Methodology and Grading of the Evidence for the Diagnosis and Management of Cough

ACCP Evidence-Based Clinical Practice Guidelines

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Objectives: To assemble a multidisciplinary, geographically diverse panel of experts in the diagnosis and treatment of cough with the intention of developing clinically relevant practice guidelines for pulmonary and primary care physicians, including recommendations covering many etiologies of cough, adult and pediatric evaluation and treatment, and empiric yet integrative algorithms for the management of the patient with cough.

Methods: The Duke University Center for Clinical Health Policy Research was selected to review and summarize the current evidence in this area. The expert panel established clinical recommendations and algorithms founded on the synthesis of this evidence.

Conclusions: This section describes the approach used to develop the guidelines, including identifying, evaluating, and synthesizing the evidence, assessing the strength of evidence pertinent to individual guidelines, and grading the guideline recommendations.

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Key words: clinical practice guidelines; cough; evidence-based medicine

Abbreviations: ACCP = American College of Chest Physicians; AECB = acute exacerbations of chronic bronchitis; RCT = randomized controlled trial

In 1998, the American College of Chest Physicians (ACCP) published Managing Cough as a Defense Mechanism and as a Symptom: A Consensus Panel Report of the American College of Chest Physicians.1

Five years later, the Health and Science Policy committee of the ACCP, with the endorsement of the Board of Regents, chose to reassess this topic based on currently available scientific literature. The new publication is intended not only as an update but also as an overhaul that would use the knowledge gleaned by the first panel and augmenting it with a new and methodologically rigorous evidence review to produce a guideline that is more explicitly steeped in evidence. The Duke University Center for Clinical Health Policy Research was selected to review and summarize the current evidence in this area. The international panel of experts provided clinically relevant recommendations that were synthesized from the results of the evidence review, and were targeted toward an audience of pulmonary and primary care physicians in their management of patients with cough.

Panel Selection and Composition

Richard S. Irwin, MD, FCCP, of the University of Massachusetts Medical School in Worcester, MA, served as Chair of this international panel of 26 experts representing seven clinical specialties. Many were members of the ACCP, but representatives from other medical associations, including the American College of Physicians, Canadian Thoracic Society, and American Thoracic Society, also participated on the panel. These experts convened on several occasions, including a panel conference in Boston, MA, in November 2004, in which they deliberated the final content and recommendations, the rating of the quality of the evidence, the estimation of benefits

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Authors were selected, or in some cases writing committees were formed, for each topic to review evidence, write an article, and draft guidelines. These assignments were made by the steering committee based on the authors’ known expertise in that specific area of the diagnosis and treatment of cough, and their research and writing skills. Some of the authors were panelists on the consensus statement of 1998; however, most were not. There was an attempt to make this panel multidisciplinary and geographically diverse, without compromising the highest level of expertise in the topic area.

Funding and Conflicts of Interest

Funding for both the evidence review and guideline development was provided through unrestricted educational grants from AstraZeneca and Altana/ Pfizer. No representatives from these companies were granted the right of review or were allowed to participate in any portion of the guideline development.

The ACCP has a very stringent approach to the issue of potential or perceived conflicts of interest. This policy is published on the ACCP Web site at www.chestnet.org. All conflicts of interest within the preceding 5 years were required to be disclosed by all panelists, including those who did not have writing responsibilities, at face-to-face meetings, the final conference, and prior to submission for publication. The most recent of these are documented in the published guideline supplement. Furthermore, the panel was instructed in this matter, verbally and in writing, prior to the deliberations of the final conference.

Scope

The panel chose the following topics for review and analysis for possible inclusion in the guideline:

- Anatomy and neurophysiology of the cough reflex;
- Global physiology and pathophysiology of cough;
- Complications of cough;
- Etiologies of cough, including definitions, epidemiology, pathophysiology, pathogenesis, diagnosis, and specific treatment for each condition;
- Evaluating cough in immunocompetent and immunocompromised adults;
- Evaluating chronic cough in pediatrics;
- Treatment of cough, including an empiric and integrative approach to the management of these patients;
- Assessing cough severity and efficacy of therapy; and
- Potential future therapies.

The section on etiologies of cough is further divided into the following causes:

I. Common causes
   A. Chronic upper airway cough syndrome (previously referred to as postnasal drip syndrome) secondary to rhinosinus diseases
   B. Cough and the common cold
   C. Asthma
   D. Gastroesophageal reflux disease
   E. Bronchitis
      1. Acute bronchitis
      2. Chronic bronchitis
      3. Acute exacerbation of chronic bronchitis
      4. Nonasthmatic eosinophilic bronchitis
   F. Bronchiectasis including
      1. Cystic fibrosis
      2. Mycobacterium avium-intracellulare complex infection
      3. Nonbronchiectatic suppurative airway disease
         a. Associated with inflammatory bowel disease
         b. Bronchiolitis
         c. Other suppurative airway diseases
   G. Postinfectious cough including
      1. Pertussis infection (whooping cough)
   H. Lung tumors
      1. Primary malignant
      2. Primary benign
      3. Metastatic
   I. Cough and aspiration of food and liquids due to oral/pharyngeal dysphagia
   J. Angiotensin-converting enzyme inhibitor-induced cough
   K. Habit cough and psychogenic cough
   L. Chronic interstitial pulmonary disease including
      1. Sarcoidosis
      2. Hypersensitivity pneumonitis
   M. Occupational and environmental causes of cough
   N. Chronic cough due to tuberculosis and other infections
   O. Peritoneal dialysis and cough

II. Cough in the immunocompromised host

III. Uncommon causes

IV. Unresolved cough (previously referred to as idiopathic cough)

The scope of therapy included not only treatments that were directed at specific etiologies but also symptomatic treatments; these included nonspecific antitussive therapies and protussive therapies, both pharmacologic and mechanical.
Evidence Review

The evidence review procedures included section-specific targeted searches as well as a formal systematic review on selected topics. The authors of each section of the guideline were encouraged to conduct computerized bibliographic literature searches to identify relevant literature. For the section-specific searches, the bibliographic databases, search terms, and selection procedures varied by topic, and are described separately in each section of the guideline.

Formal systematic reviews on selected topics covered in the guideline were performed by the Center for Clinical Health Policy Research at Duke University Medical Center. These reviews covered the efficacy of selected treatments for cough associated with the common cold and acute bronchitis. Treatments included inhaled bronchodilators, antitussive (cough suppressant) therapies, and protussive therapies. Antitussive therapies (i.e., cough suppressants) included drugs that affect mucociliary factors, the afferent limb of the cough reflex, the cough center, the efferent limb of cough reflex, and the skeletal muscles. Protussive therapies were subdivided into pharmacologic treatments and mechanical devices. The review of mechanical devices contained evidence on inspiratory muscle training, huffing, positive expiratory pressure, chest physiotherapy and postural drainage, autogenic drainage, high-frequency air flow oscillation devices such as the Flutter (Scandipharm; Birmingham, AL) and Acapella (DHD Healthcare; Wampsville, NY), devices that provide high-frequency chest compressions (ThAIRapy bronchial Drainage System or ABI Vest; Hill-Rom; St. Paul, MN), percussive devices (Percussionaire device; Medical Specialties; New Orleans, LA), mechanical insufflation/exsufflation devices such as the In-Exsufflator, Coffaltor, Cough-Alator (J.H. Emerson; Cambridge, MA), electrical stimulation of respiratory muscles, and assisted cough with manual compressions of the lower thorax and abdomen.

The following three key questions were addressed in the formal systematic reviews for these selected topics:

1. Do inhaled bronchodilators improve cough symptoms in patients with the common cold, acute bronchitis, chronic bronchitis, or acute...

Table 1—Inclusion Criteria for Systematic Literature Review Questions*

<table>
<thead>
<tr>
<th>Question</th>
<th>Patients</th>
<th>Interventions</th>
<th>Study Design</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Presenting with symptoms of cough due to acute bronchitis, AECB, common cold with or without comorbid diagnosis of asthma, or COPD</td>
<td>Inhaled bronchodilators (eg, β-agonists, albuterol, metaproterenol); and anticholinergic agents (eg, ipratropium bromide, tiotropium); or cromolyn sodium</td>
<td>RCTs</td>
<td>Cough symptoms; cough clearance (a nuclear medicine study); clinical events (pneumonia hospitalization, and long-term changes in FEV1/spirometry); quality of life</td>
</tr>
<tr>
<td>2</td>
<td>Same as above with addition of bronchiectasis</td>
<td>Antitussives; antihistamines; inhaled steroids; decongestants (oral or topical); mast cell stabilizers; tobacco cessation; antibiotics; mucolytics; opiates; and protussive therapy; pharmacologic</td>
<td>RCTs</td>
<td>Cough symptoms; cough clearance (a nuclear medicine study); clinical events (pneumonia hospitalization, and long-term changes in FEV1/spirometry); quality of life</td>
</tr>
<tr>
<td>3</td>
<td>Bronchiectasis, cystic fibrosis, chronic bronchitis, or AECB</td>
<td>Positive expiratory pressure; chest physiotherapy and postural drainage; autogenic drainage; oscillatory devices; devices that provide high-frequency chest compressions; percussive devices; mechanical insufflation devices; electrical stimulation of respiratory muscles; assisted cough with manual compression of lower thorax and abdomen</td>
<td>RCTs; other controlled trials; before-after design clinical trial</td>
<td>Same as above plus sputum volume/weight; method of measurement of sputum clearance is used as a quality measure, with tagged studies rated as being of higher quality</td>
</tr>
</tbody>
</table>

Note: neuromuscular disease excluded

*AECB = acute exacerbations of chronic bronchitis. The literature review only includes the systematic review performed by the Duke University Center for Clinical Health Policy Research. RCT = randomized controlled study.
exacerbations of chronic bronchitis? And, was asthma specifically ruled out in the acute bronchitis studies?

2. Do cough suppressant and pharmacologic protussive therapies improve cough symptoms or outcomes in patients with the common cold, acute bronchitis, chronic bronchitis or bronchiectasis, or acute exacerbations of chronic bronchitis?

3. Do mechanical protussive techniques/devices improve cough symptoms or cough clearance in patients with bronchiectasis, cystic fibrosis, and chronic bronchitis?

The Duke University research team conducted a systematic and comprehensive literature review that began with searches of MEDLINE from 1966 through August 2003 with limits of articles published in the English language and with human subjects. Search terms included the medical subject heading term “cough” combined with a published strategy for identifying randomized controlled trials (RCTs). A separate search combined the medical subject heading terms “bronchiectasis,” “cystic fibrosis,” and “respiratory therapy” with the RCT strategy. However, searches using terms related to the therapeutic use of specific agents, including “antitussive agents,” “expectorants,” “bronchodilator agents,” “ipratropium,” “albuterol,” “orciprenaline,” and “cromolyn sodium” had poor specificity in the absence of the term “cough,” and thus were not used. Additional searches were targeted to double-blind RCTs of nonspecific antitussive therapy and protussive drugs (eg, expectorant, mucolytic, mucus-modifying agents) for all indications other than those listed in question

<table>
<thead>
<tr>
<th>Quality of Evidence</th>
<th>Substantial</th>
<th>Intermediate</th>
<th>Small/Weak</th>
<th>None</th>
<th>Conflicting</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>A</td>
<td>A</td>
<td>B</td>
<td>D</td>
<td>I</td>
<td>D</td>
</tr>
<tr>
<td>Fair</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
<td>I</td>
<td>D</td>
</tr>
<tr>
<td>Low</td>
<td>B</td>
<td>C</td>
<td>C</td>
<td>I</td>
<td>I</td>
<td>D</td>
</tr>
<tr>
<td>Expert opinion</td>
<td>E/A</td>
<td>E/B</td>
<td>E/C</td>
<td>I</td>
<td>I</td>
<td>E/D</td>
</tr>
</tbody>
</table>

Table 3—Relationship of Strength of the Recommendations Scale to Quality of Evidence and Net Benefits

Table 2—Components Used in the Grading of the Quality of Evidence and Recommendations

<table>
<thead>
<tr>
<th>Scales</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of evidence</td>
<td>Evidence is based on good RCTs or metaanalyses</td>
</tr>
<tr>
<td>Good</td>
<td>Fair Evidence is based on other controlled trials or RCTs with minor flaws</td>
</tr>
<tr>
<td>Fair</td>
<td>Low Evidence is based on nonrandomized, case-control, or other observational studies</td>
</tr>
<tr>
<td>Low</td>
<td>Expert opinion Evidence is based the consensus of the carefully selected panel of experts in the topic field. There are no studies that meet the criteria for inclusion in the literature review</td>
</tr>
<tr>
<td>Net benefit</td>
<td>Substantial There is evidence of benefit that clearly exceeds the minimum clinically significant benefit and evidence of little harm</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Clear evidence of benefit but with some evidence of harms, with a net benefit between that defined for “substantial” and “small/weak”</td>
</tr>
<tr>
<td>Small/weak</td>
<td>There is evidence of a benefit that may not clearly exceed the minimum clinically significant benefit, or there is evidence of harms that substantially reduce (but do not eliminate) the benefit such that it may not clearly exceed the minimum clinically significant benefit</td>
</tr>
<tr>
<td>None</td>
<td>Evidence shows that either there is no benefit or the benefits equal the harms</td>
</tr>
<tr>
<td>Conflicting</td>
<td>Evidence is inconsistent with regard to benefits and/or harms such that the net benefit is uncertain</td>
</tr>
<tr>
<td>Negative</td>
<td>Expected harms exceed the expected benefits to the population</td>
</tr>
</tbody>
</table>

Recommendations

A Strong recommendation
B Moderate recommendation
C Weak recommendation
D Negative recommendation
E/A Strong recommendation based on expert opinion only
E/B Moderate recommendation based on expert opinion only
E/C Weak recommendation based on expert opinion only
E/D Negative recommendation based on expert opinion only
2 that reported on cough clearance or cough symptoms and had been published since the previous ACCP cough guidelines were published. The trials identified in this search were provided to the section authors.

It is important to note that the outcomes measured and reported in many of the studies were not cough symptoms or complications, but, rather, sputum production. The relationship between sputum production and cough symptoms or complications is not predictable. Thus, for these reviews, authors used data on cough symptoms and complications (and in some cases on cough clearance), which in many cases were secondary outcomes or were merely described and not analyzed.

In addition to MEDLINE, we searched the National Guideline Clearinghouse and the Cochrane Library (including the Cochrane Database of Systematic reviews, the Cochrane Controlled trial register, and the Database of Abstracts of Reviews of Effectiveness). Additional studies were identified from the reference lists of review articles and by querying experts in the field.

The formal systematic searches identified 1,974 citations, of which 275 were selected and reviewed in their full-text format. The criteria for the inclusion and exclusion of articles were developed for each research question and are shown in Table 1. The abstracts of all articles were reviewed by two physicians (one with methodological expertise and one with content area expertise), and those meeting the inclusion criteria were selected for review in full text. Details from “included” articles were extracted and recorded into evidence tables. No quantitative synthesis, such as metaanalysis, was performed, but aggregated data were described and analyzed qualitatively.

**Grading of the Evidence and Recommendations**

The recommendations were graded, by consensus of the panel, using the ACCP Health and Science Policy Grading System, which is based on the following two components: quality of the evidence; and the net benefit of the diagnostic or therapeutic procedure. The quality of evidence is rated according to the study design and strength of the other methodologies used in the included studies. The net benefit of the recommendation is based on the estimated benefit to the specific patient population described in each recommendation and not for an individual patient. The authors of each recommendation proposed their best estimate of the net benefit, and the entire panel considered these choices for each recommendation. At the conference, the panel revised the assessments of net benefit for many recommendations to be consistent across all recommendations. Usually, the net benefit is a clinical benefit to the population of patients defined in the first phrase of the recommendation but, in recommendations for future research or other nonclinical recommendations, it may be a societal benefit. Both the quality-of-evidence and net benefit components are listed after each recommendation; their interaction defines the strength of the recommendation, as indicated in Tables 2 and 3.

There are recommendations in this guideline with a grade of “D.” These are intended to be strong statements that the panel recommends against the use of the indicated technique or therapy in the patient population described at the beginning of the recommendation.

When there was insufficient evidence, the panel used informal group consensus techniques to refine or develop recommendations based on the expert opinion of the panel. Eighty percent of the panel was in attendance at the final conference to collaborate on the final wording and grading of the recommendations. Even those recommendations that were based on expert opinion were considered to be worthy of inclusion, as they were the recommendations of an international and multidisciplinary team with considerable expertise in the diagnosis and treatment of patients with cough.

**Guideline Writing and Validation Process**

The executive committee of the panel extensively reviewed each section of the guideline manuscript during the writing process. The November 2004 conference provided an opportunity for the entire panel to review the latest drafts. Following final revisions and one final review by the executive committee, each section of the guidelines was reviewed and approved by the Clinical Pulmonary Medicine, Respiratory Care, Pediatric Chest Medicine, Environmental and Occupational and Airways Disorders NetWorks of the ACCP, as well as the ACCP Health and Science Policy Committee, and subsequently by the ACCP Board of Regents. The guidelines have not been field-tested.

**References**

1 Irwin RS, ed. Managing cough as a defense mechanism and as a symptom: a consensus panel report of the American College of Chest Physicians. Chest 1998; 114(suppl):133S–181S