Bronchiectasis in Childhood

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KEYWORDS

• Bronchiectasis • Chronic cough • Endobronchial suppuration • Exacerbations • Pediatrics
• Wet cough

KEY POINTS

- Bronchiectasis in children is a heterogenous condition, which is being increasingly recognized as a cause of chronic respiratory disease.
- As earlier diagnosis and management improves long-term outcomes in children, clinician awareness leading to early recognition is crucial in refusing the future disease burden.
- Although pediatric bronchiectasis shares some common features with adult data, the substantial differences include clinical presentation features, lower airway microbiota, and prognosis.

INTRODUCTION

Pediatric bronchiectasis is defined as a chronic lung condition characterized by chronic wet cough and recurrent acute respiratory exacerbations[1] with high-resolution computed tomography (HRCT) evidence of bronchial dilation (bronchoarterial ratio $\geq$0.8; c.f. 1–1.5 in adults).[2] It is being increasingly recognized as a cause of chronic respiratory morbidity in not only low-middle income countries (LMICs) and indigenous populations, but also in nonindigenous adult and pediatric populations in developed countries.[3–5] Incidence of bronchiectasis in children is highly variable, ranging from 0.2 to 735 per 100,000 children annually, based on extrapolation of published data.[3] With increasing awareness and diagnosis in children and adults globally, bronchiectasis has been termed the new global epidemic.[5] Despite being more prevalent than cystic fibrosis (CF), pediatric bronchiectasis remains an often neglected, undertreated, and underserviced.[6] Furthermore, parents of children with bronchiectasis mistrust health services because of delayed diagnosis.[7] In this article, we focus on data specific to pediatric bronchiectasis.

INCIDENCE AND PREVALENCE

The diagnosis of bronchiectasis requires physician awareness and accessible radiology service specific for undertaking and interpreting pediatric CT scans. Delayed diagnosis occurs when either is unavailable.[8] Although data from children in specific disadvantaged populations in Australia, New Zealand, and Canada have shown high prevalence,[3] its prevalence in the LMICs as well as high-income countries is increasingly being recognized.[3]

Mortality trends due to bronchiectasis have changed with time and are setting dependent; those who receive suboptimal care have substantially earlier mortality.[9] Data from England and Wales suggest that between 2001 and 2007, there were 5745 deaths due to bronchiectasis with a 3% annual rise in mortality.[10] Six of 91 children in New

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Clin Chest Med 43 (2022) 71–88
https://doi.org/10.1016/j.ccm.2021.11.006

Zealand died during a median follow-up period of 6.7 years in a tertiary center. In Australia, in 2018, pediatric deaths related to bronchiectasis were rare, 96% of deaths where bronchiectasis was an underlying cause occurred in people aged ≥60 years.[11]

BURDEN

Bronchiectasis causes significant anxiety and stress in children and their parents, especially during exacerbations,[12] some of which require hospitalization and increase economic burden.[13] In a prospective study of 69 children followed for 900 child-months, 36 exacerbations (23%) required hospitalization.[14] Another study showed mean 3.3 exacerbations (SD 2.2) per child-year; 11.4% required hospitalization.[15] In Germany, from 2005 to 2011, the annual proportion of all (adult and pediatric) bronchiectasis-associated hospitalizations among the overall number of hospitalizations significantly increased from 0.048% to 0.054%; average annual increase of 2.0% (95% confidence interval [CI] 1.0–3.6; $P = .0001$)[16] and the rate of hospitalization in the youngest age group (0–24 years) also increased in both sexes. The sole pediatric study reporting cost of bronchiectasis-related hospitalization described mean duration of hospitalization of 12.3 days, costing AUD30,182 each,[17] which is a substantial cost to the health system.

ETIOLOGY OF BRONCHIECTASIS

Bronchiectasis is a common endpoint from various etiologies and associations. The relative common causes of pediatric cases of bronchiectasis are different from those in adults. It is heterogeneous and different cohorts report different percentages of associations (eg, post-infection, primary immunodeficiency, primary ciliary dyskinesia, congenital malformations, aspiration, etc).[3,18,19] Infectious causes, such as tuberculosis, whooping cough, and measles,[20,21] could be identified where these conditions are still prevalent, whereas oropharyngeal aspiration (with underlying neuromuscular or swallowing disorders), allergic bronchopulmonary aspergillosis, and immunodeficiency are identified when investigated with a high index of suspicion.[1,22,23] Previous history of pneumonia has been reported as a risk factor.[24] Rare causes of bronchiectasis include Mounier-Kuhn syndrome[4] and William Campbell syndrome[4] (**Table 1**).

ROLE OF NUTRITION

Appropriate nutrition is important for both reduction of acute respiratory infections[25] and maintaining good lung function in bronchiectasis.[26] Indeed, in a case-control, clinical interventional study of 17 children with bronchiectasis and 13 with interstitial lung diseases compared with 40 healthy controls showed that 56.67% of studied patients were moderately malnourished and 23.33% were severely malnourished; 66.7% of studied patients were underweight and 50% of patients had stunted growth. Furthermore, nutritional rehabilitation significantly improved patient anthropometry, body composition, decreased bronchodilator use, number of days of school absence, acute exacerbations, and hospitalization.[27] On the other hand, a study of 141 Polish children with recurrent bronchitis found higher levels of body fat and muscle mass deficiency compared with reference ranges for healthy children.[28] Comparing these children's body mass index (BMI) with healthy controls showed a high prevalence of overweight and obesity (~25%) and a relatively low proportion of underweight children (2%) in the children with bronchitis. In a study comparing indigenous children with bronchiectasis from 3 countries, there was a statistically significant difference between the groups in nutritional status with more Australian children having low weight-for-age z-scores (18% underweight) compared with the Alaskan and New Zealand groups.[29]

PATHOLOGY AND PATHOGENESIS

The pathogenesis of bronchiectasis is described in another chapter. Here we focus on relevant pediatric data. In children, the histopathological classification is similar to adults, that is, tubular characterized by smooth dilation of the bronchi; varicose in which the bronchi are dilated with multiple indentations; and cystic in which dilated bronchi terminate in blind-ending sacs were based on bronchographic findings also reflect the pathologic changes.[30] HRCT scoring systems describe cylindrical and saccular changes as markers of disease severity.[30]

Like adults, the pathogenesis of bronchiectasis is the end result of the interplay between various factors involving the host such as genetics discussed earlier, the environment (inhaled pathogens and environmental pollutants), and local factors, including airflow limitation,[31] change in the character of mucous,[32] and changes in mucous clearance.[23,33,34] However, the relative contributions of each of these factors possibly differ, for example, inhaled foreign body is an important cause of pediatric bronchiectasis as the risk of foreign body aspiration, for example, nuts is

Table 1
Etiology of bronchiectasis

Condition	Description of Condition	Diseases (Reference)
Cystic fibrosis	Two genes or homozygous state produces CF genotype, almost 2000 mutations in the CFTR gene have been identified	Bronchiectasis has been identified in patients with CF from early on in life. Bronchiectasis patients with a single CFTR mutation can have more severe disease.
Immunodeficiency	Primary immune deficiencies, especially untreated can lead to bronchiectasis. Disruption of B cell differentiation causes recurrent pyogenic sinopulmonary infections and may lead to bronchiectasis in XLA. Recurrent sinopulmonary infections are seen in CVID. Eczema, recurrent lung and skin infections, skeletal anomalies, and coarse facial features are seen in HIES.	Bronchiectasis has been reported in children and adults with immunodeficiency.
Acquired immunodeficiency	HIV	Acquired immunodeficiency can lead to recurrent infections and bronchiectasis.
PCD and heterotaxy syndromes	Causes impaired mucociliary clearance by structural or functional defects of motile cilia in the airway. Can be associated with infertility and organ laterality defects. More than 200 genes have been identified.	PCD, Kartagener syndrome
Congenital tracheobronchomegaly	Atrophy of smooth muscles and elastic tissue in the trachea and main bronchi causes tracheobronchomegaly, can be associated with tracheal and bronchial diverticula.	Mounier-Kuhn syndrome, Williams-Campbell syndrome Ehlers-Danlos syndrome
Syndromes	Triad of obstructive azoospermia, sinusitis, and bronchitis or bronchiectasis, possibly related to mercury exposure. Triad of yellow and thickened nails, lymphedema, and respiratory manifestations Disorder of connective tissue caused by the mutation of gene encoding the extracellular matrix protein fibrillin-1.	Young syndrome Yellow nail lymphedema syndrome Marfan syndrome

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Table 1
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Condition	Description of Condition	Diseases (Reference)
Recurrent Chest Infections	Previous pneumonia Recurrent respiratory tract infections, recurrent PBB Tuberculosis Allergic bronchopulmonary aspergillosis	Previous hospitalization for severe pneumonia is associated with increased bronchiectasis risk in children. Recurrent PBB is a risk factor for bronchiectasis. Cause of bronchiectasis in low-income and middle-income countries. Allergic bronchopulmonary aspergillosis is associated with bronchiectasis in adults.
Aspiration	Aspiration secondary to neuromuscular disorders	Tracheoesophageal fistula or gastroesophageal reflux.[128] Reflux is seen in 10%–18% of children with bronchiectasis.
Local Obstruction	Bronchiectasis found in up to 25% of patients' foreign body missed for >30 d. Local/endobronchial tumors can cause bronchiectasis secondary to airway obstruction.	Inhaled foreign body Tumor Bronchial stenosis
Inflammatory conditions	Rheumatoid arthritis	Bronchiectasis has been described in adult patients with rheumatoid arthritis.

Abbreviations: HIV, human immunodeficiency virus; PBB, protracted bacterial bronchitis; PCD, primary ciliary dyskinesia; CFTR, Cystic fibrosis transmembrane conductance regulator; XLA, X-linked agammaglobulinemia; CVID, Common variable immunodeficiency; HIES, Hyperimmunoglobulin E syndrome.

substantially higher in otherwise well young children c.f. adults.

Also, another pathophysiology association is protracted bacterial bronchitis (PBB). Bronchoalveolar lavage (BAL) studies have indicated an interplay of infection and host immune defects in the pathogenesis of bronchiectasis (**Fig. 1**). This clinical spectrum of chronic wet cough aligns with Coles' vicious cycle of chronic infection.[35] Chronic wet cough due to infections, if left untreated, for example, in PBB might progress to bronchiectasis,[36] initially reversible and eventually irreversible bronchiectasis (**Fig. 2**).[37] A prospective study of 161 children with PBB showed that risk factors of development of bronchiectasis during the follow-up period were recurrent PBB (>3 episodes/y, $OR_{adjusted}$ = 1.5, 95% CI 2.3–56.5) and finding *Haemophilus influenzae* infection in the BAL (hazard ratio = 7.6; 95% CI 1.7–34.3, P = .009 compared with no *H influenzae* infection).[38]

Increased expression of innate immune receptors (eg, receptors TLR2, TLR4, and CD14) and cytokine responses (eg, IL-8 and IL-1β) seen in adults[39] with bronchiectasis also occurs in children with PBB and bronchiectasis.[40]

Although primary immunodeficiency is another important cause of pediatric bronchiectasis, other subtle immune dysregulation has also been shown, for example, poor response of interferon-gamma (IFN-γ) to non typeable haemophilus influenzae (NTHi).[41] Comparing the stimulated peripheral blood mononuclear cells of 80 children with chronic suppurative lung disease (CSLD) and 51 controls, Pizzutto and colleagues found that those with CSLD produced significantly less IFN-γ in response to NTHi than healthy controls.[41] Furthermore, in a study of efferocytosis in children, a reduced ability of alveolar macrophages from children with bronchiectasis or PBB to phagocytose NTHi has been shown.[42] It has been proposed that children and adults with bronchiectasis likely have the necessary

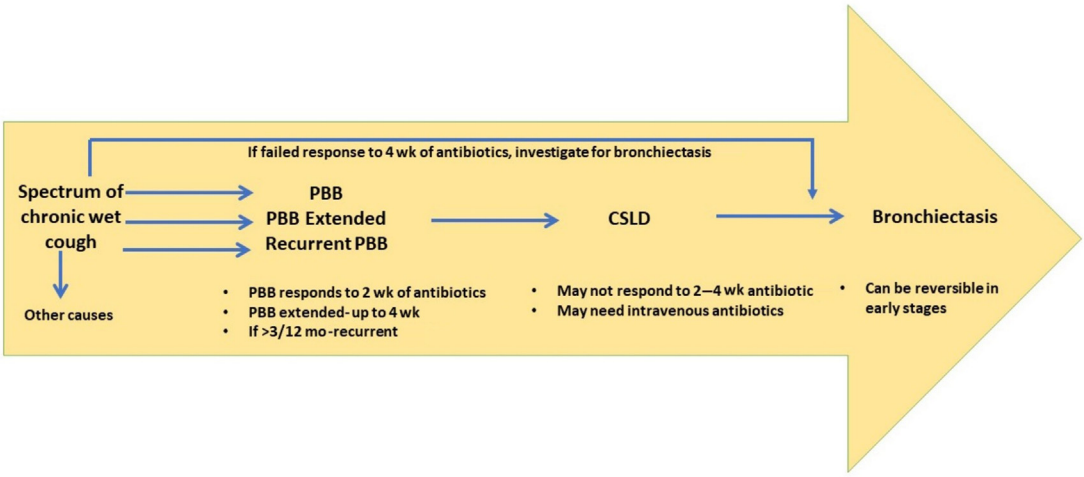

Fig. 1. Proposed spectrum and progression of chronic wet cough, PBB, and bronchiectasis.

cell-mediated immune architecture to respond to NTHi. Children with recent onset disease and adults with established bronchiectasis have a universal capacity to produce IFN-γ that is similar to healthy controls, but fail to do so in response to NTHi.[43]

MICROBIOLOGY

The common lower airways bacteria in pediatric bronchiectasis are variable depending on setting, type of specimen, and definition of infection (**Table 2**). *Pseudomonas aeruginosa*, seen in up to 25% of adult bronchiectasis patients, is less common in children with bronchiectasis.[44,45]

A study comparing microbiota from children with PBB, CF, and bronchiectasis with adults with CF and bronchiectasis found that the 3 pediatric disease cohorts shared similar core respiratory microbiota that differed from adult CF and bronchiectasis microbiota.[46]

Viruses like measles have been historically implicated in bronchiectasis pathogenesis. It has been suggested that after infection with influenza, respiratory syncytial virus (RSV), or adenovirus, there might be impaired immune responses to bacterial infections including desensitization to toll-like receptor signals and impaired macrophage and neutrophil responsiveness.[47] A retrospective study of 193 children with adenovirus infection in Canada found that of 27 children who had long-term follow-up, 8 of 10 who had a CT scan of the chest had bronchiectasis.[48] In our

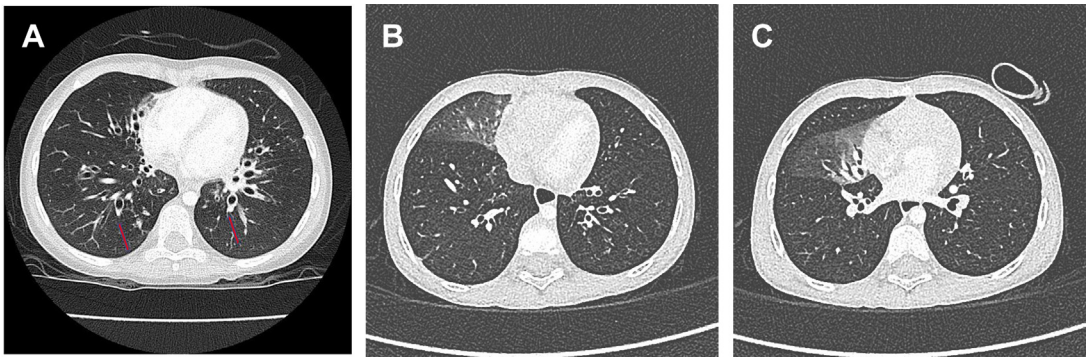

Fig. 2. Chest CT scan findings in bronchiectasis. (*A*) Chest HRCT scan image of a 4-year-old child with bronchiectasis. She presented with a history of recurrent pneumonia and had finger clubbing. Note dilated airways in both lower lobes. The bronchoarterial ratio is compared between the inner diameter of the airway with the outer diameter of the adjacent artery along the short axis, present within 1 mm of distance to each other. Note the classical "signet ring" or "pearl ring" appearance of various airways (*arrows*). If the airway and artery are oblique, that is, the ratio of the largest diameter and the smallest diameter is greater than 1.5, they should not be considered. (*B*) HRCT scan image in a 29-month-old child with a history of recurrent wet cough. Note dilated airways in both lower lobes. (*C*) HRCT scan image of the same child in 2-B showing atelectasis and dilatation of airways in the right middle lobe.

Table 2
Lower airway microbiology in children bronchiectasis in various settings

	Hare et al 2010[129] (n = 45)	Kapur et al 2012[44] (n = 113)	Maglione et al 2014[130] (n = 158)	Behcecci et al 2016[131] (n = 110)	Pizzutto et al[43] (n = 860)	Verwey et al 2017[132] HIV n = 52[b] No HIV n = 14[b]		De Vries et al 2018[133] (n = 138)
Study Design	Prospective	Retrospective	Retrospective	Retrospective	Summary	Retrospective		Retrospective
Setting	Remote Indigenous Australia	Queensland Australia	Multicentre (Europe), PCD Cohort	Izmir Turkey	6 Countries, which includes 2 studies[44,129] in Table	Johannesburg South Africa HIV Positive	Negative	Queensland Australia
Males (%)	67	57	51	51	NS	48	36	138
Period	2007–2009	1992–2009	1990–2011	2005–2015	2003–2012	2011–2013		2010–2016
Median age, mo (range)	28 (8–122)	63 (3–195)	60 (24–192)	Mean 167 (SD 39)	Range 0.4–19 y	11 (IQR 7–13)	7 (IQR 6–8)	31 (6–71)
Indigenous ethnicity (%)	100	23	NS	NS		96.9		NS
Specimen type	BAL	BAL	Sputum	BAL	BAL, sputum, UA	BAL, sputum, TA		BAL
Diagnostic threshold for BAL studies[a]	$>10^4$ cfu/mL	$>10^5$ cfu/mL	Repeated samples (>3)	NS	Mixed	Unclear		$>10^4$ cfu/mL
Respiratory pathogens (%)				Unclear				
H influenzae	47	32	48	8	40	36	38	66
S pneumoniae	18	14	11	5	20	13	12	24
M catarrhalis	20	8	3	NS	9	12	8	20
S aureus	4	5	15	1	8	11	11	7
Pseudomonas aeruginosa	Not detected	6	7	5	8	7	3	4
Mycoplasma pneumoniae	NS	2	NS	NS	NS	NS	NS	Not detected

Klebsiella species	NS	Not detected	NS	1	NS	6	4	Not detected
NTM	NS	Not detected	NS	NS	NS	NS	NS	Not detected
Aspergillus species	Not detected	Not detected	NS	NS	NS	NS	NS	Not detected
Respiratory viruses	NS	12	NS	NS	NS	NS	NS	31
No pathogens	42	51	NS	NS	NS	NS	NS	12

The Australian BAL findings are supported by studies from other countries that included on average older children where both upper airway specimens and sputum were cultured.[62]

Abbreviations: BAL, bronchoalveolar lavage; cfu, colony-forming units; HIV, human immunodeficiency virus; NS, not specified; PCD, primary ciliary dyskinesia; SD, standard deviation; TA, tracheal aspirate; UA, upper airway; NTM, Nontuberculous mycobacteria.

[a] Respiratory infection considered present for any growth of *Pseudomonas aeruginosa,* or mycobacterial species, and if *Mycoplasma pneumoniae* or respiratory viruses (mainly adenovirus, respiratory syncytial virus, or parainfluenza 3) were detected by polymerase chain reaction assays.

[b] Number of children but paper reported on all 166 specimens in the groups (145 specimens in HIV-positive and 52 in HIV-negative groups).

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current era, human adenovirus (HAdV)-C was the major HAdV species detected in the lower airways of children with PBB and bronchiectasis when in stable state.[49] Younger age appears to be an important risk factor for HAdV+ of the lower airways and influences the likelihood of bacterial co-infection. In a prospective cohort of children with chronic wet cough, viral-bacterial co-infection has also been shown to be associated with the highest median percentage neutrophils in airways compared with bacteria only, viruses only, and no infection.[50]

DIAGNOSIS

Bronchiectasis is a syndrome in children with associated clinical signs and symptoms and objectively confirmed radiologically with a CT scan of the chest using pediatric criteria.

CLINICAL FEATURES

The most common symptom in children with bronchiectasis is chronic wet cough.[23] If antibiotics are used in the initial treatment of chronic wet cough, failure of the wet cough to respond to 4 weeks of antibiotics predicts the presence of bronchiectasis (adjusted odds ratio [OR_{adj}] 20.9, 95%CI 5.4 to 81.8).[51] Children often have a wet cough starting in the first year of life and persisting for months or years before the diagnosis is made or considered.[52,53] Indeed, many adults newly diagnosed with bronchiectasis have had symptoms since childhood and these adults have worse lung function and more severe radiological features than those with a shorter duration of chronic cough.[54,55]

Other symptoms in pediatric patients may be absent, but a history of exertional dyspnea, recurrent wheezing, recurrent chest infections, hemoptysis, digital clubbing, and/or chest wall deformity in the presence of chronic wet cough increase the likelihood of underlying bronchiectasis.[53,56–61] Crackles on auscultation[18] or a history of wheeze or asthma-like symptoms[18] may be present but asthma itself does not cause chronic wet cough or bronchiectasis.[36] However, people with bronchiectasis have a higher prevalence of airway hyper-responsiveness and hence an asthma-type phenotype may co-exist in some children.[62]

RADIOLOGICAL DIAGNOSIS OF BRONCHIECTASIS

Bronchoarterial ratio (BAR), defined as the ratio of the inner diameter of an airway to the outer diameter of adjacent artery that is within 5 mm in a non-tangential plane, is used to define dilatation of the airway, which is the pathognomonic sign of bronchiectasis on HRCT scan.[22] Although the adult cut-off of BAR to define bronchiectasis is >1 to 1.5, a ratio $\geq$0.8 is more appropriate for the pediatric age group,[2,63] as BAR increases with age in the absence of disease.[64] The recently published European guidelines recommend using multidetector computerised tomography (MDCT) with HRCT in children[1] as conventional HRCT scan alone is less sensitive than the former. Although a group has suggested using the outer diameter of the airway (instead of inner diameter),[65] this has not been clinically validated.

Owing to the inherent risk of radiation with HRCT (one excess case of leukemia and one excess case of brain tumor per 10,000 head CT scans),[66,67] other modalities for diagnosis of bronchiectasis have been explored. Chest high-field 3.0-T MRI has been shown to be effective in assessing the extent and severity of lung abnormalities and diagnosing bronchiectasis[68] but concordance with HRCT is poor unless the disease is moderate-severe.

FURTHER INVESTIGATIONS

After a diagnosis of bronchiectasis is made, a minimal panel of further investigations is recommended for evaluating if an underlying etiology of bronchiectasis can be identified[1] as knowing the underlying etiology can change management and outcomes of children with bronchiectasis.[69] The recommended panel are as follows: (1) sweat test, (2) lung function tests (in children/adolescents who can perform spirometry), (3) full blood count test, (4) test for immunodeficiency, (5) test for lower airway bacteriology, and (6) test for primary ciliary dyskinesia in the appropriate setting.[70] **Table 3** outlines a summary of spirometry and lower airway microbiology findings.

DEFINING SEVERITY

In children, spirometry indices may not reflect disease severity in early disease but when bronchiectasis is severe, there is concordance between radiological scores and FEV_1 %predicted.[4] Several multidimensional grading systems classifying bronchiectasis severity exists in adults but no pediatric-specific severity scoring systems yet exists. The items in these scores (eg, FEV_1 and breathlessness scores) render these scores unsuitable for pediatrics. Likewise, there are no pediatric bronchiectasis-specific quality of life (QoL) tools. Although a parent-proxy QoL questionnaire for pediatric chronic cough has been used in pediatric bronchiectasis studies,[71] it is likely that it is

Table 3
Summary of spirometry and lower airway microbiology

	Indication	Key Findings	Additional Comments
Spirometry	Routine when age appropriate (usually when aged >3 y in specialist centers and >6 y in other centers)	Normal in mild disease. In later disease, spirometry is predominantly obstructive, but some children may have primarily restrictive or mixed obstructive and restrictive patterns.	Spirometry is insensitive both for detection and monitoring of disease severity compared with CT scans.
Lower airway specimen	Routine for assessment of airway microbiology	Respiratory pathogens identified. Summarised from review and supplement table (excluding study with unclear denominator) *H. influenzae* 32%–55% *S. pneumoniae* 10%–37% *M. catarrhalis* 2%–20% *S. aureus* 0%–17% *P. aeruginosa* 0%–16% *M. pneumoniae* 0%–2% *Klebsiella* sp 0%–6% NTM 0 *Aspergillus* 0 Respiratory viruses up to 12% No pathogens up to 51%	Obtaining suitable respiratory specimens to guide antibiotic therapy is difficult in nonexpectorating preschool children. Upper airway samples and induced sputum in preschool children are unreliable at predicting lower airway microbiology in young children with bronchiectasis. Although bronchoalveolar lavage enables collection of lower respiratory specimens, it is invasive and is restricted to initial investigations for bronchiectasis or if patients fail therapy and atypical or antibiotic-resistant pathogens are suspected. Various specimen types and different diagnostic thresholds used between studies.
Bronchoscopy	Focal disease, suspected airway lesions, foreign body inhalation, nonresponse to antibiotic treatment, especially if sputum is unavailable or unexplained deterioration	Airway suppuration. These correlate with disease severity.	

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less sensitive. There is a need for such tools to be developed for pediatric bronchiectasis.

EXACERBATIONS IN BRONCHIECTASIS

Respiratory exacerbations are not only common but also important as it impacts QoL and is a significant predictor of FEV_1 decline when severe (ie, hospitalized exacerbations).[72] In New Zealand of 91 children followed up for a median of 6.1 years described that 71% were hospitalized for bronchiectasis exacerbation at least once and they declined by 45% despite being followed-up in a tertiary respiratory clinic.[73] Therefore, identifying and treating exacerbations promptly will lead to better outcomes in children.

Although a research-based consensus statement is currently not available for pediatric bronchiectasis, the European Respiratory Society clinical practice guideline recommended the following for clinical use. "In children/adolescents with bronchiectasis, we suggest that a respiratory exacerbation is considered present when a child/adolescent has increased respiratory symptoms (predominantly increased cough $\pm$ increased sputum quantity and/or purulence) for $\geq$3-days" and "In children/adolescents with bronchiectasis, we recommend that the presence of dyspnea (increased work of breathing) and/or hypoxia is considered a severe exacerbation, irrespective of the duration."[1] A pediatric study to define a respiratory exacerbation in children with bronchiectasis,[14] proposed a combination of criteria based on clinical (symptoms and signs) and blood profiles. The major criteria are as follows: (1) significant frequency of cough (median cough score $\geq$ 2 over 72 hours) and (2) wet cough for 72 hours. The minor criteria are as follows: sputum color $\geq$ 3 on a BronkoTest, presence of: parent/child perceived breathlessness, chest pain, crepitations, wheeze, or hypoxia. The laboratory criteria are as follows: C-reactive protein >3 mg/L, serum interleukin-6 (IL-6) >2 ng/L, serum amyloid A (SAA) >5 mg/L, and raised (age-appropriate) neutrophils.

VIRAL AND BACTERIAL INFECTION IN EXACERBATIONS

It has been recognized that a virus can be identified at the beginning of 48% to 53% of exacerbations.[74,75] The common viruses identified are human rhinovirus (HRV), human coronaviruses, influenza, parainfluenza, HAdV, and RSV, respectively.[74,75] When compared with nonviral exacerbations, viral-related exacerbations are associated with worse severity and hospitalization.[23] Although there appears to be an association between a respiratory exacerbation of chronic airway inflammation and HRV in the airways, there are insufficient data to establish a causal relationship as respiratory viruses have been isolated in studies in as many as 40% of asymptomatic children.[76,77]

The role of bacteria during exacerbations is reflected in the effectiveness of antibiotic treatment on bacterial load, and consequent clinical and objective improvement has been shown in adults but there are no such pediatric data presumably related to the difficulty in obtaining sputum in a large pediatric cohort. Following antibiotic treatment in adults, improvements have been reported in 24-hour sputum volume, sputum bacterial clearance, systemic and airway inflammation, exercise capacity, and health-related QoL.[78,79] When managing exacerbations, obtaining sputum when possible is nevertheless important as new pathogens such as *P aeruginosa* may be present and require intensive treatment.[1]

MANAGEMENT

Bronchiectasis is best managed in a multidisciplinary clinic. Despite being a chronic condition, children with bronchiectasis often have poor access to multidisciplinary clinics and end up with poorer lung function outcomes.[6] Furthermore, children with bronchiectasis have been shown to have a worse outcome in growth, as well as in poor parental mental health compared with children with CF.[80] Treatment and long-term management is aimed at preventing the cycle of infection and inflammation. The 4 principles followed for management are as follows:

1. Prompt management of acute exacerbations.
2. Interventions to decrease the frequency of exacerbations.
3. Treatment of the underlying cause if identified, for example, immunodeficiency-specific treatments.
4. Treatment of treatable associated conditions like aspiration, malnutrition, and structural lesions like tracheoesophageal fistula.

TREATMENT OF ACUTE EXACERBATIONS OF BRONCHIECTASIS

Antibiotics

Antibiotics have been shown to be useful in treating exacerbations of bronchiectasis.[79,81–83] Depending on the severity of an exacerbation, the antibiotics used can be oral and/or inhaled or intravenous antibiotics. A large multicenter placebo-controlled, double-dummy, double-blind randomized controlled trial (RCT; BEST-1), of children experiencing mild-to-moderate exacerbations who received amoxicillin-clavulanate,

azithromycin, or placebo for 14 days demonstrated that oral amoxicillin-clavulanate was superior to placebo.[74] Azithromycin was also superior to placebo, but the overall effect size was outside *a-priori* defined level of significance. Furthermore, the exacerbations treated with amoxicillin-clavulanate were significantly shorter in duration compared with placebo, whereas the difference in exacerbation duration between azithromycin and placebo was not statistically significant. This trial provided robust evidence to support the current recommendation in guidelines for using amoxicillin-clavulanate as an empirical oral antibiotic for nonsevere exacerbations in children.[1,84] Another multicenter, randomized, double-dummy noninferiority study (BEST-2), that showed 21-days of oral azithromycin is noninferior (within 20% margin) to oral amoxicillin-clavulanate for treating nonsevere exacerbations of bronchiectasis in children.[75] Although azithromycin was found to be noninferior to amoxicillin-clavulanate, the exacerbations took significantly longer to resolve and increased the risk of inducing macrolide resistance.[75] Hence, although azithromycin might be used for some patients, such as those with penicillin hypersensitivity or where less frequent dosing might improve adherence, this further supports the use of amoxicillin-clavulanate as the first-choice empirical antibiotic.[75] More severe episodes or failure to improve with 4 weeks of oral antibiotics may require hospitalization for intravenous antibiotics.[85] There are no prospective data on managing exacerbations caused by *P aeruginosa,* although the recent guidelines recommend eradication therapy for *P aeruginosa.*[1]

Mucolytics and Mucokinetics

Mucolytics are drugs that degrade polymers in mucus secretions. Mucokinetics are medications that increase mucociliary efficiency or cough efficiency.[86] There are various mucokinetics and mucolytics used for exacerbations of airway inflammation. The common ones are hypertonic saline (HS), N-acetyl cysteine (NAC), recombinant human-deoxyribonuclease, and inhaled dry powder mannitol (IDPM).[86,87] A recent pediatric randomized crossover control trial in 52 children has shown that incorporating HS into airway clearance is an effective strategy to improve dynamic lung volumes and morbidity in children with bronchiectasis.[88] NAC is infrequently used in children but is commonly used for chronic obstructive pulmonary disease (COPD) and bronchiectasis, although evidence for its benefit is equivocal.[89] Recombinant human-deoxyribonuclease[90] has been found to be harmful in adult bronchiectasis and is not recommended.[91] IDPM has been shown to be well tolerated and beneficial in airway clearance in adult bronchiectasis.[92–94] It is not commonly used in children either. Bronchodilators have been used to assist airway clearance in neutrophilic diseases, but the evidence is equivocal.[95,96]

Airway Clearance Techniques

As exacerbations are associated with hypersecretion of mucus, with or without impaired mucociliary clearance, airway clearance techniques form an important component of treatment in acute exacerbations. Physiotherapy is a mainstay therapy for bronchiectasis in stable state, as well as during exacerbations.[97,98]

MAINTENANCE THERAPY

The aim of maintenance therapy is to decrease the airway inflammation and decrease the number of pulmonary exacerbations in patients with bronchiectasis. In doing so, QoL is optimized and decline in lung function may be prevented.

Antibiotics

Laboratory studies show that macrolides decrease airway inflammation by inhibiting neutrophil migration to the respiratory epithelium and blocking the production of proinflammatory cytokines and mediators. Their role has been promoted as a maintenance therapy to decrease the number of pulmonary exacerbations. Use of maintenance azithromycin in children, halves exacerbation frequency compared to placebo, (incidence RR = 0.50, 95% CI 0.35–0.71).[99,100] Inhaled antibiotics like ciprofloxacin, tobramycin, and gentamycin have been shown to be of benefit in adult patients with bronchiectasis with *Pseudomonas* infection as maintenance therapy but these are not routinely used in children.[101] Further research is needed to identify the selection of children for prophylactic antibiotics, duration, formulation (oral vs inhaled), and type of treatment and when to stop the maintenance antibiotic are required.

Steroids and Bronchodilators

There is not enough evidence to support the use of inhaled corticosteroids in patients with bronchiectasis either alone or in combination with long-acting beta-agonists.[102,103] In a pediatric study,[104] although there was a significant increase in bronchial hyper-reactivity, 12 weeks after the withdrawal of inhaled steroids in children with bronchiectasis, there was no change in number of exacerbations or antibiotic use. This was associated with a significant decrease in neutrophil apoptosis, but no

change in sputum inflammatory markers after the 12-week withdrawal of inhaled steroid treatment in children with bronchiectasis.[104]

Mucolytics and Mucokinetics

Summary data of the 3 available studies on HS in adults with bronchiectasis revealed limited benefits only in some QoL domains.[1] A small (n-63) crossover RCT using 3% HS in children for 8 weeks found, compared with placebo, consistent benefit (lung function, reduced exacerbations rate) only in the first arm of the study.[88] For mannitol, the benefit was also present only in some QoL domains, sputum characteristics, and time to next exacerbation.[1] The European respiratory society (ERS) pediatric bronchiectasis guideline recommended that HS and inhaled mannitol not be routinely used but may be considered in selected patients, for example, those with high daily symptoms, frequent exacerbations, difficulty in expectoration, and/or poor QoL.[1] When used, pretreatment with a short-acting bronchodilator is recommended to avoid bronchospasm, which occurs in up to 30% of patients.

Airway Clearance Techniques

ACT is a standard treatment in all bronchiectasis guidelines. Available studies suggest that airway clearance techniques are beneficial with improved QoL and exercise capacity and reduced cough and sputum volumes.[1] Thus age and cognitive-appropriate chest physiotherapy is recommended in a form that maximizes potential benefit and minimizes burden of care.[1] Postural drainage, standard therapy for children with CSLD/bronchiectasis in the past, is now rarely used as it may increase gastro-esophageal reflux disease (GERD) and possible aspiration. 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 undertake physical activity. Children with bronchiectasis are known to be insufficiently active for health benefit. Although there are no data on the benefits of exercise training, exercise improves airway clearance and exercise training significantly improves cardiovascular fitness and QoL in children with asthma and CF.[105]

VACCINES

An RCT with the 10-valent pneumococcal *H. influenzae* protein D conjugate vaccine in children with chronic suppurative lung disease and bronchiectasis showed that children who received the 10vPHiD-CV were less likely to have respiratory symptoms in each fortnight of surveillance (incidence density ratio [IDR] 0.82, 95% CI 0.61 to 1.10) and required fewer short-course (<14-days duration) antibiotics (IDR 0.81, 95% CI 0.61, 1.09).[106]. However, there are no specific data on the efficacy or effectiveness of influenza vaccine in patients with bronchiectasis,[107] even though it is recommended in guidelines.[1] A Cochrane review based on a single open-label study in 167 adults supports the use of 23-valent pneumococcal vaccine as routine management in adults with bronchiectasis. It also noted that expert opinion also supports the use of routine 23-valent pneumococcal vaccination in children with bronchiectasis.[108] A systematic review of 6 RCTs (440 patients) reported that oral whole-cell, killed, NTHi vaccine reduced the incidence of bronchitic episodes at 3 months after vaccination (rate ratio 0.69; 95% CI 0.41,1.14) and at 6 months after vaccination (rate ratio 0.82; 95% CI 0.62,1.09),[109] although in a larger review including 557 patients with COPD and chronic bronchitis NTHi oral vaccination did not yield a significant reduction in the number and severity of exacerbations. There is ongoing research toward the development of a vaccine for NTHi.[110]

NEWER TREATMENTS

New treatments in adults targeting specific pathways in bronchiectasis pathogenesis are promising. Brensocatib, an oral reversible inhibitor of dipeptidyl peptidase 1 (DPP-1), over 24 weeks improved clinical outcomes by reducing neutrophil serine protease activity in a phase II study.[111] Similarly an open-label adult study has shown reduction in exacerbation by using pidotimod, a synthetic dipeptide molecule with immunomodulatory activity on both innate and adaptive responses.[112] Such RCTs are also required in children.

SURGERY

Surgical intervention is uncommon in children in most high-income countries. However, those with severe, poorly controlled, localized disease, or recurrent hemoptysis may require surgical resection of a bronchiectatic lobe.[113–116] A recent retrospective study compared 29 children who underwent lobectomy and were followed up for at least 4 years before surgery and 4 years to 34 age- and gender-matched bronchiectasis patients who were medically treated without surgery in the same period. The study showed that surgical management of non-CF bronchiectasis has no

significant effect on BMI, z scores, number of pulmonary exacerbations, and lung function tests of patients. Surgical management led to significant improvement in height of patients and decrease in need for intravenous antibiotics.[117]

EDUCATION AND MANAGEMENT PLANS

Self-management is recognized as an important part of chronic disease management, recommended by the World Health Organization.[118] Information provision and support is key to facilitating self-care by patients (and families) to improve care and outcomes.[118] Adherence to treatment in adults with bronchiectasis can be low (16%) but patients who adhere to treatment have less exacerbations and less treatment burden scores.[119] Educating individuals with explanation of bronchiectasis, recognizing infective exacerbations, and a personalized management plan with approaches and options to treatment is recommended.[120] It has been recommended that high-quality information and education resources facilitating self-management advancements, improvements in adherence, and consequent physical and psychological health improvements should be produced for the management of bronchiectasis.[121] This has further been shown to be feasible and effective in a small study in adults,[122] but no studies yet exist in children. Readers are referred to the Web site www.improvebronchiectasis.org for links to education resources.

LONG-TERM PROGNOSIS

There is evidence to prove that with diligent management, pediatric bronchiectasis in its early stages can be stabilized and even reversed, which contradicts traditional definitions that bronchiectasis is an irreversible dilatation of the airways.[123,124] Also, with optimal management, the lung function of children with bronchiectasis improves[125] or at least stabilizes.[72,126] A recent study of 131 indigenous children at a single follow-up visit (median 9-year after first-visit) using standardized questionnaires, review of medical records, and undertaking clinical examinations, reported that with increasing age, rates of acute lower respiratory infections declined and median FEV_1 was 90% predicted, IQR 81 to 105. The study reported that the respiratory outcomes in late childhood or early adolescence are encouraging.[127] This highlights the importance of early diagnosis and managing these patients in a multidisciplinary setting as other studies have also described mortality due to pediatric bronchiectasis.[73]

CLINICS CARE POINTS

- Bronchiectasis is common in children and high index of suspicion is required for diagnosis.
- Chronic wet cough could be the only presenting feature.
- Bronchiectasis in children should be managed in clinics having experience with paediatric bronchiectasis using paediatric protocols for diagnosis and management.
- If identified early and managed diligently, progression of paediatric bronchiectasis can be stopped.
- Attempts should be made to identify the cause of bronchiectasis.6. All exacerbations should be treated promptly.
- Bronchiectasis should be treated in a multidisciplinary clinic.

DISCLOSURE

The authors have nothing to disclose.

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