutrophils ± bands	Most cases <15,000; lymphocytes	Most cases <15,000; neutrophils	Most cases <15,000; neutrophils, monocytes
Sputum	Copious, purulent; neutrophils, abundant bacteria	Scant mucoid; epithelial, mononuclear cells	Scant mucoid; mixed mononuclear cells/ neutrophils	Scant to copious; neutrophils (if copious)
Diagnostic tests	Sputum Gram stain, culture; blood culture	Nasal wash, throat, bronchoscopy specimen for antigen detection, polymerase chain reaction (PCR); acute and convalescent serology	Throat, nasal, bronchoscopy specimen for PCR; cold agglutinins (≥12 years); acute and convalescent serology	Gastric aspirate; sputum stain and culture; tuberculin skin test or interferon γ release assay (IGRA) (≥5 yr old)

Several studies using complex diagnostic methods have confirmed the specific cause of pneumonia in 45% to 85% of cases.[77–81] Viral causes predominate, and most are amenable to diagnosis.[77] The efficacy trial and postmarketing studies of PCV7 infer that *Streptococcus pneumoniae* is a relatively common cause of pneumonia with patchy or consolidative infiltrates.[82,83] Use of the urine antigen detection test in children with lobar pneumonia also supports the important role of *S. pneumoniae*[84]; however, the test is positive for more than 15% of children with asymptomatic colonization and not recommended for diagnosis.[85]

A Cochrane systematic review of clinical symptoms and signs of *Mycoplasma* pneumonia found the absence of wheezing and presence of chest pain were significant associations.[86] Serologic testing for *M. pneumoniae* using an IgM enzyme immunoassay is problematic because of false-positive test results.[62,87] Detection in throat or nasal specimens using polymerase chain reaction methods is highly sensitive, but the meaning requires clinical interpretation and further study. Ascribing a causal role of pneumonia to *Chlamydophila pneumoniae* is confounded by the findings of prolonged asymptomatic carriage and inconsistent serologic results among studies.[88]

HEMOPTYSIS

Hemoptysis, defined as coughing up blood that originated below the larynx, is uncommon in children. More commonly, blood originates from the upper airway due to epistaxis or other sources. Mechanisms of hemoptysis include bleeding from congenital or acquired abnormal bronchial or pulmonary blood flow, venous obstruction, or vascular abnormalities; immune-mediated endothelial damage; or infectious or traumatic erosion of tracheal, bronchial, or bronchiolar epithelium. Hemorrhage can be mild (e.g., tracheitis, tracheobronchitis) or massive (e.g., congenital malformations, foreign body, bronchiectasis, pulmonary hemosiderosis).

Causes of hemoptysis in children are listed in Table 21.10. Infection is a common cause of hemoptysis, including pneumonia from various causes, including tuberculosis and *Aspergillus*. In a 10-year retrospective study from Texas Children's Hospital, cystic fibrosis patients accounted for 68% of hemoptysis episodes overall.[89]

A chest radiograph, bronchoscopy, coagulation studies, and computed tomography are useful diagnostic modalities in most cases of hemoptysis. If negative, a cardiac evaluation including echocardiography and studies for autoimmune vasculitides may be indicated. Digital subtraction angiography, pulmonary arteriography, or lung biopsy may be indicated.

All references are available online at www.expertconsult.com.

TABLE 21.10 Causes of Hemoptysis in Children

Epithelial Damage	Vascular Abnormality or Damage
Acute infection (bacterial, fungal, mycobacterial)	Congenital heart disease or pulmonary vascular anomalies (venous obstruction, arteriovenous fistula)
Bronchiectasis (cystic fibrosis, non–cystic fibrosis, immunodeficiency)	Congenital malformation (pulmonary sequestration)
Foreign body	Autoimmune vasculitis (systemic lupus erythematosus, microscopic polyangiitis, granulomatosis with polyangiitis, inflammatory bowel disease, Goodpasture syndrome, Henoch-Schönlein purpura, Churg-Strauss)
Trauma (airway or chest, suffocation)	Idiopathic pulmonary hemosiderosis
Tumor (primary airway or pulmonary, metastatic)	Nonspecific endothelial damage (chemical, drug)
Miscellaneous (inhalation medications, factitious)	Coagulopathy
	Tumors

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