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State of the Art

Chronic Wet Cough: Protracted Bronchitis, Chronic Suppurative Lung Disease and Bronchiectasis

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Summary. The role of persistent and recurrent bacterial infection of the conducting airways (endobronchial infection) in the causation of chronic respiratory symptoms, particularly chronic wet cough, has received very little attention over recent decades other than in the context of cystic fibrosis (CF). This is probably related (at least in part) to the (a) reduction in non-CF bronchiectasis in affluent countries and, (b) intense focus on asthma. In addition failure to characterize endobronchial infections has led to under-recognition and lack of research. The following article describes our current perspective of inter-related endobronchial infections causing chronic wet cough; persistent bacterial bronchitis (PBB), chronic suppurative lung disease (CSLD) and bronchiectasis. In all three conditions, impaired muco-ciliary clearance seems to be the common risk factor that provides organisms the opportunity to colonize the lower airway. Respiratory infections in early childhood would appear to be the most common initiating event but other conditions (e.g., tracheobronchomalacia, neuromuscular disease) increases the risk of bacterial colonization. Clinically these conditions overlap and the eventual diagnosis is evident only with further investigations and long term follow up. However whether these conditions are different conditions or reflect severity as part of a spectrum is yet to be determined. Also misdiagnosis of asthma is common and the diagnostic process is further complicated by the fact that the co-existence of asthma is not uncommon. The principles of managing PBB, CSLD and bronchiectasis are the same. Further work is required to improve recognition, diagnosis and management of these causes of chronic wet cough in children. **Pediatr Pulmonol. 2008; 43:519–531.**

Key words: cough; bronchiectasis; asthma.

INTRODUCTION

In countries where data are available, cough is consistently the most common symptom that results in new medical consultations.[1,2] In Australia, 7.3% of patient visits to general practitioners are for a coughing illness[3] and these figures do not include visits to specialists. A significant proportion of these patients have chronic cough. Chronic cough (>4 weeks[4,5]), considered trivial to some health professionals, is associated with significant morbidity,[6] and a burden to parents.[7,8] This is also reflected in the cost of over the counter cough medications consumed worldwide. Also chronic cough may be reflective of an underlying serious disorder and delayed diagnosis (e.g., foreign body) may cause chronic respiratory morbidity.[9] In this review we discuss relevant clinical issues relating to diagnosis and endobronchial infections associated with chronic wet cough.

Defining a symptom and/or disease facilitates consistent, effective and accurate communication in the

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clinical arena as well as in clinical and epidemiological research. Ideally definitions should be scientifically based where their reliability and validity have been examined. In less ideal situations, definitions may require modification when appropriate research data become available. With respect to the definition of chronic cough, readers are referred to available pediatric-specific reviews[10] and guidelines.[4,5,11] The American College of Chest Physicians Guideline recommends defining chronic cough in children as daily cough lasting >4 weeks.[5] The definition of recurrence that is abnormal (as opposed to within normal limits) is poorly classified but logically should be age dependent. The frequency of acute respiratory illnesses (ARI) is age and to lesser extent gender dependent. Children aged 1-year have 6 ARI episodes per year whilst those aged 6 years have 2–3 per year.[12] In otherwise well children, these illnesses usually resolve within 2 weeks.[12,13]

WET COUGH

What Is Wet Cough?

The sound of a cough is due to vibration of larger airways and laryngeal structures during turbulent flow in expiration.[14,15] In the laboratory, productive and non-productive cough can be differentiated using cough sound analysis (spectrogram and time-expanded waveform).[16] At a clinical level even when airway secretions are present, young children rarely expectorate sputum. Hence wet/moist cough is the preferable term rather than productive cough.[4,17]

Presence of a wet cough indicates presence of excessive airway mucus. However it is not known how much mucus is required and where it has to be located for the human ear to detect presence of a moist cough in humans. It is likely that mucus in the large airways (as opposed to small airways) is required for detectable difference in cough quality. Laminar airflow, which occurs in smaller airways, is inaudible.[18] In an animal model, Korpas et al.[19] showed that a certain amount of mucus is required to alter cough sound; 0.5 ml of mucus instilled into the trachea of cats altered cough sound, too little mucin had no effect on cough quality whilst too much mucin impaired breathing. The rheological properties of airway mucus also influence cough sound,[15] and it is also unknown how airway secretions in the more peripheral airways influences the sound of cough. Whether the sound of wet cough relates to shearing of the secretions from the airway wall is unknown.

The clinical validity of dry and wet/moist cough as descriptors in children has been shown. Parental assessment of cough quality (wet/dry) had good agreement with clinicians' assessment (Kappa (K) = 0.75, 95%CI 0.58–0.93).[20] When compared to bronchoscopy findings clinicians' cough assessment had the highest sensitivity (0.75) and specificity (0.79) and was only marginally better than parent(s). This is in contrast to the poor validity of wheeze and other respiratory sounds reported by parents.[21–23] Dry cough however may represent the early phase of a process where wet cough may occur, as the minimal bronchoscopic secretions may be present in children with dry cough.[20]

Mucus hypersecretory states in human diseases can occur from a variety of mechanisms which include; hypersecretion of stored mucin, hypertrophy or hyperplasia of goblet cells and/or increased synthesis from overexpression of mucin genes.[24] In children, situations where hypersecretory states occur chronically are relatively limited. These include bronchitis, aspiration lung disease, bronchiectasis, lung abscess, atypical pulmonary infections (tuberculosis, etc.) with or without a long list of risk factors (e.g., exposure to tobacco smoke, neuromuscular disorders, tracheo-bronchomalacia, inhaled foreign body, etc.) which is associated with the preceding conditions. Conceptually poor clearance may also contribute to the presence of excessive airway mucus. Aspiration and other risks factors associated with chronic wet cough is beyond the scope of this review. Here we limit our review to three inter-related conditions; bronchiectasis, chronic suppurative lung disease (CSLD) and protracted bacterial bronchitis. We have also not discussed the multitude of etiological factors and associations with chronic cough in children. These, including management guidelines, are freely available elsewhere.[4,5,11,25]

ABBREVIATIONS

ALRI	Viral acute lower respiratory infection
ARI	Acute respiratory infection
CSLD	Chronic suppurative lung disease
PBB	Protracted bacterial bronchitis
RCT	Randomized controlled trial
TLR	Toll-like receptor

BRONCHIECTASIS AND CHRONIC SUPPURATIVE LUNG DISEASE (CSLD)

In most developed countries, childhood bronchiectasis has significantly reduced in frequency. The reduced incidence over time has been ascribed to reduced crowding, improved immunization programs, better hygiene and nutrition, and early access to medical care.[26,27] However bronchiectasis remains common in poorer countries[28–31] and among disadvantaged Indigenous groups in developed countries such as the Alaskan Yupik children in the USA,[32] Indigenous children in Australia[17] and Maori and Pacific Islanders in New Zealand.[33]

The dominant symptom of bronchiectasis is the presence of excessively prolonged wet cough. In older children cough may be productive and purulent. Other symptoms include recurrent chest infections or/and

recurrent wet cough responsive to antibiotics, exertional dyspnoea, symptoms of reactive airway disease (asthma-like condition) and growth failure. In children hemoptysis occurs rarely except in advanced disease. Clinical signs include clubbing, chest wall deformity, adventitious sounds on chest auscultation and/or hyperinflation,[17,34] but absence of these signs do not indicate absence of bronchiectasis. In advanced disease chronic hypoxemia and signs of pulmonary hypertension may be present.

The consequences of bronchiectasis range from increased mortality,[28,35] morbidity from the illness itself (increased hospitalization and medical needs, poor quality of life, etc.[36–38]) and increased co-morbidities (cardiac disease, asthma, malnutrition, pulmonary hypertension, etc.[39,40]). People with bronchiectasis have more rapid decline in lung function[39] and accelerated death.[35] The effects of bronchiectasis extends beyond the respiratory system; systemic,[41] cardiac (e.g., left ventricular diastolic function[42] and psychological (anxiety and depression)[43]) effects have been demonstrated. Furthermore, in adults chronic bronchitis/respiratory infection is an independent risk factor for atherosclerosis and coronary heart disease.[44,45] Effective management of bronchiectasis reduces the short[46] and long[47] term morbidity of the disease as well as mortality from the disease.[47] Thus prevention, early diagnosis and proactive management of bronchiectasis are advocated.[17,29,32,33] A brief review of possible interventions for the management of bronchiectasis is presented in Table 1. As bronchiectasis is a condition that has received relatively little research especially intervention trials in children, it is hardly surprising that there is little high level evidence on interventions for the management of CSLD or bronchiectasis. Further detailed information on bronchiectasis is available elsewhere.[48–50] Here we limit information relating to chronic wet cough and highlight the controversy of diagnostic terms.

The definition of bronchiectasis by Laenec was originally based on post mortem histopathology[51] in 1819. Bronchograms first described in 1951[52] then became the gold standard and this has been largely replaced by chest high-resolution computerized tomography (HRCT) scans. Currently bronchiectasis defined by ''irreversible dilatation of peripheral airways,'' is usually diagnostically established radiologically by chest HRCT scans.[53,54] The key features of bronchiectasis in HRCT scans are dilated bronchi in the periphery of the lung and bronchial wall thickening, and lack of tapering.[54,55] Other features include a linear array or cluster of cysts, decreased attenuation on the expiratory scan, mucous plugging, etc.[56] On a clinical level, particularly in children, this radiology based definition is problematic for the following reasons:

(1) A significant number of children have the clinical syndrome of bronchiectasis but their chest HRCT scans do not meet the criteria for radiological bronchiectasis. It is unknown at what stage of the disease process HRCT signs of bronchiectasis occur. While HRCT is the current standard, it has been shown to be less sensitive then bronchography in adults.[57,58] False negative results are more likely to occur when the disease is mild and focused.[57] As children are likely to have less severe bronchiectasis compared to adults, it is thus possible that the CT scans in a subgroup of children with clinical symptoms of bronchiectasis do not have radiological bronchiectasis.
(2) HRCT findings of bronchiectasis were derived from adult studies[59] but scans in adults are not necessarily equivalent to those in children. Airways and morphologic changes in the lung occur with maturation and aging.[60,61] One of the key HRCT signs of bronchiectasis is increased bronchoarterial ratio (defined as the diameter of the bronchial lumen divided by the diameter of its accompanying artery) of $>1-1.5$. This ratio is influenced by age ($r = 0.768$, $P < 0.0001$), as described by Matsuoka et al.[62] in a study of 85 adults without cardiopulmonary illness. Thus it is likely that the normal bronchoarterial ratio is lower in children than in adults and hence a lower ratio required to define abnormality representative of bronchiectasis in children.
(3) To truly fulfill the criteria of ''irreversible dilatation'' a minimum of two HRCT scans would be required. Performing more than one HRCT scan purely for diagnostic reasons (as opposed for management issues) in children is controversial because of (a) the increased cancer risk from CTs in children[63] as well as (b) the cost implications.
(4) Chest HRCT scans performed in different states of ''wellness'' may yield different results. While HRCT scans are ideally performed in a ''non-acute state,'' this state is difficult to define. A ''non-exacerbation state'' is not necessarily the same as ''post-treatment'' state. Clinicians have long realized that this is a significant limitation and this has been recently confirmed by Gaillard et al.[59] The Liverpool group described that post-medical treatment bronchial dilatation resolved completely in 6 of the 21 children with bronchiectasis.[59]

Thus for the reasons above, some clinicians use the term CSLD.[26] The term CSLD (as opposed to bronchiectasis) is used to describe a diagnosis where there are clinical symptoms of bronchiectasis without HRCT evidence of bronchiectasis. The dominant symptom of CSLD is the presence of excessively prolonged moist cough. Other than the lack of HRCT features, the symptoms of CSLD is otherwise identical to that of bronchiectasis. In contrast, protracted bacterial bronchitis is typified by the presence of isolated wet cough, that is, without the other symptoms and signs of CSLD or bronchiectasis.

TABLE 1—Possible Interventions for the Management of Bronchiectasis or CSLD

	Evidence type/study	Summary of results	Notes
Anti-microbials (by type)			
General	Cochrane review,[106] other systematic rev[107]	Generally beneficial	
Macrolides[108]	RCTs and review[109] for 2–6 months	Exacerbations significantly reduced in Rx arm[108] and reduction in sputum and symptoms, some with PFT improvement[109]	Consideration to microbial resistance
Nebulized tobramycin[110]	Double blind cross-over RCT in 30 adults with *P. aeruginosa*, 6-month each	Number and days of admissions less in tobramycin arm	Resistance and nebulized tobramycin poorly tolerated in some[111]
Anti-microbials (by time)			
Short term (<1 month)	Multiple cohort studies (e.g.,[46,112])	General clinical improvement	
Medium term (1–11 months)	Cochrane review,[106] other systematic revs[107,109]	Improvement with amoxil[113] and macrolides (see above). Adults with PsA-reduced hospitalization but no change in QOL[114]	
Long term (≥12 months)	RCTs[114,115]	Adults with PsA-reduced hospitalization frequency and days.[114] Reduced general disability in those on tetracycline[115] compared to placebo	
Anti-inflammatories			
Oral NSAIDs	Cochrane review[116]	No RCTs	Cohort study,[117] 25 mg tds indomethacin for 28 days reduced neutrophil chemotaxis but no change in sputum albumin, elastase, MPO
Inhaled indomethacin	RCT[118] in 25 adults, some with CSLD	Reduced sputum and improved dyspnoea score	
[0,1-4]Mucolytics			
Bromhexine	Cochrane review[119]	Studies only in acute phase	Not universally available
rhDNAse[120]	Systematic review[119]	Increased exacerbation rate and accelerated FEV_1 decline	
Airway clearance			
Chest physiotherapy	Cochrane review[121]	2 small trials on bronchiectasis	
Inhaled hyperosmolar agents	Cochrane review,[122] additional RCT (non-blinded) using 7% HS[123]	2 small short term studies on mannitol showed benefit in QOL only	
Asthma therapies			
Inhaled corticosteroids (ICS)	Cochrane review[124] and other RCTs	No significant effect of ICS in Cochrane review[124] Additional RCTs show some benefit. Reduced exacerbation rate only seen in those with P aeruginosa[125]	Limited applicability in children-high dose ICS and children less likely to have *P. aeruginosa*
Oral corticosteroids	Cochrane review[126]	No RCTs	No data[a]
Anti-cholinergics	Cochrane review[127]	No RCTs	No data[a]
$Beta_2$ agonist	Cochrane review[128,129]	No RCTs	No data[a]
LTRA	Cochrane review[130]	No RCTs	No data[a]
Physical training			
	Cochrane review[131] and RCT[132] which was included in Cochrane as an abstract (data changed)	Pulmonary rehabilitation improves exercise tolerance, no additional advantage of simultaneous inspiratory muscle training	
Oxygen (domiciliary)	No data as sole therapy[a]	Consider data from COPD showing benefit in survival[133,134]	

Surgery	Cochrane review[135]	No RCTs. Cohort studies suggest beneficial in selected cases[31]	Adverse events of surgery[135–137]
Vaccines			
Pneumococcal 23	Cochrane review[138]	No RCTs	Advocated as vaccines prevent respiratory infections
Influenza	Cochrane review[139]	No RCTs	
Acupuncture	RCT[140]	Improvement in QOL but not in sputum or 6 min walking test	
Model of follow up			
Nurse led	Cochrane review[141]	No difference in exacerbations but increase in hospitalizations in nurse led care compared to doctor led	Increased health care cost implications

HS, hypertonic saline; NPPV, non-invasive positive pressure ventilation; QOL, quality of life; PFT, pulmonary function test; PsA, *Ps. aeruginosa*; RCT, randomized controlled trial; Rev, review; Rx, treatment.
[a]No other data based on single reviewer search on Pubmed (Oct 2007) on studies in both adults and children. Table was modified and updated from a previous publication.[50]

PROTRACTED BACTERIAL BRONCHITIS (PBB)

What Is PBB?

PBB sometimes truncated to protracted bronchitis is a pediatric condition clinically defined as (a) the presence of isolated chronic (>4 weeks) wet/moist cough, (b) resolution of cough with antibiotic treatment, and (c) absence of pointers suggestive of an alternative specific cause of cough.[5,64,65] This condition has long been recognized by pediatric pulmonologists[66–68] but has only been adequately characterized (by BAL and clinically) recently.[64,65,69] In a prospective study that fully evaluated the etiology of chronic cough in children, bacterial infection of the airways (endobronchial infection) was the most common cause (40%).[64] In the 108 children enrolled for the study, significant colonization (≥10E5) by bacterial pathogens was detected in the BAL of 43 (40%) children, whereas respiratory viruses (examined using PCR) were detected in very few of these children. Airway neutrophilia was also present and respiratory pathogens found in the endobronchial infection were *Haemophilus influenza*, *Streptoccus pneumoniae*, and *Moraxella catarrhalis*.[64,69] PBB has been officially recognized by the Thoracic Society of New Zealand and Australia[5] and the British Thoracic Society.[11]

What Is Known About the Clinical Profile of Children With PBB?

Children with PBB are typically young (<5 years of age, median age—3 years[64,69]). They have a chronic wet cough and some parents may report a ''wheeze.'' Systemic effects are generally minimal or non-specific such as tiredness or lack of energy. While some of these are attributable to disturbed sleep, others are probably attributable to the chronic infection. These symptoms usually improve before the cough resolves when appropriate treatment is commenced. Symptoms worsen during inter-current viral infections and the combination of a persistence of a ''night time cough'' and viral exacerbations frequently lead to a misdiagnosis of asthma. As children with PBB do not respond to bronchodilator therapy they are sometimes erroneous labeled as having severe asthma.[64,69] The diagnosis is further complicated when asthma and bacterial bronchitis co-exist. On clinical assessment however, they usually do not have wheeze but instead have a ''ruttle'' (a rattling sound) reflective of airway secretions.[69]

Like children with chronic cough,[8] children with PBB have significant morbidity. Parents typically have seen multiple medical practitioners for their child's chronic cough in the last 12 months. In PBB the child's cough resolves only after a prolonged course (at least 10–14 days) of appropriate antibiotics. The diagnosis of PBB should only become definite when the response to treatment is

dramatic, that is, the child becomes asymptomatic. When a typical course (5 days) of antibiotics is used, the cough either relapses within 2–3 days, or slightly subsides but does not resolve completely. This is in contrast to the short course of antibiotics (5–7 days) required to treat community acquired pneumonia in otherwise well children.[70] Children with PB also have higher Canadian Acute Respiratory Infection Scale (CARIFS)[71] scores in subsequent respiratory illness.[72] Figure 1 shows the CARIFS scores when parents of children with PB and healthy controls scored their child's next respiratory illness. We compared these with children with acute asthma and found that at day 1 of illness there was no difference between groups. Days 7, 10, and 14 later, children with PB had significantly ($P < 0.0001$ for all) higher CARIFS scores.[72]

Their chest X-rays may be reported as ''normal'' but usually show peribronchiolar changes.[64,69] Hyperinflation is rare and if present should raise a concern for asthma alone or asthma with PBB. CT scans should be reserved until after an unsuccessful therapeutic trial as findings of bronchiectasis can occur after acute respiratory infections but resolve several months later. In addition, severity and persistence of symptoms do not necessarily correlate with CT changes.

Treatment of PBB

Unlike asthma, PBB is generally a curable condition. Our collective experience suggest that the principals of managing PBB, CSLD, and bronchiectasis are the same. Treatment is based on eradicating the bacteria with antibiotics and measures to improve cough effectiveness and keeping the airways free of infection to allow healing.

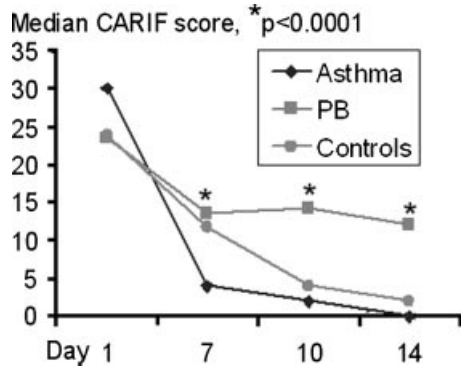

Fig. 1. Comparison of Canadian acute respiratory infection scale (CARIFS)[71] scores in children with acute asthma, protracted bronchitis and healthy controls during an acute respiratory infection. The CARIFS score consists of the sum of 18 items, each with a 4 point ordinal score (0–3). Thus a scale range of 0 (best health) to 54 (worst health) is obtained. On day 1 of the illness there was no difference between groups. On days 7, 10, and 14 later, children with PBB had significantly ($P < 0.0001$ for all) higher CARIFS scores.

There are no published randomized trials specifically on PBB. However two studies[73,74] on prolonged wet cough summarized in a Cochrane review (albeit with limitations), described that the wet cough responded to antibiotics with a number needed to treat (NNT) of 3 (95%CI 2, 4).[75] However it was unclear how many of the 140 children had PBB.[75] The progression of illness (defined by requirement for further antibiotics) was significantly lower in the group that received antibiotics, with NNT of 4 (95%CI 3, 5).[76] The initial treatment duration of antibiotics, targeted to the organisms mentioned above, vary from 2 to 4 weeks in general. Children with recurrent PBB (>2 episodes per year) should be evaluated for bronchiectasis[5] (e.g., assessment of immunoglobulins, functional antibody responses to vaccinations, full blood count, sweat test, HRCT scan, bronchoscopy, etc).

Pathogenesis of Endobronchial Infections

PBB like CSLD and bronchiectasis, is associated with persistent bacterial infection in the airways[64,69] and it is widely accepted that persistent bacteria infection is harmful to the airways.[77] The organisms most commonly identified in the airways (sputum or bronchoalveolar lavage) of children with PBB are the same as those seen in early stages of bronchiectasis, that is, non-typeable *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*.[64,69] They may well seed the lower conducting airways from the upper airways when muco-ciliary clearance is impaired for a critical period of time. Transient viral acute lower respiratory infections (ALRI) in early childhood commonly precede PBB as the most common initiating event, but colonization may be secondary to conditions that impair effective cough such as neuromuscular disease, mucus plugging in asthmatics or mucosal damage secondary to aspiration. Persistent airway colonization and the neutrophilic inflammation can evolve to chronic mucus hypersecretion, airway inflammation, and chronic cough. In some cases, cumulative airway injury from recurrent or persistent bacterial infection can lead to bronchiectasis. This may be very rapid if the degree of airway injury is severe, such as after adenoviral ALRIs, or more gradual with repeated less virulent ALRIs.

PBB is also likely to be heterogenous, with neutrophilic airway inflammation developing by a variety of mechanisms. It is likely that an innate immune dysfunction or immature adaptive immunity is present in a subgroup of these children. We found that bacterial colonization of the lower airways in children with chronic wet cough was associated with neutrophilic inflammation and reduced expression of both the toll-like receptor (TLR)-4 and the preprotachykinin gene, TAC1, that encodes substance P.[78] Substance P has a defensin-like function[79] which may explain the association between reduced TAC1 and

persistent bacterial infection. However the nature and duration of such immune dysfunction has been not defined, nor is it clear whether the dysfunction is specific to the lower airways or is more generalized and also involves circulating leukocytes. We however did not find a dysfunctional host response to bacterial infection, as an elevated gene expression for neutrophil chemoattractant chemokine IL-8 cellular receptor (CXCR1) was detected.

Innate immune studies have not been performed in children with non-CF bronchiectasis. The importance of innate immunity dysfunction is increasingly recognized in pulmonary disease.[80] The pathogenesis of progression of PBB to CSLD and bronchiectasis is unknown. We however speculate that untreated PBB leads to intensification of airway neutrophilia with subsequent airway destruction, progressing to CSLD and subsequently bronchiectasis. Further speculation is beyond the scope of this article and there is limited data on the pathogenesis of bronchiectasis in children. Readers are referred to review articles on the current knowledge on the pathogenesis of bronchiectasis.[49,50,81,82]

What Else Remains Unknown About PBB?

Currently the mechanisms underpinning the development and the natural history of PBB are unknown; the importance of these was addressed in a recent editorial.[83] Also the medium term consequences of PBB are unknown.[83] PBB is clearly differentiated from acute bronchitis (cough is of shorter duration ($\leq$2 weeks) in pediatric acute bronchitis[4,5]). Whether PBB is antecedent to bronchiectasis in some children is unknown and important to evaluate.[65,69,83] Children with PBB do not have established bronchiectasis[5] as those with established bronchiectasis usually have a different clinical profile and are unlikely to recover after 10–14 days of oral antibiotics (Table 2). Nevertheless there may be a link between PBB and bronchiectasis based on vicious circle hypothesis[84] and experimentally on old natural history data.[85] We thus advocate intervening in children with PBB and not waiting until bronchiectasis develops.

The Overlap Between PBB, CSLD, and Bronchiectasis

The similarities among these 3 conditions include the presence of a chronic wet cough with or without ruttles, as well as the process of neutrophilic airway inflammation, endobronchial bacterial infection and impaired mucociliary clearance. Types of micro-organisms are also similar in PBB and the early stages of CSLD/bronchiectasis. The key differences lie in the severity of symptoms and signs, the response to 2–4 weeks of oral antibiotics, and chest HRCT findings (Table 2).

In the clinical model depicted as ''disease entities,'' there is clearly an overlap between PBB and CSLD as well as between CSLD and radiological bronchiectasis. Whether these conditions are different conditions or reflect severity as part of a spectrum (Fig. 2) is yet to be determined. It is however conceivable that children with established bronchiectasis would have CSLD, at some stage earlier in the disease process. Similarly children with CSLD would also have PBB at some stage earlier in the disease process. However the risk factors and proportion of children with PBB who develop CSLD are unknown.

ASTHMA AND WET COUGH

The relationship of cough and asthma was previously reviewed in a ''state of the art'' article.[86] Further studies[64] and reviews[87–89] have further consolidated the fact that while cough can co-exist with other symptoms and present as asthma, isolated cough is a poor marker for asthma, first raised by McKenzie.[90] Here we focus on wet cough and asthma.

Australian[91] and British guidelines[92] on pediatric asthma clearly state that cough in children with asthma is usually dry. The USA guidelines however do not refer to the type of cough.[93] Can a wet cough that co-exists with other symptoms occur in children with asthma? This is undoubtedly yes, as by chance alone the probably of co-existence of common symptoms is high.[94] While a chronic wet cough does not exclude asthma, in the majority of children the presence of chronic wet cough does not equate to asthma.[64,65,91,92] Asthma exacerbations in childhood asthma are often triggered by viral infections[95] and cough in these circumstances (acute and subacute) may well be wet. When the wet cough becomes chronic (>4 weeks), PBB is likely present (as opposed to asthma alone). Viral infections causes transient innate immunity dysfunction in the airways which then predisposes the airway to bacterial and other endobronchial infection.[96]

Evidence of co-existent PBB in a subgroup of children with asthma is further gleaned from other studies.[97–99] Just et al.[100] described presence of common bacteria in children undergoing flexible bronchoscopy for three reasons including wheezing associated with productive cough. Although they[100] did not describe this as PBB, the BAL characteristics described have common characteristics to that of children with PBB. There are no randomized controlled trials that have evaluated this in children with asthma (there are trials on antibiotics for acute asthma[101] but none on chronic wet cough and asthma). A RCT examining the above is clearly needed. Nevertheless the approach of treating young children with asthma who have a chronic wet cough with a therapeutic trial of antibiotics is logical based on (a) cohort

TABLE 2—Comparison of Features in PBB, CSLD, and Bronchiectasis

Clinical profile	PBB	CSLD	Bronchiectasis
Symptoms[a]			
Chronic wet cough	+	++	+++
Wheeze	− (but asthma may co-exist)	+/−	+/−
Dyspnoea	−	+/−	+/−
Hemoptysis	−	−	+/−
Recurrent pneumonia	−	+/−	+/−
Pulmonary hypertension	−	−	+/−
Signs[a]			
Digital clubbing	−	+/−	+/−
Pectus carinatum	−	+/−	+/−
Crackles/crepitations	+/−	+/−	Usually +
Growth failure	−	+/−	+/−
Hypoxemia	−	−	+/−
Radiology[a]			
Chest radiograph	Normal or peribronchiolar changes	Peribronchiolar changes	Tram track signs may or may not be present
HRCT changes of bronchiectasis	−	−	+
BAL or sputum			
Cell differential	Airway neutrophilia	Airway neutrophilia	Airway neutrophilia
Micro-organisms	*H. influenza*, *S. pneumoniae*, *M. catarrhalis*	*H. influenza*, *S. pneumoniae*, *M. catarrhalis*	*H. influenza*, *S. pneumoniae*, *M. catarrhalis*. In advanced disease and depending on underlying cause, other organisms such as pseudomonas may be present
Management			
Response to antibiotics	Complete response with short term antibiotics	Usually require longer course of antibiotics or intravenous antibiotics	Usually require longer course of antibiotics or intravenous antibiotics
Other treatment	None required	See Table 1	See Table 1
Investigations	CXR and spirometry^	CXR, spirometry^ and further investigations for BE	CXR, spirometry^ and further investigations for BE such as immune function, etc.
Diagnostic criteria	Chronic wet cough responding to 2–4 weeks of antibiotics, spirometry normal	Symptoms and/or signs of BE but no HRCT signs of BE. Spirometry may or may not indicate obstructive pattern	Symptoms and/or signs of BE with HRCT signs of BE.[54] Spirometry may or may not indicate obstructive pattern

+, Present with +++ reflecting increased severity; −, absent; +/−, may be present.
BE = bronchiectasis; spirometry^ = if age appropriate.
[a]At presentation and/or initial evaluation.

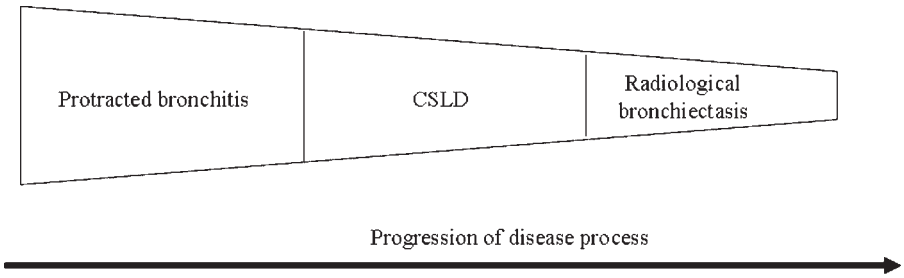

Fig. 2. Using the pathophysiological model, protracted bacterial bronchitis (PBB), chronic suppurative lung disease (CSLD) and radiological bronchiectasis likely represents different ends of a spectrum. This is however speculative and yet to confirmed. Untreated it is likely that some (but not all) children with PBB will progress to develop CSLD.

data showing most children with wet cough have an endobronchial bacterial infection,[64,69,102] (b) Cochrane review data describing the benefit of antibiotics for chronic wet cough,[76] and (c) our collective clinical experience. In a child with a cough, when other symptoms of asthma are absent, the diagnosis of asthma should be revisited.[86–88] Indeed the British[92] asthma guidelines make particular reference to this point. Antibiotics for acute cough or acute asthma are not advocated.

In a cross-sectional survey of 2,397 Seattle 11–15 years old students, Carter et al.[103] described that ''current asthma'' and tobacco smoke exposure were independently associated with chronic productive cough (defined as daily cough productive of phlegm for at least 3 months out of the year), odds ratio of 6.4 (95%CI 4.5, 9.0) and 2.7 (1.8–4.1) respectively. However the authors indicated that the study was not designed to determine whether asthma was the actual cause of the cough in this population of children.[103] Thus whether these children had symptoms attributed to asthma[89] or really had asthma is unknown.

A further complicating factor in the study of relating wet cough with asthma relates to the fact that parental reporting of wheeze is poor.[21–23] At least two groups have shown that parental reports of wheeze and other respiratory sounds are often not accurately reported in a clinic setting.[21–23] The agreement between parents' and clinicians' reports of wheeze and asthma was only 45%.[23] In the Sheffield cohort of children with PBB, parents misreported ruttles as wheeze.[69] Furthermore wheeze in young children may not representative of asthma but may reflect airway narrowing from presumably airway edema related to endobronchial infection. The BAL findings (positive bacterial culture) described in Saito and colleagues' cohort of young USA children[104] with wheeze and cough were similar to that found in PBB.[64,69] The quality of cough was not described in this study but as infection was present, it is likely wet. In a study of young children undergoing bronchoscopy, BAL airway cellularity and presence of common respiratory microorganisms related to the amount of secretions quantified at bronchoscopy.[102]

Thus chronic wet cough may co-exist in children with asthma. When it is present in a subset of selected children, it is likely related to PBB and not a marker of asthma severity. Like the data on isolated cough and asthma,[86–88,90] wet cough in isolation is also rarely indicative of asthma in children. If there is a clinical indication to try asthma therapies in these children, failure of the cough to respond within the ''time to response'' of 2–4 weeks, the asthma medications should not be escalated and the diagnosis reconsidered.[4,5]

SUMMARY

Reasons for the little recent attention on chronic wet cough likely include the intense focus on asthma that distracts clinicians from the role of chronic airway infection in children with chronic wet cough. The prevalence of chronic wet cough in children is unknown, in part because a standard definition for ''chronic'' has not been universally accepted. Pediatric literature addressing chronic cough using the definition of chronic bronchitis in adults, that is, >3 months, overlooks those children with persistent productive cough lasting 4 weeks to 3 months. In children with a wet cough of >4 weeks duration, PBB is a diagnosis that needs to be considered. Definitive diagnosis of PBB rests on isolation of bacteria and neutrophils in BAL at bronchoscopy but can also be considered clinically on the basis of the characteristic history, witnessing the cough, and using high doses of appropriate antibiotics for at least 2 weeks. On antibiotic therapy, the cough will resolve in 10–14 days, but it may take longer in a minority of children. Recurrent episodes of PBB and/or wet cough not resolving to simple therapies should prompt further evaluations of other causes of chronic wet cough (aspiration, CSLD and bronchiectasis). Management of PBB is essentially the same as that for bronchiectasis. Managing PBB is important as it is curable and it is likely that non-treatment may lead to development of CSLD in some children, such as at-risk populations (e.g., Indigenous children).

PBB, CSLD and bronchiectasis probably represents different parts of the spectrum of the same underlying

process of airway neutrophilia, endobronchial bacterial infection and impaired muco-ciliary clearance. CSLD and bronchiectasis have a similar clinical profile. CSLD is differentiated from bronchiectasis only in the absence of HRCT findings in CSLD and reasons for this were discussed. These diagnoses represent our current understanding and further research will alter and/or refine these nomenclatures alike the improvements that occurred in bronchopulmonary dysplasia.[105] Future clinical and research challenges include understanding the natural history, defining the common etiology and risk factors and, the ability to better define, monitor and improve the management of these conditions.

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