

Protracted Bacterial Bronchitis: The Last Decade and the Road Ahead

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Summary. Cough is the single most common reason for primary care physician visits and, when chronic, a frequent indication for specialist referrals. In children, a chronic cough (>4 weeks) is associated with increased morbidity and reduced quality of life. One common cause of childhood chronic cough is protracted bacterial bronchitis (PBB), especially in children aged <6 years. PBB is characterized by a chronic wet or productive cough without signs of an alternative cause and responds to 2 weeks of appropriate antibiotics, such as amoxicillin-clavulanate. Most children with PBB are unable to expectorate sputum. If bronchoscopy and bronchoalveolar lavage are performed, evidence of bronchitis and purulent endobronchial secretions are seen. Bronchoalveolar lavage specimens typically reveal marked neutrophil infiltration and culture large numbers of respiratory bacterial pathogens, especially *Haemophilus influenzae*. Although regarded as having a good prognosis, recurrences are common and if these are frequent or do not respond to antibiotic treatments of up to 4-weeks duration, the child should be investigated for other causes of chronic wet cough, such as bronchiectasis. The contribution of airway malacia and pathobiologic mechanisms of PBB remain uncertain and, other than reduced alveolar phagocytosis, evidence of systemic, or local immune deficiency is lacking. Instead, pulmonary defenses show activated innate immunity and increased gene expression of the interleukin-1 β signalling pathway. Whether these changes in local inflammatory responses are cause or effect remains to be determined. It is likely that PBB and bronchiectasis are at the opposite ends of the same disease spectrum, so children with chronic wet cough require close monitoring. *Pediatr Pulmonol.* 2016;51:225–242. © 2015 Wiley Periodicals, Inc.

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INTRODUCTION

Cough is the single most common reason given for patients seeking treatment in primary care.^{1,2} In Australia, 7% of acute medical consultations (1.38 million/year) are for a coughing illness.^{1,3} Among these presentations are children with a chronic cough >4-weeks duration where in the previous 12 months as many as 80% are likely to have seen a doctor for their symptoms on more than five occasions.⁴ Chronic cough in childhood is also associated with considerable morbidity⁵ and decreased quality of life (QoL) scores,^{4,6} which normalize once the cough resolves following appropriate therapy.⁷

Of the many possible etiologies, single⁸ and multi-center studies⁷ recruiting primarily from pediatric referral centers have found that protracted bacterial bronchitis (PBB) is the most common cause of chronic cough in childhood, exceeding by two-to-threefold other underlying diagnoses, including asthma. This article summarizes current knowledge of PBB in children, presents further preliminary data on underlying disease mechanisms, and identifies research priorities to help further close the information gap for this common, but poorly understood condition.

DEFINITIONS

The term PBB was first defined a priori and was based on our clinical experience before being applied to a subgroup of children in our prospective study evaluating

the etiology of chronic cough.⁸ The diagnostic criteria were: (i) history of chronic wet cough; (ii) positive bronchoalveolar lavage (BAL) fluid cultures for respiratory bacterial pathogens at densities $\geq 10^4$ colony-forming units (CFU)/ml of BAL fluid without serologic or polymerase chain reaction (PCR) assay evidence of infection by either *Bordetella pertussis* or *Mycoplasma pneumoniae*; and (iii) cough resolution after a 2-week course of oral antibiotics (amoxicillin-clavulanate).⁸

However, undertaking flexible bronchoscopy and BAL on every young child with a chronic wet cough is impractical and many older children are also unable to expectorate sputum of sufficient quality for reliable culture. Consequently, we altered our original definition of PBB to a more pragmatic one (Table 1). This acknowledges the multiple causes of chronic wet cough in children.^{7,9}

Diagnostic Criteria Validity

While the initial PBB criteria were derived from clinical observations, each of the initial PBB criteria have now been validated. For criterion-(i), for example, chronic wet cough (>4 weeks), our urban-based study of parental recognition of wet cough showed excellent agreement with pediatric pulmonologists ($\kappa = 0.75$, 95% confidence interval (CI) 0.58–0.93) and bronchoscopic findings of endobronchial secretions (area under the receiver operating curve = 0.85, 95%CI 0.77–0.92).¹⁰ Also, prospective^{11,12} and retrospective¹³ studies have demonstrated that BAL cultures from children with chronic wet cough have respiratory bacterial densities ($\geq 10^4$ CFU/ml) indicating lower airway infection. Further, increased amounts of secretions detected on bronchoscopy were associated with increased likelihood of infection and airway neutrophilia.¹¹

The original criterion-(ii) required BAL specimens to have positive respiratory bacterial cultures $\geq 10^4$ CFU/ml,⁸ which is a threshold often used for diagnosing lower airway infection.^{14–16} The common pathogens (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*) reported initially in PBB⁸ have been reaffirmed by several other groups.^{13,17–19}

Finally, a Cochrane review of two randomized controlled trial (RCTs) found that antibiotics (criterion-iii) improved the odds of curing chronic wet cough in children odds ratio (OR) = 7.7 (95%CI 3.1–16.7).²⁰ Although both RCTs were limited by small numbers (total n = 140), they nevertheless provided experimental data that supported clinical observations. These results have been confirmed recently by a double-blind RCT.²¹

Diagnostic Criteria Limitations

Nonetheless, each criteria described above has their limitations. Recognizing wet cough is dependent upon clinical setting. The child's age, the accuracy of their

ABBREVIATIONS:

AdV	adenovirus
BAL	bronchoalveolar lavage
BTS	British Thoracic Society
CF	cystic fibrosis
CFU	colony-forming units
CI	confidence interval
CSLD	chronic suppurative lung disease
CT	computed tomography
hBD2	human β -defensin 2
IL	interleukin
IQR	interquartile range
IRAK	IL-1 receptor associated kinase
MBL	mannose-binding lectin
MMP	matrix metalloproteinase
NNT-B	number needed to treat for benefit
NTHi	non typeable <i>Haemophilus influenzae</i>
OR	odds ratio
PBB	protracted bacterial bronchitis
PCR	polymerase chain reaction
QoL	quality of life
RAGE	receptor for advanced glycation end-products
RCT	randomized controlled trial
SP-A	surfactant protein-A
sRAGE	soluble receptor for advanced glycation end-products
TLR	toll-like receptor
TNF	tumor necrosis factor

TABLE 1—Diagnostic Criteria for Protracted Bacterial Bronchitis

1. Original microbiologic-based case definition⁸(also termed PBB-micro)
 - i. Presence of chronic wet cough (>4 weeks)
 - ii. Lower airway infection (recognized respiratory bacterial pathogens growing in sputum or at BAL at density of a single bacterial specieses $\geq 10^4$ colony-forming units/ml)
 - iii. Cough resolved following a 2-week course of an appropriate oral antibiotic (usually amoxicillin-clavulanate)
2. Modified clinical-based case definition⁴⁵ (also termed PBB-clinical)
 - i. Presence of chronic wet cough (>4 weeks)
 - ii. Absence of symptoms or signs of other causes of wet or productive cough¹
 - iii. 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

¹Specific cough pointers^{45,94,95} 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 sino-pulmonary 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].

parent/caregiver’s history, and healthcare personnel training and experience can influence accurate identification. For example, unlike urban-based parents,¹⁰ Australian Indigenous caregivers reporting of current cough is often inaccurate.²² It is also easier to recognize spontaneous wet cough in a young child. Agreement between clinicians and parents for cough quality (dry/wet) is better in children aged ≤ 2 years ($\kappa = 0.85$, 95%CI 0.57–1.0) than in older children ($\kappa = 0.70$, 95%CI 0.49–0.92).¹⁰ In our experience, older children may have an underlying productive cough despite it sounding dry when asked to cough in the clinic (“cough on request”). This may be partially related to the secretion volume relative to airway size, which has been described in animal studies where the amount of secretions alters sound characteristics.²³

While lower airway infection is often defined as bacterial growth $\geq 10^4$ CFU/ml in BAL,^{14,15} the most robust cut-off remains unknown.²⁴ Thus, different studies employing BAL have used slightly different definitions of PBB (Tables 2–4).

Although the response to 2 weeks of antibiotics is one of the criteria used to diagnose PBB, we⁹ and others^{18,19} have

observed that some children require a longer treatment of 4 weeks. The number needed to treat for benefit (NNT-B) by 2 weeks found in the Cochrane review²⁰ and the RCT²¹ was 3–4 (95%CI 2–27) and it is possible that using a longer course may reduce the NNT-B (see below).

The variation in definitions is similar to pediatric asthma where varying definitions depend upon age, clinical and/or research setting, and availability of tests for airway cellularity, lung function, and airway hyper-responsiveness. Given these limitations, the definition of PBB may be refined further; particularly if a simple biomarker is identified that predicts the response to antibiotics.

Proposed PBB Definition

To advance the field for clarity, we propose the following definition:

1. PBB-micro = original definition.⁸
2. PBB-clinical = the modified criteria where criterion-ii (BAL component) is replaced by: “absence of other causes of wet/productive cough.”

TABLE 2—Current National Pediatric Chronic Cough Guidelines

First author, publication year	Country	Society	PBB mentioned or specified	Definition used ¹
Chang [2006] ⁴⁵	Australia	Thoracic Society of Australia and New Zealand	Yes	PBB-clinical \pm BAL
Chang [2006] ⁹⁴	USA	American College of Chest Physicians	Yes	Chronic wet cough and response to 2–4 wks of antibiotics
Gibson [2008] ⁹⁶	Australia	Australian Lung Foundation	Yes (pediatric section)	PBB-clinical \pm BAL
Kohnno [2006] ⁹⁷	Japan	Japanese Respiratory Society	No	Not applicable
Leconte [2008] ⁹⁸	Belgium	Primary care	Yes	Not defined
Lu [2014] ⁹⁹	China	Multiple societies	Yes (based on translated article)	PBB-clinical \pm BAL
Shields [2008] ⁴⁸	England	British Thoracic Society	Yes	Chronic wet cough and response to 4–6 wks of antibiotics
Zacharasiewicz [2014] ¹⁰⁰	Austria	Austrian Society of Pediatrics, Austrian Society of Pneumology	Yes	PBB-clinical \pm BAL

¹See Table 1.

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.

HISTORICAL CONTEXT

When we first described PBB in 2006,⁸ its existence as a distinct diagnostic entity was controversial.²⁵ However, it is becoming recognized increasingly and is now incorporated into pediatric chronic cough guidelines (Table 2) and into the European pediatric respiratory training curriculum.²⁶

Astute clinicians alluded to PBB-like conditions previously, but did not consolidate these observations into a clinical entity supported by laboratory-based data. Various definitions used in the 1970–80s described “childhood chronic bronchitis” ranging from productive cough for 3 months/year to recurrent episodes of cough lasting >2 weeks with/without wheeze.²⁷ During this period, a single center review of 20 children undergoing bronchoscopy and diagnosed with chronic bronchitis found all had evidence of bronchial wall inflammation and purulent endobronchial secretions, and most improved after a course of antibiotics.²⁸ In the 1940s, a series of studies on childhood bronchiectasis raised the possibility of a pre-bronchiectasis state,²⁹ which was reversible by aggressive antibiotic treatment, while another study suggested a link between chronic bronchitis and bronchiectasis.³⁰ A later report described chronic bacterial bronchitis in children with tracheo-bronchomalacia,³¹ and more recently others have suggested that some children with so called “difficult asthma,” persistent wheeze³² or asthma-bronchitis might have PBB (parents of children with PBB often describe wheezing illnesses).^{18,33} Indeed, a retrospective French study reported one in eight children undergoing bronchoscopy for “severe chronic asthma” had lower airway infection (defined as >10⁵ CFU/ml or >10⁴ CFU/ml with activated neutrophils).³⁴

DISEASE BURDEN

Several cohort studies of children with chronic cough have documented the disease burden, QoL scores, medication use and number of doctor visits for the subgroup with PBB.^{4,7}

Prevalence

The true prevalence of PBB cases presenting to community clinics is unknown. Studies from specialist clinics from Australia^{7,8} and Turkey^{35,36} found PBB to be among the top three diagnoses in children with chronic cough (Table 3). Using a standard management approach,³⁷ a priori definitions and validated cough outcome measures,

an Australian multicenter study⁷ found that 142/346 (41%) children newly referred for chronic cough had PBB, which predominated in younger children.⁷ A United Kingdom (UK)-based retrospective study reported PBB was the most common diagnosis made in their clinic in children referred with difficult asthma or a chronic cough, and this disorder was increasing annually.¹⁸

Quality of Life

There are limited data on the QoL of children with PBB and that of their parents. In a multi-center study, the generic health-related (PedsQL³⁸) and chronic cough-specific (PC-QoL) QoL scores of children with PBB were similar to other different diagnostic groups (asthma, bronchiectasis, those whose chronic cough resolved without treatment) presenting to pediatric pulmonologists.^{39,40} Importantly, QoL scores normalize once the cough resolves.⁴¹

Treatment Burden

Typically, before diagnosis, children with PBB have received multiple medications and consulted several health physicians.^{4,7} A Sheffield study¹⁸ reported that at the time of referral, 59% of 81 children with PBB were taking asthma treatments, while an Australian multicenter study found 70% of 138 children with this diagnosis had received asthma medications and 76% had seen >5 doctors previously because of persistent cough.⁴⁰ However, these findings were also similar to children with chronic cough from other causes.⁴⁰

CLINICAL PHENOTYPE

There are relatively few clinical studies of children with PBB (Tables 4 and 5). By definition, they all have a chronic wet cough. Although children with PBB are typically young (mean or median age 1.8–4.8 years, Table 4), PBB also occurs in older (>12 years) children.^{7,42,43} Our first cohort of 43 children with PBB lacked systemic symptoms, including evidence of sinusitis and ear disease.⁸ This was confirmed in a subsequent prospective cohort of 104 children.³³ Compared to “disease controls” undergoing bronchoscopy for non-cough-related indications (e.g., stridor or apnea), children with PBB were more likely to have attended childcare (OR = 8.4, 95%CI 2.3–30.5), but their tobacco smoke exposure (~30%^{8,33}) was similar to that of the “controls.”³³ The strong association with childcare attendance raises the possibility of respiratory viruses having a role in initiating PBB, at least in some children.

Children with PBB typically appear well. They have normal growth and development, and lack signs of underlying chronic suppurative lung disease (CSLD), such as digital clubbing, chest wall deformity, and adventitious auscultatory chest findings,³³ although

TABLE 3—Prospective Studies on Children With Chronic Cough Describing PBB Within Their Cohort (Adapted From Article¹⁰¹)

First author, publication year, country	Setting	Inclusion criteria; exclusion	No. enrolled, no. completed, age	How cough was measured	Diagnoses, a priori defined; FU length	Period effect considered ¹	Prevalence of PBB in cohort (%)
Marchant [2006], ⁸ Australia	Single center, Resp OPD	>3 wks cough, age <18 yrs, and newly referred; Exc: NR	108, 103, median = 2.6 yrs, IQR 1.2–6.9 yrs	Cough diary ¹⁰²	Yes; FU: max 12 mo for Dx, post-Dx NR	Yes	42
Chang [2013], ⁴¹ Australia ²	Multicenter, Resp OPD	Aged <18 yrs, >4 wks cough, newly referred; Exc: chronic resp illness	270, 253, mean = 4.5 yrs, SD = 3.7 yrs	At 6 wks: cough resolution by cough diary, ¹⁰² PC-QOL ³⁹	Yes; FU: max 12 mo for Dx and 6 mo, post-Dx	Yes, 2 wks of treatment	42
Asilsoy [2008], ³⁵ Turkey	Single center, pediatric OPD	>4 wks cough; Exc: NR	108, 108, mean = 8.4 yrs, range 6–14 yrs	Cough-unspecified	Partial; FU: NR	ND	23
Chang [2012], ⁷ Australia ²	Multicenter, Resp OPD	Aged <18 yrs, >4 wks cough and newly referred; Exc: chronic resp illness	346, 346, mean = 4.5 yrs, SD 3 yrs	Cough resolution by cough diary, ¹⁰² PC-QOL ³⁹	Yes; FU: max 12 mo for Dx and 6 mo, post-Dx	Yes, 2 wks of treatment	41
Karabel [2014], ⁴³ Turkey	Single center, Resp OPD	>4 wks cough; Exc: NM, cardiac, syndromes, RTI in last 4 wks	270, 270, mean = 6.5 yrs, range 7 mo–17 yrs	ND	Partial; FU: 12 mo	ND	6
Usta [2014], ³⁶ Turkey	Single center, pediatric allergy OPD	Inclusion: NRExc: see footnote ³	156, 156, Mean = 8.4 yrs SD 2.6 yrs	Cough-unspecified	Partial; FU: max 18 mo for Dx, NR post-Dx	ND	12

Dx, diagnosis; Exc, exclusion criteria; FU, follow-up; IQR, interquartile range; mo, months; ND, not described; NM, neuromuscular; No, number; NR, not reported; OPD, outpatient; PBB, protracted bacterial bronchitis; PC-QOL, Parent Cough-Specific Quality of Life; Resp, Respiratory; RTI, respiratory tract infection; SD, standard deviation; wks, weeks; yrs, years.

¹Period effect considered: temporal relationship between medication use and outcome was defined a priori.

²Children in this RCT were from a subset of the same cohort.⁷

³Preterm birth, neuromotor-developmental delay, developmental-growth retardation, chest wall deformity, tobacco smoke exposure, clubbing, cardiac disease, any known chronic disease and/or pulmonary disease, and those unable to undertake pulmonary function tests.³⁶

TABLE 4—Prospective Studies Involving Children With Protracted Bacterial Bronchitis

Ist author, publication year; country	Setting; study design	Inclusion criteria; Exc or definitions	No. enrolled, no. completed; age	Main aim(s)	Key findings of the PBB component	Specimen; microbiology results	Other main findings
Marchant [2008], ⁸ Australia	Single center, Resp OPD	>3 wks cough, age <18 yrs and newly referred Exc: NR	No. with PBB = 43; median age of whole cohort = 2.6 yrs (IQR 1.2–6.9)	In children with chronic cough to: (a) evaluate the use of an adult-based algorithmic approach in the management and (b) describe the etiology profile, airway cellularity and promoters of neutrophilic inflammation in BAL of children	BAL median total cell count and neutrophil% in PBB ($350 \times 10^6/L$, 40%) was significantly higher than "natural resolution" group (228, 4%)	BAL: Hi = 47%, Spn = 35%; Meat = 26%	IL-8 levels significantly correlated with BAL neutrophil% and MMP-9
Marchant [2008], ⁵⁷ Australia	Single center, Resp OPD; cross-sectional	PBB = chronic wet cough (>3 wks), BAL bacterial culture ($\geq 10^4$ CFU/ml) and response to Abs (cough resolved 2 wks); other etiologies = other causes of chronic cough in cohort, ⁸ controls = children with stridor; but without chronic cough	PBB = 38, other DX = 25, SR = 22, controls = 15; respective median age (IQR): 2.4 yrs (0.9–4.2), 2.6 yrs (1.1, 9.6), 3.8 yrs (0.9, 6.8), 2.8 yrs (0.6, 9.8)	To: (a) describe the clinical profile, airway cellularity and promoters of neutrophilic inflammation in BAL of children with PBB compared to controls without cough and (b) explore innate immunity signaling receptors, specifically TLR-2, -4	BAL in PBB group had significantly elevated total cell counts, airway neutrophilia, IL-8, and active MMP-9 compared to other groups; TLR-2 and -4 mRNA relative expression ratio in BAL of PBB group was significantly higher than controls	BAL: Hi = 45%, Spn = 32%; Meat = 24%	IL-8 levels significantly correlated with BAL neutrophil% and MMP-9
Chang [2012], ⁷³ Australia	Single center, Resp OPD; cross-sectional	PBB = chronic wet cough, response to Abs with resolution of cough within 2 wks and absence of signs or symptoms of other disease; PBB well = previous PBB, but no cough when FB done	Current PBB = 61, PBB well = 20, controls = 21; respective mean age (SD) = 2.5 yrs (2.3), 4.2 yrs (3.0), 2.2 yrs (2.8)	To determine whether BAL levels of hBD2, SP-A, and MBL: (a) differed between children with current PBB, PBB well, and controls; and (b) related with airway neutrophilia and endobronchial infection	hBD2 and MBL levels in BAL were significantly higher in children with PBB compared with PBB well group and controls. hBD2 levels were associated with airway infection and are related to airway neutrophilia and MBL	BAL: microbiology NR	SP-A levels in the BAL and cytokine production of stimulated BAL cells similar between groups
Marchant [2012], ²¹ Australia	Single center, Pediatric and Resp OPD; RCT	Aged 0.5–18 yrs, doctor observed wet cough >3 wks; Exc: chronic lung, cardiac, or neurodevelopmental disorders, Abs in last 2 wks or if acutely unwell	50, 3 lost to FU that were analyzed as failures. Mean = 1.8 yrs for treatment gp and 2.8 yrs for placebo group	Efficacy of 2 wks of oral amox-clav (compared with placebo) in achieving cough resolution in children with chronic wet cough	Amox-clav effective for wet cough - cough resolution rates (48%) in amox-clav group versus placebo (16%), $P = 0.016$	BAL: Hi = 38%, Spn = 24%; Meat = 19%. All amox-clav sensitive	BAL in subgroup (n = 37); results consistent with PBB
Wurzel [2014], ³³ Australia	Single center, Resp OPD; cross-sectional	PBB = clinical def; controls = chronic resp symptoms, but no PBB, CSLD	PBB = 104, controls = 21; respective median age (IQR) = 19 mo (12–30), and 20 mo (8–63)	To provide extensive clinical, laboratory, and BAL characterization of PBB	Previous parent-reported wheeze (81%), but no increased propensity to atopy (IgE and RAST normal). Normal immunoglobulin levels and antibody responses (Hb and tetanus vaccines)	BAL: in PBB grp; Hi = 72%, Spn = 39%; Meat = 43%; Adv = 23%; any virus = 38%	PBB and childcare attendance-elevated serum NK-cell levels; tracheo-broncho-malacia common, but similar rates in controls
Baines [2014], ⁵⁶ Australia	Single center, Resp OPD; exp and validation cohorts	PBB = clinical definition; resolved PBB = previous PBB, but no cough at FB	Exp: PBB = 21; controls = 33; respective mean ages = 2.3 and 9.7 yrs; validation: PBB = 36; controls = 11; respective mean ages = 2.0 and 0.7 yrs	To evaluate the IL-1 and TNF- α /NF- κ B pathways and mediators in 2 cohorts of PBB and control children	Increased expression of neutrophil-related mediators in PBB, including IL-1 pathway members, neutrophil- α -defensins, and the chemokine receptor CXCR2	BAL: microbiology NR	IL-1 β protein levels correlated with BAL neutrophilia and duration and severity of cough symptoms

TABLE 4—(Continued)

1st author, publication year, country	Setting; study design	Inclusion criteria; Exc or definitions	No. enrolled, no. completed; age	Main aim(s)	Key findings of the PBB component	Specimen; microbiology results	Other main findings
Wurzel [2014], ⁶⁷ Australia ¹	Single center, Resp OPD; cross-sectional	PBB = clinical def; BE = Dx on CT scan	PBB = 159, BE = 112; median (IQR) age: PBB with Adv = 17 mo (12–22), PBB without Adv = 26 mo (15–56)	To identify: (a) the prevalence of Adv;(b) diversity of genotypes and species; and (c) whether presence of Adv increased the odds of bacterial coinfection	Adv-C (genotypes 1, 2) was the major Adv species in BAL; lower airway bacterial infection, (with Hi, Mcat and Spn, but not S4) increased in those with Adv	BAL: in Adv + grp; Hi = 68%; Spn = 39%; Mcat = 35%; In Adv- grp; Hi = 47%; Spn = 22%; Mcat = 19%	Younger age independent predictor of Adv with respiratory bacteria co-infection
Van der Gast [2014], ⁶⁹ USA and Australia	Multi-center, Resp OPD; cross-sectional	PBB = clinical def; BE = Dx on CT scan; CF = sweat test	PBB = 12, BE = 19; CF = 25; respective mean (SD) age: 8.9 yrs (4.7), 2.3 yrs (1.7), 12.5 yrs (3.5)	To compare: (a) the core and satellite microbiota in cohorts of children with different diseases and (b) the respiratory metacommunities in PBB and pediatric and adult CF and bronchiectasis cases	Similar resp sample core microbiota in the three diseases; microbiota from adults with CF and BE differed significantly from each other and from those of children with the same disease	BAL and sputum; traditional and non-traditional organisms described	
Chang [2014], ⁴⁰ Australia	Multi-center, Resp OPD	PBB = clinical definition	PBB = 138, asthma = 52, BE = 20, self-resolved = 40. Median age (IQR) PBB = 2.4 yrs (1.2, 4.8), BE = 3.9 (2.2, 6.4), self-resolved = 5.2 (2.1, 8.2)	In children newly referred for chronic cough, to describe data relating specific cough pointers of the three most common etiologies	At presentation (preDx), cough score, ¹⁰² PC-QOL, PedQL scores, number of doctors' visits between groups were similar	Not applicable	Likelihood ratios, sensitivity, specificity of the different symptoms/signs presented
Hodge [2015], ⁸⁰ Australia	Single center, Resp OPD; cross-sectional	PBB-micro; controls = no cough and FB undertaken for other reasons (e.g., stridor); BE = CT defined with clinical symptoms	PBB = 13, BE = 55, controls = 13. Median ages and IQR:PBB = 6.5 mo (1.6, 14), BE = 22 mo (14, 33), controls = 5.5 (4, 9.9)	(a) Quantify phagocytosis of airway apoptotic cells and NTHi by alveolar macrophages in children with PBB and BE and (b) determine if phagocytic capacity was associated with clinical or demographic variables, and differing patterns of airway inflammation	Macrophage phagocytic capacity significantly lower in PBB and BE c.f. controls ($P = 0.003$ and <0.001 for efferocytosis and 0.041 and 0.004 for phagocytosis of NTHi; PBB and BE, respectively); median phagocytosis of NTHi: BE = 13.7% (IQR 11–16%) PBB = 16% (11–16%), controls = 19.0% (13–21%); median efferocytosis: BE = 14.1% (10–16%), PBB = 16.2% (14–17%), controls = 18.1% (16–21%)	NR	IL-1 β levels significantly correlated BAL neutrophil% ($r = 0.93$, $P = 0.0001$). Negative, but non-significant correlations between IL-1 β and phagocytosis of apoptotic cells or NTHi ($r = -0.37$, $P = 0.080$, $-0.43, 0.099$, respectively)

¹Some children in this cohort³³ were also in other cohorts.^{56,67}

TABLE 5—Retrospective Studies on Children Including Children With Protracted Bacterial Bronchitis

First author, publication year, country	Setting; study design	Definition of PBB used	No. in study; age	Main aim(s)	Key finding(s)	Specimen; microbiology	Other main findings	Comment
Donnelly [2007], ⁴³ England	Resp OPD; review of clinic letters (random)	Persistent, wet cough present for 1 mo that resolved with "appropriate" AB treatment	81; median = 3.8 yrs (range 0.4–14.8)	Review the outcomes in 81 randomly selected patients diagnosed with PBB	95% cured with AB use; 48% reported "wheeze," but had a "rattle" instead	BAL (n = 19), cough swab (n = 51). Of infected specimens (~50%); Hi = 81%.	59% symptomatic for >1 yr; bronchiectasis in 4/14 who had chest CT scan; 31% with concomitant "asthma" (BDR demonstrated or responsive to steroids)	Not all children had PBB based on original definition of PBB
Kompare [2011], ¹⁹ USA	Resp and allergy OPD	Cough, wheeze or noisy breathing for >1 mo without other diagnoses, BAL ($\geq 10^4$ CFU/ml) and response to ≥ 2 wks AB treatment	70; summary age NR	Review all BAL ($\geq 10^4$ CFU/ml) cultures of children aged <5 yrs with cough, wheeze, or noisy breathing for >1 mo without other diagnoses so as to determine if PBB was present	Tracheo- or broncho-malacia present in 74%	BALHi = 56%, Spn = 37%, Mcat = 59%	Outcome data (available in 87%); symptoms resolved with AB treatment in all but one child	Bronchitis itself may cause malacia
Pfritts [2013], ⁴² Greece and England	Resp OPD	Children with chronic cough suspected of PBB who had PB to confirm diagnosis	Greece = 18, England = 39; median age = 4.8 yrs (range 0.9–14.4)	To (a) determine specific serotypes of Spn and NTHi in BAL samples and (b) compare Spn serotypes between the two countries and Spn vaccination	PCV-13 Spn serotypes in all Greek BALs, but only in 72% of English BALs (significantly different b/w countries)	Greek BAL: Hi = 61%, Spn = 27.6%; Mcat = 52%; Sa = 66%; English BAL restricted to Spn+ specs	Vaccine Spn serotypes rarely found in immunized children (OR = 0.02; 95%CI 0.003–0.115); 26 NTHi isolates (English BAL) had unique genotypes	Recent or current AB use NR. Evidence of serotype replacement disease in Spn-immunized children
Narang [2014], ⁶² England	Pediatric and Resp OPD; 50 consecutive notes	Suspected PBB (ND)	50; median age = 2.9 yrs (IQR 1.7, 4.4)	Review BAL and chest radiograph results, and assess the bacterial distribution across lung lobes	Bacterial distribution in PBB was heterogeneous	BAL: Hi = 50%, Spn = 16%, Mcat = 28%, Sa = 22%	Limiting sampling to 1–2 lobes will underestimate the microbiology of the lung (70% positive vs. 82%)	Positive culture undefined as quantitative culture was not done
Pritchard [2014], ⁵⁵ England	Pediatric and Resp OPD	AB responsive wet cough and positive BAL culture	43; median = 2.7 yrs (IQR 1.5, 4)	Review of treatment outcomes for children with PBB	Cough resolved in 77% after initial AB course (6–8 wks) but only 24% remained cough free (i.e., 76% relapsed)	BAL: Hi = 63%, Spn = 23%, Mcat = 51%, Sa = 19%	Of the 10 whose cough did not resolve after 6–8 wks ABs, 7 required prolonged ABs and 3 had other resp conditions	BE more likely to be present when wet cough unresponsive to 4 wks of ABs. ⁴⁹ Thus, likely some in cohort did not have PBB

ABs, antibiotics; AdV, human adenovirus; Amox-clav, amoxicillin-clavulanate; BAL, bronchoalveolar lavage; BE, bronchiectasis; BDR, bronchodilator responsive, btw, between, CF, cystic fibrosis, CFU, colony-forming units, CSLD, chronic suppurative lung disease; CT, computed tomography, CXCR2, chemokine (C-X-C Motif) receptor 2, Dx, diagnosis, Exc, exclusion criteria, Exp, experimental; FB, flexible bronchoscopy; FU, follow-up; hBD2, human β -defensin-2; Hi, *Haemophilus influenzae*, Hib, *Haemophilus influenzae* type b, IL, interleukin; IQR, interquartile range, MBL, mannose-binding lectin; Mcat, *Moraxella catarrhalis*, MMP, matrix metalloproteinase, mo, months, mRNA, messenger RNA, ND, not described, NF-kB, nuclear factor kappa-light-chain enhancer of activated B cells, NK, natural killer cell, No, number, NR, not reported, NTHi, nontypeable *Haemophilus influenzae*, OPD, outpatient department, OR, odds ratio, PBB, protracted bacterial bronchitis, PC-QOL, parent cough-specific quality of life, PCV-13, 13 serotype pneumococcal conjugate vaccine; PedQL, pediatric quality of life, Pros, Prospective, RAST, radioallergosorbent test, RCT, randomized controlled trial, Resp, respiratory, Retro, retrospective; Sa, *Staphylococcus aureus*, SD, standard deviation, SP-A, Surfactant protein-A; Spn, *Streptococcus pneumoniae*, *SR, spontaneous resolution of cough without therapy or, if this was tried the cough resolved more than 2 weeks after ceasing treatment.

*Spontaneous resolution (SR) defined as resolution of cough without therapy or, if this was tried the cough resolved more than 2 weeks after ceasing treatment.

occasionally a “rattly chest” and crackles are heard. The chest radiograph is normal or near-normal, showing only peri-bronchial changes.^{9,40,44} When performed, both spirometry⁴⁰ and respiratory system reactance and resistance measured by the forced oscillatory technique (unpublished) are also normal.

The prevalence of atopic features (eczema, systemic and airway eosinophilia, elevated IgE, or positive radioallergosorbent test) is similar to children without PBB.³³ While many parents report previous “ever wheeze” (41–81%^{18,33}), auscultation-confirmed wheeze by doctors is unusual. In the Iowa City BAL-based retrospective cohort of children with PBB,¹⁹ 17/70 (24%) children had “noisy breathing” (five also wheezed) and 27 (39%) parents reported wheezing. In the Sheffield cohort study,¹⁸ 36/81 (45%) children were referred for “difficult asthma” and 35 (43%) reported “shortness of breath,” which was attributable to coughing bouts. While most children in this cohort¹⁸ had PBB, some did not based upon our definition since 11 (13%) required more than six courses of antibiotics for recurrent chronic wet cough and 4 (5%) had radiographic-confirmed bronchiectasis.

In children, differentiation between acute bronchitis and PBB is based on the fact that acute bronchitis cough usually resolves within 2–4 weeks.^{45,46} Nevertheless, difficulties arise when recurrent and acute bronchitis episodes overlap, especially during the “respiratory virus” season. Furthermore, PBB can co-exist with other illnesses, including asthma, while recurrent episodes need to be differentiated from bronchiectasis where chronic wet cough and repeated respiratory exacerbations may not respond to oral antibiotics, physical signs of CSLD may develop and irreversible bronchial dilation and wall thickening are seen on plain radiographs or computed tomography (CT) scans of the chest.^{9,47}

TREATMENT

In PBB, the child’s cough resolves only after a prolonged (2 weeks) course of appropriate antibiotics.^{8,21} When a typical five to seven day course of antibiotics is prescribed the cough either relapses or does not resolve completely. However, some children require up to 4 weeks of treatment. In our RCT,²¹ many of the children whose cough was not cured by 2 weeks of antibiotics had underlying tracheo-bronchomalacia and needed a longer course of antibiotics before their cough disappeared. We speculate that children in this RCT²¹ were also at the more severe end of the disease spectrum and more likely to require a longer antibiotic course. Hence the larger NNT-B (4, 95%CI 2–27) compared to the Cochrane review (3, 95%CI 2–5).²⁰

In contrast, the 2008 British Thoracic Society (BTS) cough guidelines⁴⁸ suggest all children with PBB should receive 4–6 weeks of antibiotics. This recommendation,

however, was based upon expert opinion as at the time no supportive high-quality studies existed. Further studies are now needed to help identify whether those with PBB requiring a longer course of antibiotics are different (e.g., outcomes) from those responding to shorter courses.

While some children with PBB may need longer antibiotic treatment, we still advocate the shorter 2-week course initially. This reflects the principles of good antimicrobial stewardship and should also reduce drug-related adverse events. Furthermore, a recent study showed that children with a chronic wet cough failing to resolve after 4 weeks of appropriate oral antibiotics have increased likelihood of bronchiectasis on a chest CT scan.⁴⁹ In this retrospective study, all chest multi-detector CT scans performed over a 28 month period for assessment of chronic wet cough were reviewed.⁴⁹ Among the 105 children with persistent cough despite at least 4 weeks of antibiotics, 88 (83.8%) had bronchiectasis, while of the 24 children whose cough resolved after antibiotics, only six (25.0%) received this diagnosis (adjusted OR 20.9; 95%CI 5.36–81.8).⁴⁹

Chest airway clearance is now standard therapy in bronchiectasis management.⁴⁷ The BTS guidelines⁴⁸ also suggest physiotherapy for children with PBB. While this may be beneficial, the evidence to support this recommendation is limited. Furthermore, the time required for performing airway clearance techniques should not be underestimated.

Ideally, a lower airway specimen for microbiologic testing is obtained before treatment. Indeed, the BTS guidelines⁴⁸ recommend that before making a diagnosis of PBB, sputum should be cultured first and other underlying conditions excluded. However, most children with chronic wet cough are young (Tables 4 and 5) and unable to expectorate, even following sputum induction. Thus, obtaining reliable lower respiratory secretions requires bronchoscopy, which will be impractical in most clinical settings. Nevertheless, if a bronchoscopy is performed, purulent secretions and evidence of bronchitis (Fig. 1) are usually present.

Consequently, from a pragmatic perspective, in children with an “isolated” chronic wet cough, who have a normal or near normal chest radiograph and are without symptoms and signs of another diagnosis (e.g., aspiration lung disease, bronchiectasis, cystic fibrosis (CF), inhaled foreign body, tuberculosis, etc.) PBB should be suspected and we recommend they receive 2 weeks of an appropriate oral antibiotic. The most widely used first line empiric antibiotic is amoxicillin-clavulanate,²¹ (as commonly associated pathogens, such as *H. influenzae* and especially *M. catarrhalis*, can be amoxicillin-resistant) although depending upon local pathogen susceptibility patterns, alternatives such as an oral cephalosporin, trimethoprim-sulfamethoxazole, or macrolide may be used when immediate hypersensitivity to penicillin exists.

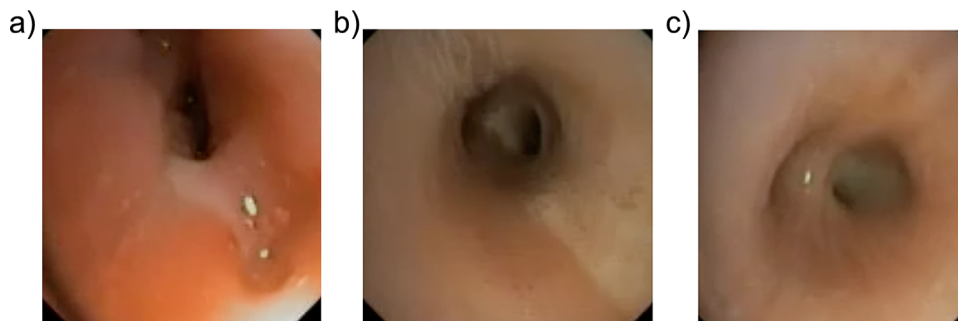


Fig. 1. Bronchoscopic images from several children with protracted bacterial bronchitis. The bronchoscopy usually shows secretions in several bronchi and features of bronchitis (airway edema and inflammation Fig. 1a). In Fig. 1a, bronchomalacia and mucus (LB10) are also present. Sometimes secretions are seen in the trachea (Fig. 1b), but more often purulent secretions are seen in the bronchi (Fig. 1c—secretions seen at the right lower lobe bronchus).

While antibiotics are generally well tolerated, caregivers should be counseled about possible adverse events (e.g., gastrointestinal complaints, rashes, hypersensitivity) occurring.⁵⁰ When a child can expectorate, a sputum specimen should be obtained. In a minority of children, the cough will not respond to treatment and the antibiotic can be extended to a maximum of 4 weeks. However, if by this time the wet cough has not improved substantially, the child should be investigated for other causes of chronic wet cough.^{9,49}

PBB can also co-exist with other conditions (e.g., asthma, tracheo-bronchomalacia)^{7,18} and these conditions should be diagnosed and managed concurrently. As with all children at risk of chronic lung disease, clinicians should also counsel on preventative care including avoidance of tobacco smoke and other inhaled environmental toxicants, timely vaccinations, ensuring good nutrition, and emphasizing the importance of physical activity.

PROGNOSIS

PBB often recurs at some point, particularly in the very young as recurrent respiratory infections are more common in this age group.⁵¹ The definition of recurrence (number of episodes per year) remains uncertain, but historically either at least three or more than three lower respiratory infections per year has been used.^{52,53} Adopting the latter definition, a prospective BAL-based study was undertaken in 106 children with PBB followed for a median 25 months (IQR 24–28) after this investigation.⁵⁴ Their median age at bronchoscopy was 23 months (IQR 14–53). Compared with healthy controls (median age 27 months, IQR 26–29) children with PBB at baseline were significantly more likely to have had wet cough and to have visited their family doctor in the preceding 12 months. At the 24 month follow-up, children with PBB were more likely to be coughing compared with controls (44% vs. 12% of respective cohort, $P=0.005$) and to have

had parent-reported wheeze in the preceding 12 months (58% vs. 16%, $P=0.001$). By the end of the study, 66 (62%) of those with PBB (and complete follow-up) had experienced recurrent episodes (>3 per year) and 13 (12%) had bronchiectasis diagnosed by chest CT scans.⁵⁴ The major independent risk factors for bronchiectasis were *H. influenzae* lower airway infection and having ≥ 2 siblings. *H. influenzae* infection conferred >6 times higher risk of bronchiectasis than a *H. influenzae* negative state (hazard ratio = 6.8, 95%CI 1.5–30.8).

A UK-based retrospective study⁵⁵ described 33 children whose wet cough resolved with antibiotics (“PBB”). During the median follow-up period of 11.3 months (IQR 8.3–14.7) only eight (24%) remained cough free, while three (9%) had three or more recurrent episodes of persistent wet cough and nine were prescribed long-term antibiotics. Another retrospective study¹⁹ reported that 43 of 70 children had recurrent symptoms (timeframe not provided). These studies suggest that physicians should warn parents about future recurrences and physicians themselves need to be aware that some children may progress to bronchiectasis.

Nevertheless, the actual rate and risk factors of PBB recurrence are likely dependent on the sampling frame and definition. Factors in those severe enough to proceed to bronchoscopy are likely different from those enrolled from the community. Additional longer term studies are warranted as recurrent PBB is associated with more intense and possibly persistent activation of interleukin (IL)-1 signalling pathways in the airways.⁵⁶

PATHOBIOLOGY

Lower airway bacterial infection and neutrophilia are present in children with PBB.^{8,19,57} Protracted cough implies injurious chronic airway inflammation and mucus hypersecretion,^{58,59} while on-going endobronchial bacterial infection is harmful to the lungs.^{60,61}

Microbiology

Bacteria

In the first description of PBB,⁸ BAL cultures grew the common respiratory bacterial pathogens, *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. Subsequently, several other groups confirmed these BAL findings.^{8,18,19,21,33,55} One retrospective study also identified *Staphylococcus aureus* in 11/50 children with PBB,⁶² but quantitative bacteriology was not performed making interpretation difficult. This latter study⁶² also evaluated BAL sampling of one versus six lobes and reported sampling only one lobe in 41 children would have missed 17 potential bacterial pathogens in 15 patients. While it is generally accepted that more than one lobe should undergo BAL, additional prospective studies employing quantitative bacteriology with concomitant inflammation marker assays are needed. Data relating to current or recent antibiotic use and vaccination status should also be recorded as it is likely that antibiotics, vaccine types, and host immune response influence lower airway bacteriology in children suspected of PBB⁴² and CSLD.^{63,64}

H. influenzae (range 47–81%) is the most common bacteria reported in all but one¹⁹ of the published studies describing the lower airway bacteriology in children with PBB.^{8,21,33,42,55,62} Most *H. influenzae* are non-typeable *H. influenzae* (NTHi) strains representing diverse genotypes,⁴² a finding consistent with the increasing importance of NTHi in chronic pulmonary disorders in children and adults.^{65,66}

In some studies,^{8,21} *S. pneumoniae* (24–39%) was the second most common organism detected in BAL cultures, but in others^{33,42,55,62} *M. catarrhalis* (range 19–43%) was found more commonly. However, these BAL studies are difficult to compare as samples came from different sites and numbers of lobes, some accepted all positive culture results,^{55,62} while others used quantitative bacteriology to diagnose infection.^{8,19,21,33} *S. pneumoniae* serotypes were reported in one recent study involving immunized children in the UK and Greece undergoing BAL for suspected PBB.⁴² Although both vaccine and non-vaccine-related serotypes were isolated from BAL cultures, vaccine serotypes were found significantly less often in children who had received pneumococcal conjugate vaccines.⁴² Finally, culturing two or more bacterial pathogens was reported frequently (22–48%) in several studies,^{8,42,55,62} but how this influenced clinical presentation or outcomes was not commented upon.

Viruses

Surprisingly, only one study has examined systematically for the presence of respiratory viruses in children with PBB.³³ This study reported higher rates of virus detection by PCR in the BAL fluid from 104 PBB cases than from 49 other chronic respiratory disease controls

(38% vs. 9%; OR = 6.3, 95%CI 2.1–19.1). The most common virus identified was adenovirus (AdV),³³ which upon genotyping belonged predominantly to AdV species C.⁶⁷ Children in the PBB AdV positive group were, however, significantly younger than those in the PBB AdV negative group (median 17 (IQR 12–22) vs. 26 (IQR 15–56) months; $P = 0.001$) and the positive association found between AdV detection and bacterial infection disappeared after adjusting for age.⁶⁷ An extended panel for 17 viruses was undertaken in a subset of 27 children, which found rhinovirus in 11 (41%) and human bocavirus and human coronavirus in 1 (4%) each of the participants.³³ The prevalence of these other viruses was similar in the control group.³³ Other studies also report a similar prevalence of these viruses in asymptomatic children.⁶⁸

Microbiota

The microbiota of the lungs of children with PBB has been examined in a single cross-sectional study.⁶⁹ Using bacterial 16S rRNA gene pyrosequencing, phylogenetic analysis and ecologic statistical tools, the core microbiota in the sputum and BAL specimens from 60 children (PBB $n = 12$, bronchiectasis = 19, CF = 25, controls = 4) and 68 adults (bronchiectasis = 38, CF = 30) with chronic pulmonary disorders were compared.⁶⁹ 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 (Fig. 2a).⁶⁹ However, while all three pediatric cohorts shared remarkably similar core microbiota, with *H. influenzae* making the greatest contribution to the observed similarity, the lung microbiota in children were significantly different from that observed in adults with CF and bronchiectasis (Fig. 2b).⁶⁹ These findings suggest that chronic airway infections begin similarly with defective airway clearance of otherwise normal airway microbiota, but over time with antibiotic treatment and perhaps the effects of the underlying disease the microbiota in these disease groups progressively diverge from one another.

Biofilm

Biofilms may be another speculative reason for the chronicity and the need for longer antibiotic courses for PBB treatment. Our group first documented biofilms in the BAL fluid of children with bronchiectasis,⁷⁰ and our preliminary data show that biofilms are also present in the BAL fluid of children with PBB. None of these children had *Pseudomonas aeruginosa*.

Immunity, Inflammation, and Associated Signalling Pathways

A prospective study showed that children with PBB have higher and more prolonged “children’s acute

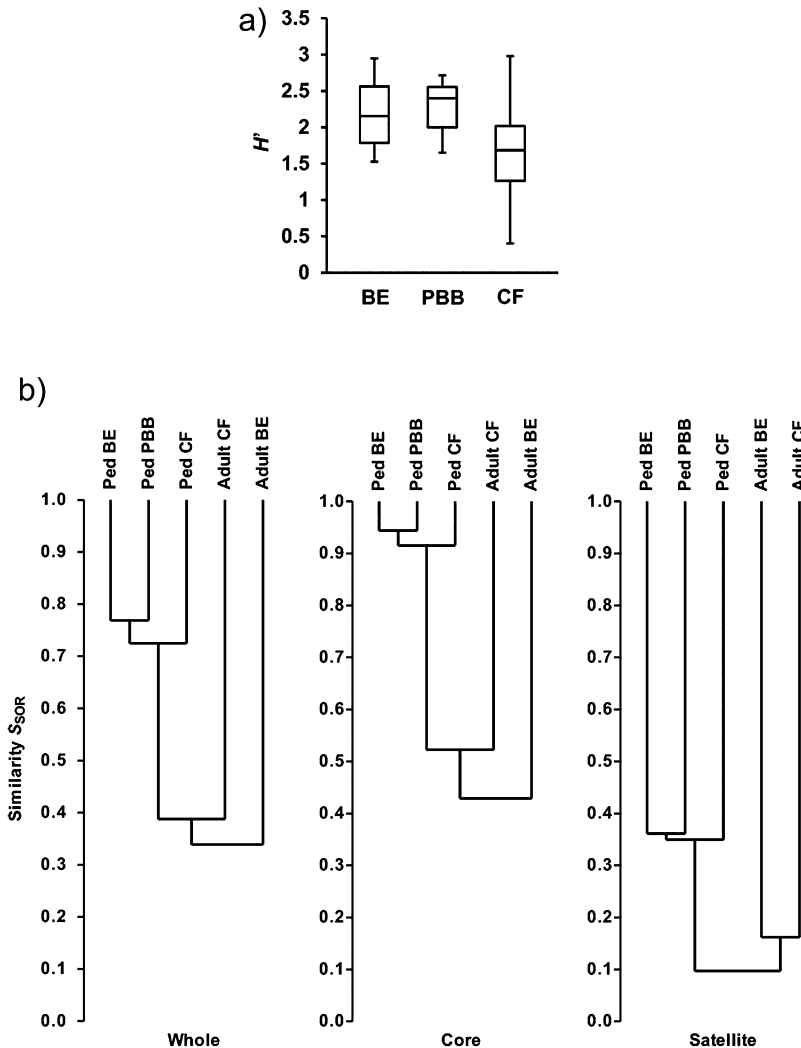


Fig. 2. (Reprinted with permission of the American Thoracic Society. Copyright 2015 American Thoracic Society. van der Gast CJ et al. Three Clinically Distinct Chronic Pediatric Airway Infections Share a Common Core Microbiota. *Ann Am Thorac Soc* 2014;11:1039–1048. The *Annals of the American Thoracic Society* is an official journal of the American Thoracic Society). **2a:** Shannon–Weiner index (H'), which reflects the diversity of species present, depicting that protracted bacterial bronchitis (PBB) was similar to bronchiectasis (BE), but significantly different to cystic fibrosis (CF). Species diversity is richer in the PBB and BE groups. **2b:** Dendrograms of community membership similarity between the pediatric (ped) BE, PBB, and CF bacterial metacommunities and compared with adult CF and BE metacommunities. Given are whole, core, and satellite microbiota. Metacommunity profiles were compared using the Sørensen index of similarity and unweighted pair-group method using arithmetic mean (UPGMA).⁶⁹ Sørensen index varies from 0 (no similarity) to 1 (entirely similar) and accounts for the number of species present in each community and those that are shared.⁶⁹

respiratory illness and flu” (CARIF) scores⁷¹ with respiratory illnesses than healthy controls and children with asthma.⁷² PBB is also characterized by airway neutrophilia and high densities of common respiratory pathogens in their lower airways,^{8,33} suggesting that host immunological responses play a role in its pathogenesis.

Immunity

Both our initial⁸ and subsequent studies³³ describing systemic immunity in children with PBB have confirmed

the absence of an overt immunodeficiency. Serum levels of IgA, IgM, IgG, and IgE are normal and responses to protein (tetanus) and conjugated protein-polysaccharide (*H. influenzae* type b) vaccines are robust.³³ Humoral immunity, therefore, seems to be intact and no abnormalities in lymphocyte subsets have been found.³³

Innate immunity among children with PBB also appears to be activated rather than deficient.^{57,73} In one study,⁵⁷ innate immunity was assessed by examining toll-like receptors (TLRs). TLR-2 and TLR-4 are signaling

pattern recognition receptors that play a key role in responding to invading bacteria, especially gram-positive and gram-negative bacteria, respectively.⁷⁴ Compared to controls, BAL samples from children with PBB had significantly elevated TLR-2 and TLR-4 mRNA relative expression⁵⁷ (Table 6). Whether the BAL of children with PBB had reduced TLR expressions levels prior to early infection is unknown. An opportunistic study of children undergoing gastroscopy for gastrointestinal symptoms, found that TLR-4 mRNA relative expression was significantly lower in children with chronic cough and BAL evidence of bacterial infection ($\geq 10^4$ CFU/ml) than those without infection.⁷⁵

A second larger study evaluated pulmonary levels of three innate immunity components (human β -defensin 2 [hBD2], mannose-binding lectin [MBL], and surfactant protein-A [SP-A]) and the cytokine production of lipopolysaccharide-stimulated BAL cells in 61 children with current PBB, 20 with previously treated PBB and 21 disease controls undergoing bronchoscopy for airway assessment of stridor.⁷³ Median hBD2 and MBL levels were significantly higher in the current than previous PBB group and controls (Table 6). SP-A levels and cytokine production of stimulated BAL cells were similar among all the groups.⁷³

In a preliminary study, the systemic immune responses (cytokine production) against NTHi in 20 children with PBB were similar to 20 healthy control subjects,⁷⁶ however, the caspase-1 dependent, proinflammatory pathways were activated in PBB children.

Deficient efferocytosis (impaired clearance of apoptotic cells by alveolar macrophages)⁷⁷ is another possible mechanism in PBB pathobiology. It is postulated that the apoptotic cells may undergo secondary necrosis with pro-inflammatory effects contributing to the perpetuation of chronic inflammation, infection and tissue damage.^{78,79} Support for this hypothesis comes from a small BAL-based study showing significantly decreased ability of alveolar macrophages to phagocytose apoptotic bronchial cells and NTHi in children with bronchiectasis (n = 55) and PBB (n = 13) compared controls (n = 13).⁸⁰ For both types of impaired phagocytosis, values in children with PBB were intermediate to those with BE and controls⁸⁰ (Table 4).

Inflammation and Associated Signaling Pathways

Neutrophil influx is an important feature of the innate immune response. We and others have described intense airway neutrophilia (median 40–44%) in children with PBB,^{8,19,57} but whether this is a pathologically disproportionate response to infection is unknown.

There are also marked pro-inflammatory mediator responses (IL-8, matrix metalloproteinase (MMP)-9 active, IL-1 β) that correlate with BAL neutrophil percentages.^{56,81} Median BAL levels of IL-8 and MMP-9 in children with PBB were 5.4- to 19.1-fold higher than in controls and in those whose cough resolved without specific treatment.⁵⁷ Levels of IL-8 and MMP-9 were also significantly correlated ($r = 0.61, P < 0.0001$).⁵⁷

We have shown in experimental and validation cohorts that children with PBB have significantly higher BAL fluid levels of IL-1 β , α -defensin, IL-1 pathway members, and CXCR2 gene and protein expression than non-PBB disease controls.⁵⁶ IL-1 β levels correlated with duration and severity of cough,⁵⁶ and with elevated expression of α -defensins 1–3 in PBB cases. In those with recurrent PBB (>3 in the next 12 months), the baseline (at bronchoscopy) gene expression of the IL-1 β signaling molecules pellino-1 and IL-1 receptor associated kinase (IRAK)-2 were significantly higher than those without recurrent PBB, suggesting this pathway’s involvement in recurrence.⁵⁶

Other innate immune factors related to wet cough and airway neutrophilia, but not specifically studied in children with PBB include the pattern recognition receptor for advanced glycation end-products (RAGE), which plays an important, but complex role in many inflammatory responses within the lungs.⁸² Soluble RAGE (sRAGE) levels within the circulation and BAL fluid were associated with age and airway inflammatory cell profiles (lower sRAGE in airway neutrophilia), highlighting a potentially important role for sRAGE in pediatric lung disease.⁸²

Association With Large Airway Lesions

Older studies have showed an association among airway lesions, chronic cough,^{83,84} and chronic bronchitis.³¹ While some clinicians believe tracheo-bronchomalacia

TABLE 6—Innate Immunity Markers From Two Different Cohorts of Children^{57,73}

Variable	Median (IQR)		P-value
	PBB	Controls	
TLR-2 mRNA relative expression	2.0 (1.1–2.5)	0.9 (0.7–1.3)	0.013
TLR-4 mRNA relative expression	2.4 (2.2–3.7)	2.0 (1.6–2.4)	0.009
Human β -defensin 2, pg/ml	164.4 (0–435.5)	3.6 (0–126)	0.018
Mannose-binding lectin, ng/ml	1.7 (0.4–4)	0.4 (0.02–79)	0.013

IQR, interquartile range; mRNA, messenger RNA; PBB, protracted bacterial bronchitis; TLR, toll-like receptor.

causes chronic cough, it is more likely that infection predisposes the individual to prolonged, inefficient airway clearance. Since the cough resolves once the underlying infection is treated, this suggests malacia has a limited causative role.⁸ Nevertheless, tracheo-bronchomalacia impairs airway clearance,⁸⁵ increasing the likelihood of persistent lower airway infection and inflammation. Tracheo-bronchomalacia is also found commonly in children with PBB.^{8,19} 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^{86,87}). One retrospective study reported tracheo-bronchomalacia was present in 52/74 (74%) children with PBB.¹⁹ 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).³³ Nevertheless, these proportions are higher than estimates for the general population (1 in 2,100)³¹ and there is little doubt that children with tracheo-bronchomalacia have a higher frequency of respiratory infections and symptoms.^{88,89}

THE OVERLAP BETWEEN PBB, CSLD, AND BRONCHIECTASIS

In 2008, we proposed a paradigm (Fig. 3) where PBB, CSLD, and bronchiectasis shared common underlying pathobiologic mechanisms and progressed variably along an increasing spectrum of severity.⁹ The current evidence

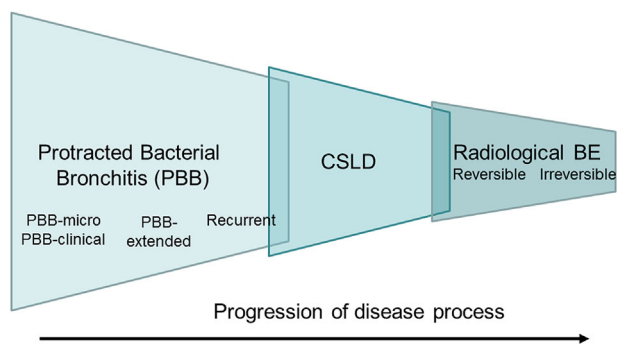


Fig. 3. (Modified with permission from Chang AB, Redding GJ, and Everard ML. (2008), Chronic wet cough: protracted bronchitis, chronic suppurative lung disease and bronchiectasis. *Pediatr Pulmonol*;43:519–531; doi: 10.1002/ppul.20821) Using the pathobiologic model, protracted bacterial bronchitis (PBB), chronic suppurative lung disease (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.

suggests that this paradigm still remains clinically useful, ensuring that children with bronchiectasis are not missed. PBB overlaps with CSLD, which in turn overlaps with radiographic-confirmed bronchiectasis.⁹ Children with established bronchiectasis would have had CSLD, at some stage earlier in the disease process, while those with CSLD would have had PBB previously.

The potential for injury with persistent infection and inflammation is probably more important in the growing and developing lungs of young children than in the mature lung. This is supported by animal and human studies where early lung insults are most likely to have adverse long-term effects.^{90–92} As children with PBB are typically very young,^{8,9} it is plausible that recurrent PBB episodes are a risk factor for developing CSLD or bronchiectasis.

The similarities between these three conditions include chronic wet cough, \pm rattling breathing, or “rattles,” as well as impaired regional muco-ciliary clearance, endobronchial bacterial infection and neutrophilic airway inflammation. The core microbiota⁶⁹ and cultured classical respiratory bacterial pathogens are also similar in PBB³³ and pediatric CSLD and bronchiectasis.^{16,67} The key differences between these three entities lie in the severity of symptoms and signs, the response to 2–4 weeks of oral antibiotics, chest high-resolution CT scan findings, and consequent management. CSLD is differentiated from bronchiectasis only by lacking the radiographic signs of bronchiectasis on chest high-resolution CT scans.^{9,93}

SUMMARY

PBB is recognized increasingly as a common cause of chronic wet cough in children. In most PBB cases, 2 weeks of oral antibiotics are sufficient, but some will require a 4-week course. The pathobiology of PBB involves lower airway bacterial infection with intense airway neutrophilia accompanied by increased inflammatory markers involving IL-1 β signaling. The pulmonary innate immune system is upregulated, but so far no systemic or local immune dysfunction has been identified, other than of decreased efferocytosis and phagocytosis of NTHi.⁸⁰ Recurrent episodes (>3 per year) occur in some, and these children have increased gene expression of the IL-1 β signaling molecules pellino-1 and IRAK-2, and are more likely to have bronchiectasis diagnosed within the next 2 years. Hence, those with PBB should be monitored closely.

The Road Ahead

In addition to consolidating the preliminary data presented above, other important research questions remain to be answered in this surprisingly common, but poorly recognized pulmonary disorder. Some of these

TABLE 7— Research Priorities for PBB

Epidemiology

- Determining the burden of disease (e.g., incidence, prevalence, QoL, economic cost) in the general community
- Establishing modifiable risk factors
- Ascertaining the long-term outcomes of children with recurrent and non-recurrent episodes
- Clarifying whether children with PBB-extended have different long term outcomes

Pathobiology

- Identifying the underlying developmental and pathobiologic mechanisms
- Uncovering host biological susceptibility factors, including the role of airway malacia
- Describing the frequency and mechanisms of virus-induced PBB episodes

Management

- Detecting a biomarker that can predict response to antibiotics and risk of recurrence
- Determining if longer courses of antibiotics of up to 4 weeks duration reduce recurrences
- Performing multicenter intervention trials to help identify those requiring longer antibiotic courses of up to 4 weeks evaluating the role of prophylactic antibiotics in patients with frequent (>3 annually) recurrences, but still lacking disease pointers and evidence of bronchiectasis

epidemiology, pathobiologic, and management research goals are listed in Table 7.

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