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26 BRONCHITIS

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Bronchitis is a component of almost all (if not all) airway diseases. In the literal translation of the word, *bronchitis* refers to inflammation of the bronchus or bronchi. However, bronchitis has different major overlapping constructs based on duration (e.g., acute, subacute, chronic), inflammation type (e.g., neutrophilic, eosinophilic, lymphocytic, neurogenic), phenotype, and clinical syndromes (e.g., acute bronchitis, laryngotracheobronchitis, protracted bacterial bronchitis, aspiration bronchitis) (Fig. 26-1). A diagnostic entity may have varying types of airway inflammation (Table 26-1). For example, acute viral bronchitis is associated with both lymphocytic and neutrophilic inflammation. Although the type of airway inflammation does not distinguish etiology of the bronchitis in children, it provides supportive diagnosis. Cough is the dominant symptom when bronchitis is present, other than when bronchitis is very mild.

General Annotations on Cough

In countries where data are available, cough is the most common symptom that results in new medical consultations.[1,2] In the United States, 29.5 million doctor visits per year are for cough.[3] In Australia, acute bronchitis/bronchiolitis is consistently the most common new problem encountered by general practitioners, ranging from an annual rate of 2.2 to 3.2 per 100 encounters (1999 to 2009 data).[2] The burden of cough is also reflected in the billions of dollars spent annually on over-the-counter (OTC) cough medications, as well as the number of consultations (per child) sought for cough. In an Australian pediatric study, the number of medical consultations for coughing illness in the last 12 months was high: >80% of children had ≥5 doctor visits, and 53% had >10 visits.[4]

Evaluating Cough

Children with cough require a systematic evaluation and approach. A complete review of cough is beyond the scope of this chapter, and readers are referred elsewhere for an evidenced-based approach[5] and guidelines.[6–8] The overall evaluation entails defining the etiology (which includes assessing if further tests and or treatment are required); the exacerbation factors (e.g., exposure to environmental tobacco smoke [ETS]), and the expectations and effect on the child and family. Treatment should be etiology-based. When a clear etiology cannot be identified and medications are trialed, reassessment of the child is recommended in 2 to 3 weeks (the "time to response" for most medications).[6,7] Also, clinicians should be cognizant of the "time-period effect" and "placebo effect." The placebo effect is as high as 80% in cough studies.[9] The time-period effect[10] refers to the spontaneous resolution of cough with time. It has been described that parents who wanted medicine at the initial visit reported more improvement at follow-up, regardless of whether the child received drug, placebo, or no treatment.[11] Therefore, one must predetermine the time factor and *a-priori* definition of what constitutes an improvement in cough because the studies that do not predefine these issues have limited validity.

Defining Etiology

The most likely etiology depends on the setting; selection criteria of children studied; follow-up rate; and depth of clinical history, physical examination, and investigations performed. In defining the etiology, it is helpful to define cough types in accordance to different constructs. Pediatric cough can be classified in several constructs based on (1) timeframe (acute, chronic), (2) likelihood of an identifiable underlying primary etiology (e.g., specific and nonspecific cough), and (3) characteristic (wet versus dry). For clinical practicality, timeframe is commonly used, divided into acute (<2 weeks), subacute (2 to 4 weeks) and chronic (>4 weeks) cough. No studies have clearly defined when cough should be defined as chronic (variably defined from >4 to 8 weeks).[6–8] Cough related to an upper acute respiratory infection (ARI) resolves within 10 days in 50% of children and by 25 days in 90%;[12] Arguably, childhood chronic cough should be defined as persistent daily cough of >4 weeks. This duration includes a "safety factor" in the recognition that foreign body airway aspiration is not uncommon in children, and thus a systematic approach is required in those with chronic cough because they are likely to have a complicated ARI or other etiology.

Exacerbation Factors

When reviewing any child with cough irrespective of etiology, exacerbation factors including exposure to environmental pollutants (e.g., ETS) should be explored. However, outside of epidemiologic studies, chronic cough should not be simply ascribed to ETS exposure. Cohort studies on children with chronic cough have shown that cough resolution was still achieved in children exposed to ETS,[13,14] including a cohort with high exposure rates (56%).[13] This suggests that, while ETS is undoubtedly associated with increased coughing illnesses and is an important contributing factor, ETS alone is not the sole etiology. Other exacerbation factors include exposure to other pollutants[15] and secondary gain from having a cough (e.g., attention from parents, missing school).

Expectations and Effects

Parents of children with chronic cough do not have symptoms of anxiety or depression but are stressed.[4] This is in contrast to adults with chronic cough, which is

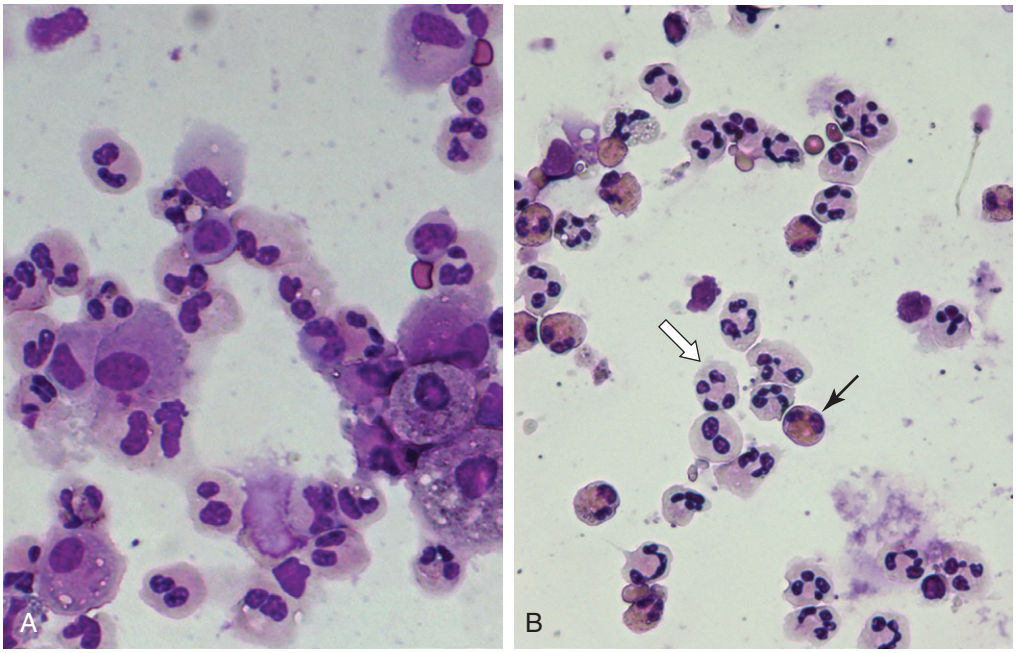

FIGURE 26-1. Micrographs of BAL cytospins showing different types of inflammation. **A,** Neutrophilic inflammation in BAL of a child with protracted bacterial bronchitis. **B,** BAL showing eosinophilic *(black arrow)* and neutrophilic *(clear arrow)* inflammation in a child with bronchiectasis and strongyloides infection.

TABLE 26-1 DOMINANT TYPE OF AIRWAY CELLULARITY IN COMMON CHILDHOOD DISEASES WITH BRONCHITIS

INFLAMMATION TYPE	EXAMPLES OF DISEASE	OTHER KEY AIRWAY MAKERS
Neutrophilic	Acute viral infection[69] Bronchiectasis[70,71] Cystic fibrosis[72] Protracted bacterial bronchitis[44] Chronic lung disease of prematurity[73] Severe bronchiolitis[74] Aspiration lung disease	Soluble intercellular adhesion molecule-1 Elevated IL-8, neutrophil elastase, TNF-α Elevated IL-8, neutrophil elastase, proteases Elevated IL-8, MMP-9 Proinflammatory cytokines and chemokines Myeloperoxidase, CD11b
Eosinophilic	Atopic asthma[75] Helminth infections (e.g., toxocara and strongyloides)*[71] Allergic bronchopulmonary aspergillosis*[76]	Elevated nitric oxide in steroid naïve Neutrophilic inflammation may also be present with elevated IL-8 and MMP-9[76]
Lymphocytic	Acute viral infection[69] Bronchiolitis obliterans[77] Autoimmune disease*[78]	Soluble intercellular adhesion molecule-1
Neurogenic	Post-RSV infection[79] Cough with gastroesophageal reflux[80]	substance P, nerve growth factor

*Data from nonpediatric studies.
IL, Interleukin; *MMP,* matrix metalloproteinase.

associated with the presence of depression and anxiety.[16] Thus clinicians need to be cognizant of the stress parents have when dealing with children with chronic cough and discuss expectations and fears. The reasons for parental fears and concerns include etiology of the cough, risk of choking, and the possibility of long-term respiratory damage.[4,17,]

Clinical Phenotypes or Syndromes of Childhood Bronchitis

While bronchitis is present in airway diseases, several clinical phenotypes of childhood bronchitis are characteristic and discussed in the following paragraphs. Other conditions associated with bronchitis (e.g., aspiration,

asthma, bronchitis associated with other pathogens such as tuberculosis, and laryngotracheobronchitis) are discussed in other chapters. The precise mechanisms underpinning acute bronchitis will vary depending on the insulting agent (i.e., the properties of the infectious agent) and the host's characteristics (e.g., pre-existing conditions) and response (e.g., the host's innate and adaptive immunity, and genetic predisposition to intensity of inflammation).

Acute Bronchitis

Acute bronchitis has a dedicated code in the International Classification of Disease (ICD). It is a nonprecise term and often overlaps with other conditions of the respiratory tract. The most common cause of acute cough, acute bronchitis is caused by viral ARIs.[18] Fifty-six percent of children with ARI are still unwell 4 days after initial consultation. The percentage decreases to 26% on the 7th day and to 6% by the 14th day.[19] However, cough was not specifically reported in the study.[19] A systematic review on the natural history of acute cough in children 0 to 4 years of age in primary care reported that the majority of children improve with time, but 5% to 10% progress to develop protracted bronchitis or pneumonia.[20] A prospective community-based study in 600 families in Melbourne, Australia,[21] found that most acute bronchitis episodes last 2 to 5 days. Leder and colleagues[21] also described that children younger than 2 years of age were more likely to have at least one respiratory infection, a higher number of episodes per person, and the longest episode duration (6.8 days).[21] The frequency of ARIs was age-dependent, with a reduction in incidence with increasing age. Yearly rate per person was 3.8 in children 0 to 1 years of age; 3.3 in children 2 to 3 years of age; 2.8 in children 4 to 5 years of age; 2.2 in children 6 to 10 years of age; and 2 in children 11 to 20 years of age.[21] Bearing in mind the different definitions and sampling frames, studies from developing countries show higher rates of ARIs (3.7 to 14.9 per child per year).[21]

Etiology of Acute Bronchitis

Any pathogen that infects the respiratory tract can cause bronchitis. These include viruses, bacteria, mycoplasma, chlamydia, fungi, and helminths. However, only viruses, bacteria, mycoplasma, and chlamydia are considered in the clinical phenotype of acute bronchitis. Respiratory viruses are the most common etiology.[22,18] Importantly, 17% to 33% of infections involve co-infections with (single or multiple) viruses or bacteria.[23,24] In developed countries, both viral and bacterial infections are likely to be self-limited. Common respiratory viruses in children are human rhinovirus (HRV), coronaviruses, respiratory syncytial virus (RSV) (A and B), parainfluenza (1 to 3), influenza, adenovirus, and human metapneumovirus (hMPV).[18] In birth cohort studies,[22] the most common respiratory pathogens were found to be HRV, followed by RSV and coronavirus. More and more new respiratory viruses are being identified, and recent additions include subtypes of HRV, human enteroviruses (HEVs), and human parechoviruses (HPeVs).[25] Although some viruses are more commonly associated with certain syndromes (e.g., RSV causes bronchiolitis and parainfluenza causes croup), any of these respiratory pathogens can cause acute bronchitis. With modern molecular techniques, co-infections are also found[25] in both symptomatic and asymptomatic children.[18,26] In a study on children with asthma exacerbations, viral co-detections occurred in 25.6% of children.[27] While co-infections were associated with lower asthma quality of life scores upon presentation than were single viral detections, the recovery phase (including symptoms of acute bronchitis) was not influenced by the presence or absence of virus.[25] There is no consensus in the literature about the relationship between clinical severity and co-detection of viruses. Persistence of symptoms is most likely to indicate a bacterial infection, either as a consequence of altered immunity from the initial viral insult[28] or a primary infection.[29]

Management of Acute Bronchitis

Viral ARIs are the most common cause of acute cough in children, and most affected children do not visit doctors. However when they do, children need to be assessed adequately for other respiratory etiologies (e.g., inhalation of a foreign body) and other infections (e.g., pneumonia and bronchiolitis). Complications develop in 8% to 12% of children with upper ARIs.[12] Fever alone, or fever with chest signs was found to be good predictors for complications in children with cough. However, the discriminatory ability is weak[30] and, to date, there is insufficient data to predict who will develop complications of acute bronchitis. Acute cough may also be the presenting symptom of an underlying disorder, and the presence of specific pointers (Table 26-2) should alert practitioners to the possibility of an underlying problem (e.g., a congenital/developmental respiratory or immunologic disorder). Differentiating uncomplicated ARIs from pneumonia has been relatively widely studied in developing countries where chest wall retractions and respiratory rate are good predictors of pneumonia.[31] Use of chest radiographs does not improve outcome in ambulatory children with acute lower respiratory infection.[32]

TABLE 26-2 POINTERS TO THE PRESENCE OF SPECIFIC COUGH*

Auscultatory findings such as crackles and wheezes
Cardiac abnormalities
Chest pain
Chest wall abnormality
Digital clubbing
Daily moist or productive cough
Dyspnea
Dysphagia
Exertional dyspnea
Hemoptysis
Immune deficiency (primary or secondary)
Neurodevelopmental abnormality
Recurrent pneumonia
Respiratory noises (stridor, wheeze)
Systemic symptoms (fever, weight loss, failure to thrive)

*Cough related to an underlying lung disease

Interventions

The American Academy of Family Physician's guidelines discourage the use of antimicrobials except when rhinosinusitis and cough is present and has not improved after 10 days.[33] Meta-analysis on antimicrobials for acute bronchitis (recent onset of productive cough without chronic obstructive pulmonary disease, sinusitis, or pneumonia) in children showed that patients receiving antibiotics were less likely to have a cough 7 to 14 days after initiation of treatment and less likely to show no improvement on the clinician's global assessment They were more likely to have shorter duration of cough, and feel ill.[30] However the benefits were small and translate into a reduction of symptoms for only a fraction of a day.[30] Thus the NICE recommends a "no antibiotic prescribing strategy or a delayed antibiotic prescribing strategy," unless the patient is systemically very unwell, has symptoms and signs that suggest serious illness or complications, or has high risk of serious complications because of pre-existing comorbidity (e.g., heart, lung, renal, liver, or neuromuscular disease; immunosuppression; cystic fibrosis; and young children who were born prematurely).[30] Other logical inclusions in this list are children with airway lesions with impaired airway clearance (tracheobronchomalacia), suppurative lung disease, and recurrent protracted bronchitis.

Parents' and caregivers' concerns and expectations should be determined and addressed, and advice about the usual natural history of the illness (up to 3 weeks for acute bronchitis) should be given.[30] OTC medications for cough confer no benefit in the symptomatic control of cough in children.[34,35] Moreover "OTC medications can be associated with significant morbidity and even mortality in both acute overdoses and when administered in correct doses for long periods of time."[36] The use of steam inhalation, vitamin C, zinc, echinacea, or lozenges for upper ARIs confer little benefit or have not been specifically examined for the symptomatic relief of cough.[37] A single RCT reported that treatment with nimesulide was associated with clinically significant improvement in cough and other signs and symptoms (rhinorrhea, nasal obstruction, pharyngeal redness, swelling of lymph nodes and cough), but this drug is not licensed in North America, the United Kingdom, Australia, or New Zealand because of safety concerns.[38] There is also no data of sufficient quality on the efficacy of Chinese herbs for acute bronchitis.[39] In ambulatory children with acute cough (1 to 10 days) with no history of asthma and a normal chest examination, oral albuterol was not effective in reducing cough frequency or duration in children.[40] In addition, β_2-agonists are not efficacious in reducing cough in children with acute bronchitis who do not have airflow obstruction.[41]

Protracted Bacterial Bronchitis

Acute bronchitis can progress to protracted bacterial bronchitis (PBB). PBB, a type of chronic airway inflammation in children, is a recently recognized clinical entity.[14] It was previously called various names including *chronic bronchitis*. Bronchitis related to suppurative lung disease is discussed in Chapter 30. The term *chronic bronchitis* should no longer be used as a diagnosis in children, as the etiologic underlying cause of any bronchitis that is chronic should be defined and appropriately treated.

Symptoms of PBB have long been recognized by pediatric pulmonologists (but have only been adequately characterized recently.[14,42–44] The original description of PBB required three criteria; (1) a history of chronic wet cough, (2) positive BAL culture ($\geq 10^5$ colony-forming units [CFU]/mL) (Fig. 26-2), and (3) response to antimicrobial treatment with cough resolution within 2 weeks.[14] PBB sometimes truncated to *protracted bronchitis (PB)* is clinically defined as (1) the presence of isolated chronic (>4 weeks) wet/moist cough, (2) resolution of cough with antimicrobial treatment, and (3) absence of pointers suggestive of an alternative specific cause of cough.[6,45] The criterion of demonstration of endobronchial airway infection by culturing respiratory pathogens from BAL is not feasible in the routine clinical setting.

PBB is differentiated from acute bronchitis by cough of shorter duration (≤2 weeks in acute bronchitis). Children with PBB are typically young (younger than 5 years of age) and do not have any other systemic symptoms such as clinical sinusitis or ear disease. Some parents may report a "wheeze." Tracheomalacia or bronchomalacia may coexist. On clinical assessment however, they usually do not have wheeze but a "ruttle or rattle" reflective of airway secretions.[42] Many of these children have been misdiagnosed as having asthma.[14,42] Their chest x-rays usually show peribronchial thickening or may be reported as "normal."[42,46] Like children with chronic cough, children with PBB have significant morbidity; parents typically have seen multiple medical practitioners for their child's chronic cough in the

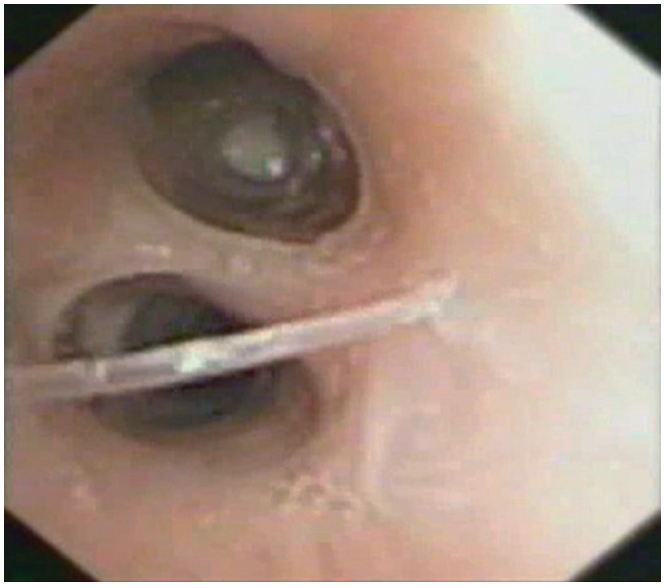

FIGURE 26-2. Bronchoscopic appearances of protracted bacterial bronchitis. A strand of mucus is present, just proximal to the left lower lobe bronchus, and there are prominent secretions in the lingula bronchus. The BAL cultured *H. influenzae* and *S. pneumoniae,* both at a density of $\geq 10^5$ CFU/mL. Polymerase chain reaction tests were negative for respiratory viruses (influenzas A and B, RSV, parainfluenzas 1 and 2, adenovirus, and human metapneumovirus), Mycoplasma, and Chlamydia.

last 12 months.[45] In PBB the child's cough resolves only after a prolonged course of appropriate antibiotics (12 to 14 days).

Pathogenesis of Protracted Bacterial Bronchitis

PBB is associated with bacterial infection in the airways,[42,14] and it is widely accepted that persistent bacterial infection is harmful.[47] The organisms most commonly identified in the airways (sputum or BAL) of children with PBB are common respiratory bacteria such as nontypeable *H. influenzae, S. pneumoniae,* and *M. catarrhalis*.[42,14] Transient viral ARIs in early childhood commonly precede PBB as the most common initiating event. However, colonization may be secondary to conditions that impair cough such as neuromuscular disease, mucus plugging in asthmatics, airway lesions that impede efficient airway clearance (e.g., tracheobronchomalacia), or mucosal damage secondary to aspiration. Tracheobronchomalacia is a common finding in children with PBB,[14] which may be a primary phenomenon (airway malacia predisposes to PBB through reduced efficiency in airway clearance) or a secondary phenomenon (malacia occurs as a consequence of intense airway inflammation).[48] Persistent airway colonization and neutrophilic inflammation may evolve to chronic mucus hypersecretion and further airway inflammation. In some cases, cumulative airway injury from recurrent or persistent bacterial infection can lead to bronchiectasis.[45] Repeated microbial exposure, especially during childhood, likely shapes later immune system responses.[49]

PBB is also likely to be heterogeneous, with neutrophilic airway inflammation developing by a variety of mechanisms. It is likely that an innate immune dysfunction or immature adaptive immune response is present, at least in a subgroup of these children. In 150 children without lung disease undergoing gastroscopy, a group of children with bacterial colonization, airway neutrophilia, and protracted cough was identified.[50] Bacterial colonization of the lower airways in these children was associated with reduced expression of both the toll-like receptor (TLR) -4 and the preprotachykinin gene, *TAC1,* that encodes substance P,[51] which also has a defensin-like function.[52] These data suggest that a dysfunction of innate immunity plays a role in PBB (at least in a subgroup of children), but the nature and duration of such immune dysfunction has been not defined.

Outcomes of Children with Protracted Bacterial Bronchitis

Long-term cohort data are currently not available. However, some children with PBB have recurrent episodes or a relapse of PBB weeks after initial treatment. These children should be investigated along the lines for a child with chronic suppurative lung disease (CSLD) (Chapter 30). It is also likely that recurrent PBB is a risk factor for chronic suppurative lung disease and bronchiectasis. Indeed it is highly likely that PBB, CSLD, and bronchiectasis represent part of a spectrum.[45] The likely link between PBB and bronchiectasis is based theoretically on a vicious circle hypothesis[53] and, experimentally, on old natural history data.[54,55]

Plastic Bronchitis

Plastic bronchitis is rare (and becoming more rare in the current era) and is characterized by the formation of bronchial casts that cause obstruction of the airways (Fig. 26-3). Bronchial casts have been divided into two types. Type I casts are inflammatory, consist mainly of fibrin with cellular infiltrates, and occur in inflammatory diseases of the lung. Type II, or acellular casts, consist mainly of mucin with a few cells and usually occur following surgery for congenital cardiac defects.[56] However analysis of casts may not fit neatly into either category.[57] Many etiologic factors have been associated with plastic bronchitis; these include cardiac defects (particularly after Fontan's procedure),[58] sickle cell disease (acute chest syndrome),[59] asthma, aspergillosis, pneumonia, cystic fibrosis,[60] pulmonary lymphatic disorders,[57] and neoplastic infiltrates.[61] The pathogenesis of cast formation is unknown but probably involves abnormal mucin accumulation, with reduced airway clearance and dehydration, in a genetically predisposed person.[57]

Children with plastic bronchitis usually present with cough and respiratory distress (with or without wheezing). Chest pain may also be present, and chest radiograph usually reveals atelectasis. Life-threatening events were higher in patients with cardiac defects (41%) than in those with asthma (0%, p = 0.02).[56] Diagnosis is made by bronchoscopy, which is also therapeutic (see Fig. 26-3). There are some case reports on the use of rhDNase.[59] Others have reported the use of inhaled corticosteroids, tissue plasminogen activator, macrolides, and inhaled heparin.[57] An alternative is direct instillation of dilute bicarbonate solution by fiberoptic bronchoscopy (used by

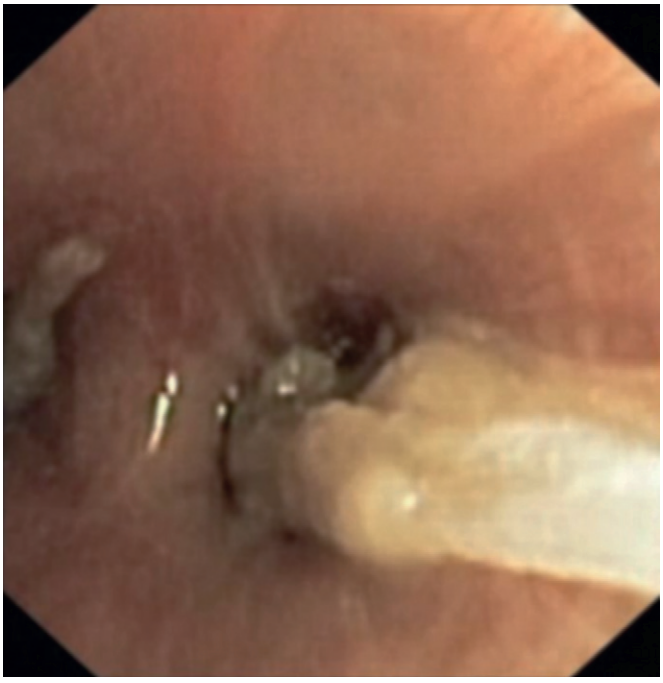

FIGURE 26-3. Bronchoscopic appearances of plastic bronchitis related to allergic bronchopulmonary aspergillosis and cystic fibrosis. The child presented with chronic cough and chest pain (no respiratory distress). The chest radiograph showed persistent changes in the lingula. The cast was removed bronchoscopically with resolution on the chest radiograph.

the author with resolution; unpublished data). It remains unclear which is the best treatment strategy. Reported mortality from plastic bronchitis is 16% and increases to 29% in patients with cardiac defects.[56]

Other Causes of and Contributors to Bronchitis

A complete review on the effects of pollutants and other possible causes of bronchitis (e.g., silent aspiration)[62] or associations (e.g., allergic rhinitis, gastroesophageal reflux) are described in other chapters. The most clinically important air pollutant in childhood bronchitis is tobacco smoke (*in-utero* and *ex-utero*). This has been extensively reviewed[63] and always requires addressing by counseling[64] and other modalities. Systematic reviews have described the link between cough and air pollution (indoors and outdoors).[15,65] It is increasingly appreciated in human and animal studies that environmental pollutants may have additive effects[66] and may influence the respiratory apparatus directly and indirectly through the immune system[67] and neural[68] pathways. However, irrespective of exposure, cough should not be simply ascribed to pollutants (see the "Exacerbation Factors" section) in clinical settings.

References

The complete reference list is available online at www.expertconsult.com