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26 Bronchiectasis and Chronic Suppurative Lung Disease

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Introduction

Worldwide, there are more people with bronchiectasis unrelated to cystic fibrosis (CF) than with CF and although regarded in affluent countries as an "orphan disease," bronchiectasis remains a major contributor to chronic respiratory morbidity in affluent[1,2] and less affluent countries.[3,4] With the increasing appreciation of bronchiectasis in adults,[5–7] the renewed interest in bronchiectasis has resulted in greater research depth, albeit[7–9] there is still proportionately little research in children. Indeed, bronchiectasis is regarded by the European Respiratory Society[10] as "one of the most neglected diseases in respiratory medicine." This chapter addresses childhood bronchiectasis, chronic suppurative lung disease (CSLD), and protracted bacterial bronchitis (PBB) unrelated to CF. Other underlying pulmonary host defense deficiencies such as ciliary dyskinesia syndromes and immunodeficiencies are covered elsewhere in this textbook.

Definitions

BRONCHIECTASIS, CHRONIC SUPPURATIVE LUNG DISEASE, PROTRACTED BACTERIAL BRONCHITIS

Bronchiectasis, CSLD, and PBB share common features but are different diagnostic entities with overlaps (Fig. 26.1).[11] Bronchiectasis is a pathologic state of the conducting airways manifested by radiographic evidence of bronchial dilation and clinically by chronic productive cough. Bronchiectasis can be focal with recurrent wet or productive cough and infectious exacerbations, or it can be diffuse, resulting in generalized airway obstruction and destruction with eventual respiratory failure. The diagnostic criteria for bronchiectasis are based on radiographic features of chest high-resolution computerized tomography (c-HRCT), although the sensitivity of adult-defined radiographic criteria has been questioned when applied to children.[12,13] Bronchiectasis may also occur in patients with interstitial lung diseases, because traction on the airways causes secondary bronchial dilation. Traction bronchiectasis in the absence of wet or productive cough will not be considered further.

CSLD describes a clinical syndrome where symptoms of chronic endobronchial suppuration exist without c-HRCT evidence of bronchiectasis. The presenting symptoms are identical to bronchiectasis, including a prolonged moist or productive cough responsive to antibiotics with or without exertional dyspnea, increased airway reactivity, and recurrent chest infections. The absence of physical signs and symptoms other than wet or productive cough do not reliably exclude either bronchiectasis or CSLD. Lung abscess and empyema (previously included as CSLD) have distinct radiological characteristics and will not be discussed further. Whether bronchiectasis and CSLD are different clinical entities or simply reflect a spectrum of airway disease remains undetermined.[12] Both are chronic suppurative airway diseases and respond to similar treatment regimens.

The sole reliance of radiographic features to distinguish between bronchiectasis and CSLD is in question for several reasons:

1. It is unknown when radiological changes consistent with bronchiectasis occur in the context of a patient with symptoms of CSLD/bronchiectasis. Adult studies have shown that bronchography (the old gold standard for diagnosis of bronchiectasis) is superior to c-HRCT scans in mild disease.[14,15] In the last decade, studies have shown that contiguous 1-mm slices of c-HRCT images identify more bronchiectasis than conventional techniques (1 mm slice every 10 to 15 mm).[16,17] Hill et al. reported that the contiguous 1-mm slices protocol demonstrated 40 extra lobes with bronchiectasis not identified on conventional HRCT in 53 adults.[16] False negative results are more likely to occur when the disease is mild and localized.[14] Thus, in the current era, tertiary centers generally use multidetector CT (MDCT) scans with HRCT reconstructions used to define airway lesions. It is likely that c-HRCT protocols (without MDCT scans) have insufficient sensitivity to detect early signs of bronchiectasis in some children with symptoms of bronchiectasis.
2. A significant number of children have clinical characteristics of bronchiectasis, but their c-HRCT do not meet the criteria for the adult-based radiological bronchiectasis criteria. c-HRCT findings of bronchiectasis were derived from adult studies,[13] but scans in adults are not necessarily equivalent to those in children. Airway and morphologic changes in the lung occur with maturation and aging.[18] One of the key signs of bronchiectasis is increased bronchoarterial ratio (diameter of the bronchial lumen divided by the diameter of its accompanying artery) of greater than 1 to 1.5. This ratio is influenced by age.[19] Thus, a lower bronchoarterial ratio should be used in children to diagnose bronchiectasis. In young children (aged <5 years), the normal bronchoarterial ratio is around 0.5[20]; and in older children (<18 years), the upper limit is less than 0.8.[13]
3. To fulfill the criteria of "irreversible dilatation," at least two scans are required. Performing more than one c-HRCT scan purely for diagnostic reasons may be impractical

ABSTRACT

Bronchiectasis, chronic suppurative lung disease, and protracted bacterial bronchitis (PBB) are increasingly recognized conditions. Bronchiectasis is now again increasingly diagnosed, and its renewed interest has resulted in further in-depth studies in children and adults. However, diagnostic labeling of childhood bronchiectasis by radiology using adult-derived criteria has substantial limitations. Thus, pediatric-derived criteria are advocated. A paradigm presenting a spectrum related to airway bacteria, with associated degradation and inflammation products causing airway damage if untreated, entails PBB (at the mild end) to irreversible airway dilatation with cystic formation as determined by chest computed tomography (CT) scan (at the severe end of the spectrum). Increasing evidence suggest that progression of airway damage can be limited by intensive treatment, even in those predestined to have bronchiectasis (e.g., immune deficiency). Treatment is aimed at achieving a cure in those at the milder end of the spectrum to limiting further deterioration in those with severe "irreversible" radiological bronchiectasis.

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KEYWORDS

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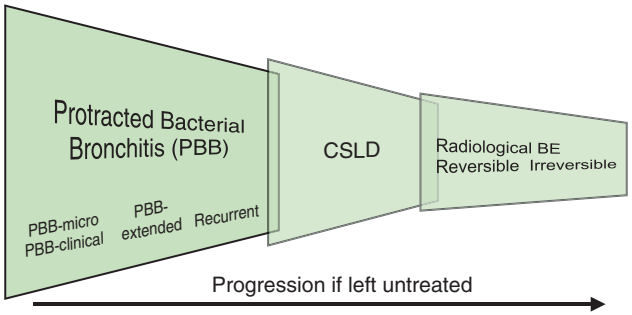

Fig. 26.1 Schema of the interrelationship between protracted bacterial bronchitis (PBB), chronic suppurative lung disease (CSLD), and bronchiectasis (BE). "Using the pathobiologic model, PBB, CSLD and radiographic-confirmed bronchiectasis likely represents different ends of a spectrum with similar underlying mechanisms of airway neutrophilia, endobronchial bacterial infection and impaired mucociliary clearance. Untreated it is likely some (but not all) children with PBB will progress to develop CSLD and some will ultimately develop bronchiectasis, initially reversible and subsequently irreversible if left to progress. There is a degree of overlap between each of the entities." (Chang AB, Upham JW, Masters IB, et al. State of the art. Protracted bacterial bronchitis: the last decade and the road ahead. *Pediatr Pulmonol*. 2016;51:225-242; Reproduced with permission from John Wiley and Sons Pediatr Pulmonol 2015; epub ahead doi: 10.1002/ppul.23351.)

and poses safety concerns regarding cancer risks from radiation in children, adolescents, and young adults.[21]

4. The timing of c-HRCT scans to diagnose bronchiectasis is important. Scans performed in different clinical states, such as during an acute pulmonary exacerbation, immediately following treatment, or when clinically stable, may yield different results. C-HRCT scans are ideally performed in a "non-acute state," but this state may differ from a posttreatment state. Bronchial dilatation resolved completely in 6 of 21 children with radiologically defined bronchiectasis when c-HRCT scans were repeated immediately following intensive medical therapy.[22]

Thus, we recommend that HRCT scans are best performed in a nonacute state and bronchiectasis be diagnosed if symptoms of CSLD are present when HRCT findings meet the pediatric[13] rather than adult radiological criteria.

PBB is a condition that is likely a prebronchiectasis state. It was first described as a diagnostic entity in 2006 with clear clinical criteria supported by laboratory studies,[23] although astute clinicians had long recognized PBB-like conditions.[11] PBB is discussed later in the chapter as a separate entity.

Bronchiectasis and Chronic Suppurative Lung Disease

EPIDEMIOLOGY, PREVALENCE, AND BURDEN OF DISEASE

Prevalence Across Time and Countries

In most affluent countries, the prevalence of childhood bronchiectasis has substantially declined since the 1940s. Field reported on 160 children with bronchiectasis over a 20-year period noting a decline in the incidence from 48 to 10 cases per 10,000 people from the 1940s to the 1960s.[24] By 1994, an English study found that only 1% of 4000 children referred to a respiratory specialty service had bronchiectasis.[25] The reduced incidence over time has been ascribed to reduced crowding, improved immunization programs, better hygiene and nutrition, and early access to medical care. However, bronchiectasis is now increasingly recognized worldwide as an important contributor to chronic respiratory morbidity in less affluent countries[4] and both indigenous[26] and non-indigenous populations in affluent countries.[27] Indeed bronchiectasis is not rare in affluent countries,[1,5,27] but is more common among certain groups for example, the Alaskan Yupik children in the United States, Aboriginals in Australia, and Maori and Pacific Islanders in New Zealand.[26,28] Among these populations, the prevalence of childhood bronchiectasis is 147 to 200 per 10,000 children.[26] A Canadian study conservatively estimated that the prevalence of bronchiectasis among Inuit children living in Nunavut was 20 per 10,000.[29] The only available national incidence data on children is that from New Zealand with a rate of 3.7 per 100,000 under 15 year old children per year,[30] which is almost twice that of CF. In the Northern Territory (Australia with a high proportion of Indigenous people) the incidence in the first year of life is 12 per 10,000.[31]

In adults, the estimated prevalence rate has been increasing (annual change of 8.8% from 2000 to 2007) based on a 5% sample of outpatient Medicare claims in the United States.[32] In the United Kingdom (UK), the prevalence of bronchiectasis in people aged 18 to 29 years increased from 29.3 (95% confidence interval [CI] 20.4 to 41.9) per 100,000 in 2004 to 43.4 (32.3 to 58.4) per 100,000 in 2013.[2] These estimates far exceed the prevalence of CF. Given the need for a CT scan to diagnose bronchiectasis, prevalence or incidence data would be an underestimation. Furthermore, recognition of bronchiectasis is physician dependent and it is not surprising that many cases in children and adults are misdiagnosed as "difficult asthma"[33,34] or chronic obstructive pulmonary disease (COPD). A proportion of adults with COPD (29% of 110) have underlying bronchiectasis.[35] Importantly, the majority of bronchiectasis in adulthood has its roots in childhood.[36,37] One study of adults with bronchiectasis found that 80% of patients had chronic respiratory symptoms from childhood.[38]

Hospitalization rates for adults with non-CF bronchiectasis in the United States have also increased in the last two decades; from 1993 to 2006, the age-adjusted rate increased significantly with an average annual percent increase of 2.4% among men and 3.0% among women.[39] German hospital statistics for 2005–2011 have also increased over that period with an annual age-adjusted rate for bronchiectasis of 9.4 hospitalizations per 100,000 population.[40] Likewise, an Australian state (Queensland) documented an increase in hospitalization from 65 to 83 per 100,000 population between 2005 and 2009.[41]

Data from less affluent countries suggest that bronchiectasis is still associated with poor outcomes, for example, 22% with respiratory failure in a 6.6-year Tunisian follow-up study.[42] Mortality from pediatric bronchiectasis is rarely reported. Arguably, no child without a serious comorbidity should die from bronchiectasis. However, an England and Wales study reported 12 deaths in the 0 to 14 years age group between 2001 and 2007,[43] and 6 (7%) of 91 children

died while attending a single New Zealand center between 1991 and 2006.[44] The premature mortality from bronchiectasis may carry over into young adulthood particularly in circumstances with nonoptimal management. This is depicted by a retrospective cohort study of 120 Central Australian Indigenous adults with bronchiectasis (50 diagnosed as children) hospitalized between 2000 and 2006 that reported 34% died during the period at a median age of 42.5 years.[45] In the UK, a recent study described that the crude mortality for men aged 18 to 49 years with bronchiectasis was 13.1 (95% CI 3.4 to 22.8) per 1000 population and 6.4 (0.8 to 12.0) for women compared to the general population, which are rates of 1.3 (1.3 to 1.4) and 0.8 (0.7 to 0.8), respectively.[2] These represent excess mortality rates of 8 to 10 times the general population.

Economic Cost

There is little data on the economic cost of bronchiectasis and none specific to children. In an United States-based case-control study involving 9146 children and adults (6.7% were aged <18 years), the direct medical cost increased by US$2319 per patient per year relative to the matched control from the preceding year.[46] The cost specifically for children was not described. An earlier study found that in the United States, adults with bronchiectasis averaged 2.0 (95% CI 1.7 to 2.3) additional days in hospital and that the average total annual medical-care expenditures (in 2001) were US$5681 ($4862 to $6593) higher for bronchiectasis patients than age, gender matched controls with other chronic diseases such as diabetes, COPD, and congestive heart failure.[47]

Other Burden of Disease

In recent years, four pediatric studies in three different continents evaluated the impact of bronchiectasis on the child's and/or parents' health-related quality of life (QoL).[3,48–50] Using the Parent Cough-Specific Quality of Life (PC-QoL)[51] and the Depression, Anxiety and Stress (DASS-21) questionnaires, a Malaysian[3] study described that children with CF had better parental mental health compared to children with non-CF CSLD. Overall, 77% of parents had abnormal DASS-21 scores (54% stressed and 51% depressed).[3] An Australian study[49] examined PC-QoL and DASS-21 scores during the stable-state and exacerbations in 69 children (median age 7 years) and their parents. In the stable state, the median PC-QoL was 6.5 (interquartile range [IQR] 5.3 to 6.9) and DASS-21 was 6 (0 to 20). Both scores were significantly worse during exacerbations (PC-QoL = 4.6 [3.8 to 5.4], $P \leq .001$ and DASS = 22 [9 to 42], $P < .001$).[49] DASS score showed that 38% had elevated anxiety and that 54% had abnormal depression/stress scores during the exacerbation. In the stable state, poorer QoL was significantly recorded with younger children, but QoL did not relate to the radiological extent, lung function, or underlying etiology.[49] In contrast, a Turkish study[48] described that the severity and frequency of symptoms were inversely related to the pulmonary function and the QoL scores (nonpediatric scales were used) in 42 children aged 9 to 18 years. Another Turkish study[50] involving 76 Caucasian children with bronchiectasis and 65 controls used self-reported questionnaires to evaluate the psychological status (using the Child Depression Inventory, State-Trait Anxiety Inventories for Children, and Pediatric Quality of Life Inventories). In this older cohort of children (mean age 11.7, SD 2.6 years), depression and trait anxiety scores were not elevated in those with bronchiectasis, but the child-rated physical health QoL scores were significantly lower in those with bronchiectasis compared to controls.[50] The determinants of QoL were related to age, forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) % predicted, and dyspnea severity.[50]

The differences between the Australian[49] and Turkish[48,50] studies likely relate to the different QoL scales used and severity of disease. It is likely that QoL scores correlate to disease severity only in more severe disease, similar to the relationship between spirometry and radiological extent of bronchiectasis; spirometry is often normal in mild or localized disease,[52] and significant correlations between spirometry indices and radiology scores are seen only in more severe disease.[53] Nevertheless, all studies showed the negative impact of bronchiectasis on the children and/or their parents QoL and mental health. Poor sleep quality has also been reported.[54]

Etiologic Risk Factors

Bronchiectasis is the result of a variety of airway insults and predisposing conditions that ultimately injure the airways and lead to recurrent or persistent airway infection and destruction. Examples of these conditions are listed in Table 26.1. Bronchiectasis develops in some individuals when structural airway abnormalities, such as bronchomalacia, endobronchial tuberculosis, central airway compression, or retained aspirated foreign bodies impair mucus and bacterial clearance. However, there is currently no evidence of airway malacia causing bronchiectasis in human studies. *Persistent* airway injury and narrowing associated with bronchiolitis obliterans (BO; due to viral injury or following lung transplantation) can lead to bronchiectasis. *Recurrent* airway injury, such as occurs with aspiration syndromes, can also result in bronchiectasis. Selected pediatric cohorts from various settings and countries that describe the frequencies of these associated conditions are summarized in Table 26.2.

Impaired upper airway defenses may also predispose to bronchiectasis based on the common association between rhinosinusitis and bronchitis/bronchiectasis. Indeed, the sinuses and Eustachian tubes have been considered a "sanctuary site" for bacterial pathogens and cytokines that may predispose to recurrent lower airway infection. Finally, there are variations in host inflammatory responses, for example, cytokine and metalloproteinase levels, and counterbalancing antiinflammatory mechanisms, for example, antioxidants and antiproteases, which may explain why some children develop bronchiectasis, while others do not despite similar exposures and living conditions.[26]

Previous Acute Lower Respiratory Infections

It is well documented that acute lower respiratory tract infections (ALRIs) in children can lead to subsequent respiratory morbidity and lung function abnormalities.[60,61] Classic epidemiological studies have linked acute ALRIs from adenovirus and other infections with chronic bronchitis and productive cough later in childhood.[62,63] Recent large epidemiological studies have also shown that those with ALRIs in early childhood are at risk of lower lung function in adulthood.[64,65] Although low lung function at birth may be the underlying

Table 26.1 Causes of Bronchiectasis

Primary Pathophysiology	Diseases	Major Associations
Impaired immune function[a]	Severe combined immunodeficiency	Gastrointestinal bacterial infections
	Common variable immunodeficiency	
	Natural killer cell deficiency	EBV infection
	Bare lymphocyte syndrome	
	X-linked lymphoproliferative disease	
	Ectodermal dysplasia	Abnormalities of teeth, hair, eccrine sweat glands
	Ataxia-telangiectasia	Cerebellar ataxia, telangiectases
	Bloom syndrome	Telangiectasia, altered pigmented skin
	DNA ligase I defect	Sun sensitivity
	T-cell deficiency	Thymus aplasia
	HIV	
	Cartilage-hair hypoplasia	Short-limb dwarfism
Ciliary dyskinesia	Primary	Sinusitis
	Functional	
Abnormal mucous	Cystic fibrosis	Pancreatic insufficiency
Clinical syndromes	Young's syndrome	Azoospermia
	Yellow nail lymphedema syndrome	Nail discoloration
	Marfan syndrome	Phenotypic appearance
	Usher syndrome	Retinitis pigmentosa
	Autosomal Dominant Polycystic kidney disease	Kidney disease
Congenital tracheobronchomegaly	Mounier-Kuhn syndrome, Williams-Campbell syndrome	
	Ehlers-Danlos syndrome	Phenotype appearance
Aspiration syndromes	Recurrent small volume aspiration	Neurodevelopmental problems
	Primary aspiration	
	Tracheoesophageal fistula	
	Gastroesophageal reflux disease	
Obstructive bronchiectasis	Foreign body, tumors, lymph nodes	
Other pulmonary disease associations	Interstitial lung disease	Systemic disease, dyspnea
	Bronchiolitis obliterans	Past severe ALRI
	Allergic bronchopulmonary aspergillosis	Wheeze
	Bronchopulmonary dysplasia	Extreme prematurity
	Tracheobronchomalacia	Brassy cough
Others	Alpha-1 trypsin or protease inhibitor deficiency	Liver disease
	Posttransplant	
	IgG4 related disease	Pancreatitis, skin lesions
	Autoimmune diseases	
	Post toxic fumes	
	Eosinophilic lung disease	
	Prolidase deficiency	Leg ulcers, pulmonary cysts

[a]List is incomplete for immune deficiency.
ALRI, Acute lower respiratory tract infection; *EBV,* Epstein-Barr Virus; *HIV,* human immunodeficiency virus; *IgG4,* immunoglobulin G_4.

factor of the significant association found, single severe ALRIs and multiple ALRIs in early childhood can undoubtedly lead to CSLD and bronchiectasis.[1,66] These single ALRIs associated with bronchiectasis have been described with tuberculosis, pertussis, adenovirus, measles, and severe viral pneumonia. Although these infections do not frequently cause bronchiectasis, they remain common ALRIs in less affluent countries[4] and are still considered important antecedents to childhood bronchiectasis.

In cohort studies, the most common associated cause or ascribed etiology for the bronchiectasis is past pneumonic events with lobar or diffuse alveolar infiltrates (see Table 26.2). In the sole case-control study of childhood pneumonia and radiographically proven bronchiectasis, a strong association between hospitalized pneumonia and bronchiectasis was found.[67] Children who had been previously hospitalized due to pneumonia were 15 times more likely to develop bronchiectasis.[67] A dose effect was also shown; recurrent (>1) hospitalization for pneumonia and more severe pneumonia (episodes with longer hospital stay or oxygen requirement) increased the risk of bronchiectasis later in childhood.[67] Bronchiectasis was 3 times more likely in children with four or five episodes of pneumonia and 21 times more likely if they had 6 or more pneumonias. The overall number of pneumonias rather than the site of pneumonia were associated with bronchiectasis.[67] In an Alaskan cohort, there was no association between lobe affected by first ALRI and the eventually bronchiectatic lobe, but there was an association between lobe most severely affected by ALRI and the lobes later affected by bronchiectasis.[56] Specific infectious etiologies were not described in these studies. A review on the long-term effects of pneumonia in young children[66] described a mixture of obstructive and restrictive lung deficits when followed up long term. However, the majority of studies in the review[66] were limited with case ascertainment and follow-up issues.

Some authors have suggested that bronchiolitis is an important precursor of bronchiectasis. An Alaskan 5-year case-control follow-up of children hospitalized in infancy specifically with severe RSV infections described that they were not more likely to have been diagnosed with bronchiectasis.[68] In contrast, a study of Indigenous children hospitalized with bronchiolitis in Australia found that on CT scans performed at a median 13 months (range 3 to 23)

Table 26.2 Selected Studies on Etiologies of Childhood Bronchiectasis Published in Last 20 Years From Various Regions and Settings

Study	Nikolaizik et al.[25] N = 41	Edwards et al.[55] N = 60	Singleton et al.[56] N = 46	Chang et al.[52] N = 65	Santamaria et al.[57] N = 105	Kapur et al.[58] 2012 N = 113	Brower et al.[59] 2014 N = 989[a]
Setting n (%)	City, England	City, New Zealand	Remote, Indigenous, Alaska	Remote, Indigenous, Australia	City, Italy	City, Australia	Mixed locations
Postinfectious (severe pneumonia)	12 (29)	15 (15)	42 (92)	58 (90)	7 (6.7)	14 (12)	174 (19)
Tuberculosis	0	0	2 (4)	1 (1)	0	0	Not described
Inherited immune deficiency	8 (20)	7 (12)	0	2 (3)	11 (10.5)	13 (12)	158 (17)
Primary ciliary dyskinesia	7 (17)	0	0	0	25 (23.8)	2 (2)	66 (7)
Congenital malformations	6 (15)	1 (1)	0	1 (1)	0	0	34 (4)
Secondary immune defects	3 (7)	0	0	0	0	5 (4)	29 (3)
Aspiration of exogenous toxicants or foreign body	2 (5)	1 (2)	1 (2)	0	0	2 (2)	Combined with below
Aspiration or GERD	0	6 (10)	1 (2)	3 (5)	4 (3.8)	12 (11)	91 (10)
Unknown	2 (5)	30 (50)	0	0	58 (55.2)	62 (55)	308 (34%)
CF-like or CF	1 (2)	0	0	0	0	0	0
Interstitial lung disease including bronchiolitis obliterans	0	0	0	0	0	3 (3)	12 (1)
"Asthma"	0	0	0	0	0	0	Not described
Others	0	0	0	0	0	0	18 (2)

[a]Although this study was called systematic review, the review was incomplete with several studies omitted.
CF, Cystic fibrosis; *GERD*, gastroesophageal reflux disease.

posthospitalization, infants with persistent cough at 3 week (n = 31) after hospitalization were significantly more likely to have bronchiectasis compared to those without a cough (n = 126), OR 3.0, 95% CI 1 to 7, $P = .03$.[69] We surmise that bronchiectasis is not a consequence of specific viruses that produce bronchiolitis.

Upper Airway Infection and Aspiration

Mechanisms by which upper respiratory infections predispose to lower airway inflammation and injury are reviewed elsewhere.[70] Bacterial pathogens colonizing the nose and mouth are shed into saliva and contaminate the lower airways. Proinflammatory cytokines from the oropharynx may also be aspirated and augment neutrophilic responses in the lower airways. Hydrolytic enzymes in infected upper airway secretions impair protective secretory molecules such as mucins in the lower airways, and thereby predispose the lower airways to infection. *In vitro* studies have shown that some bacteria produce factors that cause ciliary slowing, dyskinesia, and stasis, setting the stage for chronic bacterial colonization of the lower airways.[71] Whether the concentration or persistence of these pathogens in upper airways represents a significant risk factor for development or progression of bronchiectasis is unknown. In indigenous Australian children with bronchiectasis, a study relating nasopharyngeal to bronchoalveolar lavage (BAL) bacteria found a high density and diversity of respiratory bacteria along with strain concordance between upper and lower airways.[72] The study suggests a possible pathogenic role of recurrent aspiration of nasopharyngeal secretions.[72]

Bronchiectasis and other forms of suppurative lung disease have been described among individuals with neurologic and neuromuscular conditions that reduce the frequency and effectiveness of cough and also increase the risk of aspirating oropharyngeal contents. Brook reported on 10 children with such conditions who developed anaerobic pulmonary infections; six had poor oral hygiene.[73]

Public Health Issues

In 1949, Field wrote "Irreversible bronchiectasis is not commonly seen in the better social and economic classes. Good nutrition and home conditions probably give the child a better chance of more complete recovery from lung damaging disease."[74] Poor public health conditions, including malnutrition, crowding, lack of running water, and environmental pollution, increase the risk of ALRIs and bronchitis.[75,76] These issues are particularly important in developing countries. In affluent countries, those communities with higher prevalence of bronchiectasis are also those where poverty and low standards of housing are common.[26] In a qualitative study, community members and health care providers believed that potential contributing factors to acute and chronic lung diseases were smoke, dust, feeding practices, socioeconomic conditions, and mold.[77]

Macro and selected micro malnutrition increases infection risks, as it creates an immune deficiency state and leads to the malnutrition-infection-malnutrition cycle.[78] However, data on malnutrition specifically preceding bronchiectasis are limited and inconsistent. In Central Australia, Indigenous children with bronchiectasis are 3 times more likely to have had malnutrition in early childhood prior to the diagnosis of bronchiectasis,[67] but this is not seen in Alaska or New Zealand.[26] Breast-feeding is a known protective factor against development of bronchiectasis.[67] Bronchiectasis may itself predispose to malnutrition as a result of chronic pulmonary infection, diminished appetite, and reduced caloric intake. The caloric needs and daily oxygen consumption of children with non-CF-related bronchiectasis have not been reported. One series described that children with bronchiectasis and low (<80%) baseline FEV_1 % predicted values, and those with

immunodeficiency had significantly lower body mass index at diagnosis, and they significantly improved after appropriate therapy was instituted.[79] Also, in a double-blind randomized controlled trial on the effect of long-term azithromycin, Indigenous children randomized to the azithromycin group (c.f. placebo) had a significant improvement in weight z-score, concurrent with a reduction in exacerbations (incidence rate ratio = 0.5, 95% CI 0.35 to 0.71).[80] This suggests that effective management of children with bronchiectasis improves nutrition.

Another predisposing factor to bronchiectasis is the presence of inhaled irritants, including indoor and outdoor pollutants, particularly in the presence of impaired airway clearance. The effects of environmental tobacco smoke (ETS) on children's respiratory system are well known from both *in utero* and *ex utero* exposure and include reduced airway caliber, increased lower respiratory tract infections, and middle ear disease. Reviews of ETS and its effects on the developing lung and accelerated lung decline are available elsewhere.[81] Exposure to indoor biomass combustion increases coughing illness associated with ALRIs with an exposure-response effect.[82] Exposures to other indoor pollutants (nitrogen dioxide, gas cooking) and traffic are also associated with increased cough in children in both cross-sectional and longitudinal studies.[75] There is no direct evidence of pollutants causing bronchiectasis, and the pathogenic role is likely indirect through an increased frequency of ALRIs and increased airway mucus production. In Chile, increased arsenic exposure has been associated with a variety of chronic disorders including bronchiectasis.[83]

Genetics

The interplay between genotype, epigenetics, and environment is increasingly recognized as the key in phenotypic expression of respiratory diseases. An increased frequency of cystic fibrosis transmembrane conductance regulator (CFTR) genotypes associated with CF, presenting as heterozygotes, has been described in several case series of adults with diffuse bronchiectasis.[84] While heterozygotes for alpha-1 antitrypsin have also been described more frequently in those individuals with diffuse bronchiectasis, a causal relationship remains controversial. Older guidelines suggest optional screening for alpha-1 antitrypsin deficiency for patients with idiopathic diffuse bronchiectasis,[85] but newer guidelines described a lack of evidence and do not suggest alpha-1 antitrypsin deficiency testing for people with bronchiectasis.[86] A Turkish study (where consanguinity of parents is common) described transporter associated with antigen presentation (TAP) gene polymorphisms in their cohort of children with bronchiectasis.[87] It is interesting to note the high rate of consanguinity in several series of children with bronchiectasis from different countries.[88,89] As with other diseases, an increasing number of gene aberrations have been associated with syndromes where bronchiectasis may occur. Examples include primary ciliary dyskinesia, autosomal dominant polycystic kidney disease (PKD1 on chromosome 16p13.3 and PKD2 on chromosome 4p21),[90] and prolidase deficiency[91] (PEPD gene).

Aside from variations in specific gene frequencies, overexpression of innate pulmonary immune mechanisms, such as proinflammatory cytokine and adhesion molecule production, and receptor expression, may contribute to the development of bronchiectasis in certain children. An increased or exaggerated neutrophilic response in Australian Indigenous children as a group has been described.[92] Similarly, metalloproteinases, for example, MMP-2 and 9, have been isolated from the sputum and BAL of bronchiectatic subjects, suggesting a role in airway destruction by gelatinases and collagenases.[93,94] Whether proinflammatory cytokine and collagenase overexpression are associated with early onset disease or, particularly, progressive disease in childhood remains unknown.

PATHOLOGY AND PATHOPHYSIOLOGY

The histopathology of bronchiectasis was first described by Laënnec[95] in 1819. It includes alterations in subsegmental bronchial structure accompanied by neutrophilic inflammation, intraluminal secretion accumulation, and obliteration of distal airways. There are accompanying changes of peribronchial inflammation and fibrosis, distal lung collapse, bronchial and pulmonary vascular changes, and pleural adhesions. The macroscopic and microscopic features of bronchiectasis change as the disease progresses. Classical papers on bronchiectasis divided morphological types of bronchiectasis into tubular or cylindrical, early fusiform, late fusiform, fuso-saccular, and saccular types as different stages in the progression of disease.[36] The most commonly used classification is that of Reid's subtypes: cylindrical, varicose and cystic,[96] which were based on bronchographic findings. The latter findings are illustrated in Figs. 26.2 and 26.3 and they reflect progression of increasing severity. More recent HRCT scoring systems describe cylindrical and saccular changes as markers of disease severity.[97] Saccular and cystic changes tend to reflect clinically more advanced, severe, and irreversible disease.

Macroscopically, the airways are tortuous and dilated, at times extending to the pleural surface. Early histologic changes include bronchial wall thickening, edema, presence of inflammatory cells, development of lymphoid nodules and follicles, and mucus gland hyperplasia. Intraluminal secretions are purulent or mucopurulent (Video 26.1). Microscopic changes include loss of ciliated epithelial cells and epithelial ulcerations. With time, chronic inflammation leads to squamous cell metaplasia and fibrotic obliteration of distal conducting

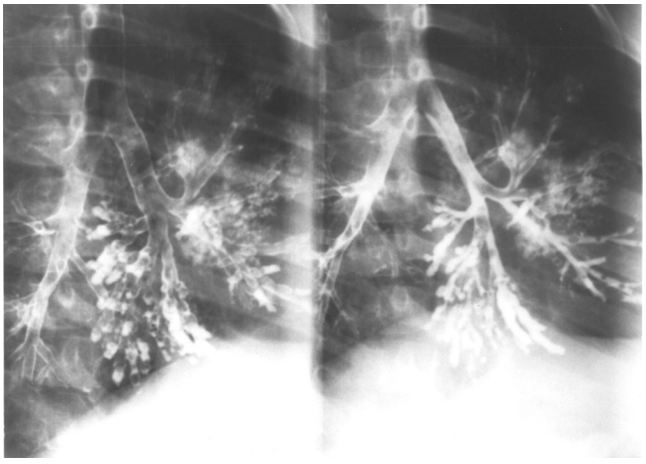

Fig. 26.2 Varicose and cystic changes characteristic of severe bronchiectasis by bronchogram.

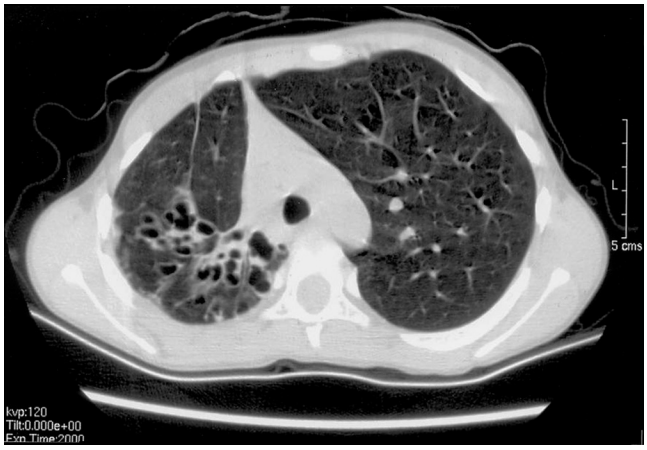

Fig. 26.3 CT scan findings of saccular bronchiectasis in the right upper lobe of a 9-year-old boy.

airways and peribronchial tissue. As bronchiectasis becomes more severe, the airway walls become thin and saccular with destruction of the airway's muscular, elastic, and cartilaginous elements.[96,98] The saccular airway walls are composed of fibrous and granulation tissue with only remnants of normal tissue. In advanced disease, mucus-filled saccular airway changes can be severe enough to appear as cystic microabscesses.

Vascular changes accompany bronchial structural changes in bronchiectasis. Large bronchopulmonary anastomosis can develop, and total bronchial arterial blood flow is increased. Extensive precapillary anastomoses between the two arterial systems can serve as a shunt between the pulmonary and systemic systems, increasing cardiac work.[98] Bronchopulmonary vascular anastomoses most often occur near distal subsegmental bronchi that have undergone saccular changes. Abnormal bronchopulmonary anastomoses and enlargement of aberrant bronchial arteries are thought to be associated with the metabolic demands of hypertrophied muscle, lymphoid tissue, and peribronchial granulation tissue during the course of the organizing pneumonitis that precedes the development of bronchiectasis.[99] The presence of significant hemoptysis is likely related to these abnormalities. Additional vascular remodeling of the pulmonary arteries and arterioles occurs in association with chronic airway obstruction and alveolar hypoxia, predisposing patients to pulmonary hypertension and cor pulmonale in severe cases.

The initial trigger for the bronchiectasis process is unknown, and there is little doubt that both host and pathogen factors play a role (Fig. 26.4). Animal models of bronchiectasis suggest that inadequate mucus clearance and persistent infection are necessary prerequisites.[101] Mucus clearance in bronchiectasis is reduced by a combination of factors including airflow limitation,[102,103] abnormal quantity and quality of mucus produced,[104] and factors produced by bacteria that cause ciliary slowing, dyskinesia, and mucus stasis.[71] Mucociliary clearance is enhanced by cough, exercise, and hyperventilation,[103,105,106] and is decreased in situations where airway caliber is diminished.[102,103] Decreased mucociliary clearance in turn leads to increased bacterial colonization and infection, setting up a vicious cycle. This concept is schematically presented in Fig. 26.4. Importantly, reduced mucociliary clearance is localized to the affected regions when bronchiectasis is produced by local injury rather than underlying deficiencies in pulmonary host defenses.[107] The role of bacteria in the pathogenesis of chronic lung infection and bronchiectasis is reviewed elsewhere.[8,108,109]

Airway and Systemic Markers

The majority of studies on airway inflammation have been performed in adults where, unlike children, assessment by using sputum is easy. Airway secretions are usually excessive in those with more severe bronchiectasis. The sputa from Alaskan native children with stable idiopathic bronchiectasis are less viscous (by one-third), less elastic (by one-fifth), less adhesive (by half), and more transportable (by 50%) compared to sputum from children with CF.[110]

Neutrophilia is the dominant type of airway inflammation,[58] although eosinophilia has also been described in some populations[111] and when treated, airway inflammation may be absent.[58] Increased percentages of neutrophils, neutrophil elastase, myeloperoxidase, mellatoproteinases, tumor necrosis factor-α (TNF-α), interleukin (IL-8), and IL-6 have been described in lower airway secretions.[112] These generally reflect neutrophilic inflammation and are not specific to bronchiectasis. The intensity of the airway and systemic inflammation is ameliorated by treatment.[112,113] An adult cohort involving 385 patients described a direct relationship between airway bacterial load and markers of airway inflammation (myeloperoxidase, neutrophil elastase, TNF-α, IL-8, and IL-1β) with a dose response such that higher inflammation correlated with higher bacterial loads.[112] High bacterial loads were associated with higher serum intercellular adhesion molecule-1 (ICAM-1), E-selectin, and vascular cell adhesion molecule-1 (VCAM-1), reflective of systemic inflammation. Using both short (14 days)- and long (12 months)-term antibiotic treatments, the study demonstrated a significant reduction in the airway bacterial load and inflammation (both airway and systemic) compared to those who did not receive antibiotic therapies.[112] However, there is a poor correlation between systemic and bronchial inflammatory mediators, suggesting that the inflammatory process is mostly compartmentalized to the airways.[114] There is paucity of data on BAL or sputum markers in children. A small study in children described increased median values of systemic markers (white cells, C-reactive protein [CRP], and fibrinogen) in children whose airways were colonized (n = 14) compared to those without identified bacteria in their sputum (white cell count: 8.2 [IQR 6.4 to 9.5] vs. 6.4 [5.8 to 7.7] × 10^3/mm^3; CRP: 0.91 [0.45 to 1.29] vs. 0.42 [0.30 to 0.77] mg/dL; fibrinogen: 433.5 [390.3 to 490.3] vs. 392.0 [327.0 to 416.0] mg/dL, $P < .05$ for all).[115] While the authors concluded that systemic inflammation was absent in children with bronchiectasis compared to controls, it is highly likely that a type-1 error was present in the study. In an in-depth study, the blood of children with bronchiectasis had a significant increase in the percentage of CD8+ T cells and T and natural killer T-cells (NKT)-like subsets expressing perforin/granzyme, interferon gamma (IFNγ), and TNFα compared with controls.[116] The proinflammatory cytotoxic T cells were more marked in Indigenous children compared to non-Indigenous children.[116]

Exaggerated or persistent pulmonary inflammation present in bronchiectasis leads to increased lung destruction by many mechanisms.[8] The balance between proteases and

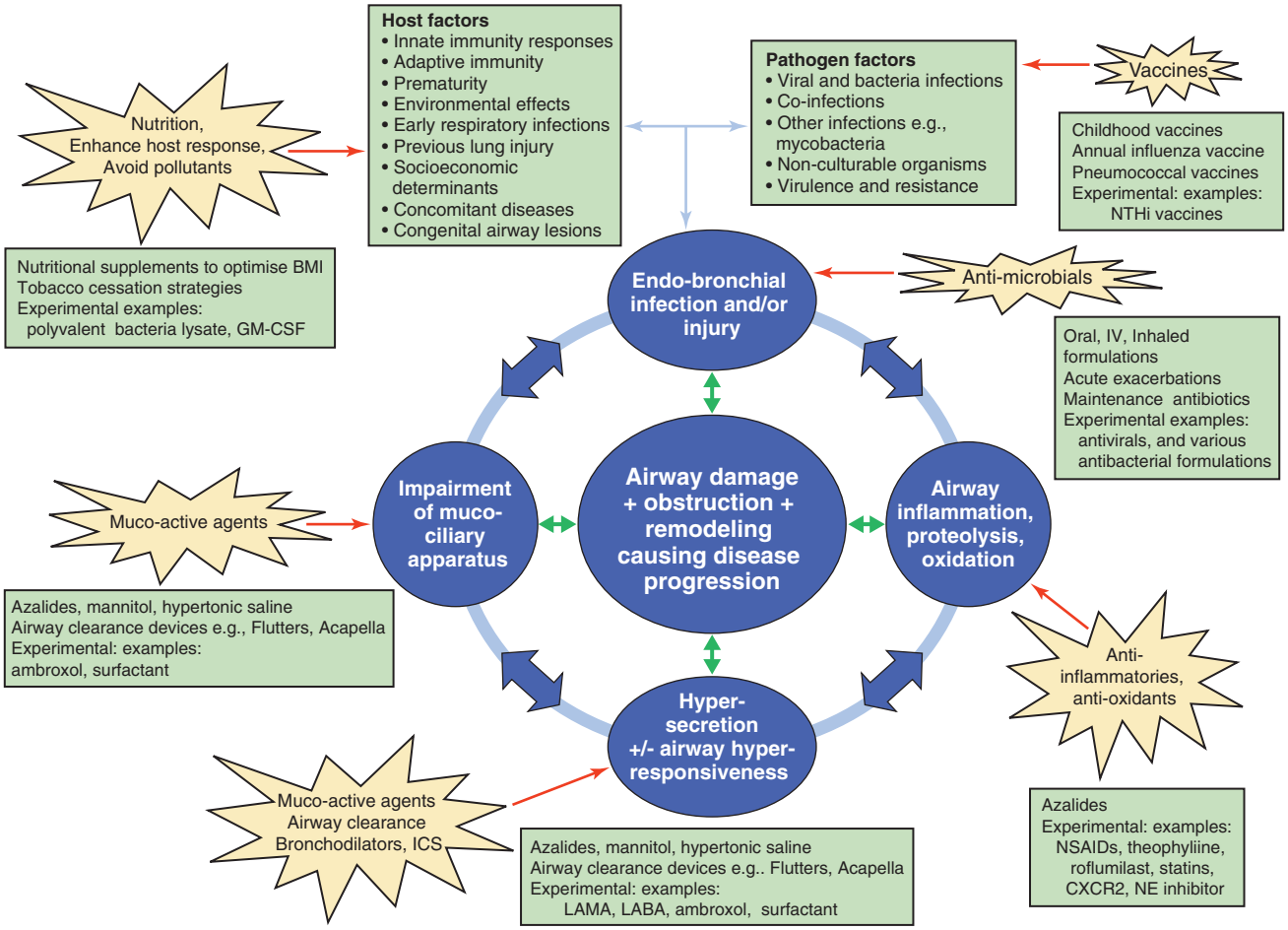

Fig. 26.4 A simplified schematic diagram of the factors contributing to the development of bronchiectasis. The initial trigger causing persistence of endobronchial infection and injury is dependent on host, environmental, and pathogen factors. This infection leads to inflammation, proteolysis, oxidation and subsequent mucous hypersecretion and/or airway hyperresponsiveness, with impairment of the mucociliary apparatus. Each factor influences each other (as in Cole's vicious cycle postulate)[100] and may lead to development, or increasing severity, of bronchiectasis (central circle) if left untreated. Possible therapeutics affecting each factor are presented in the jagged shapes. *BMI,* Body mass index; *CXCR2,* CXC chemokine receptor 2 antagonist; *GM-CSF,* granulocyte-macrophage colony-stimulating factor; *ICS,* inhaled corticosteroids; *IV,* intravenous; *LABA,* long acting beta$_2$-adrenoceptor agonist; *LAMA,* long acting muscarinic antagonists; *NE,* neutrophil elastase; *NTHi,* nontypeable *Haemophilus influenzae.*

antiproteases is increasingly recognized as important to the protection of airways against hostile agents and destruction of lung tissue. Upregulation of circulating adhesion molecules (E-selectin, ICAM-1, and vascular adhesion molecule VCAM-1) have also been suggested as playing a role in the pathogenesis of bronchiectasis.[117] Collagenase activity present in the BAL of adults with moderately severe bronchiectasis originates from neutrophils and bacteria. These collagenolytic proteases are likely contributors to tissue destruction.[118] As described above, the airways of people with bronchiectasis contains collagenolytic proteinases of bacterial origin.[118] and neutrophilic-associated cytokines that, unabated, lead to increased tissue damage (e.g., metalloproteinases [MMP-2,8, and 9]).[117] MMP-9 (but not tissue inhibitors of metalloproteinase-1) measured in exhaled breath condensate of children with non-CF bronchiectasis (42.8 ± 18.1 ng/mL) were similar to those with CF (48.9 ± 26.8) and significantly higher than controls (30 ± 3.7).[119] Endobronchial biopsies in adults with bronchiectasis demonstrated an overexpression of neutrophil matrix metalloproteinases (MMPs).[117] Using sputum from adults with bronchiectasis, Shum et al. showed that serine proteases derived from neutrophils were responsible for degradation of proteoglycans in a matrix model and that the protease secretion was stimulated by TNF-α in the presence of factors found in the sputum sol.[120]

There are additional pathogenic processes associated with bronchiectasis that contribute to the persistence of airway inflammation and obstruction. Increased airway permeability has also been described with bronchiectasis when purulent sputum and significant colonization of the respiratory tract by bacterial pathogens are present.[121] Also, resolution of inflammation is normally associated with the orderly removal of apoptotic inflammatory cells, and impaired removal of apoptotic inflammatory cells has been described in children[122] and adults[123] with bronchiectasis. The pediatric study[122] also examined specifically for phagocytic activity for nontypeable *Haemophilus influenzae* (NTHi), whereas the adult study[123] investigated apoptosis in relation to inflammation. The adult study[123] reported that impaired apoptosis occurred in a dose-response fashion with increasing neutrophil elastase, a marker of neutrophilic inflammation. In children with bronchiectasis, the macrophage phagocytic capacity of BAL cells to apoptotic cells (efferocytosis) and to NTHi was significantly lower than in controls (efferocytosis: 14.1%, IQR 10 to 16 vs. 18.1%,

IQR 16 to 21 respectively, $P < .001$ and NTHi: 13.7%, IQR 11 to 16 vs. 19.0%, IQR 13 to 21 respectively, $P = .004$).[122] Mannose receptor expression in BAL was also found to be significantly reduced in the bronchiectasis group compared to controls ($P = .019$).[122]

Other Immune Markers and Response

Innate defense mechanisms also play a role in the pathogenesis and upregulated response to infection in people with bronchiectasis.[8] However, there is little data specific to children.[27] In a study involving 26 children with human immunodeficiency virus (HIV)-related bronchiectasis,[124] the soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), an innate immune marker, was upregulated and more highly expressed than in children with CF. sTREM-1 also correlated with IL-8 and neutrophil elastase derived from BAL.[124]

The increased expression of innate immune receptors (e.g., receptors TLR2, TLR4, and CD14) and cytokine responses (e.g., IL-8 and IL-1β) seen in adults with bronchiectasis are also found in those with neutrophilic asthma and children with PBB,[125,126] a likely forerunner of bronchiectasis.[11] This raises the possibility that some people with neutrophilic asthma have unrecognized CSLD. Indeed, many of children with PBB were previously misdiagnosed with asthma[11,34] and in some settings has been classified as "difficult or severe asthma."

There is an emerging body of evidence that impaired cell-mediated immune responses and dysregulated airway inflammation are linked and could contribute to the pathobiology of CSLD. A study on systemic immunity found that children with CSLD or bronchiectasis produced significantly less IFN-γ in response to NTHi than healthy control children, whereas mitogen-induced IFN-γ production was similar in both groups.[127] The production of systemic NTHi-specific IFN-γ was significantly negatively associated with the BAL IL-6 ($P = .001$) and IL-1β ($P = .001$).[128] The presence of bacterial or viral infection and severity of bronchiectasis using modified CT Bhalla score did not influence systemic NTHi-specific IFN-γ response.[128]

CLINICAL FEATURES

Presenting Clinical Features: Symptoms and Signs

The clinical case definition of bronchiectasis is imprecise, but the diagnosis should be considered when children have a chronic "wet" sounding or productive cough with or without exertional dyspnea, recurrent wheezing and chest infections, hemoptysis, growth failure, clubbing, or hyperinflation. The most common symptom is persistent or recurrent wet/productive cough with purulent or mucopurulent sputum. Sputum color reflects neutrophilic airway inflammation.[129,130] The frequency of chest wall deformity (hyperinflation) and digital clubbing vary among case series (5% to 60%).[24,52,131] Digital clubbing can disappear after medical or surgical treatment in association with the disappearance of purulent sputum.[24,131] Although hemoptysis is much less common among children than in adults with bronchiectasis, a presenting finding of hemoptysis should raise the possibility of airway bleeding due to bronchiectasis. Chest auscultation may be entirely normal or reveal coarse inspiratory crackles over the affected regions. Reduced oxygen saturations and abnormal cardiac sounds associated with pulmonary hypertension are very late signs in bronchiectasis. Similar to any other serious chronic respiratory illness, children with bronchiectasis may have growth failure[52] that is associated with delayed diagnosis of bronchiectasis.

The median age of diagnosis of bronchiectasis unrelated to CF in affluent countries is 4 to 5 years.[52,56] A New Zealand cohort[55] was older at 9 to 10 years old at diagnosis but also experienced more advanced disease. Idiopathic bronchiectasis is rare in infancy, but when present, it is likely to reflect congenital pulmonary malformations, such as cystic lung disease or tracheobronchomegaly, or alternatively, primary ciliary dyskinesia. Only 50% of those with ciliary dyskinesia have the Kartagener triad of situs inversus, bronchiectasis, and sinusitis.[132]

Radiological risk factors for development of bronchiectasis are the presence of atelectasis[67,133] and persistent lobar abnormalities.[134] In Alaska, children were more likely to develop bronchiectasis if chest radiographs obtained in children less than 2 years of age showed lung parenchymal densities, persistent parenchymal densities greater than 6 months duration, or repeated parenchymal densities.[134] Among Aboriginal Australian children hospitalized with lobar changes on admission chest radiographs, children with alveolar abnormalities were more likely to have bronchiectasis on follow-up.[133] In a prospective radiographic study of alveolar changes (179 lobes in 112 hospitalized children), the two most common involved lobes were the right upper lobe and left lower lobes.[133] Both lobes had similar rates of radiological clearance on follow-up (22% and 27% respectively).

Comorbid Conditions

Children with postinfectious bronchiolitis obliterans and CSLD share some common clinical features (airway obstruction, chronic cough, recurrent ALRIs) in addition to the same etiological insult.[60,135] In an Australian study, 6 of 19 children with postinfectious BO developed bronchiectasis.[60] A South American cohort follow-up study (mean period of 12 years, SD 3.5) described that mean FVC increased by 11%/year (95% CI 9.3 to 12.6), FEV_1 by 9%/year (95% CI 7.7 to 10.2), and FEV_1/FVC ratio decreased by 1.9%/year (95% CI 1 to 2.8).[136] Seventy-eight percent of the 46 children in that cohort had bronchiectasis.[136]

Phenotypes of childhood wheeze have been recognized and airway hyperreactivity occurs in some individuals with bronchiectasis.[135] The presence of features of asthma has been described as a bad prognostic factor in both children[24,131] and adults[137] with bronchiectasis. The frequency of airway hyperreactivity in children with bronchiectasis varies from 26% to 74%.[52,56] As a corollary, clinicians must recognize that wheeze and cough may not be related to asthma but to increased airway secretions and airway collapse as features of bronchiectasis.

Gastroesophageal reflux disease (GERD) may coexist with any chronic respiratory illness and should be appropriately treated. However, data in adults indicate that GERD may resolve or significantly improve once the underlying respiratory disorder has been treated.[138] There is, however, no evidence-based approach to the management of GERD associated with bronchiectasis. Caution is necessary with regard

to overdiagnosis, and unnecessary treatment of GERD is given the increasing evidence of increased risk of respiratory infections in children and adults receiving proton pump inhibitors in community and hospital cohorts.[139,140] Readers are referred to the pediatric guidelines on diagnosis and treatment of GERD.[141]

Hypertrophic osteoarthropathy (clubbing, periostosis of the tubular bones, and arthritis-like signs and symptoms) may occur in children with bronchiectasis.[142] Systemic amyloidosis has also been reported as a complication or comorbidity.[143] Cardiac dysfunction, although rare, has also been reported and may not be accompanied by pulmonary hypertension. A study of 21 children with bronchiectasis showed that the ventricular systolic function was normal but some patients had changes in left ventricular diastolic function.[144] The authors also found that isovolumetric relaxation time had a significant negative correlation with the clinical severity score. Other reported comorbid conditions associated with bronchiectasis are osteopenia,[145] scoliosis, chronic suppurative ear disease, social problems, past urinary tract infections, and developmental delay.[52,56]

In adults, vitamin D deficiency has been reported to be associated with increased severity of bronchiectasis and chronic bacterial colonization of the airways.[146] However, as serum vitamin D is a negative acute phase reactant (i.e., values fall with increased inflammation), deciphering cause and effect is problematic.[147]

DIAGNOSTIC EVALUATIONS

The goals of evaluating children with suspected bronchiectasis are: (1) to confirm the diagnosis, (2) to define the distribution and severity of airway involvement, (3) to characterize extrapulmonary organ involvement associated with bronchiectasis (such as cor pulmonale), and (4) to identify familial and treatable underlying causes of bronchiectasis and contributors to its progression.

Diagnostic Criteria

Chest HRCT is the gold standard for diagnosis,[27] because plain chest radiographs are insensitive. It has been long recognized that chest x-rays can be normal in people with bronchiectasis.[148] With modern CT scanners, the images are best acquired using an MDCT scan with HRCT reconstruction which provides the best sensitivity.[27] The scan protocol must be child-appropriate to minimize radiation risk. Radiology centers inexperienced in dealing with children often utilize adult protocols that subject children to higher doses of radiation. Radiological features of bronchiectasis can also occur in association with pulmonary fibrosis, congenital lesions such as Mounier-Kuhn, and Williams-Campbell syndrome,[97] and as a result of traction in nonsuppurative lung disease.[149]

The characteristic radiographic finding on HRCT in bronchiectasis is the presence of a "signet ring" where a dilated bronchus is greater than the diameter of the accompanying blood vessel in cross section (Fig. 26.5).[97,150] However, the cutoff (>1 to 1.5) whereby the ratio is considered abnormal should be reduced to 0.8 in children when CSLD symptoms are present.[13] While this is generally appreciated by pulmonologists, radiologists may still use the adult criteria. The presence of bronchial dilatation relative to the accompanying vessel does not always equate to the presence of bronchiectasis, as this finding can also be present in other conditions (Box 26.2). Other c-HRCT signs of bronchiectasis include abnormalities in the surrounding lung may include parenchyma loss, emphysema, scars and nodular foci,[150] a linear array or cluster of cysts, dilated bronchi in the periphery of the lung, and bronchial wall thickening (Box 26.1).[154] Image quality and hence detection of bronchiectasis is dependent on the radiological technique used (tube setting, radiation dose, collimation distance, and image intervals).[155] False positive and false negative situations that may occur are listed in Box 26.2. HRCT does not differentiate the etiologies of bronchiectasis.[156]

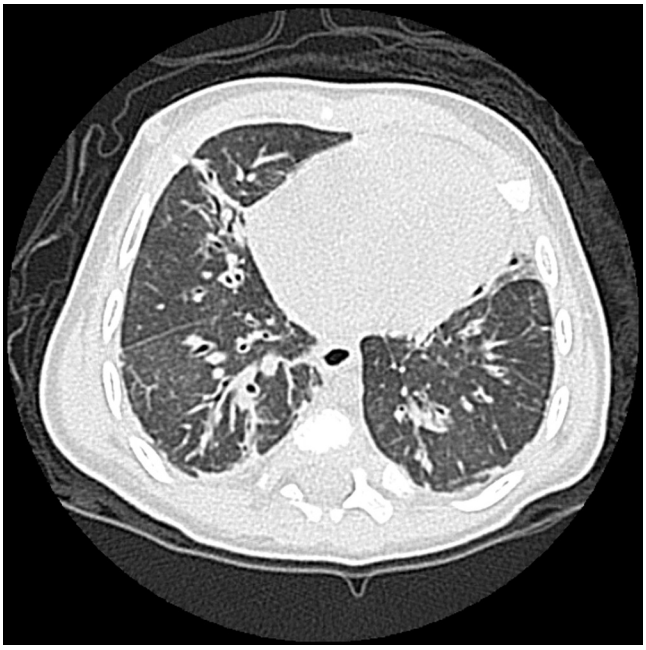

Fig. 26.5 High resolution CT finding in bronchiectasis. Image illustrates the "signet ring" appearance of a dilated airway adjacent to smaller associated pulmonary vessels. In adults, abnormal dilatation is considered present when the bronchoarterial ratio (inner diameter of bronchus: external diameter of adjacent artery) is greater than 1. In children, a cutoff of 0.8 is considered abnormal when clinical features of bronchiectasis are present.

Box 26.1 Features of Bronchiectasis on Chest High Resolution Computed Tomography Scans

1. Signet ring sign: internal diameter of bronchi is larger than accompanying vessel (diameters of both should be short axis)
2. Enlarged internal bronchial diameter
3. Failure of airway to taper normally while progressing to lung periphery
4. Presence of peripheral airways at CT periphery
5. Presence of associated abnormalities
   - Bronchial wall thickening
   - Mucoid plugging or impaction (seen as branching or rounded/nodular opacities in cross sections, tubular or Y-shaped structures or tree in bud appearance)
6. Mosaic perfusion
7. Air trapping on expiration
8. Air-fluid levels in distended bronchi

Compiled from references 97, 151-153.

Etiologic Evaluation

As most patients are usually diagnosed with bronchiectasis after many years of symptoms, it may be difficult to define the etiology. Differentiating idiopathic from postinfectious bronchiectasis is particularly problematic. A common feature of many patients is impaired local or systemic host defenses to infection.[127,157] Often, no cause is found even with extensive investigation, and many retain the label of idiopathic or presumed postinfectious bronchiectasis (see Table 26.2). Difficulties with ascribing an etiology to CSLD/bronchiectasis arise due to unavailability of certain tests, for example, functional tests for ciliary motility and extended immune testing, lack of a standardized approach to diagnosis, the population studied, and the CT definitions used.

Identifying etiology and assessing disease severity can influence surveillance frequency, treatment intensity, and prognosis.[157,158] Investigations for specific causes of CSLD/bronchiectasis are recommended, even though many patients will lack an identifiable etiology.[79] Current best practices for investigating possible etiology are outlined in Table 26.3. The diagnosis of ciliary dyskinesia[159] is addressed in another chapter (see Chapter 71).

Box 26.2 Pitfalls in Diagnosis of Bronchiectasis on Chest High-Resolution Computed Tomography Scans

False Positives

1. Physiologic constriction of pulmonary artery (creates relative bronchial enlargement)
2. Artefacts from cardiac pulsation and respiratory motion (creates pseudocystic pattern)
3. Pseudobronchiectasis or transient bronchial atresia (related to acute pneumonia or atelectasis)
4. Increased bronchoarterial ratio in normals, asthmatics or at high attitude

False Negatives

1. Inappropriate HRCT protocol (wrong electronic windows or collimation)
2. Poor image due to movement artefacts
3. Nonuse of high-resolution techniques

HRCT, High-resolution computed tomography.
Compiled from references 97, 151-153.

Bronchoscopic Findings

Bronchoscopy is indicated to identify obstructive bronchiectasis, which can be intraluminal (tumors and foreign body), in the wall (tracheobronchomalacia [TBM]), or extramural from external airway compression. Bronchiectasis is a complication of inhaled foreign bodies and occurs among 25% of patients whose diagnosis of aspiration was delayed by greater than 30 days.[160] In a prospective study involving 56 children with bronchiectasis undergoing flexible bronchoscopy, there were 25 occasions in 23 children where bronchoscopic results altered empiric treatment.[111] BAL microbiology results led to antibiotic changes in five (9%) children, and an unsuspected foreign body was found in one (2%).[111]

Bronchoscopic findings of major airways related to bronchiectasis have been described as five types: type I: mucosal

Table 26.3 Evaluation for Underlying Etiologies

Investigation Type	Details	Evaluation for:
ROUTINE		
Baseline immune function	IgG, A, M, IgG subclasses, IgE, hemagglutinins, antibodies to vaccinations	Immune deficiency states
Full blood count	White cell count	Neutropenia
HIV status	HIV antibody, HIV PCR assay	HIV infection
Sweat test and consider genotype	Sweat chloride and CF genotype	Cystic fibrosis
Radiology	Chest HRCT scan Chest radiograph	Diagnosis, congenital malformation and disease severity
Aspergillosis serology	Aspergillus specific IgE Skin test, total IgE	Allergic bronchopulmonary aspergillosis
Cilial biopsy and consider genetic testing	Electron microscopy and ciliary beat function	Ciliary dyskinesia
Sputum	Microscopy, sensitivity and culture	Number of polymorphs, microbiology
ADDITIONAL TESTS DEPENDING ON CLINICAL CHARACTERISTICS		
Bronchoscopy	Airway abnormalities BAL	Obstructive bronchiectasis Congenital airway abnormalities Microbiological assessment when sputum cannot be obtained Cellular differential count
Investigations for GERD	Esophageal pH studies, manometry and/or upper endoscopy	GERD with or without aspiration syndromes
Barium meal		Tracheoesophageal fistula, esophageal abnormalities causing secondary aspiration such as achalasia
Mantoux	PPD tuberculin and atypical	Mycobacterium TB and atypical mycobacteria
Further immune tests	Neutrophil function, CH50, etc.	Immune function
Video fluoroscopy	Oro-palatal function and assessment of laryngeal protection	Primary aspiration lung disease
Genetic tests		

BAL, Bronchoalveolar lavage; *GERD,* gastroesophageal reflux disease; *HRCT,* high-resolution computed tomography; *PPD,* purified protein derivative skin test; *TB,* tuberculosis.

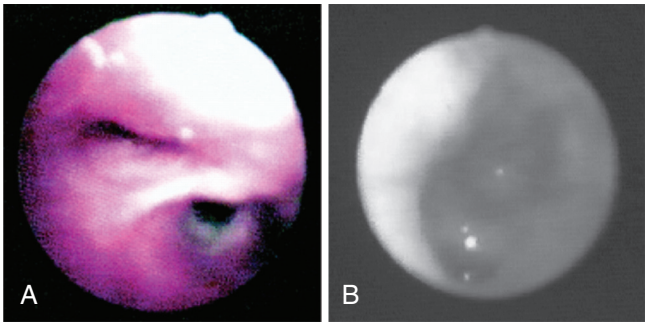

Fig. 26.6 Major airway bronchoscopic findings in bronchiectasis. (A) Bronchomalacia (airway type II) of the right middle lobe. (B) Obliterative-like lesion (airway type III) seen in the segmental bronchi (middle of picture) while the adjacent bronchi are widely patent and more inflamed. (Reproduced with permission from the BMJ Publishing Group—Chang AB, Boyce NC, Masters IB, et al. Bronchoscopic findings in children with non-cystic fibrosis chronic suppurative lung disease. *Thorax* 2002;57:935-938.)

abnormality/inflammation only; type II: bronchomalacia (Fig. 26.6A); type III: obliterative-like (Fig. 26.6B); type IV: malacia/obliterative-like combination; and type V: no abnormality.[161] The frequencies of these findings among 28 children with non-CF bronchiectasis were 58%, 17%, 17%, 4%, and 2% for types I through V respectively.[161] In the 33 children with postinfectious bronchiectasis and CSLD, structural airway lesions were present in 40%.[161] A retrospective study involving 93 Greek children (0.6 to 16.4 years) described that type III (OR 5.4, 95% CI 1.9 to 15.4) and type IV (OR 8.9, 95% CI 2.5 to 15.4) bronchoscopic lesions significantly correlated to worse radiological scores, reflecting severity, and correlated with the percentage of BAL neutrophils ($r = 0.23$, $P = .036$).[162]

Bronchomalacia associated with bronchiectasis can be related to chronic inflammation,[163] although it is unknown if bronchomalacia predates recurrent respiratory infections. Airway mucosal changes typical of chronic bronchitis are usually present in bronchiectatic airways at bronchoscopy. Bronchoscopic findings include atrophic mucosa, increased secretions, and airway friability. Airway flaccidity, hypertrophy of elements in wall, longitudinal corrugations, mucosal reddening, increased vascularity, dilated ducts, and displacement due to lobar collapse have also been described in the proximal conducting airways (Fig. 26.7).[163]

Assessment of Severity

Pulmonary Function. In children, spirometry is insensitive in detecting early structural lung damage in children with bronchiectasis, both in CF[164] and non-CF.[52] Spirometric values may be normal, but when a spirometric abnormality is present[52,165]; it is usually obstructive in the earlier stages and becomes a mixed obstructive and restrictive process when bronchiectasis is more severe. Although FEV_1 correlates with chest HRCT abnormalities in some populations, it is not a sensitive measure, especially if bronchiectasis is localized.[52,165] FEV_1 can also be normal, as in CF, in the early stages of disease even when radiological bronchiectasis was present.[164] However, when bronchiectasis is diffuse, spirometric abnormalities, although insensitive to disease activity, reflect disease severity.[164] Other pulmonary function test abnormalities described are a high residual volume, lower aerobic capacity, and lower maximal ventilation at maximal exercise.[166] Effort limitation during cardiopulmonary exercise testing does not relate to HRCT scores.[167]

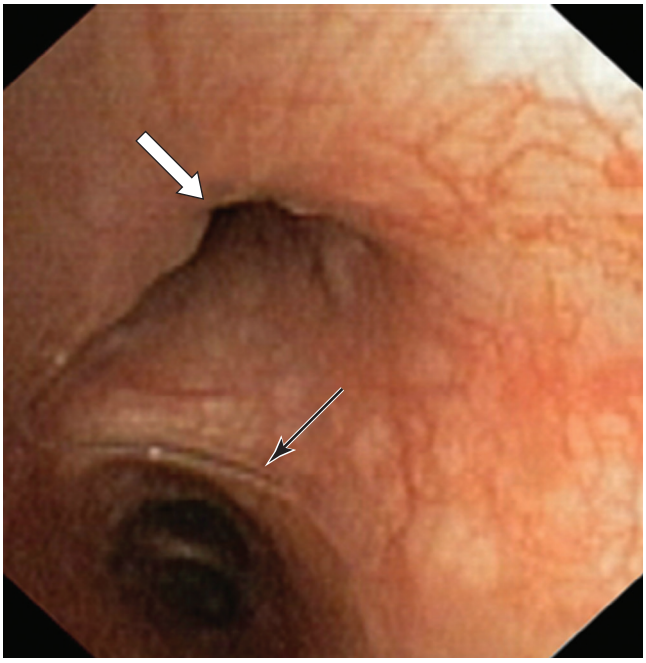

Fig. 26.7 Bronchoscopic picture from a child with bronchiectasis. Airway mucosal abnormality in child with bronchiectasis depicting mucosa erythema and irregularity, muscularis ridging *(black arrow),* and bronchomalacia (*white arrow,* right middle lobe).

There are limited data on how bronchiectasis alters respiratory system resistance or reactance measured by forced oscillatory techniques (FOT). In children, indices obtained from impulse oscillometry during exacerbations were not significantly different from the stable state.[168] In the stable state, resistance at 5 Hz was poorly sensitive to lung disease.[168] In children with CF, indices from FOT are not only insensitive at baseline but also cannot detect lung progression over 12 months.[169]

Another tool to assess severity of bronchiectasis is lung clearance index (LCI). The LCI reflects ventilation inhomogeneity in peripheral airways. Data in children with CF suggest that LCI changes occur early and before other physiological measurements when evaluating lung damage.[170] Among adults with stable non-CF bronchiectasis, the LCI negatively correlated with FEV_1 % predicted and was abnormal more often than FEV1.[171] However, a study involving 25 paired measurements of adults with non-CF bronchiectasis found that LCI was less sensitive than FEV_1 when evaluating improvement after treatment with intravenous antibiotics and physiotherapy for respiratory exacerbations.[170] While FEV_1 and vital capacity significantly improved, there was no significant change in LCI after intravenous antibiotics and physiotherapy.[170] The same study also undertook paired measurements in 25 adults with stable bronchiectasis and described that LCI indices were reproducible and, compared to controls, LCI was significantly higher.[170] There are no studies in children with non-CF bronchiectasis to know its sensitivity to early disease.

Radiology. There are at least eight radiographic scoring systems to assess severity of bronchiectasis using plain

films. However, given the insensitivity of chest radiographs in detecting bronchiectasis, these scoring systems have been superseded by chest HRCT scoring systems described by Webb et al.,[97] Bhalla et al.,[172] and Reiff et al.[156] These chest HRCT scoring systems are based on composite scores of multiple radiological findings. Some systems utilize expiratory scans,[173] while others do not.[97] The Webb composite score[97] is a summation score of severity, extent, and features of emphysema and consolidation/atelectasis. The Bhalla score[172] comprises the sum of scores assigned to each of nine categories: severity of bronchiectasis, peribronchial thickening, extent of bronchiectasis, extent of mucus plugging, sacculations, generations of bronchi involved, number of bullae, emphysema, and collapse/consolidation. One study compared these three scoring systems in a group of 59 children with non-CF bronchiectasis.[52] The correlation between the scores ranged from 0.61 to 0.8 but none related to FEV_1 values. Magnetic resonance imaging (MRI) is an emerging technique for assessing bronchiectasis, but it is currently poorer than CT in evaluating airway diseases.[174,175]

Other Markers. A UK group developed the bronchiectasis severity index for adults[6] as a stratification tool for morbidity and mortality. The index includes features that are rare in children (e.g., FEV_1 of <30% predicted) and is thus not used in children.

The world of "omics" is blooming, but there currently are no studies relevant to clinical care in bronchiectasis. In children with CF, metabolomics using mass spectrometry have described possible biomarkers of BAL neutrophilic inflammation.[176] Techniques such as expired breath analysis and breath condensate measurements described almost two decades ago have not advanced in bronchiectasis.

Assessment of Disease Progression

To date, there is little research on the most sensitive and appropriate method of assessing progression of bronchiectasis in children. Clinicians rely on frequency of respiratory exacerbations and on daily clinical symptoms, which may be perceived differently by children and their parents. There is no bronchiectasis severity score for children. QoL scores that are not specific for cough have been used in children with bronchiectasis, but to date, there is no pediatric bronchiectasis-specific QoL score.

The most sensitive objective assessment of early disease progression is based on HRCT changes, as these precede most pulmonary function changes.[52,165] However, repeated HRCT scans are not recommended purely for assessment of disease progression given the known risks of radiation in young children.[177] Other assessments of disease progression include chest radiographs which are insensitive, lung function, markers of neutrophilic airway inflammation, and possibly assessments of airway proteases. One small cross-sectional study showed significant correlations between HRCT severity scores and symptoms, FEV_1, sputum IL-8, and TNF-α levels (r values of 0.64, –0.68, 0.41 and 0.41, respectively).[53] However, there are no data relating these airway markers to imaging assessments longitudinally and disease progression.

Assessment of Infection

Sputum sampling is the easiest method of obtaining an endobronchial microbiologic profile, but young children often do not expectorate sputum even when they have substantial lower airway secretions. Hence, in young children, assessment of lower airway microbiology requires bronchoscopy to obtain BAL and lower airway samples. BAL remains the gold standard, although the criteria for defining infection remains controversial.[11,178] Studies have generally used a threshold of bacterial growth of $\geq 10^4$ colony forming unit (cfu)/mL BAL to indicate infection.[11,179]

Other methods for identifying airway pathogens from children with bronchiectasis are oropharyngeal or nasopharyngeal swabs and induced sputum. In adults with bronchiectasis, sputum culture is generally reflective of lower airway organisms obtained by bronchoscopic catheter protected brushings.[180] One study on children with bronchiectasis described that the sensitivity and negative predictive value of nasopharyngeal cultures for individual respiratory bacterial pathogens, causing lower airway infection using BAL for comparison, ranged from 75% to 100%, and the specificity and positive predictive value were lower (32% to 72%).[72]

Common respiratory pathogens in children with bronchiectasis are *Streptococcus pneumoniae* and *H. influenzae nontype b.* Other organisms include *Moraxella catarhallis* and *Pseudomonas aeruginosa.* In pediatric bronchiectasis, the pathogen isolation rate from sputum or BAL is 53% to 67%.[58,109] Pseudomonas is commonly found in adults with severe bronchiectasis, but it is uncommon in children until adolescence or when bronchiectasis is severe.[58] In adults, a systematic review[181] found that persistent pseudomonas endobronchial infection was associated with increased disease severity measured radiographically, with spirometry, with death (threefold), and with more hospitalizations and poorer QoL; there are no such data in children. While nontuberculous mycobacteria and Aspergillus are commonly found in adults with bronchiectasis, they are rarely present in children with bronchiectasis.[58,72]

A number of children with bronchiectasis are persistently colonized with potential pathogenic microorganisms.[180] The largest study to report on microbiology in children with bronchiectasis was undertaken when they were clinically stable.[58] *H. influenzae* was identified in 32%, *S. pneumoniae* in 14%, *M. catarrhalis* in 8%, and *S. aureus* in 5% of BAL cultures.[58] *P. aeruginosa* was present in seven (6%) children of whom six had bronchiectasis involving multiple lobes, and five had other comorbidities.[58] The study also reported that respiratory viruses (principally respiratory syncytial virus and adenovirus) were present in 14 (12%) children; codetection of respiratory pathogens was found in more than half of those with positive microbiology results.[58] When the adenovirus was genotyped, almost all were type C, and the presence of adenovirus was significantly associated with bacterial coinfection with *H. influenzae, M. catarrhalis, or S. pneumoniae* (OR 3.27; 95% CI 1.38 to 7.75) and negatively associated with *S. aureus* infection ($P = .03$) in the BAL.[182] Studies on the microbiota (using bacterial 16S rRNA gene pyrosequencing) in children[9] and adults[183] with bronchiectasis have been reported. However, their impact on clinical management is yet to be defined. Nevertheless, one study that compared the microbiota of children and adults with bronchiectasis reported that the respiratory microbiota significantly differed from each other.[9]

Pulmonary exacerbations among children with non-CF bronchiectasis are often triggered by viruses and an increased

density of known bacterial pathogens in sputum. The single prospective study in children that evaluated the point prevalence of viruses associated with exacerbations reported that respiratory viruses were detected during 37 of 77 (48%) exacerbations.[184] As the viruses reported included those commonly found in well children (rhinovirus [n = 20], enterovirus [n = 4] bocavirus [n = 4] coronavirus [n = 1]), it is possible that the percentage of true virus-associated triggers is lower. Classical respiratory viruses (adenoviruses, metapneumovirus, influenza, respiratory syncytial virus, parainfluenza [n = 3 each]) were found in only 15 (20%) exacerbations.[184]

Assessment and Importance of Exacerbations

There is one published study that developed a standardized definition of exacerbation in children.[168] In 69 children over 900 child months, the study described validated major and minor criteria that can be used in the hospital or primary care setting. The major criteria were the presence of a wet cough and a cough severity score of ≥2 over 72 hours (area under the curve [AUC] of 0.85 [95% CI 0.79 to 0.92] and 0.84 [95% CI 0.77 to 0.91] respectively).[168] The minor criteria were change in sputum color, chest pain, dyspnea, hemoptysis and new chest signs on physical examination. The inclusion of investigations (investigatory criteria: elevated serum C-reactive protein, amyloid-A, or IL6) to the definition improved its specificity and positive predictive value.[168] Other infrequent features of importance are reduced exercise tolerance and energy.[185] Fever and hemoptysis are uncommon in exacerbations of bronchiectasis in the pediatric age group.[168,185]

Determinants of accelerated lung function decline in adults with bronchiectasis are frequency of hospitalized exacerbations, increased systemic inflammatory markers, and colonization with *P. aeruginosa*.[186] In one study of 52 children over a 3-year interval, the only significant predictor of FEV_1 decline was frequency of hospitalized exacerbations[79]; with each exacerbation, the FEV_1 % predicted decreased by 1.95% adjusted for time.[79] It is likely that interventions that can reduce exacerbations prevent further lung dysfunction.[187] Also, exacerbations, particularly when recurrent, are one of the strongest predictors of poor QoL among adults with bronchiectasis.[188,189] A prospective study involving 93 Indigenous children in Alaska and Australia showed that factors associated with recurrent (≥2) exacerbations included age less than 3 years, respiratory-related hospitalization in the first year of life, and pneumonia or hospitalization for exacerbations in the year preceding enrollment.[1] The study also reported that with clinical care and time exacerbations occurred less frequently.[1]

Exacerbations should be treated such that at the end of treatment, there are improvements in cough character, general well-being, QoL indicators, and inflammatory markers with reduced sputum volume and purulence, decreased sputum bacterial load or pathogen clearance, and a return toward the patient's stable baseline state.[109,190]

MANAGEMENT AND TREATMENT PRINCIPLES

As early as 1933, Roles and Todd emphasized the importance of early diagnosis and treatment in reducing mortality associated with bronchiectasis.[36] Over the ensuing years, other authors such as Field[74] emphasized the importance of treatment "Even with simple medical treatment, the progress of most cases can be arrested...."[74] In bronchiectasis secondary to CF and primary ciliary dyskinesia, aggressive management of infections with antimicrobials, regular use of airway clearance methods, attention to nutrition, coupled with vigilant monitoring of long-term clinical trends, and proactive care led to improved survival and preservation of lung function.[191] CF produces a specific type of progressive bronchiectasis that differs from other forms of bronchiectasis with respect to mucus rheology, airway surface abnormalities, salt content, airway microbial pathogens, and extrapulmonary organ involvement. Although blind extrapolation of management used in CF to non-CF bronchiectasis can be harmful,[192] management of children with bronchiectasis should be arguably as intensive in children with idiopathic bronchiectasis to minimize acute exacerbations, daily symptoms, and functional limitations; thus improving the prognosis. Indeed, more recent data have provided evidence that intensive treatment of children who either have bronchiectasis or who are at risk of developing severe bronchiectasis prevents poor lung function in adulthood.[79,193] Even among children with serious underlying conditions, such as congenital immunodeficiencies and bronchiectasis, comprehensive regular care and surveillance programs have delayed decline in lung function over a period of a year.[194]

The aims of regular review include optimal postnatal lung growth, prevention of premature respiratory decline, maximal QoL, and prevention of complications due to bronchiectasis. Issues that require regular monitoring are listed in Box 26.3. Ideally, a team approach with incorporation of allied health expertise (nursing, physiotherapy, nutritionist, social work) should be used, as this model has been shown to improve health outcomes for several chronic diseases.[195] Evidence-based guidelines of management of bronchiectasis in children have been published since 2002 and subsequently updated,[190] and adults have been included.[196] An umbrella Cochrane review on the interventions for bronchiectasis has been published.[197]

Box 26.3 Management Issues for Regular Review

1. Accurate diagnoses of underlying etiology and conditions that aggravate bronchiectasis
2. Philosophy of antibiotics use (maintenance, intermittent, regular hospitalizations)
3. Airway pathogens and drug-sensitivity profiles
4. Effectiveness of mucociliary clearance techniques
5. Nutritional state and support
6. Psychosocial support and adherence issues
7. Pattern and frequency of acute respiratory exacerbations
8. Presence of comorbid conditions
9. Education and promotion of self-management
10. Preventive measures (environment assessment, vaccines)
11. Indications for surgical resection of bronchiectatic regions
12. Complications related to bronchiectasis (e.g., hemoptysis, lung abscess, pulmonary hypertension, sleep disorders, reactive airway disease)
13. Review of new therapies and therapeutic strategies as they emerge, for example, macrolide use for antiinflammatory, antisecretagogue effects.

Antimicrobials

Antimicrobial treatment is a key intervention in the management of patients with bronchiectasis.[109] In stable adult patients, there was a direct relationship between bacterial load and the risk of both subsequent and severe exacerbations (ORs of 1.2, 95% CI 1.1 to 1.3 and 1.1, 95% CI 1.0 to 1.2; respectively).[112] However, there are few published randomized controlled treatment trials on childhood bronchiectasis and none that focus on acute exacerbations.[198] Brief antimicrobial interventions significantly improve the inflammatory profile in the airways,[199,200] and blood,[199,200] sputum production, cough frequency, and QoL measures.[200,201] Use of antimicrobials for bronchiectasis was recently summarized.[109]

In general, the type of antimicrobial should target known pathogens and the route dependent on the severity of the illness and response to previous treatments.[109,190] Ideally, a sputum culture should be obtained prior to initiating antibiotics. Oral antibiotics are usually prescribed initially, but more severe episodes, or failure to improve with oral agents, require intravenous antibiotics combined with more intensive airway clearance techniques. Although robust evidence is lacking, a course of antibiotics for 14 days has been recommended by respiratory specialists.[112,190]

Comprehensive care programs for bronchiectasis have used both intermittent antibiotics to treat exacerbations and chronic or maintenance antibiotic treatment strategies. The use of maintenance antimicrobials may be suitable in selected situations where frequent exacerbations are likely to occur. Old studies in adults demonstrated that regular use of macrolides and trimethoprim reduced pulmonary inflammation, infective exacerbations and improved lung function.[202,203] A pediatric randomized controlled trial (RCT) involving 25 children (12 weeks of roxithromycin 4 mg/kg twice a day or placebo) also described a significant improvement in sputum markers and of airway responsiveness in the roxithromycin group, but improvements in FEV_1 were not observed in either group.[204] More recent studies in adults and children have confirmed these findings.[205] However, many questions remain, such as when should maintenance antibiotics be started and in whom, what is the optimal duration (studies suggest effects are evident only after 3 months), whether macrolides are the best choice of maintenance treatment, and which macrolides to use. Other questions are the optimal type and dosing regimen (daily-to-weekly) and whether associated increases in *S. aureus* and other macrolide-resistant bacteria are harmful at individual or community levels.[206] The latest Cochrane review (children and adults included) consisted of 18 studies whereby the meta-analysis showed that in patients with at least one exacerbation, the use of maintenance antibiotics (for >4 weeks) significantly reduced exacerbations compared to placebo or usual care with a reduction of 275 exacerbations per 1000.[205] Hospitalization was also reduced (50 fewer hospitalizations per 1000 people treated).[205] There was a threefold higher likelihood of antibiotic resistance in the group using maintenance antibiotics.[205] However, in the sole RCT that reported on use of antibiotics for conditions other than respiratory exacerbations, those in the antibiotic arm required 50% less other antibiotics (Incidence Rate Ratio = 0.5, 95% CI 0.31 to 0.81).[80] The factors affecting the risk of development of resistance to long-term macrolide therapy are adherence (adherence ≥70% reduces risk OR 0.34, 95% CI 0.14 to 0.81 compared to <70%) and baseline macrolide resistance rate.[207] The majority of the long-term studies used macrolides that have antiinflammatory and antisecretagogue effects.[208]

Antiinflammatory and Antioxidant Agents

In 18 children with CF and 15 children with idiopathic bronchiectasis, 6 months of beta-carotene supplementation reduced plasma levels of TNF-α and malondialdehyde, a marker of lipid peroxidation,[209] but did not change clinical status. In adults with bronchiectasis, nonsteroidal antiinflammatory agents have a major effect on peripheral neutrophil function, significantly reducing neutrophil chemotaxis and fibronectin degradation by resting and stimulated neutrophils, but they had no effect on bacterial colonization of the airways or superoxide anion generation by neutrophils.[210] There are no studies on oral nonsteroidal antiinflammatory drugs (NSAIDs), but a Cochrane review on inhaled NSAIDs found a single trial in CSLD.[211] In adults with bronchiectasis, Tamaoki et al. reported a significant reduction in sputum production over 14 days in the treatment group (4 days of inhaled indomethacin) compared to placebo and significant improvement in a dyspnea score.[212] There was no significant difference between groups in lung function or blood indices. Emerging drugs in development have been recently reviewed.[213]

Antisecretagogues and Mucoactive Agents

Mucoactive agents enhance mucus clearance from the respiratory tract in conditions where mucus clearance is impaired.[104] Mucolytics reduce mucus crosslinking and viscosity by disruption of polymer networks in the secretions through severing disulfide bonds, depolymerizing mucopolysaccharides, liquefying proteins, and degrading DNA filaments and actin.[104] In adults, high doses of bromhexine (not available in some countries) used with antibiotics eased difficulty in expectoration and reduced sputum production.[197] Recombinant deoxyribonuclease (rhDNAse) is efficacious in CF but is contraindicated in non-CF bronchiectasis. In a double-blind, RCT, multicenter study for 24-weeks in 349 adults with bronchiectasis, those given rhDNAse had higher exacerbation and hospitalization rates and more rapid pulmonary decline (decrease in FEV_1 3.6% in rhDNase group; 1.6% in placebo group).[192] Inhaled osmotic agents, such as 7% hypertonic saline and mannitol, improve airway clearance and lung function and reduce exacerbation frequency in people with CF but studies in adults with non-CF bronchiectasis show a benefit only in time to first exacerbation and QoL and not in exacerbation rates.[214] There are no studies in children and clinically selected children can be commenced on hypertonic saline. When used, pretreatment with a short-acting bronchodilator is recommended to avoid bronchospasm, which occurs in up to 30% of patients.

Antisecretagogues reduce airway mucus production and secretion. These agents include anticholinergic agents, macrolide antibiotics, and bromhexine. Fourteen-member-ring macrolides are antibiotics with antiinflammatory activities and their use is discussed in the antimicrobials section. There are no RCTs on anticholinergics in the treatment of acute or stable bronchiectasis. Some anticholinergic agents such as atropine and glycopyrrolate slow mucociliary transport and predispose to further mucus stasis. An

uncontrolled trial of tiotroprium in adults with hypersecretory states, including bronchiectasis that was resistant to macrolides, reduced daily symptoms and improved QoL with short-term use,[215] but it is not currently recommended in children.

Airway Clearance Methods

Although it is lacking a robust evidence-base,[216] airway clearance techniques (encompassing various types of chest physiotherapy) are recommended in children and adults.[190,196] Available studies suggest that airway clearance techniques are beneficial with improved QoL and exercise capacity and reduced cough and sputum volumes.[216] Thus daily chest physiotherapy is recommended in a form that maximizes potential benefit and minimizes burden of care. In the past, postural drainage was standard therapy for children with CSLD/bronchiectasis. However, this treatment may increase gastroesophageal reflux and possible aspiration.[217] Given the availability of multiple techniques for airway clearance and the lack of clear superiority of any one technique, specific choices should be individualized and pediatric-specific physiotherapist expertise sought. In addition, children with bronchiectasis should be encouraged to participate in exercise activities.

Asthma Therapy

Asthma in children with bronchiectasis should be treated on its own merits. Inhaled corticosteroids (ICS), at best, have a modest benefit in those with severe CSLD/bronchiectasis and those with *P. aeruginosa.*[218] The Cochrane review (six studies in adults, no pediatric studies) found that in the short term (ICS for <6 months duration), adults on very high doses of ICS (2 g per day of budesonide equivalent) had significantly improved FEV_1, FVC, QoL, and sputum volume but no improvement in peak flow, exacerbations, cough, or wheeze when compared to adults in the control arm (no ICS). When only placebo-controlled studies were included in the review, there were no significant differences between groups in any of the outcomes examined (spirometry, clinical outcomes of exacerbation or sputum volume). A single study on medium-term (>6 months) outcomes showed no significant effect of inhaled steroids on any of the outcomes.[218] There is no published RCT on the use of ICS for children with CSLD/bronchiectasis.[218] One study reported that 12-week withdrawal of ICS resulted in a significant increase in bronchial hyperreactivity and decrease in neutrophil apoptosis but no change in the children's clinical parameters or sputum inflammatory markers.[219] This suggests that ICS have little role in the management of CSLD/bronchiectasis in children when asthma does not coexist.

Short- and long-acting β-2 agonists also have an indeterminate role in the management of bronchiectasis,[197] and their use must be individualized. Although the presence of asthma is associated with advanced bronchiectasis and a worse prognosis, treatment of asthma to alter long-term outcomes has not been studied. It may be that the asthmatic features associated with diffuse bronchiectasis reflect the disease itself rather than a concurrent condition. Whether published guidelines for asthma care pertain to patients with wheeze and airway hyperactivity is unclear. Increased cough in children with bronchiectasis should be initially treated as an exacerbation of bronchiectasis.

Environmental Modification

In utero tobacco smoke exposure alters respiratory control and pulmonary development and physiology.[81,220] Tobacco smoke also skews the early immune function,[81] but its role in permanently altering local and systemic pulmonary immunity is unknown. Exposure to ETS increases susceptibility to respiratory infections, causes adverse respiratory health outcomes, and increases coughing illnesses.[81] Cessation of parental smoking reduces children's cough.[221] Behavioral counseling and motivational interviewing for smoking mothers reduces young children's ETS exposure in both reported and objective measures of ETS.[222]

Indoor wood smoke also increases acute respiratory infections, demonstrating an exposure-response effect.[223] Thus efforts to reduce smoke and biomass exposure including *in utero* exposure and children's exposure in the home must be maximized. There is low to moderate quality evidence that repairing houses decreases respiratory tract infections.[224]

Prevention: Vaccines

Vaccination as per national schedules is recommended. Many of the diseases described as causing bronchiectasis (e.g., pertussis and measles) are now controlled in developed countries. Vaccinations for prevention of influenza are recommended despite the lack of evidence specific for bronchiectasis.[225,226] While there is no specific evidence for influenza vaccine in those with CSLD/bronchiectasis,[225] indirect evidence suggests that annual influenza vaccinations reduce morbidity, mortality, and health care cost in "at risk" groups.[227] For pneumococcal vaccination, limited evidence supports the use of the 23-valent pneumococcal vaccine in reducing acute infective exacerbations.[226] 23-valent pneumococcal vaccine is recommended for high-risk children, including those with bronchiectasis.[228,229] Current evidence support revaccination, although the frequency of revaccination is controversial.[228] A recent study found that vaccination with the pneumococcal 10-serotype with *H. influenzae* protein D conjugate vaccine was associated with improvements in NTHi-specific cell-mediated and humoral immune responses in children with CSLD.[230] While this is promising, further confirmatory data are required.

Surgical Considerations

Surgery is considered most often when bronchiectasis is focal and medical therapy has failed. Surgery is very rarely undertaken now in affluent countries but is still a common intervention in less affluent countries.[231] Perioperative mortality for lobectomy and pneumonectomy has fallen dramatically. In a retrospective series of 109 children (mean age 7.6 years, range 1 to 15.5), 36% had minor postoperative complications (transient atelectasis in 26%, air leak 6%) and one child died within the 30-day postoperative period. Of the 83 children with an average follow-up period of 667 days, 76% showed improvement of clinical symptoms. This is similar to several reviews of surgical therapy for bronchiectasis; the compiled group of adult and pediatric patients experienced 1% mortality (6/597) and an operative complication rate of 8.5% (51/597).[232,233] Complications included empyema, bronchopulmonary fistula, hypotension, and bleeding, but surgical treatment of bronchiectasis was more effective in patients with localized disease.[233] Appearance of new

Box 26.4 Indications and Contraindications for Lobectomy

Indications

1. Poor control of symptoms (purulent sputum, frequent exacerbations) despite optimal medical therapy
2. Poor growth despite optimal medical therapy
3. Severe and recurrent hemoptysis uncontrolled by bronchial artery embolization

Relative Indications

1. Localized disease with moderate persistent symptoms

Contraindications

1. Widespread bronchiectasis
2. Young child (<6 years)
3. Minimally symptomatic disease

bronchiectasis following surgical management has been described.[52,234] Indications for surgical intervention are controversial, and data from the 1940 to 1950's cannot be applied given the major advances in antibiotics, airway clearance techniques, and nutrition supplementation, and socioeconomic standards among underserved populations. Our suggested indications for surgical intervention are outlined in Box 26.4. Although lung transplantation has been reported widely for patients with CF, this option has only been used for adults with end-stage non-CF bronchiectasis,[235] and outcomes following lung transplantation in children without CF have not been reported.

Social Determinants and Health Care

Finally, health cannot be isolated from social, economic, environmental, and educational issues. Health and health behaviors are closely linked to socioeconomic factors,[236,237] and increased poverty, with its associated consequences such as poor housing and poor water supply, is an independent risk factor for increased respiratory infections and associated mortality.[237] To effectively reduce the morbidity and mortality from CSLD and bronchiectasis in children, a multifaceted approach encompassing good clinical care and public health concerns bears consideration. Although it is beyond the scope of this article to address this important issue, future work must focus on the public health issues predisposing to childhood bronchiectasis if the disparity between developed and developing countries is to be reduced.

Delivery of chronic disease programs requires comprehensive and highly skilled culturally competent primary health care. Education of primary health providers should ideally focus on identifying children for appropriate referral and high quality local management. Initial assessment requires specialist expertise, and specialist evaluation is recommended to confirm diagnosis, investigate etiology, assess baseline severity, and develop a management plan. Similar to other chronic illnesses, individualized and multidisciplinary case management operating within an interprofessional framework is optimal. Similarly, deterioration should prompt early referral for specialist care. In addition, those with moderate or severe disease are best managed by a multidisciplinary team approach.

PROGNOSIS

Given the heterogeneity of etiological factors and host responses, regional severity, and distribution of bronchiectasis, it is not surprising that the prognosis is varied, ranging from mild respiratory morbidity to death from airway obstruction, pulmonary infection, and respiratory failure with hypercapnia. There are cases where bronchiectasis resolves radiographically with treatment.[22] However, these children remain at risk of developing bronchiectasis and should be monitored regularly for reemergence of symptoms and obstructive lung disease. More often, bronchiectasis persists on HRCT but becomes less severe clinically with fewer infectious exacerbations and less cough evident later in childhood. In a series of 46 children with HRCT–documented bronchiectasis, a third improved, a third remained symptomatic but stable, and a third worsened while receiving medical therapy[56] Both Field[131] and Landau et al.[238] reported reductions in exacerbations during the second and third decade of life despite persistence of bronchiectasis radiographically. What happens in the following decades is inferred from case series of adults with bronchiectasis, many of whom had onset of respiratory problems, if not bronchiectasis in childhood. However, these series do not depict the era of minimal symptoms that occur at adolescence and anecdotally reappear at age 35 to 40 years old.

There are three published studies (all retrospective) on longitudinal FEV_1 changes in children with non-CF bronchiectasis studied over variable intervals with varying results.[79,239,240] A British study (n = 59 over 2 years, n = 31 over 4 years) found that lung function improves with intensive treatment but does not necessary normalize.[239] Likewise, an Australian study (n = 52 over 3 years, n = 25 over 5 years)[79] found that lung function and anthropometric parameters remain stable over a 3- to 5-year follow-up period once appropriate therapy is instituted, and those with low function at diagnosis (FEV_1 % predicted <80%) improved with time.[79] In contrast, a New Zealand (NZ) study of 44 children over 4.5 years found that FEV_1 declined at 1.9% per annum.[240] The explanations for this contrast are speculative but likely include the different age groups, children from different ethnicities, and health care differences. Also, the NZ cohort had more extensive radiological disease with 89% bilateral disease (median of four diseased lobes, 95% with multilobar involvement). The Brisbane study found that the only significant predictor of FEV_1 decline (over 3 years) was frequency of exacerbations requiring hospitalization[79] The other two cohorts[239,240] did not examine for determinants of lung function decline.

Published data also suggest that delayed diagnosis is associated with poorer outcomes.[27,79] A large study of adults newly diagnosed with bronchiectasis showed that the decline in FEV_1 correlates with the duration of chronic wet cough,[37] the most common symptom of bronchiectasis.[241] For each additional year of productive cough, FEV_1% predicted declined by 0.51% in nonsmokers.[37] Adults with bronchiectasis who were symptomatic from childhood have much poorer lung function and worse chest CT scan scores than those with adult-onset symptoms.[37] In the Brisbane longitudinal study, children diagnosed earlier and hence managed earlier were significantly younger and had better long-term spirometry and growth parameters.[79] FEV_1% predicted decreased by

1.64% points for each year increase in age at diagnosis, but this was statistically nonsignificant.[79]

When bronchiectasis worsens, it may become increasingly saccular within a local lung region (see Figs. 26.2 and 26.3). Alternatively, bronchiectasis can extend to additional airways, either due to endobronchial spread of infection or evolution of disease at multiple airway sites. The frequency with which bronchiectasis extends to new lung regions varies with different series, from 2% to 35%.[242,243] Local progression of disease rather than extension to new areas is likely more common.

The most severe cases of bronchiectasis have diffuse airway involvement and are accompanied by airflow limitation, with or without concomitant airway hyperreactivity. The diagnosis of asthma in the context of an underlying lung disease may be difficult. Wheeze and asthma symptoms are common in people with CSLD/bronchiectasis, although reported prevalence varies from 11% to 46%.[57,244] While some studies describe asthma as a cause of bronchiectasis, it is more likely that wheezing illness is a secondary or coexistent condition or that asthma was initially misdiagnosed. Asthmalike symptoms in adults with bronchiectasis may be associated with an accelerated decline in lung function.[137] King reported that increased use of bronchodilators led to a trend of a greater FEV_1 decline over time in adults.[245] The NZ cohort found that while the presence of asthma was associated with lower FEV_1 at diagnosis, asthmatics had a slower rate of decline over the 5-year follow-up.[240]

Unfavorable prognostic factors for patients with bronchiectasis include presence of asthma, bilateral lung involvement,[131,246] saccular bronchiectasis,[246] frequency of exacerbations, and presence of *P. aeruginosa* in the airways.[181] The advent of better antibiotics, inhaled antibiotics, long-term oxygen therapy, and improved nutrition has improved prognosis. Cor pulmonale and right heart failure are now uncommon complications of advanced bronchiectasis in children. In one series, echocardiography in 50 children with bronchiectasis found only one child with pulmonary hypertension.[52] In addition, chronic lung infection and inflammation are independent risk factors for developing cardiovascular disease in adults.[247]

Protracted Bacterial Bronchitis

EPIDEMIOLOGY AND DISEASE BURDEN

Prior to a diagnosis of PBB, most children with a chronic wet cough received multiple medications and consulted several health physicians.[34,248] An Australian multicenter study found 70% of 138 children with PBB had received asthma medications, and 76% had seen greater than five doctors previously because of persistent cough.[249] However, these findings were also similar to children with a chronic cough from other causes.[249] QoL scores of children with PBB were similar to children with cough due to asthma or bronchiectasis presenting to pediatric pulmonologists.[249,250] Importantly, QoL scores normalized once the cough resolved.[251] While the prevalence of PBB cases in the community clinics is unknown, studies from specialist clinics (pediatrics and/or pediatric pulmonology) from Australia[23,34] and Turkey[252,253] found PBB to be among the top three diagnoses in children with chronic cough, with the prevalence ranging from 6% to 42%.[11]

PATHOLOGY AND PATHOGENESIS

Microbiology

In the first description of PBB,[23] BAL cultures grew the common respiratory bacterial pathogens, *S. pneumoniae, H. influenza,* and *M. catarrhalis* (Fig. 26.8). Subsequent studies confirmed this finding, although one retrospective study also identified *S. aureus* (11 of 50 children),[254] but quantitative bacteriology was not performed, making interpretation difficult. One study examined the presence of respiratory viruses in children with PBB.[255] This study reported rates of 39% for viruses detected by polymerase chain reaction (PCR) in the BAL fluid from 104 PBB cases compared to 9% of 49 other chronic respiratory disease controls (OR = 6.3, 95% CI 2.1 to 19.1). The most common virus identified was adenovirus (AdV),[255] which upon genotyping, belonged predominantly to AdV species C.[182]

The presence and role of biofilms in the BAL of children with PBB have not been studied, but their presence has been speculated.[11] The microbiota of the lungs of children with PBB has been examined in a single cross-sectional study.[9] One-way analysis of variance showed the Shannon-Weiner index (a measure of species diversity) of the lower airway microbiota in children with PBB, and bronchiectasis were similar and statistically higher (i.e., richer) than in CF. The lung microbiota in children were significantly different from those observed in adults with CF and bronchiectasis, suggesting that chronic airway infections begin similarly with

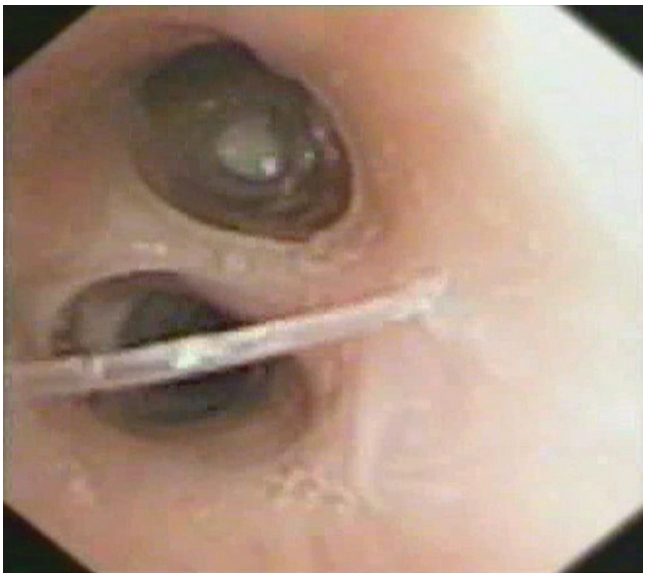

Fig. 26.8 Bronchoscopic picture from a child with protracted bacterial bronchitis. The picture shows a strand of mucus just proximal to the left lower lobe bronchus and prominent secretions in the left lingula bronchus. The bronchoscopic appearances in children with protracted bacterial bronchitis are similar to those seen in mild bronchiectasis. The bronchoalveolar lavage from this child cultured *Haemophilus influenzae* and *Streptococcus pneumoniae,* both at a density of greater than 10^5 cfu/mL. Polymerase chain reaction for respiratory viruses (influenza A and B, RSV, parainfluenza 1-2, adenovirus, human metapneumovirus), Mycoplasma and Chlamydia were negative.

defective airway clearance of otherwise normal airway microbiota. Over time with antibiotic treatment and perhaps the effects of the underlying disease, the microbiota in these disease groups progressively diverge.[11,182]

Immunity and Inflammation. Studies on immunity in children with PBB[11] reported the following features: (1) absence of an overt systemic immunodeficiency (normal serum IgA, IgM, IgG, and IgE levels), (2) robust responses to protein (tetanus) and conjugated protein-polysaccharide *(H. influenzae type b)* vaccines,[255] and (3) upregulated innate immunity (e.g., elevated TLR-2, TLR-4, human β-defensin 2 [hBD2], and mannose-binding lectin [MBL][125]). A small BAL-based study described significantly decreased ability of alveolar macrophages to phagocytose apoptotic bronchial cells and NTHi in children with PBB (n = 13) compared to controls (n = 13).[122] For both types of impaired phagocytosis, the values in children with PBB were intermediate to those with bronchiectasis and controls (median phagocytosis of NTHi: bronchiectasis = 13.7% [IQR 11% to 16%], PBB = 16% [11 to 16], controls = 19.0% [13 to 21]; and median efferocytosis values were 14.1% [10 to 16], 16.2% [14 to 17] and 18.1 [16 to 21], respectively).[122]

BAL from children with PBB typically shows intense airway neutrophilia (median 40% to 44%).Whether this is a pathologically disproportionate response to infection is unknown.[11] There are also marked proinflammatory mediator responses (increased IL-8, MMP-9, and IL-1β) that correlate with BAL neutrophil percentages.[256,257] Median BAL levels of IL-8 and MMP-9 in children with PBB were 5- to 19-fold higher than controls and children whose cough resolved without treatment.[256] Children with PBB had significantly higher BAL fluid levels of IL-1β, α-defensin, IL-1 pathway members and CXCR2 gene and protein expression than non-PBB disease controls.[257] IL-1β levels correlated with duration and severity of cough,[257] and with elevated expression of α-defensins 1 to 3 in PBB cases. In those with recurrent PBB (>3 in the next 12 months), gene expression of the IL-1β signaling molecules pellino-1 and IL-1 receptor associated kinase (IRAK)-2 (in BAL at initial bronchoscopy) were significantly higher than those without recurrent PBB, suggesting this pathway's involvement in recurrence.[257] Thus, "PBB is characterized by increased IL-1β pathway activation. IL-1β and related mediators were associated with BAL neutrophils, cough symptoms, and disease recurrence, providing insight into PBB pathogenesis."[257]

Large Airway Lesions. While some clinicians believe TBM causes chronic ineffective cough, it is as likely that the airway malacia predisposes individuals to prolonged, inefficient airway clearance and hence increases risk of infection. Since the cough resolves once the underlying infection is treated, this suggests malacia has a limited causative role.[23] Nevertheless, TBM is found commonly in children with PBB.[23,258] This association may be primary (airway malacia predisposes to PBB through reduced efficiency in airway clearance) or secondary (malacia developing because of intense airway inflammation and infection).[161,259] One retrospective study reported TBM was present in 52/74 (74%) children with PBB.[258] However, a prospective study involving 104 children with PBB found that these airway abnormalities were no more common in children with PBB than in those undergoing bronchoscopy for other respiratory indications at a tertiary pediatric hospital (68% vs. 53%, respectively).[255] However, it has been shown in a prospective study that, children with TBM (c.f. controls) have a higher frequency of respiratory infections and symptoms.[260,261]

CLINICAL FEATURES

Symptoms and Signs

Children with PBB have a chronic wet cough but otherwise typically appear well with an absence of recurrent nasal or ear disease. They have normal growth and development, and lack signs of underlying CSLD. The prevalence of atopic features (eczema, systemic and airway eosinophilia, elevated IgE, or positive radioallergosorbent test) is similar to children without PBB.[255] While many parents report previous "ever wheeze" (41% to 81%),[255,262] wheeze on auscultation confirmed by doctors is unusual. Occasionally, a "rattly chest" can be palpated and crackles are heard.

Imaging and Pulmonary Function Tests

The chest radiograph is normal or near-normal, showing only peribronchial changes.[12,249,263] When performed, both spirometry[249] and respiratory system reactance and resistance measured by FOT are normal.[11] Laboratory findings, when undertaken, show absence of serum neutrophilia or systemic inflammation (CRP and erythrocyte sedimentation rate [ESR] normal).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Defining Protracted Bacterial Bronchitis

When PBB was first described in 2006,[23] its existence as a distinct diagnostic entity was controversial. However, it is becoming recognized increasingly and is now incorporated into all national pediatric chronic cough guidelines.[11] It is also forms part of the European pediatric respiratory training curriculum.[264] PBB was first defined *a priori* and was based on clinical experience before being applied to a subgroup of children in a prospective study evaluating the etiology of chronic cough.[23] The diagnostic criteria were (1) history of chronic wet cough, (2) positive BAL cultures for respiratory bacterial pathogens at densities $\geq 10^4$ cfu/mL without serologic or PCR assay evidence of infection by either *Bordatella pertussis* or *Mycoplasma pneumoniae,* and (3) cough resolution after a 2-week course of oral antibiotics (amoxicillin-clavulanate).[23] The consideration of feasibility in day-to-day clinical practice and further research has resulted in definitions (Box 26.5) based on recurrence and clinical setting.[11] Each criteria has been validated.[11] However, uncertainties remain and include (1) diagnosis can only be determined after a trial of therapy, (2) lack of research data on an optimal length of antibiotics, and (3) uncertainty of the diagnostic threshold for determining lower airway infection.[11]

Differentiation between acute bronchitis and PBB is because acute bronchitis cough usually resolves within 2 to 4 weeks. Difficulties arise when recurrent and acute bronchitis episodes overlap, especially during the "respiratory virus" season.[11] Furthermore, PBB can coexist with other illnesses, including asthma, and recurrent episodes need to be differentiated from

bronchiectasis when chronic wet cough does not respond to greater than 4 weeks of oral antibiotics.[268] Among 105 children with persistent cough despite at least 4 weeks of antibiotics, 88 (83.8%) had bronchiectasis; of the 24 children whose cough resolved after antibiotics, only six (25.0%) received this diagnosis (adjusted OR 20.9; 95% CI 5.4 to 81.8).[268]

Box 26.5 Diagnostic Criteria for Protracted Bacterial Bronchitis

1. Original microbiologic-based case definition[23] (also termed PBB-micro)
   a. Presence of chronic wet cough (>4 weeks)
   b. Lower airway infection (recognized respiratory bacterial pathogens growing in sputum or BAL at density of a single bacterial specifies $\geq 10^4$ colony-forming units/mL)
   c. Cough resolved following a 2-week course of an appropriate oral antibiotic (usually amoxicillin-clavulanate)
2. Modified clinical-based case definition[265] (also termed PBB-clinical)
   a. Presence of chronic wet cough (>4 weeks)
   b. Absence of symptoms or signs of other causes of wet or productive cough[a]
   c. Cough resolved following a 2-week course of an appropriate oral antibiotic (usually amoxicillin-clavulanate)
3. PBB-extended = PBB-clinical or PBB-micro, but cough resolves only after 4 weeks of antibiotics.
4. Recurrent PBB = recurrent episodes (>3 per year) of PBB.

[a]Specific cough pointers[265–267] are: chest pain, history suggestive of inhaled foreign body, dyspnea, exertional dyspnea, hemoptysis, failure to thrive, feeding difficulties (including choking/vomiting), cardiac or neurodevelopmental abnormalities, recurrent sinopulmonary infections, immunodeficiency, epidemiological risk factors for exposure to tuberculosis, signs of respiratory distress, digital clubbing, chest wall deformity, auscultatory crackles, chest radiographic changes (other than perihilar changes), lung function abnormalities.

BAL, Bronchoalveolar lavage; *PBB*, protracted bacterial bronchitis.

Chang AB, Upham JW, Masters IB, et al. State of the art. Protracted bacterial bronchitis: the last decade and the road ahead. Pediatr Pulmonol. *2016;51:225-242.*

Differential Diagnosis

There are many causes of chronic wet cough in children, and further investigation to elucidate the cause is necessary when the child does not respond to antibiotics and/or has other clinical features, for example, coughing with feeds.[11,179] These are addressed elsewhere in this textbook.

Bronchitis is a component of many 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 (acute, subacute, chronic), inflammation type (neutrophilic, eosinophilic, lymphocytic, neurogenic), phenotype, or clinical syndromes (e.g., acute bronchitis, larygnotracheobronchitis, PBB, aspiration bronchitis). A diagnostic entity may have varying types of airway inflammation (Table 26.4). For example, acute viral bronchitis is associated with both lymphocytic and neutrophilic inflammation. Although the types of airway inflammation do not distinguish etiology of the bronchitis in children, it provides support for the diagnosis. Cough usually occurs when bronchitis is present.

Chronic (>4 weeks) wet cough in children signifies the persistence of increased airway secretion production or decreased airway clearance in the large airways.[283] The greater the amount of secretions seen at bronchoscopy, the higher the likelihood of bacterial infection and intense neutrophilia in the airways.[284] Clinicians need to be cognizant that recognition of wet cough is dependent on the clinical setting, and it is also likely age dependent. It is easier to detect a wet cough in young children, while older children may have a productive cough but may have a dry cough when asked to cough. Parents and clinicians have varying ability to recognize cough quality. In Australia, Brisbane-based parents were more accurate in determining the type of cough (compared to pulmonologists [kappa = 0.75, 95% CI 0.58

Table 26.4 Dominant Type of Airway Cellularity in Selected Childhood Diseases With Bronchitis

Inflammation Type	Examples of Disease	Other Key Airway Makers
Neutrophilic	Acute viral infection[269]	Soluble intercellular adhesion molecule-1
	Bronchiectasis[116,128]	Elevated IL-8, neutrophil elastase, TNF-α, IL-1β
	Cystic fibrosis[270]	Elevated IL-8, neutrophil elastase, proteases
	Protracted bacterial bronchitis[11,257]	Elevated IL-8, MMP-9, IL-1β and related mediators that reflect IL-1β pathway activation
	Chronic lung disease of prematurity[271]	Proinflammatory cytokines and chemokines
	Severe bronchiolitis[272,273]	Myeloperoxidase, CD11b RSV proteins and mRNA transcripts in severe RSV bronchiolitis
	Bronchiolitis obliterans[274]	Elevated IL-6, IL-8, TNF-α, IL-1β
	Aspiration lung disease[275]	Index of lipid-laden macrophages (nonspecific marker), amylase, pepsin (still needs validation)
Eosinophilic	Atopic asthma[276]	Elevated nitric oxide in steroid naive
	Helminth infections[111] e.g., toxocara and strongyloides	
	Allergic bronchopulmonary aspergillosis[277]	Neutrophilic inflammation may also be present with elevated IL-8 and MMP-9
	Hypersensitivity, eosinophilic pneumonia[278]	
Lymphocytic	Acute viral infection[269]	Soluble intercellular adhesion molecule-1
	Bronchiolitis obliterans[279,274]	CD8+T lymphocytes
	Autoimmune disease*[280]	
Neurogenic	Post RSV infection[281]	substance P, nerve growth factor
	Cough with gastroesophageal reflux[282]	Calcitonin G-related peptide

to 0.93] and flexible bronchoscopy findings),[283] whereas Indigenous caregivers were less accurate.[285]

MANAGEMENT AND TREATMENT

There is high-quality evidence that in children with greater than 4 weeks' duration of wet or productive cough, the use of appropriate antibiotics improves cough resolution.[179] In PBB, the child's cough resolves only after a 2-week course of appropriate antibiotics, in contrast to shorter durations of treatment.[23,286] Meta-analyses of three RCTs that used 10 to 14 days of antibiotics for chronic wet cough found that the number needed to treat (for benefit by end of study) was 3 (95% CI 2.0 to 4.3) Although the British Thoracic Society (BTS) cough guidelines[287] suggest all children with PBB should receive 4 to 6 weeks of antibiotics, there is no prospectively derived evidence for this. While some children with PBB may need longer antibiotic treatment, we advocate the shorter 2-week course initially.[11]

PROGNOSIS

The rate and risk factors of PBB recurrence are likely dependent on the sampling frame and definition. Factors in those severe enough to need to bronchoscopy and BAL sampling are probably different from those enrolled from the community. The sole prospective study to date was undertaken in 106 children with PBB followed for a median of 25 months (IQR 24 to 28).[288] Their median age at bronchoscopy was 23 months (IQR 14 to 53). At the 24-month follow-up, children with PBB were more likely to be coughing compared with controls (44% vs. 12% of respective cohort, $P = .005$) and to have had parent-reported wheeze in the preceding 12 months (58% vs. 16%, $P = .001$). By the end of the study, 66 (62%) of those with PBB had experienced recurrent episodes (>3 per year) and 13 (12%) had bronchiectasis diagnosed by chest CT scans.[288] The major independent risk factors for bronchiectasis were *H. influenzae* (mainly NTHi) lower airway infection and having ≥2 siblings. *H. influenzae* infection conferred greater than six times higher risk of bronchiectasis than a *H. influenzae* negative state (hazard ratio = 6.8, 95% CI 1.5 to 30.8).[288]

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Access the reference list online at ExpertConsult.com.

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