

Children With Chronic Wet or Productive Cough—Treatment and Investigations

A Systematic Review



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BACKGROUND: Systematic reviews were conducted to examine two related key questions (KQs) in children with chronic (> 4 weeks' duration) 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 they be referred for further investigations?

METHODS: The systematic reviews were undertaken based on the protocol established by selected members of the CHEST expert cough panel. Two authors screened searches and selected and extracted data. The study included systematic reviews, randomized controlled trials (RCTs), cohort (prospective and retrospective) studies, and cross-sectional studies published in English.

RESULTS: Data were presented in Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowcharts, and the summaries were tabulated. Fifteen studies were included in KQ1 (three systematic reviews, three RCTs, five prospective studies, and four retrospective studies) and 17 in KQ2 (one RCT, 11 prospective studies, and five retrospective studies). Combining data from the RCTs (KQ1), the number needed to treat for benefit was 3 (95% CI, 2.0-4.3) in achieving cough resolution. In general, findings from prospective and retrospective studies were consistent, but there were minor variations.

CONCLUSIONS: There is high-quality evidence that in children aged ≤ 14 years with chronic (> 4 weeks' duration) wet or productive cough, the use of appropriate antibiotics improves cough resolution. There is also high-quality evidence that when specific cough pointers (eg, digital clubbing) are present in children with wet cough, further investigations (eg, flexible bronchoscopy, chest CT scans, immunity tests) should be conducted. When the wet cough does not improve by 4 weeks of antibiotic treatment, there is moderate-quality evidence that children should be referred to a major center for further investigations to determine whether an underlying lung or other disease is present. CHEST 2016; 149(1):120-142

KEY WORDS: cough; evidence based; systematic review; treatment

ABBREVIATIONS: BAL = bronchoalveolar lavage; FB = flexible bronchoscopy; KQ = key question; NNT = number-needed-to-treat; PBB = protracted bacterial bronchitis; RCT = randomized controlled trial

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DOI: <http://dx.doi.org/10.1378/chest.15-2065>

The burden of chronic cough in children and the importance of early diagnosis and management were recently highlighted.^{1,2} It has long been recognized by clinicians that early diagnosis and management of chronic productive cough are likely important for future lung health.^{3,4} Because young children do not usually expectorate, wet cough is substituted for productive cough in this age group. When children can expectorate, the term productive cough is preferred.

Chronic wet cough is common among children whose parents sought medical consultations.⁵ Using a standard management approach,⁶ a priori definitions, and validated cough outcome measures, an Australian multicenter study⁵ found that 63.9% of the 346 children newly referred to pediatric pulmonologists for chronic cough (> 4 weeks' duration) had wet or productive cough. Of the 346 children, the two most common conditions associated with wet cough were protracted bacterial bronchitis (PBB) in 142 children (41%) and chest CT scan-proven bronchiectasis in 31 children (9%).⁵

Appropriate management of children with chronic wet cough is arguably important for several reasons. First, chronic wet cough can signify an underlying illness such as aspiration lung disease,⁷ cystic fibrosis, or non-cystic fibrosis bronchiectasis.⁵ Second, the long-term outcomes for these underlying conditions are likely better when diagnosed and appropriately managed early in the disease course. For example, in children, unlike in

adults, early bronchiectasis (most commonly manifested by chronic wet cough) that is unassociated with pneumonia may be reversible when appropriately managed,^{4,8} whereas disease progression may occur with suboptimal management.⁹ The study by Gaillard et al⁸ assessed the scans of 22 children with a radiologic diagnosis of bronchiectasis following a median scan interval of 21 months (range, 2-43 months). Bronchial dilatation resolved completely in six children, and there was improvement in appearances in an additional eight children, with medical treatment. Third, regardless of the underlying cause, improving the quality of life of those affected is important. Generic health-related and cough-specific quality of life scores of children with chronic cough and their parents are poor; these scores normalize when the cough resolves.¹⁰

The overall goal of the present article was to evaluate 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). We undertook systematic reviews to examine two related key questions (KQs) in children with chronic (> 4 weeks' duration) 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 they be referred for further investigations?

Materials and Methods

The systematic reviews were conducted based on the protocol¹¹ established by selected members of the CHEST expert cough panel. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement was used for reporting.

The searches for both questions were conducted by librarians from the University of Massachusetts Medical School between July 19, 2015, and July 27, 2015, using the search strategies outlined in [e-Table 1](#) and [e-Table 2](#). For the CHEST cough guidelines, it was determined a priori that the age cutoff for pediatric and adult components was 14 years. However, to ensure that all relevant studies were captured, the search filter included studies in subjects up to 18 years of age. We included only studies published in English. Duplicates found between Scopus and PubMed searches were identified and removed by the librarians before sending the abstracts to the two authors (A. B. C. and J. J. O.) who reviewed the abstracts.

The two reviewers independently reviewed all abstracts and agreed on which full-text articles to retrieve to assess for potentially eligible studies. It was planned that disagreements that could not be resolved by consensus would have been adjudicated by a third reviewer (R. S. I.).

For randomized controlled trials (RCTs), both reviewers independently assessed the risk of bias criteria by using measures in Cochrane reviews. The criteria used were: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). For cohort studies, data were extracted by a single author (A. B. C.) and checked by a second author (J. J. O.). In cohort studies, the study's setting, number enrolled and completing the study, inclusion and exclusion criteria, and main results related to the respective KQs are reported ([Tables 1-4](#)). For KQ2, we also described studies that reported on the association between duration of chronic wet cough and outcomes ([Table 5](#)) and mechanistic or pathobiology studies ([Table 6](#)).

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