CHEST

Management of Children With Chronic Wet Cough and Protracted Bacterial Bronchitis

CHEST Guideline and Expert Panel Report

Anne B. Chang, MBBS, PhD, MPH; John J. Oppenheimer, MD; Miles M. Weinberger, MD, FCCP; Bruce K. Rubin, MD; Cameron C. Grant, MBChB, PhD; Kelly Weir, BSpThy, MSpPath, PhD, CPSP; and Richard S. Irwin, MD, Master FCCP; on behalf of the CHEST Expert Cough Panel

BACKGROUND: Wet or productive cough is common in children with chronic cough. We formulated recommendations based on systematic reviews related to the management of chronic wet cough in children (aged ≤ 14 years) based on two key questions: (1) how effective are antibiotics in improving the resolution of cough? If so, what antibiotic should be used and for how long? and (2) when should children be referred for further investigations?

METHODS: We used the CHEST expert cough panel's protocol for systematic reviews and the American College of Chest Physicians (CHEST) methodologic guidelines and GRADE framework (the Grading of Recommendations Assessment, Development and Evaluation). 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 (eg, flexible bronchoscopy, chest CT scans, immunity tests) should be undertaken when specific cough pointers (eg, digital clubbing) are present. When the wet cough does not improve following 4 weeks of antibiotic treatment, 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.

CONCLUSIONS: Compared with 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.

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KEY WORDS: children; cough; evidence-based; guidelines; management

ABBREVIATIONS: FB = flexible bronchoscopy; KQ = key question; PBB = protracted bacterial bronchitis; RCT = randomized controlled trial

AFFILIATIONS: From the Menzies School of Health Research (Dr Chang), Darwin, NT, Australia; Department of Respiratory and Sleep Medicine (Dr Chang), Lady Cilento Children's Hospital, South Brisbane, QLD, Australia; Queensland University of Technology (Dr Chang), QLD, Australia; New Jersey Medical School, Pulmonary and Allergy Associates, Morristown, NJ (Dr Oppenheimer); UMass Memorial Medical Center, Worcester, MA (Dr Irwin); Griffith University (Dr Weir), Gold Coast, QLD, Australia; Children's Hospital of Richmond at Virginia Commonwealth University (Dr Rubin), Richmond, VA; Department of Paediatrics: Child and Youth Health (Dr Grant), Faculty of Medicine and Health Sciences, The University of Auckland, Auckland, New Zealand; and the Pediatric Allergy, Immunology, and Pulmonology Division (Dr Weinberger), University of Iowa Children's Hospital, Iowa City, IA.

CORRESPONDENCE TO: Anne B. Chang, MBBS, PhD, MPH, Department of Respiratory and Sleep Medicine, Lady Cilento Children's Hospital, South Brisbane, QLD 4101, Australia; e-mail: annechang@ausdoctors.net

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Summary of Recommendations/Suggestions

1. For children aged ≤ 14 years with chronic (> 4 weeks' duration) wet or productive cough unrelated to an underlying disease and without any specific cough pointers (eg, 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 ≤ 14 years with chronic wet or productive cough unrelated to an underlying disease and without any specific cough pointers (eg, 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 ≤ 14 years with PBB with lower airway (bronchoalveolar lavage or sputum) confirmation of clinically important density of respiratory bacteria (≥ 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 ≤ 14 years with chronic wet or productive cough unrelated to an underlying disease and without any specific cough pointers (eg, 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 ≤ 14 years with chronic wet or productive cough unrelated to an underlying disease and without any specific cough pointers (eg, coughing with feeding, digital clubbing), when the wet cough persists after 4 weeks of appropriate antibiotics, we suggest that further investigations (eg, 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 (eg, coughing with feeding, digital clubbing), we recommend that further investigations (eg, 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 (eg, 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).

Chronic wet cough is common among children whose parents seek medical consultations from specialty centers.[1] Young children do not usually expectorate. Thus the term wet cough is used instead, and this is defined by its loose, self-propagating sound, was substituted for productive cough in this age group.[2] When children can expectorate, the term productive cough is preferred.[3] Decades ago, astute clinicians recognized that early diagnosis and management of chronic productive cough were likely important for future lung health.[4,5] Additional reasons why the recognition and treatment of chronic wet/productive cough in children are important were highlighted previously.[3]

The 2006 American College of Chest Physicians (CHEST) guidelines on chronic cough in children[6] advocated that when a wet cough was present and there were no other symptoms and signs (eg, dysphagia or digital clubbing), antibiotics should be prescribed. However, this recommendation was made with the use of limited evidence. For the present update as required by the CHEST Guideline Committee, we undertook systematic reviews addressing key questions (KQs) concerning the management of children with chronic wet or productive cough unrelated to established chronic lung disease (ie, when children first present to clinicians with a previously undiagnosed condition).[3] The present article is a summary of the evidence behind the recommendations formulated on findings of the systemic reviews that examined two related KQs in children with chronic (> 4 weeks) wet or productive cough not related to bronchiectasis. KQ1 was as follows: How effective are antibiotics in improving the resolution of cough? If so, what antibiotic should be used and for how long? KQ2 was as follows: When should children be referred for further

investigations? The present article should be read with the accompanying systematic review.[3]

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. Although the recommendations address 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 (ie, 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 performed externally by librarians (Nancy Harger, MLS, and Judy Nordberg, MLS) from the University of Massachusetts Medical School, Worcester, Massachusetts. These searches were conducted between July 19 and July 27, 2015, using an a priori established protocol for each KQ.[3] The evidence for the KQs was summarized in a previous publication.[3]

The systematic review[3] 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 six recommendations and/or suggestions were derived from findings from our systematic reviews that addressed the aforementioned KQs.[3] Diagrams according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement and included studies were presented in the prior publication.

Summary of Evidence and Interpretation

The efficacy of antibiotic treatment for resolving chronic wet cough in children was evident from three randomized controlled trials (RCTs) in which the forest plot from the combined RCT data showed a clear benefit (number needed to treat for benefit by end of study was 3 [95% CI, 2.0-4.3]).[3] Consistent with RCT data, all other studies included in the systematic review reported benefit irrespective of the study design (eg, prospective and retrospective studies).

However, our systematic review[3] found lower level evidence with regard to the type and duration of antibiotics required. The duration of treatment ranged from 1 to 8 weeks; prospective studies used a shorter duration (7 days[10,11] to 2 weeks[12-17]), whereas the retrospective studies reported longer durations (4-6 weeks[18] and 6-8 weeks[19]). 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.[3,20] The British Thoracic Society cough guidelines[21] suggest the use of 4 to 6 weeks of antibiotics in children suspected of having protracted bacterial bronchitis (PBB). However, our systematic review did not identify any prospective study-derived evidence for this statement. Although a full 4 weeks or longer course may be needed in a minority of patients, a shorter initial course is advocated in the current era of judicious antimicrobial stewardship. Furthermore, one 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.[22]

Prospective and retrospective studies have found clinically important levels of respiratory bacteria density

($\geq 10^4$ CFUs/mL) in the BAL of children with chronic wet cough.[3] The common lower airway bacteria pathogens reported in prospective studies of children with chronic wet cough were *Haemophilus influenzae* (nontypeable when typing was done), *Moraxella catarrhalis,* and *Streptococcus pneumoniae*.[20] Other retrospective studies also reported *Staphylococcus aureus* in some (11 of 50) children with PBB,[23] but quantitative bacteriologic testing was not performed, making interpretation difficult. Amoxicillin-clavulanate was the most commonly used single antibiotic (the primary antibiotic in seven studies[11,13,15,16,18,19,24]) followed by clarithromycin in three studies,[12,14,17] erythromycin in one study,[10] and cefaclor in one study.[25] The retrospective studies used a variety of antibiotic types.[18,19,24,25]

PBB was first described in 2006.[15] The criteria in the original description of PBB were as follows: (1) presence of chronic wet cough; (2) response (cough resolution) to antibiotics (amoxicillin-clavulanate) within 2 weeks of use; and (3) lower airway infection defined as the presence of respiratory pathogens at a density $\geq 10^4$ CFUs/mL BAL,[15] in the absence of evidence of infection with *Bordetella pertussis, Mycoplasma pneumoniae*, or chlamydia infection (according to polymerase chain reaction and/or serologic testing). In a double-blind, placebo-controlled RCT[16] in which a flexible bronchoscopy (FB) was performed pretreatment (amoxicillin-clavulanate or placebo) in a subgroup of children with chronic wet cough, their BAL data were consistent with PBB. However, it was not feasible or warranted that all children with chronic wet cough undergo a FB. Thus, it has been advocated that the third criterion be replaced by absence of other causes of wet or productive cough.[26] Our systematic review found mechanistic or pathobiologic studies that provide firm evidence of PBB as a diagnostic clinical entity. We also identified several studies that used cough management pathways in which a key step was the use of antibiotic treatment in children with chronic wet cough who did not have other symptoms or signs.[3] FB was not performed in these studies when the cough resolved with antibiotic treatment, supporting the concept of the diagnosis of PBB without lower airway microbiology confirmation (ie, clinically defined PBB).

1. For children aged ≤ 14 years with chronic (> 4 weeks' duration) wet or productive cough unrelated to an underlying disease and without any specific cough pointers (eg, 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 ≤ 14 years with chronic wet or productive cough unrelated to an underlying disease and without any specific cough pointers (eg, 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 ≤ 14 years with 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 ≤ 14 years with chronic wet or productive cough unrelated to an underlying disease and without any specific cough pointers (eg, 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[22] were in agreement with those on the use of cough management pathways[27] with regard to undertaking investigations when cough pointers (eg, coughing with feeding, digital clubbing) (Table 1) 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 depended on the child's clinical features.[3] However, the time frame used for "nonresolution" following a course of antibiotics differed among studies, although most studies used a cutoff of 4 weeks.[12-15,28] Our systematic review[3] also identified two studies[19,22] that described an increased risk of the presence of underlying lung disease such as bronchiectasis when the cough did not respond to 2 to 4 weeks of antibiotic treatment. One additional study[29] determined that longer cough duration was associated with worse radiologic features (higher Bhalla[30] score)

TABLE 1] Extended List of Cough Pointers (Modified From Previous Articles[6,26,33])

Systemic	Pulmonary
• Cardiac abnormalities	• Chest pain
• Digital clubbing	• Daily moist or productive cough
• Failure to thrive	• Hemoptysis
• Medications or drugs associated with chronic cough (angiotensin-converting enzyme inhibitors, illicit drug use)	• Abnormal cough characteristics (brassy, plastic bronchitis, paroxysmal with/without posttussive vomiting, staccato, cough from birth)
• Neurodevelopmental abnormality	• Recurrent pneumonia
• Fever	• Hypoxia/cyanosis
• Immunodeficiency (primary or secondary)	• History of previous lung disease or predisposing causes (eg, neonatal lung disease, foreign body aspiration)
• Feeding difficulties	• Exertional dyspnea
• History of contacts (eg, TB)	• Dyspnea at rest or tachypnea
	• Chest wall deformity
	• Auscultatory findings (eg, stridor, wheeze, crackles)
	• Chest radiograph abnormalities
	• Pulmonary function test abnormalities

and more structural airway abnormality (type of airway obstruction[31]). The Bhalla score is a CT scan-derived score in which a higher score indicates worse bronchiectasis.

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

5. For children aged ≤ 14 years with chronic wet or productive cough unrelated to an underlying disease and without any specific cough pointers (eg, coughing with feeding, digital clubbing), when the wet cough persists after 4 weeks of appropriate antibiotics, we suggest that further investigations (eg, 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 (eg, coughing with feeding, digital clubbing), we recommend that further investigations (eg, 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 earlier, our systematic review[3] was limited by the small number of studies. In addition, all but one study were conducted 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 centers. 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.[27]

7. For children aged ≤ 14 years with chronic wet or productive cough unrelated to an underlying disease and without any specific cough pointers (eg, 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 the performance of multicenter cohort studies.
2. Multicenter, parallel-group RCTs addressing the efficacy of antibiotics for the treatment of chronic wet cough in primary care, using validated cough outcome measures[32] and a priori definitions of cough resolution. Ideally, an objective cough outcome (eg, cough counts) should also be included as an outcome.
3. Determining the optimal length of antibiotics in different circumstances (eg, relating to prevention of recurrence, duration of chronic cough, type of bacteria, 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 antibiotic treatment.
5. Intervention studies to prevent recurrence of PBB, especially for those having very frequent recurrences.

Conclusions

This update of the 2006 CHEST Cough Guidelines[6] relating to chronic wet cough in children has resulted in new recommendations formulated from systematic reviews addressing two 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 the data are scarce.

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