Management of children with chronic wet cough and protracted bacterial bronchitis

Chang, Anne; Oppenheimer, JJ; Weinberger, M; Rubin, BK; GRANT, C; Weir, Kelly; Irwin, Richard

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Anne B. Chang, FRACP, PhD, John J. Oppenheimer, MD, Miles Weinberger, MD, FCCP, Bruce K. Rubin, MD, FRCPC, Cameron C. Grant, FRACP, PhD, Kelly Weir, PhD, Richard S. Irwin, MD, Master FCCP

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Anne B Chang, FRACP, PhD; John J Oppenheimer, MD; Miles Weinberger, MD, FCCP; Bruce K Rubin, MD, FRCPC; Cameron C Grant, FRACP, PhD; Kelly Weir, PhD; Richard S Irwin, MD, Master FCCP

on behalf of the CHEST Expert Cough Panel

Affiliations: Menzies School of Health Research (Chang); Respiratory Dept, Lady Cilento Children’s Hospital, Qld Uni of Technology Queensland, Australia (Dr Chang); New Jersey Medical School, Pulmonary and Allergy Associates, Morristown, New Jersey, USA (Dr Oppenheimer); UMass Memorial Medical Center, Worcester, MA, USA (Dr Irwin); Griffith University, Gold Coast, Qld, Australia (Dr Weir); Children’s Hospital of Richmond at Virginia Commonwealth University, Richmond, VA, USA (Dr Rubin); Department of Paediatrics: Child and Youth Health, Faculty of Medicine and Health Sciences, The University of Auckland, Auckland, New Zealand (Dr Grant); Pediatric Allergy, Immunology, and Pulmonology Division, University of Iowa Children’s Hospital, Iowa City, Iowa, USA (Dr Weinberger).

Corresponding author

Prof Anne Chang

Dept of Respiratory and Sleep medicine

Lady Cilento Children’s Hospital, South Brisbane, Queensland 4101, Australia
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Abstract

Background: Wet or productive cough is common in children with chronic cough. We formulated recommendations based on systematic reviews relating to the management of chronic wet cough in children (aged ≤14-years) based on key questions (KQ1)-how effective are antibiotics in improving the resolution of cough? If so, what and for how long? and; (KQ2)-when should children be referred for further investigations?

Methods: We used the CHEST expert cough panel’s protocol for the systematic reviews and the American College of Chest Physicians (CHEST) methodological guidelines and GRADE framework. Data from the systematic reviews in conjunction with patients’ values and preferences and the clinical context were used to form recommendations. Delphi methodology was used to obtain consensus for the recommendations/suggestions made.

Results: Combining data from the systematic reviews, we found high quality evidence in children aged ≤14-years with chronic (>4-weeks duration) wet/productive cough that using appropriate antibiotics improves cough resolution and; further investigations (e.g. flexible bronchoscopy, chest CTs and immunity tests) should be undertaken when specific cough pointers (e.g. digital clubbing) are present. When the wet cough does not improve following 4-weeks of antibiotics there is moderate quality evidence that further investigations should be considered to look for an underlying disease. New recommendations include the recognition of the clinical diagnostic entity of protracted bacterial bronchitis.

Conclusion: Compared to the 2006 Cough Guidelines, there is now high quality evidence for some, but not all, aspects of the management of chronic wet cough in specialist settings. However, further studies particularly in primary health are required.
**Abbreviation list**

ACCP=American College of Chest Physicians

BAL=bronchoalveolar lavage

BTS=British Thoracic Society

CI=Confidence Interval

FB=flexible bronchoscopy

KQ=Key Question

LR=Likelihood Ratio

NNT- number needed to treat

OR=Odds ratio

PBB=Protracted bacterial Bronchitis

PC-QOL= Parent Cough-Specific Quality of Life

PV=Predictive Value

QoL=Quality of Life

RCT=Randomized Controlled Trial

TSANZ=Thoracic Society of Australia and New Zealand
Summary of recommendations/suggestions

1. For children aged \( \leq 14 \)-years with chronic (>4 weeks duration) wet or productive cough unrelated to an underlying disease and without any specific cough pointers (e.g., coughing with feeding, digital clubbing), we recommend that children receive 2 weeks of antibiotics targeted to common respiratory bacteria (Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis) and local antibiotic sensitivities (Grade 1A).

2. For children aged \( \leq 14 \)-years with chronic wet or productive cough unrelated to an underlying disease and without any specific cough pointers (e.g., coughing with feeding, digital clubbing) and whose cough resolves within 2 weeks of treatment with antibiotics targeted to local antibiotic sensitivities, we recommend that the diagnosis of protracted bacterial bronchitis (PBB) be made (Grade 1C).

3. For children aged \( \leq 14 \)-years with protracted bacterial bronchitis (PBB) with lower airway (bronchoalveolar lavage or sputum) confirmation of clinically important density of respiratory bacteria (\( \geq 10^4 \) cfu/ml), we recommend that the term ‘microbiologically-based-PBB (or PBB-micro) be used to differentiate it from clinically-based-PBB (PBB without lower airway bacteria confirmation) (Grade 1C).

4. For children aged \( \leq 14 \)-years with chronic wet or productive cough unrelated to an underlying disease and without any specific cough pointers (e.g., coughing with feeding, digital clubbing) when the wet cough persists after 2 weeks of appropriate antibiotics, we recommend treatment with an additional 2 weeks of the appropriate antibiotic(s) (Grade 1C).

5. For children aged \( \leq 14 \)-years with chronic wet or productive cough unrelated to an underlying disease and without any specific cough pointers (e.g., coughing
with feeding, digital clubbing), when the wet cough persists after 4 weeks of appropriate antibiotics, we suggest that further investigations (e.g. flexible bronchoscopy with quantitative cultures and sensitivities with or without chest computed tomography) be undertaken (Grade 2B).

6. For children aged ≤ 14-years with chronic wet or productive cough unrelated to an underlying disease and with specific cough pointers (e.g. coughing with feeding, digital clubbing), we recommend that further investigations (e.g. flexible bronchoscopy and/or chest computed tomography, assessment for aspiration and/or evaluation of immunologic competency) be undertaken to assess for an underlying disease (Grade 1B).

7. For children aged ≤ 14-years with chronic wet or productive cough unrelated to an underlying disease and without any specific cough pointers (e.g., coughing with feeding, digital clubbing), we suggest that randomized controlled trials on the efficacy of different durations of antibiotics be undertaken in various clinical settings (particularly in primary care) to determine its influence on the number to treat and recurrence. When doing so, we suggest that validated cough outcomes and a-priori definitions be used (Ungraded Consensus–based Statement).
**Introduction**

Chronic wet cough is common among children whose parents seek medical consultations from specialty centers. As young children do not usually expectorate, wet cough is defined by its loose, self-propagating sound, was substituted for productive cough in this age group. When children can expectorate, the term productive cough is preferred. Decades ago, astute clinicians recognized that early diagnosis and management of chronic productive cough was likely important for future lung health. Further reasons why the recognition and treatment of chronic wet/productive cough in children are important were previously highlighted.

The 2006 American College of Chest Physicians (CHEST) guidelines on chronic cough in children advocated that when a wet cough was present and there were no other symptoms and signs (e.g. dysphagia or digital clubbing), antibiotics should be prescribed. However, there was limited evidence upon which this recommendation was made. For this update as required by the CHEST Guideline Committee, we undertook systematic reviews addressing key questions concerning the management in children with chronic wet or productive cough unrelated to established chronic lung disease (i.e. when children first present to clinicians with a previously undiagnosed condition). Here, we present the summary of evidence behind the recommendations formulated on findings of the systemic reviews that examined two related key questions (KQs) in children with chronic (>4 weeks) wet or productive cough not related to bronchiectasis; (KQ1): How effective are antibiotics in improving the resolution of cough? If so what antibiotic should be used and for how long? (KQ2): When should children be referred for further investigations? This manuscript should be read with the accompanying systematic review.
In line with the CHEST cough guidelines, it was determined a-priori that the age cutoff for pediatric and adult components was to be 14 years. While the recommendations addresses children aged < 14 years, premature infants and neonates are excluded from these recommendations. In premature infants and neonates, respiratory illnesses are much more likely to manifest as tachypnea, dyspnea and/or hypoxemia and rarely by chronic cough.

**Materials and methods**

We used a standard method as previously used by panel members:7 “(The methodology used by the CHEST Guideline Oversight Committee to select the Expert Cough Panel Chair and the international panel of experts, perform the synthesis of the evidence and develop the recommendations and suggestions has been published.8,9 Key questions and parameters of eligibility were developed for this topic. Existing guidelines, systematic reviews, and primary studies were assessed for relevance and quality, and were used to support the evidence-based graded recommendations or suggestions. A highly structured consensus-based Delphi approach was employed to provide expert advice on all guidance statements. The total number of eligible voters for each guideline statement varied based on the number of managed individuals recused from voting on any particular statements because of their potential conflicts of interest. Transparency of process was documented. Further details of the methods have been published elsewhere.8,9)” In line with the CHEST guideline methodology,8,9 a comprehensive, systematic review of the literature was undertaken to provide the evidence base for recommendations outlined here.

**Guideline Framework**

As previously described,7 “the ACCP has adopted the GRADE framework (The Grading of Recommendations Assessment, Development and Evaluation). This framework separates the
process of rating the quality of evidence from that of determining the strength of recommendation. The quality of evidence is based on the five domains of risk of bias, inconsistency, indirectness, reporting bias and imprecision. The quality of evidence (i.e., the confidence in estimates) is rated as high (A), moderate (B), low or very low (C). The strength of recommendation is determined based on the quality of evidence, balance of benefits and harms, patients’ values and preferences and availability of resources”. Recommendations can be strong vs weak or Grade 1 vs 2 or ungraded.

State of the available evidence

Searches for the systematic reviews were externally undertaken by librarians (Nancy Harger, MLS and Judy Nordberg, MLS) from the University of Massachusetts Medical School, Worcester, MA USA. These searches were undertaken between 19-27 July 2015, using an a-priori established protocol for each key question (KQ). The evidence for the KQs was summarized in a previous publication.

The systematic review identified high-quality evidence to support some recommendations but not all. Where there was insufficient evidence for diagnosis and management recommendations, the panel heavily considered patient values, preferences, ease and cost of tests, and availability of potential therapies. The panel also made several suggestions for future research.

Results

The first 6 recommendations and/or suggestions were derived from findings from our systematic reviews that addressed the KQs above. The PRISMA diagrams and included studies were presented in the publication.
Summary of evidence and interpretation

The efficacy of antibiotic treatment for resolving chronic wet cough in children was evident from three RCTs where the forest plot from the combined RCT data demonstrated a clear benefit (NNT for benefit by end of study was 3, 95% CI 2.0-4.3). Consistent with RCT data, all other studies included in the systematic review reported benefit irrespective of the study design (e.g. prospective and retrospective studies).

However, our systematic review found lower level evidence with regard to the type and duration of antibiotics required. The duration used ranged from 1 to 8 weeks; prospective studies used a shorter duration of treatment (7-days to 2-weeks) whereas the retrospective studies reported longer durations (4-6 weeks and 6-8 weeks). The summary of evidence indicates that, in general, a 2-week course is sufficient but up to 4-weeks may be required in a minority of children. The British Thoracic Society (BTS) cough guidelines suggest the use of 4–6 weeks of antibiotics in children suspected of having PBB. However, our systematic review did not identify any prospective study-derived evidence for this statement. While a full 4-weeks or longer course may be needed in a minority of patients, a shorter initial course is advocated in our current era of judicious anti-microbial stewardship. Further, a study showed that children with chronic wet cough that does not resolve after 4-weeks of appropriate oral antibiotics have an increased likelihood (adjusted OR=5.9, 95%CI 1.2-28.5) of CT scan diagnosed bronchiectasis.

Prospective and retrospective studies have shown clinically important levels of respiratory bacteria density (≥10^4 cfu/ml) in the BAL of children with chronic wet cough. The common lower airway bacteria pathogens reported in prospective studies of children with chronic wet
cough were *Haemophilus influenzae* (non-typeable when typing done), *Moraxella catarrhalis* and *Streptococcus pneumoniae*. Some retrospective studies also reported *Staphylococcus aureus* in some (11/50) children with PBB, but quantitative bacteriology was not performed making interpretation difficult. Amoxicillin-clavulanate was the most commonly used single antibiotic (the primary antibiotic in 7 studies) followed by clarithromycin in 3 studies, erythromycin in one and cefaclor in one. The retrospective studies used a variety of antibiotic types.

PBB is a condition first described in 2006. The criteria in the original description of PBB were: (i) presence of chronic wet cough, (ii) response (cough resolution) to antibiotics (amoxicillin-clavulanate) within 2-weeks of use, and, (iii) lower airway infection defined as presence of respiratory pathogens at a density of $\geq 10^4$ cfu/ml BAL, in the absence of evidence of infection with *Bordetella pertussis*, *Mycoplasma pneumoniae* or chlamydia infection (by PCR and/or serology). In a double-blind placebo controlled RCT where a flexible bronchoscopy (FB) was performed pre-treatment (amoxicillin clavulanate or placebo) in subgroup of children with chronic wet cough, their bronchoalveolar lavage (BAL) data were consistent with protracted bacterial bronchitis (PBB). However, it was not feasible or warranted that all children with chronic wet cough undergo a FB. Thus, it has been advocated that criterion-(iii) be replaced by absence of other causes of wet or productive cough. Our systematic review found mechanistic or pathobiological studies that provide firm evidence of PBB as a diagnostic clinical entity. We also identified several studies that used cough management pathways where a key step was the use of antibiotic treatment in children with chronic wet cough who did not have other symptoms or signs. FB was not undertaken in these studies when the cough resolved with antibiotic treatment, supporting the concept of the
diagnosis of PBB without lower airway microbiology confirmation (i.e. clinically defined PBB).

1. For children aged $\leq 14$-years with chronic (>4 weeks duration) wet or productive cough unrelated to an underlying disease and without any specific cough pointers (e.g. coughing with feeding, digital clubbing), we recommend that children receive 2 weeks of antibiotics targeted to common respiratory bacteria (Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis) and local antibiotic sensitivities (Grade 1A).

2. For children aged $\leq 14$-years with chronic wet or productive cough unrelated to an underlying disease and without any specific cough pointers (e.g., coughing with feeding, digital clubbing) and whose cough resolves within 2 weeks of treatment with antibiotics targeted to local antibiotic sensitivities, we recommend that the diagnosis of protracted bacterial bronchitis (PBB) be made (Grade 1C).

3. For children aged $\leq 14$-years with protracted bacterial bronchitis (PBB) with lower airway (bronchoalveolar lavage or sputum) confirmation of clinically important density of respiratory bacteria ($\geq 10^4$ cfu/ml), we recommend that the term ‘microbiologically-based-PBB’ (or PBB-micro) be used to differentiate it from clinically-based-PBB (PBB without lower airway bacteria confirmation) (Grade 1C).

4. For children aged $\leq 14$-years with chronic wet or productive cough unrelated to an underlying disease and without any specific cough pointers (e.g., coughing with feeding, digital clubbing) when the wet cough persists after 2 weeks of appropriate
antibiotics, we recommend treatment with an additional 2 weeks of the appropriate antibiotic(s) (Grade 1C).

Summary of evidence and interpretation

Data in our systematic review on chronic wet cough were in agreement with that on the use of cough management pathways with regard to undertaking investigations when cough pointers (e.g. coughing with feeding, digital clubbing, see Table 1 for list) are present and when the wet cough does not resolve within a specific time-frame following the use of antibiotics. The type of investigations initiated were dependent on the child’s clinical features. However, the time-frame used for ‘non-resolution’ following a course of antibiotics differed among studies; although most studies used a cut-off of 4 weeks. Our systematic review also identified two studies that described an increased risk of the presence of underlying lung disease such as bronchiectasis when the cough did not respond to 2-4 weeks of antibiotics. One additional study described that longer cough duration was associated with worse radiological features (higher Bhalla score) and more structural airway abnormality (type of airway obstruction). The Bhalla score is CT scan derived score where a higher score indicates worse bronchiectasis.

Our systematic review found that in the majority of studies that described the investigation of chronic wet cough, FB with BAL and/or chest CT scans or assessment of immunity were the tests most commonly undertaken. FBs abnormalities described included tracheal and bronchial malacia, visualization of purulent secretions and/or BAL data. When BAL data were reported and was although interpreted by the study authors as being consistent with infection, quantitative bacteriology was only undertaken in some studies. The types of investigations were targeted to the population and sampling frame. For example, in settings
with high tuberculosis exposure, appropriate tests for *M. tuberculosis* infection were required.\textsuperscript{3,28}

5. **For children aged \( \leq 14 \)-years with chronic wet or productive cough unrelated to an underlying disease and without any specific cough pointers (e.g., coughing with feeding, digital clubbing), when the wet cough persists after 4 weeks of appropriate antibiotics, we suggest that further investigations (e.g. flexible bronchoscopy with quantitative cultures and sensitivities with or without chest computed tomography) be undertaken** (Grade 2B).

6. **For children aged \( \leq 14 \)-years with chronic wet or productive cough unrelated to an underlying disease and with specific cough pointers (e.g. coughing with feeding, digital clubbing), we recommend that further investigations (e.g. flexible bronchoscopy and/or chest computed tomography, assessment for aspiration and/or evaluation of immunologic competency) be undertaken to assess for an underlying disease** (Grade 1B).

**Summary of evidence and interpretation**

In addition to the lack of available information outlined above, our systematic review\textsuperscript{3} was limited by the small number of studies. Also, all but one study were undertaken in major hospitals. Large multicenter studies particularly in primary care will be required to build the evidence base to inform management outside of major hospitals or tertiary referral center.

When cough is used as a study outcome, the use of validated outcome measures would improve the quality of studies. The lack of the use of validated cough outcomes and *a priori* definitions are major limitations of many chronic cough studies in children.\textsuperscript{27}

7. **For children aged \( \leq 14 \)-years with chronic wet or productive cough unrelated to an underlying disease and without any specific cough pointers (e.g., coughing with
feeding, digital clubbing), we suggest that randomized controlled trials on the
efficacy of different durations of antibiotics be undertaken in various clinical settings
(particularly in primary care) to determine its influence on the number to treat and
recurrence. When doing so, we suggest that validated cough outcomes and a-priori
definitions be used (Ungraded Consensus–based Statement).

Areas for further research

To advance and improve the management of chronic wet or productive cough in children,
suggested areas of research include:

1. Determining the outcomes of chronic wet cough following an acute infection in
   various settings (community and hospital) through undertaking multi-center cohort
   studies.

2. Multi-center parallel RCTs addressing the efficacy of antibiotics for the treatment of
   chronic wet cough in primary care, using validated cough outcome measures and a-
   priori definitions of cough resolution. Ideally, an objective cough outcome (such as
   cough counts) should also be included as an outcome.

3. Determining the optimal length of antibiotics in different circumstances (e.g. relating
   to prevention of recurrence, duration of chronic cough, type of bacteria and age of
   children).

4. Studies to address the most appropriate time point when the child should be referred
   for further investigations when specific cough pointers (Table 1) are absent and the
   wet cough persists after antibiotics.

5. Intervention studies to prevent recurrence of PBB, especially for those having very
   frequent recurrences.
Conclusions

This update of the 2006 CHEST Cough Guidelines relating to chronic wet cough in children has resulted in new recommendations formulated from systematic reviews addressing 2 key clinical questions. The clinical diagnostic entity of PBB, not mentioned in the 2006 guidelines, is now recognized. These recommendations were endorsed by the CHEST Expert Cough Panel. There is high quality evidence relating to most of the recommendations but many questions remain particularly in primary care where there is scarcity of data.

Author contributions: AC, JO and RI drafted the key recommendations and all authors reviewed them; AC drafted the manuscript, had full access to the data and takes responsibility for the integrity of all of the data and the accuracy of the data analysis. All authors critically reviewed the manuscript.

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<td>• daily moist or productive cough</td>
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<td>neonatal lung disease, foreign body aspiration)</td>
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References


