ERS statement on protracted bacterial bronchitis in children

Ahmad Kantar[1,13], Anne B. Chang[2,3,4,13], Mike D. Shields[5], Julie M. Marchant[2,3], Keith Grimwood[6], Jonathan Grigg[7], Kostas N. Priftis[8], Renato Cutrera[9], Fabio Midulla[10], Paul L.P. Brand[11] and Mark L. Everard[12]

Affiliations: [1]Pediatric Asthma and Cough Centre, Istituti Ospedalieri Bergamaschi, University and Research Hospitals, Bergamo, Italy. [2]Dept of Respiratory and Sleep Medicine, Lady Cilento Children's Hospital, Brisbane, Australia. [3]Centre for Children's Health Research, Institute of Health & Biomedical Innovation, Queensland University of Technology, Brisbane, Australia. [4]Child Health Division, Menzies School of Health Research, Charles Darwin University, Casuarina, Australia. [5]Dept of Child Health, Queen's University Belfast, Belfast, UK. [6]Menzies Health Institute Queensland, Griffith University and Gold Coast Health, Gold Coast, Australia. [7]Blizard Institute, Queen Mary University London, London, UK. [8]Third Dept of Paediatrics, University General Hospital Attikon, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece. [9]Respiratory Unit, University Dept of Pediatrics, Bambino Gesu' Children's Research Hospital, Rome, Italy. [10]Dept of Pediatrics and Infantile Neuropsychiatry, "Sapienza" University of Rome, Rome, Italy. [11]Isala Women and Children's Hospital, Zwolle, the Netherlands. [12]School of Pediatrics and Child Health, University of Western Australia, Princess Margaret Hospital, Subiaco, Australia. [13]Both authors contributed equally.

Correspondence: Ahmad Kantar, Pediatric Asthma and Cough Centre, Istituti Ospedalieri Bergamaschi, University and Research Hospitals, via Forlanini 15, Ponte San Pietro, Bergamo, Italy. E-mail: kantar@centropediatricotosse.com

ABSTRACT This European Respiratory Society statement provides a comprehensive overview on protracted bacterial bronchitis (PBB) in children. A task force of experts, consisting of clinicians from Europe and Australia who manage children with PBB determined the overall scope of this statement through consensus. Systematic reviews addressing key questions were undertaken, diagrams in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement constructed and findings of relevant studies summarised. The final content of this statement was agreed upon by all members.

The current knowledge regarding PBB is presented, including the definition, microbiology data, known pathobiology, bronchoalveolar lavage findings and treatment strategies to manage these children. Evidence for the definition of PBB was sought specifically and presented. In addition, the task force identified several major clinical areas in PBB requiring further research, including collecting more prospective data to better identify the disease burden within the community, determining its natural history, a better understanding of the underlying disease mechanisms and how to optimise its treatment, with a particular requirement for randomised controlled trials to be conducted in primary care.

Introduction

Cough is the most common presenting symptom in those seeking primary healthcare [1]. Within this large group of patients are children similar to the child described in box 1 in having a chronic (>4 weeks) cough, where there may be considerable, but often unrecognised, morbidity adversely impacting upon their quality of life (QoL) [2, 3]. Among children referred to a specialist respiratory clinic because of chronic cough, >80% had sought medical advice on five or more occasions during the preceding 12 months and 53% had been taken to the doctor >10 times during the same period [2].

Protracted bacterial bronchitis (PBB) is characterised by an isolated chronic wet or productive cough without signs of another cause, and usually responds to 2 weeks of an appropriate oral antibiotic. The term was first described as a diagnostic entity by the Brisbane group in 2006 [4] and was recognised then in guidelines as a cause of chronic wet cough in children [5, 6]. Although the true prevalence of PBB within the community is unknown, single and multicentre studies in Australia [4, 7] and Turkey [8, 9] diagnosed PBB in 11–41% of children referred to specialist respiratory clinics, where it was found to be one of the most common causes of chronic cough.

PBB is not a new entity and PBB-like conditions were reported during the last century [10]. In the 1940s the possibility of a link between chronic bronchitis and bronchiectasis was raised [11], including suggestions that this could be interrupted by intensive antibiotic therapy [11, 12]. Later, in the 1980s, a retrospective review of 20 children with chronic bronchitis reported bronchoscopic evidence of bronchial wall inflammation, purulent bronchial secretions, containing mainly *Haemophilus influenzae*, and most improved following antibiotic therapy [13]. This report coincided with publication of Cole's [14] "vicious circle" hypothesis of chronic bacterial infection and inflammation causing bronchiectasis, which helped to provide a conceptual framework for PBB as a potential pre-bronchiectasis state in some children [15].

PBB is often misdiagnosed as asthma, resulting in inappropriate and often high doses of inhaled corticosteroids [7, 16]. Generic health-related (PedsQL [17]) and chronic cough-specific (PC-QoL) QoL scores of children with PBB were found to be similar to those recorded in children from other diagnostic groups (asthma, bronchiectasis and those whose chronic cough resolved without treatment) when the QoL measures were undertaken at the first presentation to respiratory specialists [7, 18], but normalised when the cough resolved [7].

Thus, while PBB-like descriptions are certainly not new, with the clinical features being well described in previous decades, it is now a distinct diagnostic entity and our knowledge of the clinical and pathobiological features has progressed rapidly in recent years. However, as studies of PBB have relied upon children presenting to hospital and specialist clinics, our understanding of the true underlying epidemiology and disease burden of PBB is limited by the absence of community data. This European Respiratory Society (ERS) task force position statement on PBB outlines current knowledge and provides a clinical profile, diagnostic indications and a therapeutic approach to this common disease in children. In addition, it highlights areas of future research.

Methodology

The ERS PBB task force team consisted of 11 members (general paediatricians and respiratory and infectious disease specialists) representing clinicians in Europe and Australia who manage children with chronic cough. ERS standardised procedures for conflict of interest declaration were followed. The key questions (KQ), framed in a patient intervention comparison outcome format, were developed by the group and distributed among four pairs of authors (online supplementary file 1). Author pairs undertook the systematic reviews based on the method used in the paediatric sections of the American College of Chest Physicians (ACCP) CHEST cough guidelines [19, 20] and the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (online supplementary figures S1–S7).

BOX 1   Case vignette

A 3-year-old male attends your clinic with his mother who is concerned about his persistent cough and "rattly breathing" that have both been present and unrelenting over the past 6 weeks. Upon taking the history, you learn that his symptoms were accompanied initially by a low-grade fever and nasal discharge, and while these resolved in 2 days and 7 days, respectively, his cough persisted. You identify that the cough is wet in nature. He is well grown, fully immunised and has no history of aspiration or recurrent sinopulmonary infections. There is no family history of chronic pulmonary disease, but the father smokes cigarettes outside the home. The child attends childcare. You confirm on examination the presence of a spontaneous wet cough. There are no signs of upper airway infection and no other abnormal physical findings are present. The chest radiograph shows only perihilar changes.

You consider that this child probably has protracted bacterial bronchitis (PBB). What is the evidence for the existence of PBB? How is it diagnosed and managed? What is its prognosis? What are the causes and risk factors and how can it be prevented?

The key questions (all related to children aged <18 years)

1) In children with chronic (>4 weeks) wet or productive cough unrelated to an underlying disease and without any specific cough pointers (see box 2),
   a) what is the evidence for PBB in clinical studies and clinical guidelines?
   b) what symptoms (including cough duration) and signs are used to diagnose PBB?
2) In children with chronic (>4 weeks) wet or productive cough without any specific cough pointers,
   a) what are the possible causes?
   b) which tests should be undertaken and when should they be referred for further investigations?
   c) what is the risk of harm in cases of delayed treatment and investigations?
3) In children with chronic (>4 weeks) wet or productive cough unrelated to an underlying disease and without any specific cough pointers, what bacteria are cultured from the lower airways?
4) In children with PBB, in addition to "classical" bacteriology, what else is known about the airway microbiology (viruses, virus–bacteria interactions and microbiome)?
5) In children with PBB, what is known about its pathobiology (risk factors, underlying mechanisms, cellular pathways, immunity and airway malacia)?
6) In children with chronic (>4 weeks) wet or productive cough unrelated to an underlying disease and without any specific cough pointers,
   a) how effective are antibiotics at improving clinical outcomes (*e.g.* cough resolution)?
   b) what is the most suitable antibiotic?
   c) for how long should antibiotics be prescribed?
   d) does treatment dose and duration influence risk of recurrence in the following 12 months?
7) In children with chronic (>4 weeks) wet or productive cough unrelated to an underlying disease and without any specific cough pointers,
   a) what is the role of prophylactic antibiotics?
   b) what is the risk of antibiotic resistance?
   c) how should recurrences be managed?

Searches, data extraction and summaries

Searches relating to the key questions were undertaken by four pairs of task force members, whereby one member of each reviewer pair used a standard format (online supplementary file 1) updated from and based on the ACCP's CHEST cough paediatric guidelines [19, 20]. The search criteria used for each key question are presented in online supplementary file 1. Both reviewers within each pair independently reviewed all abstracts and agreed upon which full-text articles to retrieve to assess for potentially eligible studies. It was decided that disagreements not resolved by consensus would be adjudicated by a third reviewer (AK). Risk of bias criteria was not undertaken as this was undertaken in the previous systematic review [20], and no new randomised controlled trials (RCTs) were identified in our searches for this systematic review. For cohort studies, data were extracted by a single reviewer and checked by another reviewer. In cohort studies, we reported on the study's setting, number enrolled and completing the study, inclusion and exclusion criteria and main results relating to the key questions.

Summaries of the data relating to each key question were presented to the entire group at a face-to-face meeting in April 2016. Following a review of the data and discussions, this document and statements were formulated. Consensus was defined *a priori* as agreement by >80% of the group. Key findings from the key questions and task force statements are presented below with additional details presented in the online supplementary files. Studies had components common to almost all the key questions and they are summarised in table 1.

Definition of PBB (KQ1)

As outlined recently [57], the task force considers a reliable definition of PBB for day-to-day clinical practice when all three of the following criteria are fulfilled. 1) Presence of continuous chronic (>4 weeks' duration) wet or productive cough; 2) absence of symptoms or signs (*i.e.* specific cough pointers) suggestive of other causes of wet or productive cough (see box 2); and 3) cough resolved following a 2–4-week course of an appropriate oral antibiotic.

BOX 2   Specific cough pointers [5, 6, 21]

Symptoms: chest pain, history suggestive of inhaled foreign body, dyspnoea, exertional dyspnoea, haemoptysis, failure to thrive, feeding difficulties (including choking/vomiting), cardiac or neurodevelopmental abnormalities, recurrent sinopulmonary infections, immunodeficiency or epidemiological risk factors for exposure to tuberculosis
Signs: respiratory distress, digital clubbing, chest wall deformity or auscultatory crackles
Tests: chest radiographic changes (other than perihilar changes) or lung function abnormalities

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TABLE 1 Summary of studies found in the systematic reviews of the key questions

First author, publication year; country [reference] questions	Setting, study design	Inclusion and exclusion criteria or definitions	Subjects enrolled/completed, age, length of follow-up	Main aim(s) of study	Relevant to key
Prospective studies					
ALUOCH, 1984; Kenya [22]	Single centre, general OPD, cross-sectional	Age >6 years, first attendance with main complaint of cough, sputum (>1 month) or haemoptysis Exc: NR	n=601; with sputum n=601 Median age NR and study included adults FU: NR	Yield of tuberculosis from systemic examination of first presentation	2
ASILSOY, 2008; Turkey [8]	Single centre, paediatric OPD, cohort	>4 weeks cough Exc: NR	n=108/n=108 Mean (range) age 8.4 (6–14) years FU: NR	"Evaluate children with cough in accordance with the 2006 ACCP guidelines" [8]	1, 2, 6
BAINES, 2014; Australia [23]	Single centre, respiratory OPD, exploratory and validation cohorts	PBB (clinical definition); resolved PBB (previous PBB, but no cough at FB)	Exploratory: PBB n=21, controls n=33 Mean age 2.3 and 9.7 years, respectively Validation: PBB n=36, controls n=11 Mean ages 2.0 and 0.7 years, respectively	To evaluate the IL-1 and TNF-α/NF-κB pathways and mediators in two cohorts of PBB and control children	1, 2, 3, 5
CHANG, 2005; Australia [24]	Single centre, respiratory OPD, cross-sectional	Children undergoing FB without a known underlying respiratory Dx	n=106 Median (IQR) age 2.6 (5.7) years FU: NR	Compare 1) cough quality (wet/dry and brassy/non-brassy) to FB findings of secretions and tracheomalacia, respectively; 2) parent's *versus* clinician's evaluation of cough quality (wet/dry)	2
CHANG, 2006; Australia [25]	Single centre, respiratory OPD, cross-sectional	Children undergoing FB without a known underlying respiratory Dx	n=106 Median (IQR) age 2.6 (5.7) years FU: NR	To examine the relationship between the amount of secretions seen at bronchoscopy with airway cellularity and microbiology	3
CHANG, 2012; Australia [26]	Single centre, respiratory OPD, cross-sectional	PBB (chronic wet cough, response to antibiotics with resolution of cough within 2 weeks and absence of signs or symptoms of other disease); PBB well (previous PBB, but no cough upon FB)	Current PBB n=61, PBB well n=20, controls n=21 Age 2.5±2.3 years, 4.2 ±3.0 years, 2.2±2.8 years, respectively FU: NR	To determine whether BAL levels of hBD2, SPA and MBL 1) differed between children with current PBB, PBB well and controls; 2) were related to airway neutrophilia and infection	1, 2, 3, 5
CHANG, 2013; Australia [27]	Multicentre, respiratory OPD, RCT	Age <18 years, >4 weeks cough, newly referred Exc: known chronic respiratory illness	n=270/n=253 Age 4.5±3.7 years FU 12 months for Dx, 6 months post-Dx	RCT to determine if Mx according to a standardised clinical Mx pathway improves clinical outcomes	2

TABLE 1 Continued

First author, publication year; country [reference] questions	Setting, study design	Inclusion and exclusion criteria or definitions	Subjects enrolled/completed, age, length of follow-up	Main aim(s) of study	Relevant to key
CHANG, 2015; Australia [28]	Multicentre, respiratory OPD, cohort	Age <18 years, >4 weeks cough, newly referred Exc: chronic respiratory illness	n=346/n=326 Age 4.5±3 years FU 12 months for Dx, 6 months post-Dx	In children newly referred for chronic cough, to describe data relating to specific cough pointers of the three most common aetiologies	1, 2
COREN, 1998; UK [29]	Single centre, general OPD, cross-sectional	All chest CT scans undertaken over 12 months Exc: NR	102 children had 106 CT scans Median (range) age 5 years (7 weeks–15 years) FU: NR	To determine whether use of paediatric chest CT scans was appropriate (new Dx and how it influenced Mx)	2
DARELID, 1993; Sweden [30]	3 centres, paediatric OPD, open RCT	Age 0.5–6 years, persistent cough >10 days Exc: pneumonia, allergy, acute otitis media, tonsillitis, cardiac disease, suspected pertussis	n=88/n=87# Median age 13–24 months FU 3 months	Whether 7 days of erythromycin clinically improves children aged 0.5–6 years with a cough >10 days duration	1, 6
DE BAETS, 2012; Belgium [31]	Dual-centre, respiratory OPD, cross-sectional	"Persistent respiratory symptoms, productive cough, bronchorrhoea and wheezing for ⩾3 months" Exc: premature, failure to thrive, CF, prolonged intubation, tracheotomy, dysmorphic, neurology, cardiac problems or CXR consolidation	n=124 Median (IQR) age 10 (7–14) months FU: NR	Description of results of diagnostic investigations in children with persistent respiratory symptoms despite regular asthma Rx	2, 3
GEDIK, 2015; Turkey [32]	Single centre, paediatric or allergy department, cohort	Age <17 years, persistent cough >4 weeks Exc: known chronic respiratory, neuromuscular, growth or cardiac problems, genetic syndromes, prematurity	n=563/n=563 Age 5.4±3.8 years FU: NR	The evaluation of children with chronic cough and aged-based aetiological factors	1, 2, 3, 5
GOTTFARB, 1994; Sweden [33]	3 centres, paediatric OPD, double-blinded RCT	Lower respiratory tract infection with cough >10 days, >11 coughing attacks in 24 h Exc: pneumonia, acute otitis media, clinical suspicion of pertussis	n=52/n=52 Median age 2.6–2.7 years FU 14 days	"To investigate the nasopharyngeal flora of children with persistent cough and the effects of treatment with amox-clav" [33]	1, 6
GRISSELL, 2007; Australia [34]	Single centre, gastroenterology OPD, non-bronchoscopic BAL	Children undergoing upper GI endoscopy, cough questionnaire Excl: neurodevelopmental abnormalities, underlying cardiorespiratory disease, primary aspiration Group defined on positive bacterial culture, not PBB	n=69 children n=10 positive bacterial growth from non-bronchoscopic BAL, control group n=59	To examine the expression of neurokinins, neurotrophins and TLRs in the lungs of children	5

TABLE 1 Continued

First author, publication year; country [reference] questions	Setting, study design	Inclusion and exclusion criteria or definitions	Subjects enrolled/completed, age, length of follow-up	Main aim(s) of study	Relevant to key questions
HEINO, 1990; Finland [35]	Single centre, respiratory OPD, cross-sectional	Chronic productive cough (>3 months) unresponsive to oral antibiotics and oral bronchodilators	n=7 Age range 5–11 years	To describe the ultrastructural nature of epithelial damage in respiratory symptoms	2
HODGE, 2016; Australia [36]	Single centre, respiratory OPD, cross-sectional	PBB (microbiology); controls (no cough and FB undertaken for other reasons, e.g. stridor); BE (CT scan defined with clinical symptoms)	PBB n=13, BE n=55, controls n=13 Median (IQR) age PBB 6.5 (1.6–14) months, BE 22 (14–33) months, controls 5.5 (4–9.9) months	1) To quantify phagocytosis of airway apoptotic cells and NTHi by alveolar macrophages in children with PBB and BE; 2) to determine if phagocytic capacity is associated with clinical variables, and patterns of airway inflammation	1, 3, 5
KARABEL, 2014; Turkey [37]	Single centre, respiratory OPD, cohort	>4 weeks cough Exc: neuromuscular or cardiac syndromes, respiratory infection lasting 4 weeks	n=270/n=270 Mean (range) age 6.5 (7 months–17 years) years FU 12 months	To determine the aetiology of chronic cough in children, using the ACCP guidelines	1, 2, 6
MARCHANT, 2006; Australia [4]	Single centre, respiratory OPD, cohort	>3 weeks cough, age <18 years and newly referred Exc: known chronic disease	n=108/n=103 Median (IQR) age 2.6 (1.2–6.9) years FU 12 months	In children with chronic cough, to 1) evaluate the use of an adult-based algorithmic approach in management; 2) describe aetiology	1, 2, 3, 5, 6
MARCHANT, 2008; Australia [38]	Single centre, respiratory OPD, cross-sectional	PBB (chronic wet cough (>3 weeks), BAL bacterial culture (⩾10^5 CFU·mL^{-1}) and response to antibiotics (cough resolved in 2 weeks)); other aetiologies (other chronic cough aetiologies in cohort [4]), controls (children with stridor without chronic cough)	PBB n=38, other Dx n=25, SR n=22, controls n=15 Median (IQR) age 2.4 (0.9–4.2) years, 2.6 (1.1–9.6) years, 3.8 (0.9–6.8) years, 2.8 (0.6–9.8) years, respectively	To 1) describe the clinical profile, airway cellularity and promoters of neutrophilic inflammation in BAL fluid of children with PBB compared to children with other aetiologies and controls without cough; 2) explore selected innate immunity signalling receptors, specifically TLR-2 and -4	1, 2, 3, 5
MARCHANT, 2012; Australia [39]	Single centre, paediatric and respiratory OPD, double-blinded RCT	Age 0.5–18 years, doctor-observed wet cough >3 weeks Exc: chronic lung, cardiac or neurodevelopmental disease, antibiotics in the past 2 weeks, acutely unwell	n=50/n=47 Mean (IQR) age 1.8–2.8 (0.9–5.3) years FU 2 weeks	Efficacy of 2 weeks of oral amox-clav (compared with placebo) in achieving cough resolution in children with chronic wet cough	1, 3, 5, 6
SEEAR, 1997; Canada [40]	Single centre, respiratory OPD, cross-sectional	Chronic (⩾3 months) productive or rattly cough, with or without wheezing; controls: children with asthma Exc: known causes of productive cough	n=81/n=81, controls n=60 Mean (range) age 8.4 (6–14) years FU: NR	In children with chronic productive cough, "1) do such diagnostic orphans exist?; 2) if so, can they be classified in a clinically useful manner?"	2
USTA GUC, 2014; Turkey [9]	Single centre, paediatric allergy OPD, cohort	Inclusion criteria NR Exc: cardiac or chronic disease, prematurity, neurodevelopmental disorders, chest wall deformity, smoking, clubbing, spirometry not possible	n=156/n=156 Age 8.4±2.6 years FU: maximum 18 months for Dx, post-Dx NR	"To evaluate assessment and Mx of chronic cough in children according to the British Thoracic Society guidelines"	1, 2, 6

Continued

TABLE 1 Continued

First author, publication year; country [reference] questions	Setting, study design	Inclusion and exclusion criteria or definitions	Subjects enrolled/completed, age, length of follow-up	Main aim(s) of study	Relevant to key
VAN DER GAST, 2014; USA and Australia [41]	Multicentre, respiratory OPD, cross-sectional	PBB (clinical definition); BE (Dx on CT scan); CF (positive sweat test)	PBB n=12, BE n=19, CF n=25 Age 8.9±4.7 years, 2.3±1.7 years, 12.5±3.5 years, respectively	To compare 1) the core and satellite microbiota in cohorts of children with different diseases; 2) the respiratory meta-communities in PBB and paediatric and adult CF and BE cases	1, 2, 3
WURZEL, 2014; Australia [42]	Single centre, respiratory OPD, cross-sectional	Children undergoing FB Children were categorised into wet cough, dry cough, no cough groups Exc: CF	Wet cough n=143 Median (IQR) age 26 (15–60) months Dry cough n=18 Median (IQR) age 66 (31–159) months FU: NR	To examine the relationships between cough nature, lower airway infection and severity of neutrophilic airway inflammation	2, 3, 4, 5
WURZEL, 2014; Australia [43]	Single centre, respiratory OPD, cross-sectional	PBB (clinical definition); controls (chronic respiratory symptoms, but not PBB or CSLD)	PBB n=104, controls n=21 Median (IQR) age 19 (12–30) months and 20 (8–63) months, respectively	To provide extensive clinical, laboratory and BAL characterisation of PBB	1, 2
WURZEL, 2014; Australia [44]	Single centre, respiratory OPD, cross-sectional	PBB (clinical definition); BE: Dx on CT scan	PBB n=159, BE n=112 Median (IQR) age PBB with AdV 17 (12–22) months, PBB without AdV 26 (15–56) months	To identify 1) the prevalence of AdV; 2) diversity of genotypes and species; 3) whether presence of AdV increased the odds of bacterial co-infection	1, 3, 4
Retrospective studies					
CHANG, 2002; Australia [45]	Respiratory OPD, chart review	CSLD (>4 months wet cough), indigenous children	n=65, bronchoscopy n=33 (n=28 out of 33 radiological BE) Median age 3.8 years	Children prospectively identified and charts reviewed retrospectively to describe airway abnormalities and relate these to chest HRCT scans	5
DONNELLY, 2007; UK [16]	Single centre, respiratory OPD, random review of clinic letters	"Persistent, wet cough present for 1 month that resolves with appropriate antibiotic Rx"	n=81 Median (range) age 3.8 (0.4–14.8) years FU: NR	To present "results of a retrospective review of outcomes in 81 randomly selected patients diagnosed with PBB"	1, 3, 6, 7
DOUROS, 2011; Greece [46]	Allergy-respiratory OPD, chart review	Chronic (>6 weeks) wet cough with FB undertaken for criteria¶ Exc: CF, immunodeficiency, neuromuscular disorder, aspiration	n=93 Age 5.8±3.6 years FU: NR	In children with chronic wet cough, 1) comparison of chest CT and FB in detecting airway abnormalities; and 2) exploration of radiological and FB/BAL associations	2, 3, 5

Continued

TABLE 1 Continued

First author, publication year; country [reference] questions	Setting, study design	Inclusion and exclusion criteria or definitions	Subjects enrolled/completed, age, length of follow-up	Main aim(s) of study	Relevant to key questions
GOYAL, 2014; Australia [47]	Single centre, respiratory OPD, chart and CT scan review	Chronic wet cough (>4 weeks) and having completed >4 weeks of oral antibiotics directed against likely respiratory bacteria Exc: asthma, CF, known BE or CT scans ordered by oncology, surgical, ICU or trauma services	n=144 (BE n=106) Median (range) age 4.7 (0.3–17) years FU: NR	"To determine whether a child with chronic wet cough and poor response to at least 4 weeks of oral antibiotics is more likely to have BE" (radiologically defined)	2, 6
KOMPARE, 2012; USA [48]	Single centre, respiratory and allergy OPD, bronchoscopy database review	Cough, wheeze or noisy breathing of >1 month without other diagnoses, infected BAL ($\geqslant 10^4$ CFU·mL^{-1}) and response to $\geqslant$2 weeks antibiotics	n=70 (cough n=51) Summary age NR FU: NR	Review of all infected BAL of children aged <5 years with cough, wheeze or noisy breathing lasting >1 month without other diagnoses, to determine if PBB present	1, 2, 3, 5, 6
LIM, 2012; UK [49]	Single centre, respiratory OPD, chart review	Chronic wet cough (>8 weeks) attending clinic over a 12-month period Exc: CF	n=96 children with wet cough, n=66 tested Age >2 years (summary NR) FU 18 months	"Prevalence of specific antibody deficiency in children with chronic wet cough" [49]	2
NARANG, 2014; UK [50]	Paediatric and respiratory OPD; 50 consecutive notes	Suspected PBB (ND)	n=50 Median (IQR) age 2.9 (1.7–4.4) years	Review BAL and CXR results, and assess the bacterial distribution across lung lobes	1, 2, 3
PRIFTIS, 2013; Greece and UK [51]	Respiratory OPD, dual centre, chart review	Children with chronic cough suspicious of PBB who had FB to confirm diagnosis	Greece n=18; England n=39 Median (range) age 4.8 (0.9–14.4) years	To 1) determine specific serotypes of Spn and NTHi in BAL samples; 2) compare Spn serotypes between the two countries and Spn vaccination	1, 2, 3
PRITCHARD, 2015; UK [52]	Single centre, paediatric or respiratory OPD	Antibiotic-responsive wet cough confirmed by a positive BAL culture (undefined)	n=43 (>1 lost to FU) Median (IQR) age 2.7 (1.5–4) years FU: 11.3 (8.3–14.7) months	Review of outcomes for children with antibiotic-responsive wet cough with positive BAL culture	1, 2, 3, 6, 7
ROTHER, 2015; Germany [53]	Single centre, tertiary hospital, chart review	NR with respect to key question; children with an established diagnosis of asthma, PCD, PBB, acute bronchitis, CF or pneumonia	PBB n=18 children	"To develop and test a questionnaire-based and data mining-supported tool providing diagnostic support for selected pulmonary diseases"	1
SMITH, 1985; USA [13]	Respiratory OPD, chart review	Presence of chronic bronchitis by FB evaluation Exc: CF or other abnormality that could contribute to chronic bronchitis	n=20 Mean (range) age 5.7 (0.5–15) years FU: NR	To investigate clinical, allergic, immunological and physiological characteristics of children with chronic bronchitis	1, 6

TABLE 1 Continued

First author, publication year; country [reference] questions	Setting, study design	Inclusion and exclusion criteria or definitions	Subjects enrolled/completed, age, length of follow-up	Main aim(s) of study	Relevant to key
THOMSON, 2002; Australia [54]	Respiratory OPD, chart review	Chronic cough >4 weeks	n=49 Median (range) age 39 (4 months–14 years) months	To determine 1) the referring and final diagnosis; and 2) the extent of the use of medications (asthma, GOR, antibiotics) prior to referral, and the side-effects encountered in children referred over a 12-month period to paediatric respiratory physicians for persistent cough	
WANG, 2015; China [55]	Single centre, hospitalised children in children's hospital; unclear how children were identified	Chronic cough (>4 weeks) without acute lower respiratory infection and no response to conventional Rx Exc: heart disease, immune-deficiency, pulmonary or bronchus dysplasia, neuromuscular disease, foreign body aspiration	n=66 with wet cough, of whom n=50 had PBB Median (range) age 10 (5.8–14[#]) months	To describe the clinical characteristics of children with PBB aged <3 years	1, 2, 3, 5
ZGHEREA, 2012; USA [56]	Single centre, respiratory OPD, chart review	Primary symptom of chronic (>4 weeks) wet cough who had FB Exc: CF, PCD, immunodeficiency, aspiration, asthma, genetic, known airway or neuromuscular disorders	n=197 Mean age: NR <3 years 55%; 3–7 years 36%; >7 years 9% FU: NR	"To determine the frequency of lower respiratory tract bacterial infections in children with chronic wet cough and to analyse the bronchoscopic findings"	2, 3, 5

Findings of the studies related to the key questions are outlined in online supplementary tables S1–S7. OPD: outpatients department; Exc: exclusion criteria; NR: not reported; FU: follow-up; ACCP: American College of Chest Physicians; PBB: protracted bacterial bronchitis; FB: flexible bronchoscopy; IL: interleukin; TNF: tumour necrosis factor; NF-κB: nuclear factor-κB; Dx: diagnosis; IQR: interquartile range; BAL: bronchoalveolar lavage; hBD: human β-defensin; SPA: surfactant protein A; MBL: mannose binding lectin; RCT: randomised controlled trial; Mx: management; CT: computed tomography; CF: cystic fibrosis; CXR: chest radiograph; Rx: treatment; amox-clav: amoxicillin-clavulanate; GI: gastrointestinal; TLR: toll-like receptor; BE: bronchiectasis; NTHi: nontypeable *Haemophilus influenzae*; SR: spontaneous resolution; CSLD: chronic suppurative lung disease; AdV: adenovirus; HRCT: high-resolution computed tomography; ICU: intensive care unit; ND: not defined; Spn: *Streptococcus pneumoniae*; PCD: primary ciliary dyskinesia; GOR: gastro-oesophageal reflux. [#]: it is unclear what these figures refer to, as the figure in the table differed from the text; [¶]: not all children in cohort had PBB, *i.e.* some had bronchiectasis.

The evidence for PBB in clinical studies and guidelines (KQ1)

The validity of each criterion was outlined in a recent review [57] and updated in this systematic review for duration of cough, in the absence of other symptoms and signs (online supplementary table S1.1a-b). The task force chose the 4-week diagnostic threshold based upon the inclusion criteria of the studies outlined in online supplementary table S1.1a-b. Other than the British Thoracic Society guidelines, all other national guidelines use a cough duration >4 weeks. However, the duration of cough may need adjusting if new data arise from prospective longitudinal observational studies. This was also recommended by the ACCP cough guidelines [20]. Such information is especially required from within the primary healthcare setting.

In prospective studies that are currently available (online supplementary table S1.1a), the mean or median duration of cough (at presentation) varied from 3 weeks [30] to as long as 6 months [4]. In the retrospective studies (online supplementary table S1.1b), the mean or median cough duration varied from 10 weeks [55] to 11 months [52]. The variability in central estimates and 95% confidence intervals of these studies was high, and even more so in the retrospective studies.

PBB as a diagnostic entity and cause of wet cough was well documented in prospective and retrospective studies (online supplementary table S1.1a-b). The response to oral antibiotics was used to help define PBB in almost all studies and national cough guidelines in children. However, the length of antibiotic courses to define PBB varied between studies. In all but one of the prospective studies, the duration of antibiotic treatment ranged from 10 days to 2 weeks (online supplementary table S1.1a). However, in the retrospective studies, the mean duration of antibiotic courses either varied from 17 days to 6–8 weeks or was unspecified (online supplementary table S1.1b).

Prospective studies were supported by other descriptive studies examining the associated bacteriology, inflammatory profiles and immune responses, providing further evidence of PBB as a diagnostic entity in children (online supplementary table S1.3a-b). While an adult version of PBB has not been clearly described, it has been suggested by some clinicians [58]. However, in this particular report [58], other than presence of wet or productive cough, other criteria such as duration of cough went undefined. Furthermore, another adult case series [59] described chronic productive cough unrelated to bronchiectasis, which responded only to intravenous antibiotics. However, this requirement for parenteral antibiotics is used to help to differentiate between chronic suppurative lung disease (CSLD) and PBB in children [15].

Although most current guidelines include PBB as a cause of chronic wet cough, variations exist in the definition of PBB, and some do not clearly define PBB (online supplementary table S1.2). While all definitions include the presence of chronic wet or productive cough, there is variability in the inclusion/exclusion of treatment response, microbial isolation (and method used). Some documents use BAL as a diagnostic criterion; other documents use microbiological findings, yet others just clinical criteria. As recently described [57], the original microbiology-based case definition [4] (also termed PBB-micro) criteria are as follows. 1) Presence of chronic wet cough (>4 weeks); 2) lower airway infection (recognised respiratory bacterial pathogens growing in sputum or at bronchoalveolar lavage at density of a single bacterial species >104 CFU·mL^{-1}); and 3) cough resolved following a 2-week course of an appropriate oral antibiotic (usually amoxicillin-clavulanate). PBB-clinical (modified clinical-based case definition [6, 57]) refers to presence of the following criteria. 1) Presence of chronic wet cough (>4 weeks); 2) absence of symptoms or signs of other causes of wet or productive cough; and 3) cough resolved following a 2-week course of an appropriate oral antibiotic (usually amoxicillin-clavulanate).

Typical profile of a child with PBB (KQ1)

Part of KQ1 reviewed what symptoms and signs (other than wet cough) were used (or found) in descriptions of children with PBB. The prospective studies (online supplementary table S1.3a) specified that no other symptoms (other than wet cough) or signs were present, although some had "parent-reported wheeze". The retrospective studies (online supplementary table S1.3b) commonly described wheeze or "noisy breathing" being present. Concomitant bronchodilator responsiveness was described in some studies, and was particularly common in one retrospective study (nine out of 20 children [13]), although this high proportion could have arisen through patient selection.

As summarised previously [57], while children with PBB were typically young (median age ranging from 10 months to 4.8 years), PBB was also recognised in older (age >12 years) children [7, 37, 51]. Most children with PBB lacked systemic symptoms, without evidence of sinusitis or ear disease [4, 43]. Compared to "disease controls" undergoing bronchoscopy for non-cough-related indications (e.g. stridor or apnoea), children with PBB were more likely to have attended childcare (OR 8.4, 95% CI 2.3–30.5), but their exposure to tobacco smoke (~30% [4, 43]) was similar to that of the "controls" [43]. Children with

PBB typically appeared well. They had normal growth and development, and lacked signs of underlying CSLD, such as digital clubbing, chest wall deformity or adventitial auscultatory chest findings [43], although occasionally a "rattly chest" and crackles were heard.

The prevalence of atopic features (eczema, systemic and airway eosinophilia, elevated IgE or positive radioallergosorbent test) was similar to children without PBB [43]. While many parents (41–81%) reported previous "ever wheeze" [16, 43], auscultation-confirmed wheeze by doctors was unusual.

The chest radiograph was normal or near-normal, showing only peribronchial changes [15, 28, 60]. When performed, both spirometry [28] and respiratory system reactance were also normal. While no RCTs have assessed whether ordering chest radiographs and/or spirometry in children with PBB or chronic wet cough enhanced management, a systematic review found "high-quality" evidence for improved clinical outcomes by adopting cough management protocols (or algorithms) in children with chronic cough aged <14 years [19]. Steps in these cough management algorithms included undertaking a chest radiograph and (when possible) spirometry [19]. When an abnormality in either the spirometry and/or the chest radiograph (other than peribronchial changes) in a child with chronic wet cough is present, additional investigations for an underlying cause are indicated (figure 1). PBB may co-exist with other diseases, (*e.g.* asthma and airway malacia), although for asthma, no studies including objective assessments of reversible airflow limitation to help determine whether there is any association have been undertaken.

Other causes of chronic wet cough in children (KQ2)

Data from KQ2 included evaluating causes of chronic wet or productive cough in children when they first present to doctors (online supplementary table S2.1). These other causes of chronic wet cough in children include, but are not limited to pertussis, tuberculosis, inhaled foreign body, bronchiectasis, cystic fibrosis, aspiration or congenital lung lesions. Most however have other symptoms and signs present (*i.e.* cough pointers [19, 28, 60]).

In addition, KQ2 addressed other investigations and the possible harm from having a prolonged wet cough (online supplementary tables S2.2 and 2.3). Data suggest that children should be referred for further investigations when specific cough pointers (box 2) are present or when the wet cough does not respond to 4 weeks of antibiotics. One study found that failure of the cough to respond to 4 weeks of antibiotics increased the chance of bronchiectasis being present (adjusted OR 20.9, 95% CI 5.4–81.8) [47]. Another study reported that the duration of chronic wet cough was significantly associated with increased risk of structural airway abnormalities and increased Bhalla scores on chest computed tomography (CT) scans [46].

Microbiology (KQ3 and KQ4)

Wet cough (KQ3)

The respiratory bacterial pathogens found in studies of chronic wet cough are summarised in online supplementary table S3.1. Overall, *H. influenzae* was the most common organism, found in 28–58% of children [4, 31, 32, 37, 42, 56], with *Streptococcus pneumoniae* (13–58%) and *Moraxella catarrhalis* (17–59%) the two other most frequently detected organisms. These results are similar to findings in PBB (online supplementary table S3.2).

PBB (KQ3)

The first study describing PBB detected commonly recognised respiratory pathogens (*H. influenzae* (47%), *Strep. pneumoniae* (35%) and *M. catarrhalis* (26%)) in BAL cultures at high bacterial loads ($\geqslant 10^5$ CFU·mL^{-1}) [4]. Subsequently, other studies have supported these findings (online supplementary table S3.2). As in children with chronic wet cough, *H. influenzae* was the most common pathogen (38–81%) cultured from children with PBB. Although most *H. influenzae* are likely to be nontypeable (NTHi) strains, only two studies have attempted capsular typing of *H. influenzae* isolates [51, 61]. The other commonly detected bacteria are *Strep. pneumoniae* (16–39%) and *M. catarrhalis* (19–51%), while *Staphylococcus aureus* was found (6–22%) in five of the 10 published studies (online supplementary table S3.2). Differences in the types of *Strep. pneumoniae* serotypes encountered in children with PBB from different countries have been reported and may have arisen from variations in antibiotic prescribing and vaccine practices. For example, in one comparative study, 100% of *Strep. pneumoniae* isolates from Greek children undergoing BAL for PBB were serotypes contained in the 13-valent pneumococcal conjugate vaccine, while only 28% of *Strep. pneumoniae* isolates in BAL cultures from fully vaccinated children with PBB in the UK were vaccine-type serotypes [51]. Finally, polymicrobial infections involving multiple respiratory bacterial pathogens were identified in the lower airways of 30–50% of affected children [16, 42, 50–52].
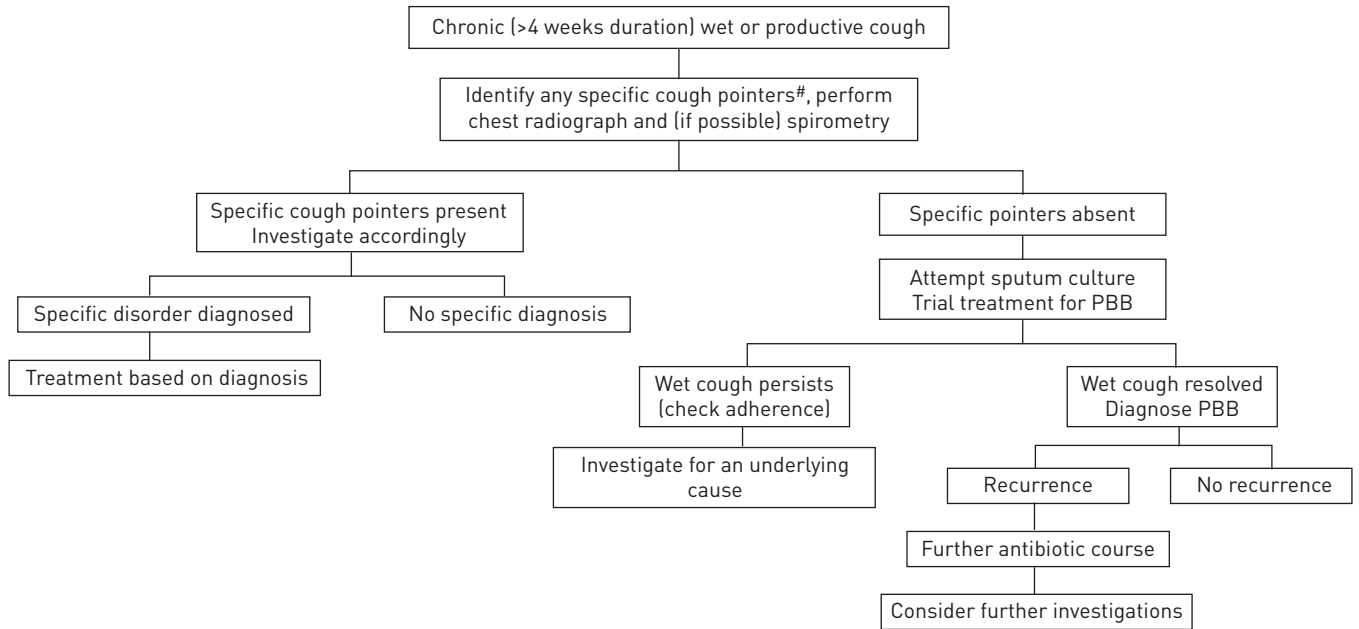
FIGURE 1 Possible approach to managing a child with a chronic (>4 weeks) wet cough. It is not a management guideline. #: see box 2.

When assessing the bacteriology of PBB it is important to note that not all BAL studies are directly comparable with one another, as only some utilised quantitative bacterial culture to describe BAL findings [50, 51]. The distribution of bacteria within the lungs is not uniform. One retrospective study reported that sampling from a single lobe would have missed 17 different organisms in 15 out of 50 patients, eight of whom would not have had any organisms cultured [50]. Nonetheless, it should be noted that this study used nonquantitative bacterial culture methods and failed to report bacterial densities between the various lobes. A summary of information on bacteria found in PBB is presented in online supplementary table S3.2.

Viruses (KQ4)

Our systematic review (online supplementary table S4.1) revealed two studies that reported on viruses in children with PBB [43, 44] and another in children with wet cough [42]. However, we found only one study that specifically systematically examined for viruses [43]. The presence of any virus was found in 38% of BAL samples from 104 children with PBB [43], which was significantly greater than in 49 children with other chronic respiratory disorders (38% *versus* 9%; OR 6.3, 95% CI 2.1–19.1). The most common virus detected in children with PBB was human adenovirus (HAdV) (23%) of which most cases were representative of the HAdV-C species (detected in 96% of HAdV[+] children) [44]. An extended molecular-based diagnostic panel for 17 respiratory viruses was performed in a subset of 27 children, which found rhinovirus in 11 (41%) subjects and human bocavirus and human coronavirus each in one (4%) participant [43]. However, the prevalence of these other viruses was similar in the control group [43]. The same study showed that lower airway infection with *H. influenzae* ($\geqslant 10^4$ CFU·mL^{-1}) was significantly associated with HAdV co-infection [43].

Microbiota (KQ4)

Our systematic review identified a single study that examined the lower airway microbiota of children with PBB [41]. It compared the microbiota of 12 children with PBB with that of 19 children with bronchiectasis and 25 with cystic fibrosis [41]. Unlike adult studies, where significant interindividual differences exist in bacterial community composition between patients with cystic fibrosis and bronchiectasis, the core microbiota in the three aforementioned conditions was similar during early childhood, with *H. influenzae* and oral aerobic (*Streptococcus mitis*) and anaerobic (*Prevotella melaninogenica*) commensals the most commonly shared core species. Subsequent to our systematic review, a larger study involving 78 children (PBB n=28, CSLD/bronchiectasis n=40, disease controls n=10), found that the microbiota in upper and lower airways helped to discriminate between these clinically defined groups [62]. Statistically significant differences have been found in the microbiota between these diagnostic groups [62].

Pathobiology (KQ5)
Risk factors (KQ5)
Besides microbiology, the pathobiology of PBB (addressed in KQ5 and summarised in online supplementary tables S5.1 and 5.2) involves risk factors, underlying structural airway lesions and host airway inflammatory and immune responses. However, few studies have described PBB risk factors, and these report a male predominance [42, 55] and a median age ranging from 10 months to 4.8 years [4, 42, 55]. In addition, a single prospective study found that childcare attendance was the single positive risk factor in 91% of PBB cases, compared with 58% of disease controls [43].

Airway inflammation (KQ5)
Studies included in the systematic review describing the BAL inflammatory profile of PBB had similar findings of intense airway neutrophilia (summarised in online supplementary tables S5.1a and S5.1b), with a percentage neutrophil median range of 25.5–44% [4, 16, 23, 26, 36, 38, 39]. The airway neutrophilia was accompanied by a raised total cell count with a median range of $188–426×10^6$ cells·L^{-1} [4, 23, 26, 36, 38, 39]. No airway eosinophilia was observed in any study and a single study described an increase in the percentage of lymphocytes [23].

An associated marked inflammatory mediator response was also found in the BAL fluid of children with PBB. Increased levels of interleukin (IL)-8, active matrix metalloproteinase-9 and IL-1β correlated with the degree of neutrophilia [35, 36, 38]. Other pro-inflammatory mediators detected at increased levels in the BAL fluid of PBB patients included α-defensin, IL-1 pathway cytokines, and CXCR2 gene and protein expression [23, 34, 63]. In addition, IL-1β and related mediators were associated with BAL neutrophils, cough symptoms and disease recurrence [23].

Immunity (KQ5)
Studies outlined in online supplementary table S5.1b consistently demonstrate that children with PBB have preserved systemic adaptive immunity with normal serum immunoglobulin levels (IgA, IgM, IgG and IgE) and normal antibody-mediated responses to both protein (tetanus) and conjugated protein-polysaccharide based (H. influenzae type b) vaccines [4, 43]. Lymphocyte subsets were normal, except for increased CD56 and CD16 natural killer cell levels for age [43, 55].

Several studies described activated pulmonary innate immune pathways [26, 38, 43, 55, 63]. Specifically, the toll-like receptors (TRLs) associated with bacterial infection (TLR-2 and -4) were elevated in PBB. Another study reported augmented human β-defensin-2 and mannose-binding lectin levels, while activated caspase-1 dependent pro-inflammatory pathways in response to NTHi were also detected in children with PBB, indicating that both innate pathogen recognition and clearance mechanisms were intact [26].

Finally, a recent study of BAL fluid samples from children with PBB discovered reduced alveolar macrophage phagocytic host responses to NTHi and to apoptotic cells (i.e. deficient efferocytosis) [36]. It is therefore possible that the combination of reduced efferocytosis and increased IL-1β pathways could lead to persistence of the activated M1 macrophage phenotype with its pro-inflammatory effects and resulting chronic neutrophilic airway inflammation [36]. Efferocytosis values in children with PBB were in between controls and children with bronchiectasis [36].

Bronchoscopic findings (KQ5)
Purulent airway secretions and large airway malacia are common bronchoscopic findings in children with PBB [15, 56, 57]. Studies seeking specifically both PBB and tracheo-bronchomalacia reported airway malacia in 74% of PBB cases in one retrospective study [48] and 68% in a prospective study [43], although in the latter 53% of disease controls also had evidence of airway malacia [43]. Systematic review of the available studies shows that it remains unclear whether one condition is an antecedent of the other. While the reduced airway clearance found in tracheo-bronchomalacia is thought to predispose to PBB, it is also possible that chronic infection and airway inflammation leads to the development of secondary airway malacia [45]. A recent study comparing clinical findings, airway cellularity and bacterial cultures in PBB patients with and without tracheo-bronchomalacia observed no differences between the two groups [55]. Hence, although it is a common finding, the role of airway malacia in the pathobiology of PBB remains largely unknown.

Therapy (KQ6)
13 studies were included in the systematic review for KQ6 and the primary studies are summarised in online supplementary table S6. One was a Cochrane review [64], three were RCTs [30, 33, 39] and the remaining nine were descriptive studies, of which four involved prospective cohorts of children with a chronic cough [4, 8, 9, 37] and five were retrospective reviews [13, 16, 47, 48, 52].

The three RCTs [30, 33, 39] were the only studies whose principal aims were to determine the efficacy of antibiotics in resolving a chronic wet cough in young children. The Cochrane review included two of these studies, one of which was open-label [30], and when both were combined they involved 140 children aged ⩽7 years [28, 33]. While concluding that antibiotics were likely to be beneficial (pooled OR 0.13, 95% CI 0.06–0.32) for children with persistent cough post-treatment), the review also raised concerns over study quality and design [64]. Both studies relied upon nasopharyngeal cultures to determine the bacterial aetiology of the suspected lower respiratory tract infection and included children with pertussis and cough duration as brief as 10 days, while outcomes were based upon physician's assessment and not defined fully. Antibiotic courses were for 7 days and included erythromycin in one trial [30] and relatively low doses of amoxicillin-clavulanate in the other [33]. One RCT had a more robust design and found that children treated with conventional doses of amoxicillin-clavulanate for 2 weeks had higher rates of cough resolution than those receiving placebo (48% *versus* 16%) [39]. However, this trial included only 25 subjects in each treatment arm and was conducted in a specialist clinic, raising the possibility of sample bias towards more severe cases. Importantly, none of the studies undertook long-term follow-up to determine recurrence rates following treatment.

The remaining evidence supporting the role of antibiotics was limited to a small number of observational studies, many involving children with chronic cough from various causes, where controls were absent and cough resolution following antibiotics was not a main outcome (online supplementary table S6). These studies suggested that a ⩾2-week course of antibiotics active against respiratory bacterial pathogens (*H. influenzae*, *Strep. pneumoniae*, *M. catarrhalis* and *Staph. aureus*) found in the lower airways of children with chronic wet or productive cough were associated with increased likelihood of cough resolution [16, 48, 52]. However, symptomatic recurrences were common [16, 48, 52], occurring in as many as 76% of cases, while a poor response to ⩾4 weeks of treatment increased the likelihood of the presence of underlying bronchiectasis [47].

While there was some evidence that antibiotics improved clinical outcomes in children with chronic wet or productive cough unrelated to underlying disease and without any specific cough pointers, larger RCTs of well-characterised children with chronic wet cough recruited from multiple centres to reduce sample bias and with prolonged follow-up are needed. The lack of comparative studies means that important knowledge gaps exist involving the choice of antibiotic, the doses to be prescribed and the treatment duration needed, to optimise the clinical response and reduce the risk of recurrent chronic wet cough.

A recent review recommended that until further evidence is available, children with an isolated chronic wet cough, lacking symptoms and signs of an underlying disease and whose chest radiograph is normal (or shows only peribronchial changes) should receive 2–4 weeks of an oral antibiotic directed against common respiratory bacterial pathogens associated with PBB [57]. As most children are too young to expectorate and provide a reliable spontaneous or induced sputum specimen, the choice of antibiotic is frequently empirical and determined by local patterns of antibiotic susceptibility. The antibiotic used most widely is oral amoxicillin-clavulanate, which is active against β-lactamase-producing strains of *H. influenzae*, *M. catarrhalis* and *Staph. aureus*, although alternatives such as oral second- or third-generation cephalosporins, trimethoprim-sulfamethoxazole or a macrolide may be used when there is a history of an IgE-mediated reaction to penicillin. However, in those with a previous IgE-mediated reaction to penicillin, oral cephalosporins with similar side chains to the implicated penicillin agent (*e.g.* ampicillin and cefalexin or cefaclor) should be avoided [65, 66]. In addition, this review recommended that investigations for an underlying cause should be undertaken in the small group of children who, despite adhering to their treatment, fail the 4-week course of antibiotic therapy [47, 57].

Treatment failure (KQ6)

There are many causes of chronic wet cough in children, of which PBB is just one [57]. In those in whom therapy fails (figure 1), possible reasons are nonadherence and/or other causes of chronic wet cough. Guidelines suggest that these children should be referred for further evaluation and investigations recommended for suspected CSLD or bronchiectasis [67]. Intravenous antibiotics are probably beneficial in those with persistent endobronchial infection, even without CT scan evidence of bronchiectasis [68], since early intervention to break the "vicious cycle" of infection, inflammation and impaired mucociliary clearance might prevent future development of bronchiectasis [69, 70].

Recurrent chronic wet cough following successful antibiotic treatment (KQ7)

A prolonged period of observation is required to determine the recurrence rate, and only limited data were available, all from three retrospective studies [16, 48, 52], which were included in the systematic review for KQ7. These studies provided little or no evidence for the role of prophylactic antibiotics, risk of increased

antibiotic resistance following treatment or how recurrences of PBB should be managed (online supplementary table S7).

The first [16] reported that while 51% of 81 children with newly diagnosed PBB were completely symptom free after two prolonged (6–8 week) courses of antibiotics, 13% required either six or more courses of antibiotics or had continuous prophylactic antibiotics for at least one winter to control symptoms, with another 5% requiring intermittent antibiotic courses and were still under active review. However, this study [16] included children with bronchiectasis and used different definition of PBB. The second [52] noted that over a 2-year period, only 25% of 33 patients remained well following their first 6–8-week course of antibiotics, despite all achieving complete resolution of their cough symptoms by day 14 of therapy. Moreover, three (10%) of these children had three or more recurrences, and overall nine (27%) received long-term prophylactic antibiotics. Like the first study, the definition of PBB was not the same as that proposed in this task force document. Finally, a third retrospective study [48] reported complete resolution of symptoms in all but one of 61 children who underwent BAL for chronic wet cough followed by ⩾2-week course of oral antibiotics. Of these children, 43 (70%) required repeated courses of treatment for recurrent symptoms.

It should be noted there was no systematic approach to starting prophylactic antibiotics, with some children beginning these after a single recurrence, while details on antibiotics, repeat treatment courses and outcome are scant. Microbiology reporting was incomplete and no antibiotic resistance data were presented. Thus, crucial knowledge gaps remain on how to best manage children with recurrent PBB, how these episodes might be prevented and the impact of long-term antibiotics upon antimicrobial resistance in this patient population.

Subsequent to the task force group meeting, the sole published long-term prospective follow-up study described a subgroup of children with PBB who subsequently received a diagnosis of bronchiectasis [61]. Multivariate logistic regression showed that recurrent episodes (more than three per year) of PBB (adjusted (a)OR 11.5, 95% CI 2.3–56.5; p=0.003) and presence of *H. influenzae* lower airway infection (aOR 7.6, 95% CI 1.5–37.8; p=0.013) were both independently associated with bronchiectasis diagnosis within the 2-year follow-up period [61].

Whether symptom duration prior to treatment impacts on clinical outcomes remains unknown, as the current definition includes everyone with a persistent wet cough, irrespective of whether it has been present for weeks, months or even years. The risk of recurrence is likely to depend upon factors that are difficult to assess, such as the composition of the respiratory microbiota, the relevance of airway malacia and/or subtle immune deficiencies. In addition, it is also unknown whether the approach to initial therapy (*i.e.* length of antibiotic treatment course) influences the risk of recurrence. Prescribing 2–4 weeks of oral antibiotic therapy targeted at the suspected (or cultured) bacterial pathogens has been part of the diagnostic process. Should the cough resolve completely, some clinicians will cease therapy at this point, while others will continue for prolonged periods. The proposed rationale for prolonged antibiotic use is that protecting the airways against the common respiratory bacterial pathogens for an extended period allows the airways to recover their integrity and resist reoccurrence. However, this practice is unproven at either a mechanistic or clinical level. In addition, prolonged antibiotic exposure disrupts resident microbiota (dysbiosis) and contributes to the pathoadaption of organisms within the lower airways, including the selection of antibiotic-resistant strains [71, 72].

Finally, while once-weekly azithromycin halved the rate of pulmonary exacerbations in children with either CSLD or bronchiectasis [73], its role in PBB remains undefined. This is especially important in the setting of the global antibiotic resistance crisis from over-prescribing antibiotics [74], where, in addition to the concerns stated above, macrolides in particular alter the host's resident microbiome [75] and provide strong selection pressure for antibiotic-resistant organisms, leading to increased treatment costs and risk of treatment failure [76, 77].

Research priorities

1) Community-based epidemiological studies to generate data that informs our understanding of the current incidence and prevalence of chronic cough in the paediatric population across several healthcare settings (countries). Such studies need to assess a random selection of those reporting chronic cough to more accurately assess the relative contributions of different diagnostic entities.
2) Prospective, longitudinal cohort studies of newly diagnosed children with PBB are needed to determine its natural history, including whether those already with early bronchiectasis or at risk of developing this complication can be identified.
3) Understanding the impaired pathogen clearance mechanisms underlying PBB, including host susceptibility factors and whether recurrences and disease progression are influenced more by the

composition of the respiratory microbiota than by individual pathogens. This information is critical for identifying susceptible infants and children and developing novel treatments and prevention strategies.

4) Strengthen the evidence-based diagnostic algorithm for a child with an "isolated" chronic wet cough and lacking specific cough pointers, to help determine those most likely to benefit from antibiotics and when to investigate for an underlying disorder.

5) Undertake multicentre RCTs in children with chronic wet cough to help identify the antibiotic class, dose and course duration that optimises cough resolution and reduces the likelihood of recurrences in children with PBB, while still minimising antibiotic resistance. Examples might include β-lactam *versus* trimethoprim-sulfamethoxazole *versus* macrolide antibiotics; higher *versus* standard dosing (*e.g.* amoxicillin-clavulanate at 90 mg·kg^{-1}·day^{-1} *versus* 60 mg·kg^{-1}·day^{-1}); or extended *versus* standard antibiotc course duration (*e.g.* 8 weeks *versus* 4 weeks *versus* 2 weeks).

6) Undertake multicentre RCTs in children with recurrent (*e.g.* more than three episodes annually) PBB to determine whether long-term oral (*e.g.* azithromycin) or inhaled antibiotics reduce the risk of further episodes of chronic wet cough and improve long-term outcomes. If successful, such studies would need to identify those most likely to benefit, for how long antibiotics should be administered and to examine the impact of this treatment upon the respiratory microbiome and resistome.

To conclude, we return to the 3-year-old boy who received a 2-week course of amoxicillin-clavulanate, following which his cough resolved completely. His parents were informed of his diagnosis of PBB and counselled that PBB is an endobronchial infection. If a flexible bronchoscopy and lavage were undertaken, we would probably find common respiratory bacteria and airway inflammation. However, we do not really know why PBB occurs in some and not in others. While we now understand some of the associations with PBB and have found that PBB can recur, we do not know who are more likely to experience recurrence or whether an even longer course of antibiotics reduces the chance of having a recurrence. Recurrence of PBB should be managed with further antibiotic courses and if more than three episodes occur per year, further investigations are indicated.

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