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CHEST Expert Panel Report

CHEST Expert Cough Panel

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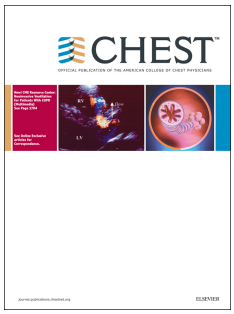

Chronic cough related to acute viral bronchiolitis in children – CHEST Expert Panel Report

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Conflict of Interests table

Author	All Key Questions were voted on by all authors
ABC	Up to Date – author and reviewer; Data safety monitoring board for a vaccine study (Glaxo); Advisor for study design of an unlicensed product (Merck). No financial or intellectual conflicts of interest regarding the content of this manuscript
JJO	American Board of Allergy and Immunology - Board of Directors; Annals of Allergy and Allergy Watch - Associate Editor; Up to Date – reviewer, Clinical Research - Astra Zeneca, Boehringer Ingelheim, Glaxo, Medimmune and Novartis; Adjudication Committee – Astra Zeneca and Novartis; Data safety monitoring board - Ohio State University; Consultant - Glaxo, Myelin, Church and Dwight, and Meda
MMW	No financial or intellectual conflicts of interest
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GCC	No financial or intellectual conflicts of interest
RSI	No financial or intellectual conflicts of interest regarding the content of this manuscript. Moreover, while RSI is the Editor in Chief of CHEST, the review and all editorial decisions regarding this manuscript were independently made by others

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Abstract

Background: Acute bronchiolitis is common in young children and some children develop chronic cough after their bronchiolitis. We thus undertook systematic reviews based on key questions (KQs) using the PICO format. The KQs were: Among children with chronic cough (>4 weeks) after acute viral bronchiolitis, how effective are the following interventions in improving the resolution of cough?: (1) Antibiotics. If so what type and for how long? (2) Asthma medications (inhaled steroids, $beta_2$ agonist, montelukast) and; (3) Inhaled osmotic agents like hypertonic saline?

Methods: We used the CHEST expert cough panel's protocol 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 these suggestions. Delphi methodology was used to obtain consensus.

Results: Several studies and systematic reviews on the efficacy of the three types of interventions listed in the introduction were found but no data were relevant to our KQs. Thus, no recommendations on using the interventions above could be formulated.

Conclusion: The panel made several consensus-based suggestions and identified directions for future studies to advance the field of managing chronic cough post-acute bronchiolitis in children.

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Abbreviation list

AAP=American Academy of Pediatrics

ACCP=American College of Chest Physicians

ALRI=Acute lower respiratory infection

CI=Confidence Interval

KQ=Key Question

NICE=National Institute for Health and Care Excellence [1]

PICO=Population, Intervention, Comparison, Outcome

QoL=Quality of Life

RCT=Randomized Controlled Trial

SIGN=Scottish Intercollegiate Guidelines Network

UK=United Kingdom

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Summary of suggestions

1. **For children with chronic cough (>4 weeks) after acute viral bronchiolitis, we suggest that the cough be managed according to the CHEST pediatric chronic cough guidelines** (Ungraded Consensus–based Statement)**.**

Remark: These include the evaluation for the presence of cough pointers and the use of 2 weeks of antibiotics targeted to common respiratory bacteria (*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*) and local antibiotic sensitivities managing in children with wet or productive cough unrelated to an underlying disease and without any specific cough pointers (e.g. coughing with feeding, digital clubbing).

2. **For children with chronic cough (>4 weeks) after acute viral bronchiolitis, we suggest that asthma medications not be used for the cough unless other evidence of asthma is present** (Ungraded Consensus–based Statement)**.**

Remark: Symptoms of asthma include the presence of recurrent wheeze and/or dyspnea.

3. **For children with chronic cough (>4 weeks) after acute viral bronchiolitis, we suggest that inhaled osmotic agents not be used** (Ungraded Consensus–based Statement)**.**

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Introduction

In pediatrics, bronchiolitis is a clinical diagnosis characterized by tachypnea, wheeze and/or crepitations/crackles in children (aged <2 years) following an upper respiratory illness.[1,2] Worldwide, bronchiolitis is one of the most common acute lower respiratory tract infection (ALRI) in very young children[1] and the most common cause of hospitalization in those aged < 1 year.[2] Bronchiolitis is characterized by extensive inflammation of the airways accompanied by increased mucus production and necrosis of airway epithelial cells and other pathobiology, the discussion of which is beyond the scope of this article. It is primarily caused by infection of the respiratory epithelial cells by a variety of viruses (e.g. respiratory syncytial virus, adenovirus, influenza, parainfluenza, human metapneumovirus, rhinovirus and coronavirus).[1,2]

Bronchiolitis is a self-limiting condition in most children but some may have on-going symptoms post the acute episode. A systematic review found that in children with bronchiolitis, 90% were cough-free by day 21 (mean time of cough resolution was 8-15 days).[3] Those with chronic symptoms (after 4 weeks) possibly represent a different clinical problem. Sometimes it is termed post-bronchiolitis syndrome.[4] The previous UK-based Scottish Intercollegiate Guidelines Network (SIGN) guideline,[5] refer to post-bronchiolitis syndrome as the presence of any respiratory symptoms that includes chronic cough. However, in the most recent UK National Institute for Health and Care Excellence (NICE) guidelines, 'post-bronchiolitis syndrome' is implied as "a chronic, relapsing episodic wheeze with subsequent viral infections may occur over the ensuing 6 months or so".[1]

Given the high prevalence of bronchiolitis[1] and the potential impact of chronic cough on the quality of life (QoL),[6] multiple doctor visits,[7] and adverse effects from inappropriate use of

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medications,[8] the American College of Chest Physicians (CHEST) panel considered several questions relating to chronic cough (>4 weeks duration) post-bronchiolitis to be important.

Using the PICO framework, we performed systematic reviews to address key questions (KQ) relating to etiologies of cough in children. Here, we present the systematic reviews for the KQs, summary of the evidence and the formulated recommendations based upon these findings utilizing CHEST's cough guidelines methods and framework.[9] The 3 KQs addressed were:

KQ1: In children with chronic cough (>4 weeks) after acute viral bronchiolitis, are antibiotics effective in improving the resolution of cough? If so, what antibiotics and for how long?

KQ2: In children with chronic cough (>4 weeks) after acute viral bronchiolitis, are asthma medications (e.g. inhaled and oral corticosteroids, $beta_2$ agonist, monteleukast) effective in improving the resolution of cough? If so, what and for how long?

KQ3: In children with chronic cough due to acute viral bronchiolitis, are inhaled osmotic agents like hypertonic saline effective in improving the resolution of cough?

Materials and methods

We undertook the systematic reviews based on the protocol[9] established by selected members of the CHEST expert cough panel. We used the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement for reporting. The KQs were framed by this paper's main authors.

Study identification and eligibility criteria

Searches for the three systematic reviews were externally undertaken by librarians (Nancy Harger, MLS and Judy Nordberg, MLS) from the University of Massachusetts Medical

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School, USA, using the search strategies outlined in the supplemental file. 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 (AC, JO) who independently reviewed the abstracts.

Data extraction and quality assessment

The two reviewers fully 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 be adjudicated by a third reviewer (RI), but there were no disagreements. As previously done,[10,11] it was also planned that data would have been extracted by a single author and checked by a second and that a GRADE-based quality assessment independently undertaken for any RCTs. However, as there were no relevant studies, our planned methods were not relevant.

Recommendation/Suggestion framework

We used a standard method[9] as previously described:[12] "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.[9,13] 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 statement(s) because of their potential

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conflicts of interest. Transparency of process was documented. Further details of the methods have been published elsewhere.[9,13] Consistent with recent recommendations from the National Academy of Medicine (previously referred to as the Institute of Medicine), the Panel conducted a comprehensive, systematic review of the literature to provide the evidence base for this guideline". During the Delphi approach, those with a 'conflict of interest' were not permitted to vote. The committee has a patient representative who approved the suggestions/recommendations during the voting process.

The CHEST approach 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. Where there is insufficient evidence, 'suggestions' are formulated instead of recommendations.

Results

The search results and PRISMA diagrams for all KQs are presented in the supplemental file. The duration of cough relating to the various interventions including antibiotics (KQ1), asthma medications (KQ2) and hypertonic saline (KQ3) was examined as an outcome in the NICE guideline.[1] However, none of the data fulfilled our KQ criteria as in all the studies, children with acute bronchiolitis were recruited and none of the studies reported on the duration of cough at or beyond 4 weeks. Combining this with our own searches, the summary is presented below.

Summary of evidence and interpretation

The single paper included in KQ1 was a recently updated Cochrane systematic review.[4] The systematic review[4] compared antibiotics with controls (placebo or no treatment) administered

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in the post-acute phase of bronchiolitis (> 14 days) but included antibiotics started in the acute phase. The Cochrane review[4] concluded that "there was insufficient evidence to inform whether antibiotics should be used to treat or prevent persistent respiratory symptoms in the post-acute phase of bronchiolitis".[4]

There were no prospective studies that have specifically recruited children with chronic cough post bronchiolitis. A study involving only Aboriginal Australian children hospitalized for bronchiolitis described that the presence of cough at follow-up (at 3 weeks post discharge) was significantly associated with future identification of radiological bronchiectasis, OR=3, 95%CI 1.1, 7, p=0.03).[14] However, these data cannot be applied to the general mainstream population, given the narrow population profile.

In our previous systematic reviews on the etiology[11] and the use of pediatric-specific cough pathways when managing children with chronic cough,[15], none of the various cohorts mentioned whether the chronic cough was related to bronchiolitis. However, given the young median age in some cohorts, it is possible (although remains unknown) how many of these cohorts included children with recent bronchiolitis. Given the burden of chronic cough including the negative effect on quality of life,[6] until more data specific to chronic cough post-acute bronchiolitis become available, we suggest that these children are managed in accordance with current CHEST pediatric cough guidelines.[11,15,16] Of the total of 23 recommendations/suggestions from these guidelines[11,15,16] the ones most likely applicable are the recommendations to evaluate for the presence of cough pointers and the use of 2 weeks of antibiotics targeted to common respiratory bacteria (*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*) and local antibiotic sensitivities managing in children with

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wet or productive cough unrelated to an underlying disease and without any specific cough pointers (e.g. coughing with feeding, digital clubbing).[15,16]

No relevant papers were identified for KQ2 or KQ3. Post publication of the AAP[2] and SIGN[1] bronchiolitis guidelines, our search identified several other RCTs that also found that hypertonic saline was not efficacious for the various clinical outcomes examined (none examined for development or treatment of chronic cough) in children with bronchiolitis. In the context that neither asthma medications nor hypertonic saline is efficacious for acute bronchiolitis,[1] both groups of interventions are also not recommended for post-bronchiolitis chronic cough. However, as current data suggest that the incidence of asthma is increased post-acute viral bronchiolitis,[17] clinicians should assess for the presence of the symptoms and signs of asthma (e.g. recurrent wheeze and dyspnea responsive to $beta_2$ agonists), which is in-line with recommendations in current CHEST chronic cough guidelines.[11,15,16]

Using CHEST's framework, as our systematic reviews found no data specific to our KQs, only suggestions could be formulated.

1. **For children with chronic cough (>4 weeks) after acute viral bronchiolitis we suggest that the cough be managed according to the CHEST pediatric chronic cough guidelines** (Ungraded Consensus–based Statement)**.**

Remark: These include the evaluation for the presence of cough pointers and the use of 2 weeks of antibiotics targeted to common respiratory bacteria (*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*) and local antibiotic sensitivities managing in children with wet or productive cough unrelated to an underlying disease and without any specific cough pointers (e.g. coughing with feeding, digital clubbing).[15,16]

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2. **For children with chronic cough (>4 weeks) after acute viral bronchiolitis we suggest that asthma medications not be used for the cough unless other evidence of asthma is present** (Ungraded Consensus–based Statement)**.**

Remark: Symptoms of asthma include the presence of recurrent wheeze and/or dyspnea.

3. **For children with chronic cough (>4 weeks) after acute viral bronchiolitis we suggest that inhaled osmotic agents not be used** (Ungraded Consensus–based Statement)**.**

Areas for further research

To advance and improve knowledge regarding the management of chronic cough post-acute bronchiolitis in children, we suggest other areas of research.

1. There are currently little data regarding the transition from acute to chronic cough.[18] While studies have reported that some children with persistent symptoms post bronchiolitis, their individual outcomes are unknown. Thus, we suggest multi-center cohort studies involving children with bronchiolitis of different severity in various clinical settings (rural-remote vs urban) to evaluate their individual outcomes focusing on cough and the etiology immediately post-bronchiolitis.
2. RCTs should include various interventions (e.g. antibiotics for wet cough and inhaled or short course oral corticosteroids for dry cough post-acute bronchiolitis) that may be efficacious for chronic cough post bronchiolitis. The RCTs should utilize validated cough outcomes and *a-priori* definitions.
3. Studies on whether tobacco smoke exposure (in-utero, post-natal and environmental) and air quality contribute to the development of chronic cough post bronchiolitis such as large cohort and/or case control studies in different settings.
4. Are there specific risk factors and/or pathogens that are likely to result in post-bronchiolitis chronic cough? For example, does the presence of poly microbial (e.g.

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mixed viral-bacteria) pathogens in the airways increase the risk of developing chronic cough?

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