# ERS statement on protracted bacterial bronchitis in children

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# ERS Task Force Document: Protracted bacterial bronchitis in children

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## 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. Also, 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.

## Case vignette

A 3 year old boy 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 last 6-weeks. Upon history taking, you learn that his symptoms were accompanied initially by a low-grade fever and nasal discharge, and while these resolved in 2 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 sino-pulmonary 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 most likely 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?

## Introduction

Cough is the most common presenting symptom in those seeking primary health care.[1] Within this large group of patients are children similar to the child described in the case vignette by 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] Amongst children referred to a specialist respiratory clinic because of a chronic cough, more than 80% had sought medical advice on five or more occasions during the preceding 12-months and 53% had been taken to the doctor more than ten 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 group from Brisbane in 2006[4] and also 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 multi-centre studies from 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 being 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 'vicious circle' hypothesis of chronic bacterial infection and inflammation causing bronchiectasis,[14] 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 (PedsQoL[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, 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 Taskforce position statement on PBB outlines current knowledge and provides a clinical profile, diagnostic indications and a therapeutic approach to this common disease in children. It also highlights areas of future research.

## Methodology

The European Respiratory Society (ERS) PBB taskforce team consisted of 11 members (general paediatricians, respiratory and infectious disease specialists) representing clinicians in Europe and Australia managing 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 (PICO) format, were developed by the group and distributed among four pairs of authors (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 (Supplementary Figures).

**The KQs** (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);
    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, what:
    a. are the possible causes?
    b. tests should be undertaken and when should they be referred for further investigations?
    c. 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, 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 (eg. 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 KQs were undertaken by 4 pairs of the taskforce members whereby one member of each reviewer pair used a standard format (Supplementary File 1) based on the ACCP's CHEST cough pediatric guidelines.[19,20] 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 unable to be resolved by consensus would be adjudicated by a third reviewer (AK). As there were no new randomised controlled trials (RCTs) following the published systematic review on chronic wet cough in children,[20] risk of bias criteria was not undertaken. 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 respective KQs.

Summaries of the data relating to each KQ 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 KQs and Task Force statements are presented below with additional details presented in the Supplementary Files. Studies had components common to almost all the KQs and they are summarised in the Table.

## Definition of PBB (KQ1)

As outlined recently,[21] the Task Force recommends that for day-to-day clinical practice, PBB is considered present when all three criteria listed below are fulfilled:

i. Presence of continuous chronic (>4-weeks duration) wet or productive cough

ii. Absence of symptoms or signs (ie. specific cough pointers) suggestive of other causes of wet or productive cough (see Box) and

iii. Cough resolved following a 2-4 week course of an appropriate oral antibiotic.

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

The validity of each criterion was outlined in a recent review[21] and updated in this systematic review for duration of cough, in the absence of other symptoms and signs (Supplementary Tables 1.1a-b). The Task Force chose the 4-week diagnostic threshold based upon the inclusion criteria of the studies outlined in the Supplementary Tables 1.1a-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 recommended by the ACCP cough guidelines.[20] Such information is especially required from within the primary health care setting.

In prospective studies that are currently available (Supplementary Table 1.1a), the mean or median duration of cough (at presentation) varied from 3-weeks[22] to as long as 6-months.[4] The lowest first quartile was 4-weeks and lowest 95th% percentile was 2.6-months. In the retrospective studies (Supplementary Table 1.1b), the mean or median cough duration varied from 10-weeks[23] to 11-months.[24] The lowest range value was 1-month[25] and lowest 95% percentile was 9.6-weeks.[23]

PBB as a diagnostic entity and cause of wet cough was well-documented in prospective and retrospective studies (Supplementary Tables 1.1a-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 (Supplementary Table 1.1a). However, in the retrospective studies, the mean duration of antibiotic courses either varied from 17-days to 6-8 weeks or was unspecified (Supplementary Table 1.1b).

Prospective studies were also 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 (Supplementary Tables 1.3a-b). While an adult version of PBB has not been clearly described, it has been suggested by some clinicians.[26] However, in this particular report,[26] other than presence of wet or productive cough, other criteria such as duration of cough went undefined. Furthermore, another adult case series[27] described chronic productive cough unrelated to bronchiectasis, which responded only to intravenous antibiotics. This requirement for parenteral antibiotics however, is used to help to differentiate between chronic suppuratives lung disease (CSLD) and PBB in children.[15]

Despite all national society chronic cough guidelines describing PBB as a cause of chronic wet cough, variations in the definition of PBB between them still exist (Supplementary Table 1.2).

## Typical profile child with PBB (KQ1)

Part of KQ1 also reviewed what symptoms and signs (other than wet cough) were used (or found) in descriptions of children with PBB. The prospective studies (Supplement Table 1.3a) specified that no other symptoms (other than wet cough) or signs were present, although some had 'parent reported wheeze'. The retrospective studies (Supplement Table 1.3b) commonly described wheeze or 'noisy breathing' being present. Concomitant bronchodilator responsiveness was also described in some studies, and was particularly common in one retrospective study (9 of 20 children,[13]) although this high proportion could have been from patient selection.

As summarised previously,[21] while children with PBB were typically young (mean or median age 1.8-4.8 years), PBB was also recognised in older (age >12-years) children.[7,28,29] Most children with PBB lacked systemic symptoms without evidence of sinusitis or ear disease.[4,30] Compared to 'disease controls' undergoing bronchoscopy for non-cough-related indications (eg. stridor or apnoea), children with PBB were more likely to have attended childcare (odds ratio (OR)=8.4, 95% confidence interval (CI) 2.3-30.5), but their tobacco smoke exposure (~30%[4,30]) was similar to that of the 'controls'.[30] 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,[30] 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.[30] While many

parents reported previous ‘ever wheeze’ (41-81%[16,30]), auscultation-confirmed wheeze by doctors was unusual.

The chest radiograph was normal or near-normal, showing only peri-bronchial changes.[15,31,32] When performed, both spirometry[31] and respiratory system reactance and resistance measured by the forced oscillatory technique (unpublished) 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 peri-bronchial changes) in a child with chronic wet cough is present, additional investigations for an underlying cause are indicated (see Figure). PBB may co-exist with other diseases, (e.g. asthma and airway malacia); although for asthma studies including objective assessments of reversible airflow limitation to help determine whether there is any association have not 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 (Supplementary Tables 2.1). These other causes of chronic wet cough in children include, but are not limited to: pertussis, tuberculosis, inhaled foreign body, bronchiectasis, cystic fibrosis (CF), aspiration or congenital lung lesions. Most however have other symptoms and signs present (i.e. cough pointers[19,31,32]).

KQ2 also addressed other investigations and the possible harm from having a prolonged wet cough (Supplementary Tables 2.2-2.3). Data suggest that children should be referred for further investigations when specific cough pointers (see Box) 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).[33] Another study reported 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.[34]

## Microbiology (KQ3 and KQ4)

### Wet cough (KQ3)

The respiratory bacterial pathogens found in studies of chronic wet cough are summarised in Supplementary Table 3.1. *H. influenzae* was overall the most common organism found in 28-58% of children,[4,29,35,36,37,38] 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 (Supplementary Table 3.2).

### PBB (KQ3)

The first study describing PBB detected commonly recognised respiratory pathogens (*H. influenzae* (47%), *S. pneumoniae* (35%) and *M. catarrhalis* (26%)) in BAL cultures at high bacterial loads ($\geq 10^5$ colony-forming units/mL).[4] Subsequently, other studies have supported these findings (Supplementary Table 3.2). 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 non-typeable (NTHi) strains, only two studies have attempted capsular typing of *H. influenzae* isolates.[28,39] The other commonly

detected bacteria are *S. pneumoniae* (16-39%) and *M. catarrhalis* (19-51%), while *Staphylococcus aureus* has been found (6-22%) in five of the ten published studies (Supplementary Table 3.2). Differences in the types of *S. 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 *S. pneumoniae* isolates from Greek children undergoing BAL for PBB were serotypes contained in the 13-valent pneumococcal conjugate vaccine, while only 28% of *S. pneumoniae* isolates in BAL cultures from fully vaccinated English children with PBB were vaccine-type serotypes.[28] Finally, polymicrobial infections involving multiple respiratory bacterial pathogens were identified in the lower airways of 30-50% of affected children.[16,24,28,38,40]

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.[28,40] 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 15/50 patients, eight of whom would not have had any organisms cultured.[40] Nonetheless it should be noted that this study used non-quantitative bacterial culture methods and failed to not report bacterial densities between the various lobes. A summary of information on bacteria found in PBB is presented in Supplementary Table 3.2.

## Viruses (KQ4)

Our systematic review (Supplementary Table 4.1) revealed 2 studies that reported on viruses in children with PBB[30,41] and another in children with wet cough.[38] However, only single study that specifically systematically examined for viruses.[30] The presence of any virus was found in 38% of BAL samples from 104 children with PBB,[30] which was

significantly greater than in 49 children with other chronic respiratory disorders (38% vs 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 were representatives of the HAdV-C species (detected in 96% of HAdV+ children).[41] 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 in one (4%) each of the participants.[30] However, the prevalence of these other viruses was similar in the control group.[30] The same study showed that lower airway infection with *H. influenzae* ($\geq 10^4$ CFU/mL) was significantly associated with HAdV co-infection.[30]

## Microbiota (KQ4)

Our systematic review identified a single study that examined the lower airway microbiota of children with PBB.[42] It compared the microbiota of 12 children with PBB with that of 19 children with bronchiectasis and 25 with CF.[42] Unlike adult studies, where significant inter-individual differences exist in bacterial community composition between patients with CF and bronchiectasis, the core microbiota in the three aforementioned conditions was similar during early childhood with *H. influenzae* and oral aerobic (*S. mitis*) and anaerobic (*Prevotella melaninogenica*) commensals the most commonly shared core species. Subsequent to our systematic review, a larger study involving 78 children (PBB=28, CSLD/bronchiectasis=40, disease controls=10), found that the microbiota in upper and lower airways helped to discriminate between these clinically defined groups.[43] Employing PERMANOVA, a type of multivariate analysis of variance using distance measurements, significant differences in the lower airway microbiota (core and satellite combined) between the disease groups ($p = 0.0001$) were found and diagnostic groups accounted for 29.2% of the total variation in the microbiota.[43]

## Pathobiology (KQ5)

## Risk factors (KQ5)

Besides microbiology, the pathobiology of PBB (addressed in KQ5 and summarised in Supplementary Tables 5.1-5.2) 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[23,38] and a median age of 10-31 months.[4,23,38] In addition, a single prospective study found childcare attendance was the single positive risk factor in 91% of PBB cases compared with 58% of disease controls.[30]

## 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 Supplementary 5.1a and 5.1b), with a percentage neutrophil median range of 25.5-44%.[4,16,44,45,46,47] The airway neutrophilia was accompanied by a raised total cell count with a median range of 188-426 x $10^6$/L.[4,44,45,46,47,48] No airway eosinophilia was observed in any study and a single study described an increase in the percentage of lymphocytes.[46]

An associated marked inflammatory mediator response was also found in the BAL fluid of children with PBB. Increased levels of interleukin (IL)-8, matrix metalloproteinase (MMP)-9 active and IL-1β correlated with the degree of neutrophilia.[44,45,49] 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.[46,49,50] Also, IL-1beta and related mediators were associated with BAL neutrophils, cough symptoms and disease recurrence.[46]

## Immunity (KQ5)

Studies outlined in Supplementary Table 5.1b 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.[4,30] Lymphocyte subset were also normal, except for increased CD56 and CD16 natural killer cell levels for age.[23,30]

Several studies described activated pulmonary innate immune pathways.[23,30,45,47,50] 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 (hBD2) and mannose-binding lectin (MBL) 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.[47]

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 (ie. deficient efferocytosis).[44] 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.[44] Efferocytosis values in children with PBB were in between controls and children with bronchiectasis.[44]

## Bronchoscopic findings (KQ5)

Purulent airway secretions and large airway malacia are common bronchoscopic findings in children with PBB.[15,21,37] Studies seeking specifically both PBB and tracheo-bronchomalacia reported airway malacia in 74% of PBB cases in one retrospective study[25] and 68% in a prospective study,[30] although in the latter 53% of disease controls also had evidence of airway malacia.[30] Systematic review of available studies shows it remains unclear whether one condition is an antecedent of the other. Whilst 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 secondary airway malacia developing.[51] 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.[23] Hence, although a common finding, the role of airway malacia in the pathobiology of PBB remains largely unknown.

## Therapy (KQs 6)

Thirteen studies were included in the systematic review for KQ6 and the primary studies are summarised in Supplementary Table 6. One was a Cochrane review,[52] three were RCTs,[22,48,53] while the remaining nine were descriptive studies, of which four involved prospective cohorts of children with a chronic cough[4,8,9,29] and five were retrospective reviews.[13,16,24,25,33]

The three RCTs[22,48,53] 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-labelled,[22] and when both were combined they involved 140 children ≤7-years of age.[31,53] 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.[52] 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[22] and relatively low doses of amoxicillin-clavulanate in the other.[53] A recent 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% respectively).[48] 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 (Supplementary Table 6). These studies suggested that at least a 2-week course of antibiotics active against respiratory bacterial pathogens (*H. influenzae, S. pneumoniae, M. catarrhalis*, *S. aureus*) found in the lower airways of children with chronic wet or productive cough were associated with increased likelihood of cough resolution.[16,24,25] However, symptomatic recurrences were common,[16,24,25] occurring in as many as 76% of cases, while a poor response to ≥4-weeks of treatment increased the likelihood of underlying bronchiectasis being present.[33]

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 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.[21] 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 antibiotic susceptibility patterns. The antibiotic used most widely is oral amoxicillin-clavulanate, which is also active against beta-lactamase producing strains of *H. influenzae, M. catarrhalis* and *S. aureus,* although alternatives such as an oral cephalosporin, trimethoprim-sulphamethoxazole or a macrolide may be used when there is a history of immediate hypersensitivity to penicillin. This review also 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.[21,33]

## Treatment failure (KQ6)

There are many causes of chronic wet cough in children, of which PBB is just one.[21] In those who fail therapy (Figure), possible reasons are non-adherence and/or other causes of

chronic wet cough. These children should be referred for further evaluation and investigations recommended for suspected CSLD or bronchiectasis.[54] Intravenous antibiotics are likely beneficial in those with persistent endobronchial infection, even without CT scan evidence of bronchiectasis,[55] since early intervention to break the 'vicious cycle' of infection, inflammation and impaired mucociliary clearance might prevent future development of bronchiectasis.[56,57]

## 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[16,24], 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 (Supplementary Table 7).

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 ≥6 courses of antibiotics or had continuous prophylactic antibiotic for at least one winter to control symptoms with another 5% requiring intermittent antibiotic courses and still under active review. However this study[16] included children with bronchiectasis and used different definition of PBB. The second[24] 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 the 14th day 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 taskforce document. Finally, a third retrospective study[25] 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.[39] Multivariate logistic regression showed that recurrent episodes (>3/year) of PBB ($OR_{adjusted}$ 11.5,95%CI 2.3-56.5, p=0.003) and presence of *H. influenzae* lower airway infection ($OR_{adjusted}$ 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.[39]

Whether symptom duration prior to treatment impacts on clinical outcomes remains unknown as the current definition includes everyone with a persistent wet cough, irrespective 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. Whether the

approach to initial therapy (ie. length of antibiotic treatment course) influences the risk of recurrence is also unknown. 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 by 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.[58,59]

Finally, while once-weekly azithromycin halved the rate of pulmonary exacerbations in children with either CSLD or bronchiectasis,[60] its role in PBB remains undefined. This is especially important in the setting of the global antibiotic resistance crisis from over-prescribing antibiotics,[61] where, in addition to the concerns stated above, macrolides in particular alter the host's resident microbiome[62] and provide strong selection pressure for antibiotic-resistant organisms, leading to increased treatment costs and risk of treatment failure.[63,64]

## Research priorities

- 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.

- 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.

- Understanding the impaired pathogen clearance mechanisms underlying PBB, including host susceptibility factors and if 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.

- 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.

- 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:
        - Beta-lactam versus trimethoprim-sulphamethoxazole versus macrolide antibiotics
        - Higher versus standard dosing (eg. amoxycillin-clavulanate at 90mg/kg/day versus 60mg/kg/day)

  - Extended versus standard antibiotc course duration (eg. 8-weeks versus 4-weeks versus 2-weeks).

- Undertake multicentre RCTs in children with recurrent (eg. >3 episodes annually) PBB to determine if long-term oral (eg. 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.

And so, back to the 3-year old boy who received a 2-week course of amoxicillin-clavulanate, following which his cough resolved completely. His parents are informed of his diagnosis of PBB and counselled that PBB is an endobronchial infection. If a flexible bronchoscopy and lavage were undertaken we would likely find common respiratory bacteria and airway inflammation. However, at this point in time, 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 PBB should be managed with further antibiotic courses and if more than 3 episode per year occur, further investigations are likely indicated.

## Figure Legend

Possible approach to a child with a chronic (>4-weeks) wet cough. It is not a management guideline.

# Table

## Summary of studies found in the systematic reviews of the key questions.

| 1st author, publication y; country | Setting; Study design | Inclusion and Exc criteria; or definitions | N enrolled, N completed; Follow-up length; Age | Main aim(s) of study | Relevant to KQs |
|---|---|---|---|---|---|
| **PROSPECTIVE STUDIES** | | | | Findings of the studies related to the KQs are in the Supplementary Tables | |
| **Aluoch[65] 1984, Kenya** | Single centre; General OPD, cross sectional | Aged >6y, first attendance with main complaint of cough, sputum (>1mo) or haemoptysis; Exc: NR | N=601; N with sputum=601; median age NR and study included adults; FU=NR | Yield of tuberculosis from systemic examination of first presentation | 2 |
| **Asilsoy,[8] 2008 Turkey** | Single centre, Paed OPD; Cohort | >4w cough; Exc: NR | N=108, N completed=108 FU:NR Mean age=8.4 y; range 6-14 | "evaluate children with cough in accordance with the 2006 ACCP guidelines"[8] | 1, 2, 6 |
| **Baines,[46] 2014; Australia** | Single centre, Resp OPD; exploratory & validation cohorts | PBB=clinical definition; Resolved PBB =previous PBB, but no cough at FB | Exp: PBB=21; Controls=33; Respective mean ages= 2.3 & 9.7 y; Validation: PBB=36; Controls=11; Respective mean age=2.0 and 0.7y | To evaluate the IL-1 and TNF-α/NF-κB pathways and mediators in 2 cohorts of PBB and control children | 1, 2, 3, 5, |
| **Chang[66] 2006 Australia** | Single centre; Resp OPD, cross-sectional | Children undergoing FB without a known underlying resp Dx | N=106; Median age=2.6y, IQR 5.7 FU=NR | Compare (a) cough quality (wet/dry and brassy/non-brassy) to FB findings of secretions and tracheomalacia respectively, (b) parent's vs clinician's evaluation of cough quality (wet/ dry) | 2 |
| **Chang[67] 2006 Australia** | Single centre; Resp OPD, cross-sectional | Children undergoing FB without a known underlying resp Dx | N=106; Median age=2.6y, IQR 5.7 FU=NR | Examine the relationship between the amount of secretions seen at bronchoscopy with airway cellularity and microbiology | 3 |
| **Chang,[47] 2012;** | Single centre, Resp OPD; | PBB=chronic wet cough, response to ABs with resolution of cough within | Current PBB=61, PBB well=20, Controls=21; | To determine whether BAL levels of hBD2, SP-A, and MBL: (a) | 1, 2, 3, 5 |

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| **Australia** | cross-sectional | 2w & absence of signs or symptoms of other disease; PBB well=previous PBB, but no cough when FB done | FU: NR<br>Respective mean age (SD) =2.5y (2.3), 4.2y (3.0), 2.2y (2.8) | differed between children with current PBB, PBB well, and controls; and (b) related with airway neutrophilia and infection | |
| **Chang[68] 2013 Australia** | Multicentre, Resp OPD, RCT | Aged <18y, >4w cough, newly referred;<br>Exc: known chronic resp illness | N enrolled=270,<br>N completed=253<br>FU=12mo for Dx, 6mo post Dx;<br>Mean=4.5 y, SD=3.7 | RCT to determine if Mx according to a standardised clinical Mx pathway improves clinical outcomes | 2 |
| **Chang[31] 2015 Australia** | Multi-centre, Resp OPD;<br>Cohort | Aged <18y, >4w cough newly referred<br>Exc: chronic respiratory illness | N of cohort=346,<br>N completed=326;<br>Follow-up=12mo for Dx,<br>6mo post Dx<br>Mean age=4.5y, SD 3 | In children newly referred for chronic cough, to describe data relating to specific cough pointers of the 3 most common aetiologies | 1, 2 |
| **Coren[69] 1998 England** | Uni-centre;<br>General OPD,<br>Cross-sectional | All CT scans undertaken over 12mo.<br>Exc: NR | 102 children had 106 CT scans.<br>FU=NR;<br>Median age=5y (range 7w-15y) | To determine whether use of paediatric chest CT scans was appropriate (new Dx and how it influenced Mx) | 2 |
| **Darelid[22] 1993 Sweden** | 3 centres Pediatric OPD;<br>open RCT | Aged 0.5-6y, persistent cough >10 days.<br>Exc: pneumonia, allergy, acute otitis media, tonsillitis, cardiac disease, suspected pertussis | N cohort=88;<br>N completed=87#<br>FU=3mo;<br>Median age group=13-24mo (IQR NR) | Whether 7 days of erythromycin clinically improves children 0.5-6y of age with a cough$^{+}$ >10 days | 1, 6 |
| **De Baets[36] 2012 Belgium** | Dual-centre;<br>Resp OPD,<br>Cross-sectional | "Persistent resp symptoms, productive cough, bronchorrhoea and wheezing for ≥3mo."<br>Exc: premature, failure to thrive, CF, prolonged intubation, tracheotomy, dysmorphic, neurology, cardiac problems, or CXR consolidation | N=124;<br>FU=NR;<br>Median age=10mo (IQR 7-14) | Description of results of diagnostic investigations in children with persistent resp symptoms despite regular asthma Rx | 2, 3 |
| **Gedik[35], 2015, Turkey** | Single centre, Paediatric or Allergy dept;<br>Cohort | Aged <17y, persistent cough >4w.<br>Exc: known chronic resp, neuromuscular, growth, cardiac problems, genetic syndromes, prematurity | N=563, N completed=563<br>FU:NR<br>Mean age=5.4y, SD 3.8 | The evaluation of children with chronic cough and aged-based aetiological factors | 1, 2, 3, 5 |

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| **Gottfard[53] 1994 Sweden** | 3 centres Pediatric OPD; DB RCT | Lower resp tract infection with cough >10 days, >11 coughing attacks in 24hrs. Exc: pneumonia, acute otitis media, clinical suspicion of pertussis | N cohort=52; N completed=52 FU=14 days; Median age=2.6-2.7y (IQR NR) | "To investigate the nasopharyngeal flora of children with persistent cough and the effects of treatment with amox-clavulanate" [+][53] | 1, 6 |
| **Grissell[49] 2007; Australia** | Single centre, Gastro OPD non-bronchoscopic BAL | Children undergoing upper GI endoscopy, cough questionnaire. Excl: neurodevelopmental abn, underlying cardioresp dis, primary aspiration *Group defined on +ve bacterial culture not PBB | 69 children; 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 |
| **Heino[70] 1990 Finland** | Single centre, Resp OPD; cross-sectional | Chronic productive cough (>3mo) unresponsive to oral ABs and oral bronchodilators | N=7; Age range 5-11y | Describe ultrastructural nature of epithelial damage in respiratory symptoms | 2 |
| **Hodge[44] 2016; Australia** | Single centre, Resp OPD; cross-sectional | PBB-micro; Controls=no cough and FB undertaken for other reasons (e.g. stridor); BE=CT scan defined with clinical symptoms | PBB=13, BE=55, controls=13. Median ages and IQR: PBB=6.5mo (1.6-14) BE=22mo (14-33) Controls=5.5mo (4-9.9) | (a) Quantify phagocytosis of airway apoptotic cells and NTHi by alveolar macrophages in children with PBB and BE; (b) Determine if phagocytic capacity associated with clinical variables, and patterns of airway inflammation | 1, 3, 5 |
| **Karabel[29] 2014 Turkey** | Single centre, Resp OPD; Cohort | >4w cough Exc: Neuromuscular, cardiac, syndromes, resp infection last 4w | N cohort=270, N completed=270; FU=12mo Mean age=6.5y, range 7mo-17y | To determine the aetiology of chronic cough in children using the ACCP guidelines | 1, 2, 6 |
| **Marchant[4] 2006 Australia** | Single centre, Resp OPD, Cohort | >3w cough, age <18y and newly referred Exc: known chronic disease | N cohort=108; N completed=103 FU=12mo; Median age=2.6y (IQR 1.2-6.9) | In children with chronic cough, to; (a) evaluate the use of an adult-based algorithmic approach in the management, (b) describe the aetiology | 1, 2, 3, 5, 6 |
| **Marchant,[45] 2008; Australia** | Single centre, Resp OPD; cross-sectional | PBB=chronic wet cough (>3w), BAL bacterial culture ($\geq 10^5$ CFU/mL) & response to Abs (cough resolved in 2w); Other aetiologies=other chronic | PBB=38, other Dx=25, SR=22, controls=15; Respective median age (IQR): 2.4y (0.9-4.2), 2.6y (1.1, 9.6), 3.8y (0.9, 6.8), 2.8y (0.6, 9.8) | To: (a) describe the clinical profile, airway cellularity and promoters of neutrophilic inflammation in BAL fluid of | 1, 2, 3, 5 |

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| | | cough aetiologies in cohort;[4] Controls=children with stridor without chronic cough | | children with PBB compared to children with other aetiologies and controls without cough , (b) explore selected innate immunity signaling receptors, specifically TLR-2 and -4 | |
| **Marchant[48] 2012 Australia** | Single centre, Paediatric and resp OPD; DB RCT | Aged 0.5-18y, doctor observed wet cough >3w; Exc: chronic lung, cardiac neuro-development disease, ABs in the last 2w, acutely unwell | N cohort=50, N completed=47 FU=2 w Mean age=1.8-2.8y, IQR 0.9-5.3 | Efficacy of 2 w of oral amoxi-clav (compared with placebo) in achieving cough resolution in children with chronic wet cough | 1, 3, 5, 6 |
| **Seear[71] 1997 Canada** | Single centre, Resp OPD, Cross-sectional | Chronic (≥3mo) productive or rattly cough, with or without wheezing; Controls: children with asthma; Exc: known causes of productive cough | N=81 N completed=81 FU:NR Mean age=8.4y; range 6-14y N controls=60 | In children with chronic productive cough, "(a) do such diagnostic orphans exist? (b) if so, can they be classified in a clinically useful manner" | 2 |
| **Usta,[9] 2014 Turkey** | Single centre, paediatric allergy OPD; cohort | Inclusion: NR Exc: cardiac or chronic disease, prematurity, neuro-development, chest wall deformity, smoking, clubbing, if spirometry not possible | N cohort=156, N completed=156, FU=max 18mo for Dx, NR post Dx; Mean age=8.4y; SD 2.6 | "Evaluate assessment and Mx of chronic cough in children according to the British Thoracic Society guidelines" | 1, 2, 6 |
| **Van der Gast,[42] 2014; USA and Australia** | Multi-centre, Resp OPD; cross-sectional | PBB=clinical def; BE=Dx on CT scan; CF=positive sweat test | PBB=12, BE=19; CF=25; Respective mean (SD) age: 8.9y (4.7), 2.3y (1.7), 12.5y (3.5) | To compare: (a) the core and satellite microbiota in cohorts of children with different diseases; (b) the respiratory meta-communities in PBB and paediatric and adult CF and BE cases | 1, 2, 3 |
| **Wurzel[38] 2014 Australia** | Single centre, Resp OPD, cross-sectional | Children undergoing FB. Children categorised into wet cough, dry cough, no cough groups; Exc: CF | Wet cough n=143 Median age=26mo (IQR 15-60) Dry cough n=18 Median age=66mo (IQR 31-159) FU=NR | Examine the relationships between cough nature, lower airway infection and severity of neutrophilic airway inflammation | 2, 3, 4, 5 |
| **Wurzel[30] 2014;** | Single centre, Resp OPD; | PBB=clinical def; Controls=chronic resp symptoms, but not PBB or CSLD | PBB=104, Controls=21; Respective median age (IQR) | To provide extensive clinical, laboratory, and BAL | 1, 2 |

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| **Australia** | cross-sectional | | 19mo (12-30), and 20mo (8-63) | characterisation of PBB | |
| **Wurzel,[41] 2014; Australia** | Single centre, Resp OPD; cross-sectional | PBB=clinical def; BE=Dx on CT scan | PBB=159, BE=112; Median (IQR) age: PBB with AdV=17mo (12-22), PBB without AdV=26mo (15-56) | To identify: (a) the prevalence of AdV; (b) diversity of genotypes and species (c) whether presence of AdV increased the odds of bacterial coinfection | 1, 3, 4 |
| **RETROSPECTIVE STUDIES** | | | | | |
| **Chang[51] 2002, Australia** | Resp OPD, Chart review | CSLD (>4mo wet cough) Indigenous children | n=65; (n=33 bronchoscopy) Med age=3.8y (*n=28 of 33 radiological BE) | Children prospectively identified and charts reviewed retrospectively to describe airway abnormalities and relate these to chest HRCT scans | 5 |
| **Donnelly[16] 2007, England** | Single centre, Resp OPD; random review of clinic letters | "Persistent, wet cough present for 1mo that resolves with appropriate AB treatment" | N=81; Median age=3.8y (range 0.4-14.8); FU=NR | To present "results of a retrospective review of outcomes in 81 randomly selected patients diagnosed with PBB" | 1, 3, 6, 7 |
| **Douros[34] 2011, Greece** | Allergy-Resp OPD, Chart review | Chronic (>6w) wet cough with FB undertaken for criteria*; Exc: CF, immuno-deficiency, neuromuscular disorder, aspiration | 93; FU=NR Mean age=5.8y, SD 3.6 | In children with chronic wet cough: (a) Comparison of chest CT and FB in detecting airway abnormalities and (b) explore radiological and FB/BAL associations | 2, 3, 5 |
| **Goyal[33] 2014 Australia** | Single centre; Resp OPD, Chart and CT scan review | Chronic wet cough (>4w) and having completed >4w of oral ABs directed against likely resp bacteria Exc: asthma, CF, known BE or CT scans ordered by oncology, surgical, ICU, trauma services | N=144 (106 with BE); FU=NR; Median age=4.7y (range 0.3-17) | "To determine whether a child with chronic wet cough and poor response to at least 4w of oral ABs is more likely to have BE" (radiologically defined) | 2, 6 |
| **Kompare[25] 2011, USA** | Single centre, Resp & allergy OPD Bronchoscopy database review | Cough, wheeze or noisy breathing of >1mo without other diagnoses, infected BAL ($\geq 10^4$ cfu/ml) and response to ≥2w ABs | 70 in cohort (cough=51) Summary age NR; FU=NR | Review all infected BAL of children aged <5y with cough, wheeze or noisy breathing of >1 mo without other diagnoses, to determine if PBB present | 1, 2, 3, 5, 6 |

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| **Lim[72] 2012 England** | Single centre; Resp OPD; Chart review | Chronic wet cough (>8w) attending clinic over a 12mo period Exc: CF | 96 children with wet cough, 66 tested; All >2y (summary NR); FU=18mo | Prevalence of specific antibody deficiency in children with chronic wet cough"[72] | 2 |
| **Narang,[40] 2014; England** | Paediatric and Resp OPD; 50 consecutive notes | Suspected PBB (ND) | 50; Median age=2.9y (IQR 1.7-4.4) | Review BAL and CXR results, and assess the bacterial distribution across lung lobes | 1, 2, 3 |
| **Priftis,[28] 2013; Greece and England** | Resp OPD, Dual centre Chart review | Children with chronic cough suspicious of PBB who had FB to confirm diagnosis | Greece=18 England=39; Median age=4.8y (range 0.9-14.4) | To (a) determine specific serotypes of Spn and NTHi in BAL samples; (b) compare Spn serotypes between the 2 countries and Spn vaccination | 1, 2, 3 |
| **Pritchard[24] 2014, England** | Single centre, Paediatric or Resp OPD | AB responsive wet cough confirmed by a positive BAL culture (undefined) | 43 (+1 lost to FU); Median age=2.7y (IQR 1.5-4); FU=11.3mo (IQR 8.3–14.7) | Review of outcomes for children with AB responsive wet cough with positive BAL culture | 1, 2, 3, 6, 7 |
| **Rother[73] 2015, Germany** | 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. | 18 children with PBB | "To develop and test a questionnaire-based and data mining-supported tool providing diagnostic support for selected pulmonary diseases" | 1 |
| **Smith[13] 1985, USA** | Resp OPD, Chart review | Presence of chronic bronchitis by FB evaluation. Exc: CF or other abnormality that could contribute to chronic bronchitis | 20, FU=NR; Mean age=5.7y (range 0.5-15) | To investigate clinical, allergic, immunological and physiological characteristics of children with chronic bronchitis | 1, 6 |
| **Thomson[74] 2002, Australia** | Resp OPD, Chart review | Chronic cough >4w | n=49 Med age=39mo (range 4mo-14y) | Determine (i) the referring and final diagnosis; and (ii) the extent of the use of medications (asthma, GOR, antibiotics) prior to referral, and the side effects encountered in children referred over a 12mo period to paediatric respiratory physicians for persistent cough | |
| **Wang,[23] 2015; China** | Single centre, Hospitalised children in children's hospital, | Chronic cough (>4w) without acute lower resp infection and no response to conventional Rx. Exc: heart disease, immune-deficiency, | 66 with wet cough, of whom 50 had PBB; median age=10mo; (5.8–14[#]) | To describe the clinical characteristics children aged <3y with PBB | 1, 2, 3, 5 |

| | | | | | |
|---|---|---|---|---|---|
| | unclear how children were identified | pulmonary or bronchus dysplasia, neuro-muscular disease, foreign body aspiration | | | |
| **Zgherea[37] 2012, USA** | Single centre, Resp OPD,<br>Chart review | Primary symptom of chronic (>4w) wet cough who had FB.<br>Exc: CF, PCD, immunodeficiency, aspiration, asthma, genetic, known airway or neuro-muscular disorders | N=197,<br>FU=NR<br>Mean=NR<br>< 3y:55%; 3-7y:36%; >7 y: 9% | "Determine the frequency of lower respiratory tract bacterial infections in children with chronic wet cough and to analyze the bronchoscopic findings" | 2, 3, 5 |

AB=antibiotics; Abn=abnormality; ACCP=American College of Chest Physicians; AdV=adenovirus; Amox-clav=amoxicillin-clavulanate; BAL=bronchoalveolar lavage; BE=bronchiectasis; CF=cystic fibrosis; CFU=colony-forming unit; Clarithro=clarithromycin; CSLD;=chronic suppurative lung disease; CT=chest computed tomography; CXR=chest radiograph; d=days; DB=double blinded; Def=definition; Dis=disease; Dx=diagnosis; Exc=exclusion criteria; Exp=exploratory; FB=flexible bronchoscopy; FU=follow-up; mo=months; Gastro=gastroenterology; GI=gastrointestinal; GOR=gastro-oesophageal reflux; Hi=*Haemophilus influenzae*; HRCT=high-resolution computed tomography; ICS=inhaled corticosteroids; ICU=intensive care unit; IL=interleukin; IQR=interquartile range; KQs=key questions; MBL=mannose binding ligand; Mcat= *Moraxella catarrhalis;* Micro=microbiology; mo=months; Mx=management; N=number; ND=not defined; NF=nuclear factor; NR=not reported; NTHi=non-typeable *Haemophilus influenzae*; OPD=outpatients department; PBB=protracted bacterial bronchitis; PCD=primary ciliary dyskinesia; RCT=randomized control trial; Resp=Respiratory; Rx=treatment; Sa=*Staphylococcus aureus;* SD=standard deviation; SPA=surfactant protein A; Spn=*Streptococcus pneumoniae;* SR=spontaneous resolution; TLRs=toll-like receptors; TNF=tumour necrosis factor; w=weeks; y=year

[*]Not all children in cohort had PBB i.e. some had bronchiectasis
[#]Unclear what these figures refer to as figure in the table differed from the text

## Box

*Specific cough pointers[5,6,75] are:

**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 sino-pulmonary infections, immunodeficiency, epidemiological risk factors for exposure to tuberculosis.

**Signs:** respiratory distress, digital clubbing, chest wall deformity, auscultatory crackles.

**Tests:** Chest radiographic changes (other than perihilar changes), lung function abnormalities.

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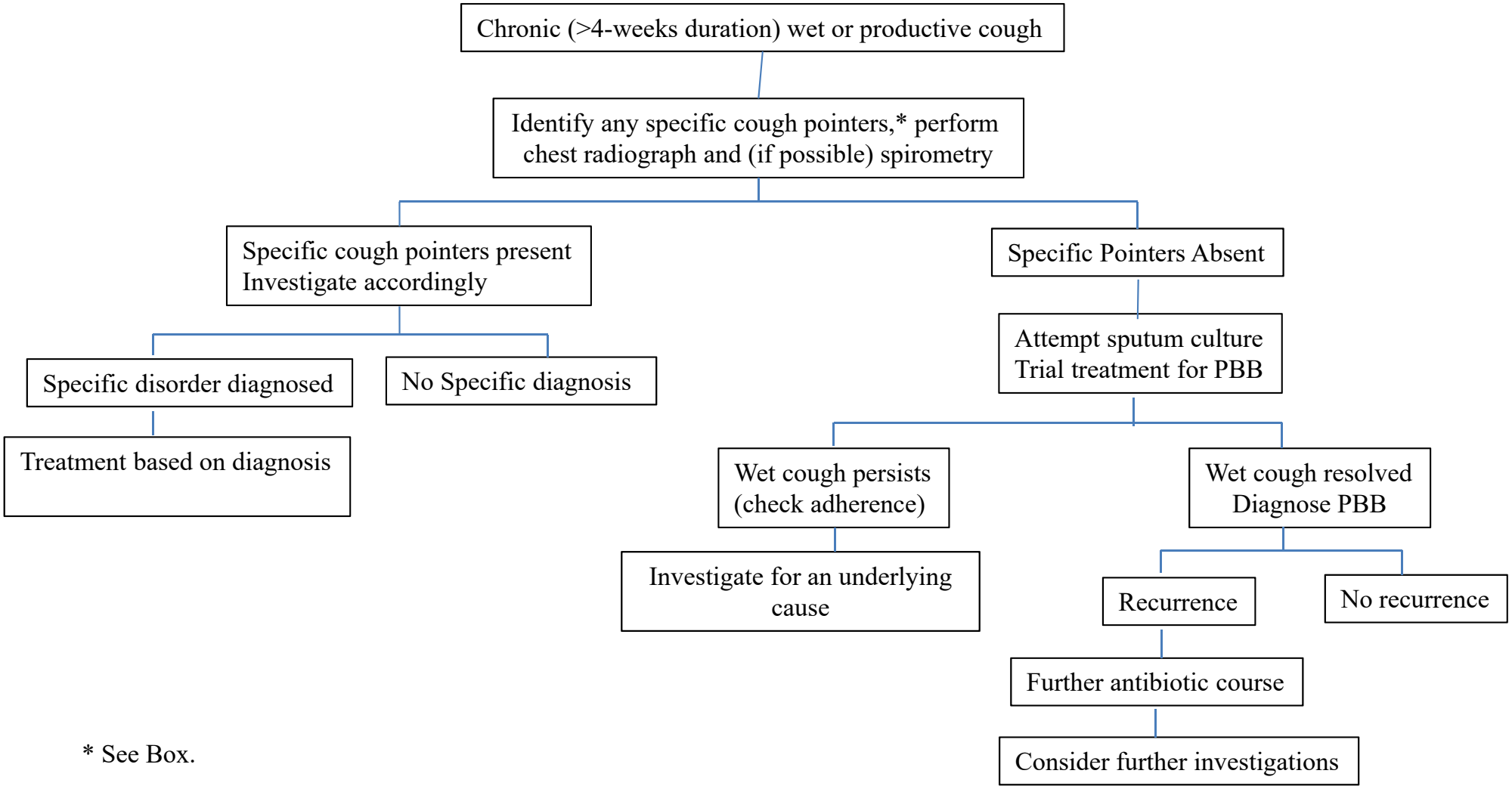
Chronic (>4-weeks duration) wet or productive cough
Identify any specific cough pointers,* perform chest radiograph and (if possible) spirometry
Specific cough pointers present Investigate accordingly
Specific Pointers Absent
Specific disorder diagnosed
No Specific diagnosis
Attempt sputum culture Trial treatment for PBB
Treatment based on diagnosis
Wet cough persists (check adherence)
Wet cough resolved Diagnose PBB
Investigate for an underlying cause
Recurrence
No recurrence
Further antibiotic course
Consider further investigations

* See Box.