

Pharmacologic and Nonpharmacologic Treatment for Acute Cough Associated With the Common Cold

CHEST Expert Panel Report



Mark A. Malesker, PharmD, FCCP; Priscilla Callahan-Lyon, MD; Belinda Ireland, MD; Richard S. Irwin, MD; Master FCCP; on behalf of the CHEST Expert Cough Panel

BACKGROUND: Acute cough associated with the common cold (CACC) causes significant impairment in quality of life. Effective treatment approaches are needed for CACC. We conducted a systematic review on the management of CACC to update the recommendations and suggestions of the CHEST 2006 guideline on this topic.

METHODS: This systematic review of randomized controlled trials (RCTs) asked the question: Is there evidence of clinically relevant treatment effects for pharmacologic or non-pharmacologic therapies in reducing the duration/severity of acute CACC? Studies of adults and pediatric patients with CACC were included and assessed for relevance and quality. Based on the systematic review, guideline suggestions were developed and voted on using the American College of Chest Physicians organization methodology.

RESULTS: Six systematic reviews and four primary studies identified from updated literature searches for each of the reviews or from hand searching were included and reported data on 6,496 participants with CACC who received one or more of a variety of interventions. The studies used an assortment of descriptors and assessments to identify CACC.

CONCLUSIONS: The evidence supporting the management of CACC is overall of low quality. This document provides treatment suggestions based on the best currently available evidence and identifies gaps in our knowledge and areas for future research.

CHEST 2017; 152(5):1021-1037

KEY WORDS: acute cough; common cold; pharmacologic and nonpharmacologic treatment

ABBREVIATIONS: CACC = cough associated with the common cold; CHEST = American College of Chest Physicians; FDA = Food and Drug Administration; NSAID = nonsteroidal anti-inflammatory drug; OTC = over the counter; RCT = randomized controlled trial; VAS = visual analogue scale

AFFILIATIONS: From the Pharmacy Practice Department, (Dr Malesker), Creighton University, Omaha, NE; Mercy Clinic (Dr Callahan-Lyon), Adamstown, MD; TheEvidenceDoc (Dr Ireland), Pacific, MO; Division of Pulmonary, Allergy, and Critical Care Medicine (Dr Irwin), University of Massachusetts Medical School, Worcester, MA.

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FUNDING/SUPPORT: CHEST was the sole supporter of these guidelines, this article, and the innovation addressed within.

CORRESPONDENCE TO: Mark A. Malesker, PharmD, FCCP, Creighton University, 2500 California Plaza, Omaha, NE 68178; e-mail: mark-malesker@creighton.edu

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DOI: <http://dx.doi.org/10.1016/j.chest.2017.08.009>

Summary of Recommendations and Suggestions

1. For adult and pediatric patients with cough due to the common cold, we suggest against the use of over the counter cough and cold medicines until they have been shown to make cough less severe or resolve sooner (Ungraded Consensus-Based Statement).

2. In adult patients with cough due to the common cold, we suggest against the use of nonsteroidal anti-inflammatory agents until they have been shown to make cough less severe or resolve sooner (Ungraded Consensus-Based Statement).

3. In pediatric patients (aged 1-18 years) with cough due to the common cold, we suggest honey may offer more relief for cough symptoms than no treatment, diphenhydramine, or placebo, but it is not better than dextromethorphan (Ungraded Consensus-Based Statement).

Remarks: Infants < 1 year of age should not be administered honey, and children < 2 years of age should not be administered dextromethorphan for cough symptoms.

4. In pediatric patients (aged < 18 years) with cough due to the common cold, we suggest avoiding use of codeine-containing medications because of the potential for serious side effects including respiratory distress (Ungraded Consensus-Based Statement).

The common cold is an acute upper respiratory syndrome, usually due to a viral infection, with symptoms including rhinorrhea and nasal obstruction.

Common cold is frequently accompanied by sore throat, sneezing, body aches, low-grade fever, and cough.

Cough associated with the common cold is a common and particularly bothersome symptom for patients in the ambulatory setting. A recent Internet survey found that cough outlasted other cold symptoms in 69% of the survey respondents.¹ Adults in the United States average two to three colds on an annual basis, and this number is even higher for children.²

Fifty-two percent of adult participants from a recent survey indicated that cough/cold impacted their daily lives a “fair amount to a lot.”³ A total of 74% of survey respondents attempted to treat the cough associated with the common cold (CACC), most commonly with over the counter (OTC) syrup (58%) or a throat lozenge (53%).¹ In 2015, the average American household made 26 trips to retail outlets and spent approximately \$338 annually on OTC products. OTC medications are sold in 540,000 pharmacies and in > 750,000 retail locations in the United States.⁴ The Consumer Healthcare Products Association indicates an increasing trend in OTC sales of cough and cold products.⁵ Total sales of OTC cough, cold, and allergy products was \$9.56 billion in the United States in 2015 according to *Drug Store News*.⁶

The current Cough Expert Panel believed it would be beneficial to perform a systematic review to update the recommendations of the 2006 guideline.⁷ The specific aim was to evaluate the evidence for clinically relevant pharmacologic and nonpharmacologic therapies in reducing the duration/severity of acute CACC.

Methods

The methodologies used by the CHEST Guideline Oversight Committee to select the Expert Cough Panel Chair and the international panel of experts perform synthesis of the evidence and develop the recommendations and suggestions that have 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 used to provide expert advice on all guidance statements. The total number of eligible voters for each guidance 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}

Systematic Review Question

The clinical question for this systematic review was generated using the Population, Intervention, Comparison, Outcome format.¹⁰ The review

question was: Is there evidence of clinically relevant treatment effects for pharmacologic or nonpharmacologic therapies in reducing the duration/severity of acute CACC?

Systematic Literature Search

The methods used for this systematic review conformed to those outlined in the article “Methodologies for the Development of CHEST Guidelines and Expert Panel Reports.”⁸ The National Guideline Clearinghouse (<http://www.guideline.gov>) and the Guidelines International Network (<http://www.g-i-n.net>) were searched for existing guidelines on pharmacologic and nonpharmacologic treatment for CACC. Systematic reviews and clinical trials were identified from searches of electronic databases (PubMed, EMBASE, the Cochrane Central Register of Controlled Trials [Cochrane Library], Google Scholar, and CINAHL, commencing from the earliest available date until April 2014. The reference lists of retrieved articles were examined for additional citations. The search terms used were common cold, cough, antihistamine, decongestant, cough suppressant, antitussive, antibiotic, zinc, expectorant, acute cough, anticholinergic, topical steroids, upper respiratory tract infection. An additional search for

TABLE 1] Eligibility Criteria

Criteria	Study Requirements	
Inclusion	English-language publication	
	Population	
	Common cold syndrome: the common cold is an acute upper respiratory syndrome of rhinorrhea and nasal obstruction, frequently accompanied by sore throat, sneezing, and cough	
	Adult (12 y and older)	
	Pediatric (< 12 y)	
	Elderly (65 y and older)	
	Intervention	Pharmacologic treatment
		Acetylcysteine
		Antihistamine alone
		Expectorant alone
Cough suppressant alone		
Antihistamine + expectorant		
Antihistamine + suppressant		
Expectorant + cough suppressant		
Antihistamine + suppressant + expectorant		
Supplements (zinc, vitamin C)		
Antihistamine + decongestants, inhaled nasal steroids, and inhaled nasal antihistamines and inhaled nasal ipratropium bromide		
NSAIDs and acetaminophen		
OTC cough and cold remedies		
Nonpharmacologic therapies		
Neti pot		
Chest rub (Vicks VapoRub)		
Honey		
Demulcents		
Cough drops		
Gelatin		
Chicken soup		
Complementary/alternative therapies		
Comparison/control	Other pharmacologic or nonpharmacologic therapies	
	Placebo	
	Head to head comparisons	
	Pharmacologic agents added to antibiotics vs no antibiotics	

(Continued)

TABLE 1] (Continued)

Criteria	Study Requirements
Outcome	Symptoms
	Severity of acute cough
	Duration of acute cough
	Side effects of therapies (benefits vs harms)
	Rating scales or VAS or HRQoL
	Cough must be mentioned as the primary symptom or can be teased out as part of a symptom complex

HRQoL = health-related quality of life; NSAID = nonsteroidal anti-inflammatory drug; OTC = over the counter; VAS = visual analogue scale.

cough and cold remedies for the cold, nonpharmacologic therapies, and complementary and alternative therapies was conducted. Since the publication of this review, the databases have been searched periodically to look for additional substantive articles.

The titles and abstracts of the search results were independently evaluated by two reviewers (M. A. M. and P. C. L.) to identify potentially relevant articles based on the eligibility criteria of the study design (randomized controlled trial [RCT], controlled clinical trial, or systematic review) and acute CACC in populations of adults or adolescents (12 years or older) and children (< 12 years) (Table 1). The full text of all potentially relevant articles was retrieved, and two reviewers (M. A. M. and P. C. L.) independently evaluated all the studies retrieved against the criteria.

Pharmacologic interventions included acetylcysteine, antihistamine monotherapy, expectorant monotherapy, cough suppressant monotherapy, antihistamine + expectorant, antihistamine + suppressant, expectorant + suppressant, antihistamine + suppressant + expectorant, supplements (zinc, vitamin C), antihistamine + decongestants, inhaled nasal steroids, inhaled antihistamines, inhaled ipratropium bromide, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and OTC cough and cold remedies. Nonpharmacologic therapies included a neti pot, mentholated chest rub, honey, demulcents, cough drops, gelatin, chicken soup, and complementary/alternative therapies. For outcome measures, cough must have been mentioned as the primary symptom or was able to be teased out as part of a symptom complex including severity of cough, duration of acute cough, side effects of therapies (benefits vs harms), and rating scales (visual analogue scale [VAS] or health-related quality of life).

Quality Assessment

Included articles underwent quality assessment. For RCTs and controlled clinical trials, quality assessment was conducted using the Cochrane Risk of Bias Tool.¹¹ For systematic reviews, the Documentation and Appraisal Review Tool (Guidelines International Network) was used.¹² Studies that were at high risk of bias or of poor quality were excluded.

Grading Recommendations

Recommendations were graded using two dimensions: quality of the body of evidence using three categories—low, moderate, or high—and strength of the supporting evidence, rated as either strong or weak.⁸ In the context of practice recommendations, a strong

recommendation applies to almost all patients, whereas a weak recommendation is conditional and applies only to some patients. In the context of research recommendations (those provided in the present guidelines), we intended for a strong recommendation (grade 1) to imply that we recommended using intervention fidelity strategies in all studies in which patients with CACC are being managed. Intervention fidelity has been identified as an important aspect of acute cough studies and is defined “as the extent to which an intervention was delivered as conceived and planned to arrive at valid conclusions concerning the effectiveness in achieving target outcomes.”¹³ The strength of recommendations here is based on consideration of three factors: balance of benefits to harms, patient values and preferences, and resource considerations. Harms incorporate risk and burdens to the patients, which can include convenience or lack of convenience, difficulty of administration, and invasiveness. These variables in

turn affect patient preferences. The resource considerations extend beyond economics and should also factor in time and other indirect costs. The authors of these recommendations have considered these parameters in determining the strength of the recommendations and associated grades.

The findings of this systematic review were used to support the evidence-graded recommendations or suggestions. A highly structured consensus-based Delphi approach was used to provide expert advice on all guidance statements. The total number of eligible voters for each guidance statement varied based on the number of managed individuals recused from voting on any particular statement because of their potential conflicts of interest. Transparency of process was documented. Further details of the methods related to conflicts of interests have been published elsewhere.⁸

Results

The flowchart in [Figure 1](#) presents the results of the systematic search. Two hundred forty records were identified, and the abstracts were screened (224 RCTs and 16 Cochrane systematic reviews). Thirty-six RCTs and nine potentially relevant systematic reviews were identified for full text review, and six systematic reviews met the inclusion and exclusion criteria. The systematic reviews were mostly of good quality. Generally, however, the relevant study data were quite limited and of low quality. Details of study quality are reflected in [Tables 2 to 7](#). An updated search for new studies was conducted in February 2015, and 3,265 records were retrieved. Of those, only three met all inclusion criteria.

The key question was: Is there evidence of clinically relevant treatment effects for pharmacologic or nonpharmacologic therapies in reducing the duration/severity of severe CACC? Because of the large number of potential pharmacologic and nonpharmacologic treatments, we further developed six separate questions for each specific therapeutic category (acetylcysteine/carbocysteine, decongestants, antihistamines, acetaminophen as a single product or in combination products, NSAIDs, honey, zinc, and OTC antitussive agents). With respect to voting, no panelist was recused.

Key Clinical Question 1

Is there evidence of clinically relevant treatment effects for acetylcysteine or carbocysteine in reducing the duration of cough ([Table 2](#))?

The Chalumeau and Duijvestijn¹⁴ systematic review identified six RCTs comparing acetylcysteine or carbocysteine vs placebo for upper or lower respiratory tract infections in pediatric patients. Only three RCTs assessed cough as a primary outcome, measuring

“reduction in cough” after 6 to 7 days. The methods of measuring cough were not discussed. Overall, these studies were very small (139 total subjects in the three RCTs that assessed cough) and had a high risk of bias. It was difficult to account for other therapies and, in many cases, antibiotics were administered. Additionally, many of the patients were hospitalized, which is not routine for the treatment of the common cold.

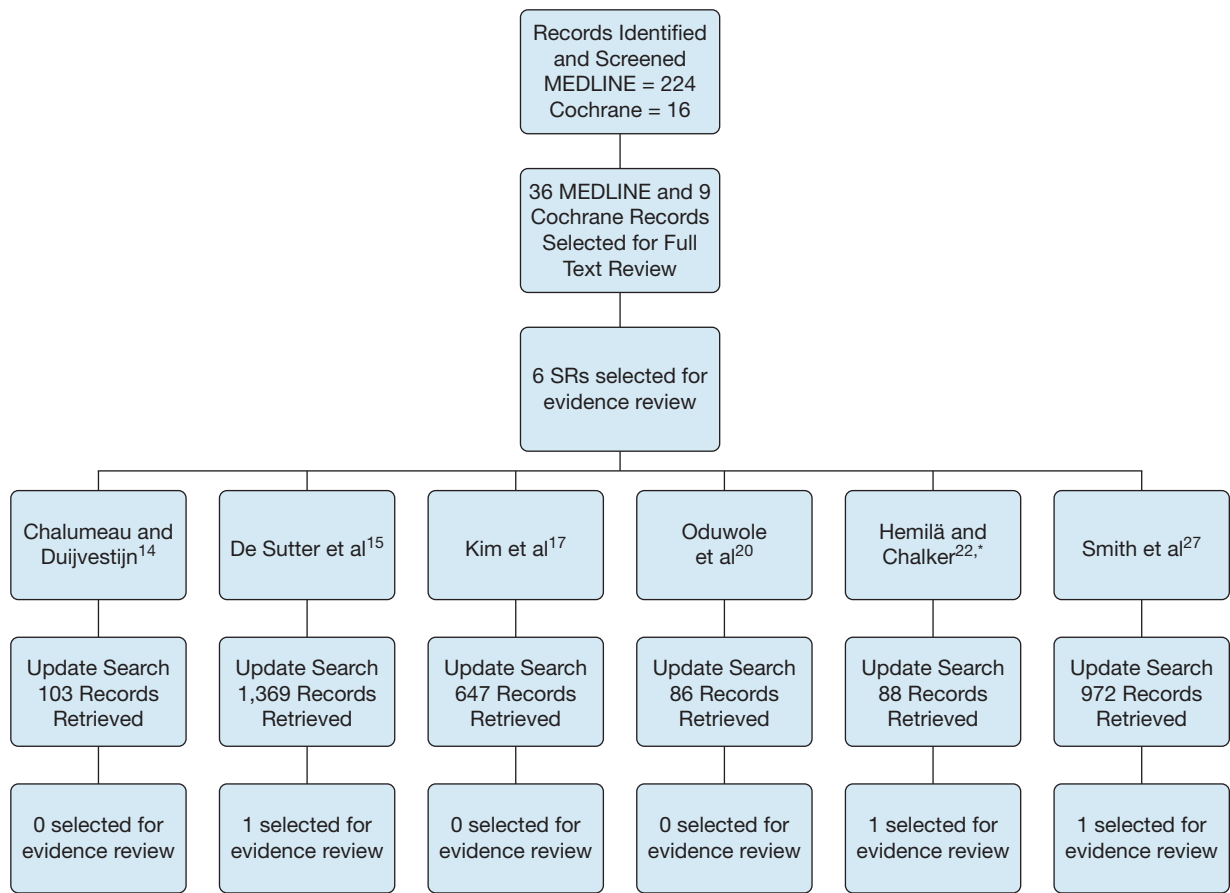
The Chalumeau and Duijvestijn¹⁴ systematic review identified 34 studies, with a total of 2,064 participants, that evaluated product safety. Although limited data are noted for children < 2 years, there were 59 cases of paradoxically increased bronchorrhea in this age group, and many (86%) required hospitalization or extended hospitalization. For other age groups, the products were generally safe, with minor GI symptoms reported in 2% of all participants.

A pooled analysis of the three RCTs that measured cough showed statistically significant effects after 6 to 7 days of treatment. As CACC is generally a self-limited disease process, with most symptoms resolving in 5 to 7 days, no specific recommendations could be made for acetylcysteine or carbocysteine.

Key Clinical Question 2

Is there evidence of clinically relevant treatment effects for decongestants and antihistamines in reducing the duration of CACC ([Table 3](#))?

The De Sutter et al¹⁵ systematic review identified four RCTs that evaluated the effects of antihistamine and decongestant combinations on the severity of cough. The data (three studies in adults and one pediatric study) included 672 cold episodes. Data pooling was not possible due to different treatments and combinations. Overall, the results were inconsistent, making it



*The original search yielded a systematic review by Singh. The Cochrane Acute Respiratory Infections Group withdrew that review in September of 2016. On December 2, 2016 we performed an updated search for systematic reviews on zinc in common cold for treatment of cough, which retrieved one eligible systematic review on the topic published since the original search.

Figure 1 – Systematic review flow diagram.^{14,15,17,20-22,27} SRs = systematic reviews.

impossible to form any conclusion regarding the effectiveness of this combination of products.

The De Sutter et al¹⁵ systematic review identified two RCTs of antihistamine and analgesic combinations. Three hundred forty-one adult subjects had cough symptoms evaluated daily for 5 days. Both trials failed to show an effect from the active treatment compared with placebo or acetaminophen for cough.

The De Sutter et al¹⁵ systematic review identified two RCTs with a total of 249 subjects treated with a decongestant and analgesic combination. No effect on cough was observed.

The De Sutter et al¹⁵ systematic review evaluated three RCTs of antihistamine, decongestant, and analgesic combinations. Two studies included 555 adult subjects, and one pediatric study included 201 children. Data pooling was not possible, and study results were

inconsistent. The two adult studies did demonstrate some treatment effect on cough with the combination of dextromethorphan, doxylamine, paracetamol, and ephedrine. The author concluded that this combination may be effective for CACC in adults. However, there is no commercially marketed product available in the United States that includes this combination of ingredients. The pediatric study using the combination of acetaminophen, diphenhydramine, and pseudoephedrine showed no effect on cough; however, dextromethorphan was not included in the combination product administered in the pediatric study.

A single potentially eligible trial was identified from an updated literature search of the De Sutter review. This trial by Dicipinigaitis et al¹⁶ studied the effect of diphenhydramine on cough reflex sensitivity in 22 healthy subjects with acute viral infection by administering a capsaicin challenge on 3 separate days. Diphenhydramine was successful in inhibiting the cough

TABLE 2] GRADE Evidence Profile: Common Cold (Acetylcysteine and Carbocysteine for Acute Upper and Lower Respiratory Tract Infections in Children)^{1,4}

No. of Studies	Quality Assessment							No. of Patients			Effect			Quality	Importance
	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	AC or CC	Placebo	Relative (95% CI)	Absolute	Quality	Importance			
Cough after 6-7 d 3 studies N = 139	RCT	Serious ^a	No serious risk	Serious ^b	Serious ^c	Undetected	74	65	0.37 (95% CI, 0.12-1.20)	10% (-19% to -1%)	Very Low				

Question: Is there evidence of clinically relevant treatment effects for acetylcysteine and carbocysteine in reducing the duration of cough? **Settings:** Many studies included only hospitalized patients. AC = acetylcysteine; CC = carbocysteine; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCT = randomized controlled trial.

^aStudies have an overall high risk of bias.

^bMany patients were hospitalized, which is not routine in common cold, and included subjects with bronchitis and acute lower respiratory tract infections.

^cStudies were very small and even when combined contributed only 139 total subjects.

reflex in subjects with acute cough during viral respiratory tract infection. After review, it was determined that this study was not relevant to the clinical question. The available currently marketed products in the United States do not include the combination of ingredients that may be effective for CACC in adults; hence, no specific recommendations could be made for the use of antihistamine, decongestant, and analgesic combinations to treat CACC in adults. In addition, there were no pediatric studies of antihistamine, decongestant, and analgesic combination products that demonstrated efficacy for CACC.

1. For adult and pediatric patients with cough due to the common cold, we suggest against the use of over the counter cough and cold medicines until they have been shown to make cough less severe or resolve sooner (Ungraded Consensus-Based Statement).

Key Clinical Question 3

Is there evidence of clinically relevant treatment effects for NSAIDs on CACC (Table 4)?

The Kim et al¹⁷ systematic review identified two RCTs of 77 patients receiving NSAIDs and 82 placebo comparisons. The 2006 cough guidelines recommended a combination of first-generation antihistamine and nasal decongestant or naproxen for CACC.⁷ The Kim et al systematic review found no clear evidence that treatment with NSAIDs is effective for treatment of CACC. These studies were very small with wide CIs.

2. In adult patients with cough due to the common cold, we suggest against the use of nonsteroidal anti-inflammatory agents until they have been shown to make cough less severe or resolve sooner (Ungraded Consensus-Based Statement).

Key Clinical Question 4

Is there evidence of clinically relevant treatment effects for honey in reducing the duration of CACC in pediatric patients (Table 5)?^{18,19}

The Oduwole et al²⁰ systematic review identified a total of three RCTs. Two RCTs included a comparison of honey to dextromethorphan for reducing the frequency of cough. Both trials were judged to be at high risk of bias. There were 149 total participants in these study arms (75 received honey and 74 received dextromethorphan). Overall, there was no difference between treatment groups.

TABLE 3] GRADE Evidence Profile: Common Cold Decongestants and Antihistamines for Acute Cough^{15,16}

No. of Studies	Design	Quality Assessment					No. of Patients		Effect	Quality	Importance
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Decongestant or Antihistamine	Comparison			
Antihistamine and decongestant (De Sutter et al) ¹⁵											
4 studies	RCT	Serious ^a	Serious ^b	No serious risk	Serious ^c	Undetected	672 cold episodes	Pooling not possible Results inconsistent	Very low		
Antihistamine and analgesic (De Sutter et al) ¹⁵											
2 studies	RCT	Serious ^a	Serious ^b	No serious risk	Serious ^c	Undetected	341 subjects	Pooling not possible No effect observed	Very low		
Decongestant and analgesic (De Sutter et al) ¹⁵											
2 studies	RCT	Serious ^a	Serious ^b	No serious risk	Serious ^c	Undetected	249 subjects	Pooling not possible No effect observed	Very low		
Antihistamine decongestant and analgesic (De Sutter et al) ¹⁵											
3 studies	RCT	Serious ¹	Serious ²	No serious risk	Serious ^c	Undetected	555 adults, 201 children	Pooling not Possible Results inconsistent	Very low		
Antihistamine and decongestant with capsaicin challenge (Dicpinigaitis et al) ¹⁶											

(Continued)

TABLE 3] (Continued)

Quality Assessment							No. of Patients		Effect	Quality	Importance
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Decongestant or Antihistamine	Comparison			
1 study	RCT	No serious risk	Serious ^c	Serious ^d	Serious ^e	Undetected	22 subjects		Mean log C5 (0.4 ± 0.55 SD; P < .01) for diphenhydramine vs placebo	Very low	

Question: Is there evidence of clinically relevant treatment effects for decongestants and antihistamines in reducing the duration of CACC? CACC = cough associated with the common cold. See Table 2 legend for expansion of other abbreviations.

^aStudies were so poorly reported that risk of bias could not be accurately assessed.

^bData were not reported in sufficient detail in the primary studies to evaluate or pool in most cases.

^cEffect sizes not reported for studies, and data could not be pooled.

^dOutcome was cough reflex challenge.

^eExtremely small study.

TABLE 4] GRADE Evidence Profile for Common Cold: NSAIDs for Cough¹⁷

Quality Assessment							No. of Patients		Effect		Quality	Importance
No. of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	NSAID	Comparison	Relative (95% CI)	Absolute		
2 studies	RCT	Serious ^a	Serious ^b	No serious risk	Serious ^c	Undetected	77	82	MD -0.05 (-0.66 to +0.56)		Very low	

Question: Is there evidence of clinically relevant treatment effects for NSAIDs on CACC? MD = mean duration (of cough). See Table 2 legend for expansion of other abbreviations.

^aStudies were so poorly reported that most risk of bias categories could not be assessed.

^bInconsistency is high as assessed by the I_2 statistic.

^cStudies were very small and the CI was wide and includes both a relative decrease and increase.

TABLE 5] GRADE Evidence Profile Common Cold: Honey for Acute Cough in Children²⁰

No. of Studies	Quality Assessment						No. of Patients		Effect		Quality	Importance
	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Honey	Comparison	Relative (95% CI)	Absolute		
Honey compared with dextromethorphan for frequency of cough												
2 studies	RCT	Very serious ^a	Serious ^b	No serious risk	Serious ^c	Undetected	75	74	MD -0.07 (-1.07 to +0.94)		Very low	
Honey compared with dextromethorphan for severity of cough												
2 studies	RCT	Very serious ^a	Serious ^b	No serious risk	Serious ^c	Undetected	75	74	MD -0.13 (-1.25 to +0.99)		Very low	
Honey compared with diphenhydramine for frequency of cough												
1 study	RCT	Very serious ^a	Serious ^b	No serious risk	Serious ^c	Undetected	40	40	MD -0.57 (-0.90 to -0.24)		Very low	
Honey compared with diphenhydramine for severity of cough												
1 study	RCT	Very serious ^a	Serious ^b	No serious risk	Serious ^c	Undetected	40	40	MD -0.60 (-0.94 to -0.26)		Very low	
Honey compared with no treatment for frequency of cough												
2 studies	RCT	Very serious ^a	No serious risk	No serious risk	Serious ^c	Undetected	75	79	MD -1.05 (-1.48 to -0.62)		Very low	

(Continued)

TABLE 5] (Continued)

No. of Studies	Quality Assessment						No. of Patients		Effect		Quality	Importance
	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Honey	Comparison	Relative (95% CI)	Absolute		
Honey compared with no treatment for severity of cough 2 studies	RCT	Very serious ^a	No serious risk	No serious risk	Serious ^c	Undetected	75	79	MD -1.03 (-1.59 to -0.47)		Very low	
Honey compared with placebo for frequency of cough 1 study	RCT	No serious risk	Serious ^b	No serious risk	Serious ^c	Undetected	225	75	MD -1.85 (-3.36 to -0.33)		Low	
Honey compared with placebo for severity of cough 1 study	RCT	No serious risk	Serious ^b	No serious risk	Serious ^c	Undetected	225	75	MD -1.83 (-3.32 to -0.34)		Low	

Question: Is there evidence of clinically relevant treatment effects for honey in reducing the duration of CACC? See Table 2, 3, and 4 legends for expansion of abbreviations.

^aPaul et al¹⁸ and Shadkam et al¹⁹ have an overall high risk of bias.

^bInconsistency is high as assessed by the I_2 statistic or cannot be assessed because it is a single study.

^cStudies were very small.

TABLE 6] GRADE Evidence Profile for Common Cold: Zinc for the Common Cold²²

No. of Studies	Quality Assessment							No. of Patients		Effect			Quality	Importance
	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Zinc	Placebo	Relative (95% CI)	Absolute	Quality	Importance		
	Cough duration 3 adult studies	RCT	No serious risk	Serious ^a	No serious risk	Serious ^b	Undetected	102	97		Cough duration reduced in subjects receiving zinc Pooled estimate was -46% (95% CI, -28% to -64%)	Low		

Question: Is there evidence of clinically relevant treatment effects for zinc in cough duration? See Table 2 legend for expansion of abbreviations.

^aInconsistency; heterogeneity was 64% as assessed by the I_2 statistic.

^bIndividual studies were very small and CIs were wide.

One trial also included a comparison of honey to diphenhydramine (40 subjects in each group). This comparison showed honey may be better than diphenhydramine in reducing the frequency of cough and severity of cough. Two other comparisons in the two RCTs showed that honey was probably better compared with no treatment in 154 participants for frequency of cough and cough severity. In the third RCT of 300 pediatric patients, evidence indicated that honey may be better than placebo in reducing cough frequency and severity.

3. In pediatric patients (aged 1-18 years) with cough due to the common cold, we suggest honey may offer more relief for cough symptoms than no treatment, diphenhydramine, or placebo, but it is not better than dextromethorphan (Ungraded Consensus-Based Statement).

Remarks: Infants < 1 year of age should not be administered honey, and children < 2 years of age should not be administered dextromethorphan for cough symptoms

Key Clinical Question 5

Is there evidence of clinically relevant treatment effects for zinc regarding the time to resolution of cough or change in the cough symptom score (Table 6)?

The Singh and Das²¹ systematic review published in 2013 identified four RCTs in which zinc was evaluated for time to resolution of cough. One study was eliminated because the zinc was administered as syrup, whereas the other three studies used zinc lozenges. In the three lozenge studies (two adult studies, one pediatric study), 122 patients received zinc lozenges and 137 patients received placebo therapy. Data pooling was not possible given the diverse populations and varying dosage frequency. The time for resolution of cough was shorter with zinc treatment. In September 2016, the Singh and Das Cochrane review was withdrawn, and we subsequently performed an updated search for systematic reviews published on the use of zinc. One review by Hemilä and Chalker²² was identified.

The Hemilä and Chalker²² systematic review identified three RCTs in adults that addressed the total duration of colds and duration of the symptoms with zinc compared with placebo. The Petrus et al²³ 1998 study included 101 adult patients, and there was a significant decrease in the mean cough score in the zinc intervention group. The Prasad et al²⁴ 2000 study included 48 adult patients, and

TABLE 7] GRADE Evidence Profile for the Common Cold: OTC Medications for Acute Cough in Children and Adults in Community Settings²⁷⁻²⁹

No. of Studies	Design	Quality Assessment					No. of Patients	Effect		Quality	Importance
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias					
Antitussive agents (Smith et al ²⁷) 6 adult studies 4 child studies	RCT	Serious ^a	Serious ^b	No serious risk	Serious ^c	Undetected	1,526 adults 327 children	Pooling not possible Studies had variable results		Very low	
Expectorants (Smith et al ²⁷) 3 studies	RCT	Serious ^a	Serious ^b	No serious risk	Serious ^c	Undetected	604	Pooling not possible Studies had conflicting results		Very low	
Mucolytic agents (Smith et al ²⁷) 1 adult study 1 child study	RCT	Serious ^a	Serious ^b	No serious risk	Serious ^c	Undetected	99 adults 40 children	Pooling not possible		Very low	
Other combinations (Smith et al ²⁷) 4 adult studies 2 child studies	RCT	Serious ^a	Serious ^b	No serious risk	Serious ^c	Undetected	836 adults 94 children	Pooling not possible Studies were very small, heterogeneous, and used very different drug preparations and dosing frequency, limiting their comparability		Very low	
Vicks VapoRub (Paul et al ²⁸) 1 child study	RCT	No serious risk	Serious ^b	No serious risk	Serious ^c	Undetected	138 children	Change in cough frequency -1.5 placebo vs Vicks VapoRub -2.5; <i>P</i> = .07	Change in cough severity -1.4 placebo vs Vicks VapoRub -2.1; <i>P</i> = .06	Low	

(Continued)

TABLE 7] (Continued)

No. of Studies	Quality Assessment							Effect	Quality	Importance
	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	No. of Patients			
Agave nectar (Paul et al ²⁹) 1 child study	RCT	No serious risk	Serious ^b	No serious risk	Serious ^c	Undetected	119 children	Change in cough frequency -2.1 placebo vs agave nectar -2.2; P = .79	Change in cough severity -2.1 placebo vs agave nectar -2.2; P = .87	Low

Question: Is there evidence of clinically relevant treatment effects for OTC medications in reducing the duration of CACC? See Table 1 and 3 legends for expansion of abbreviations.

^aStudies overall have a high risk of bias.

^bThere are conflicting results between trials in each medication group, or inconsistency cannot be assessed because it was a single study.

^cMost studies failed to provide quantitative data on cough, and quantitative data that could be combined showed wide ranges, or study sample size was very small.

zinc was associated with reduction in duration and severity of cold symptoms, including cough. The Prasad et al²⁵ 2008 study included 50 adult patients, and there was a significant reduction in the duration of cold symptoms and cough. Zinc lozenges (dosed ≥ 75 mg/d) given within 24 hours of symptom onset may reduce the duration of cold symptoms, such as cough, in healthy individuals.²²

No systematic review is available regarding the use of zinc in pediatric patients. No recommendation can be made for the use of zinc supplements to reduce the duration and severity of cough in pediatric patients. A trial by Rerksuppaphol²⁶ was identified that assessed the efficacy of 15 mg of chelated zinc (zinc bisglycinate) given once daily vs placebo for 3 months during the winter season to 100 children aged 8 to 13 years in Thailand. There was no significant difference in the incidence of common cold symptoms; however, the authors report that the duration of cough was reduced significantly in the intervention group.²⁶ Similar studies in Turkey and Iran have also shown possible reduction in cold symptoms in children who received prophylactic zinc therapy. Another trial in the United States failed to demonstrate a positive impact. No recommendation can be made for the use of zinc supplement prophylaxis.^{21,26}

Zinc deficiency is an important cause of childhood morbidity in developing countries; this may explain the differing study results. Although generally well tolerated, some zinc lozenges have a distinctive and unpleasant taste, making subject blinding for these trials very difficult. The bad taste may also affect compliance with zinc therapy. A suggestion for the use of zinc lozenges in healthy adults with cough due to common cold was considered by the expert panel. However, due to weak evidence, the potential side effects of zinc, and the relatively benign and common nature of the condition being treated, the panel did not approve inclusion of this suggestion.

Key Clinical Question 6

Is there evidence of clinically relevant treatment effects for OTC medications in reducing the duration of CACC (Table 7)?

The Smith et al²⁷ systematic review, assessed to be of good quality, included six trials with a total of 1,526 adult patients that compared antitussive agents with placebo. The antitussive agents studied included codeine, dextromethorphan, and moguisteine. Four trials of antitussive studies were identified in 327

pediatric subjects. Overall, the studies had very poor quality with variable results. Data pooling was not possible.

The Smith et al²⁷ systematic review identified three trials comparing the expectorant guaifenesin with placebo in 304 subjects. Data quality was very low, and studies had conflicting results. No studies were identified that reported outcomes with the use of expectorants in pediatric subjects.

The Smith et al²⁷ systematic review identified one trial of 99 subjects that compared the mucolytic agent bromhexine with placebo. One pediatric trial compared the mucolytic letosteine with placebo in 40 subjects. Overall, the data quality for mucolytic agents was very low, and data pooling was not possible. One trial did find reduced cough frequency with mucolytic therapy.

Four studies evaluated other product combinations against placebo in 836 adults; three of the studies found antihistamines to be no more effective than placebo in relieving cough symptoms. Two studies evaluated other product combinations in 99 pediatric patients. Overall, these studies were very small and heterogeneous, using widely varied drug preparations and dosing frequencies. These limitations do not lead to any possible data pooling. None of the pediatric studies showed a benefit over placebo for antitussive therapy, antihistamines, decongestants, or antitussive/bronchodilator treatment.

A trial by Paul et al²⁸ was identified in the updated literature search of Smith et al.²⁷ Paul et al evaluated a single dose of Vicks VapoRub (camphor, menthol, and eucalyptus oils in a petroleum base) compared with petrolatum and no treatment for nocturnal cough caused by respiratory tract infections in 138 children. The study was blinded, but parents who used VapoRub correctly guessed their treatment group 86% of the time, as did 89% of the petrolatum-treating control group. Parents rated VapoRub most favorably for symptomatic relief of nocturnal cough. This study was assessed as low quality. Although the mechanism is not completely clear, menthol has been shown to improve the nasal sensation of airflow and may lead to improved sleep.

Another trial was identified in the update of Smith et al.²⁷ Paul et al²⁹ compared the effects of agave nectar with placebo and no treatment on acute nocturnal cough in 119 infants and toddlers. This study was assessed as low quality. Although a placebo effect was demonstrated, there was no additional benefit from agave nectar.

In adult and pediatric patients with the common cold, we find no evidence to support or refute the use of OTC antitussive agents, expectorants, mucolytic agents, antihistamines, or combination products for reducing cough.

Characteristics of Included Studies

Evidence profiles were created to grade the overall quality of the body of evidence supporting each question. The six evidence profiles can be found in [Tables 2 to 7](#).

State of the Available Evidence

Even though the systematic reviews were mostly of good quality,^{14,15,17,20-22,28} in general the only studies identified in the reviews provided low-quality evidence to support a particular strategy for management of cough with the common cold. Therefore, for recommendations, the panel depended heavily on patient values, preferences, and availability of potential therapies. The panel also made several suggestions for future research.

Discussion

We addressed six key clinical questions regarding the treatment of CACC. We could make no specific recommendation regarding the use of acetylcysteine or carbocysteine for key clinical question 1. Regarding key clinical question 2, no specific recommendation can be made based on the role of decongestants and antihistamines. For key clinical question 3, we found no evidence to support the use of nonsteroidal anti-inflammatory agents. For key clinical question 4, we suggested that honey may offer more relief than diphenhydramine, no treatment, or placebo; however, honey is not more effective than dextromethorphan for adults and children. For key clinical question 5, we reviewed evidence on the use of zinc lozenges in healthy adults and children > 2 years of age; some evidence indicates that when administered within 24 hours of symptoms, they may reduce cough duration. However, the evidence was not convincing, and study results are not consistent. Due to the benign nature of the illness, no specific suggestion was made for this question. Finally for key clinical question 6, we found no evidence to support or refute the use of OTC antitussive agents, expectorants, mucolytic agents, antihistamines, or combination products.

Although no significant advancement in treatment has been identified in clinical trial data since the 2006

update,⁷ there are dozens of pharmacologic and nonpharmacologic treatment options currently available as monotherapy or combination therapy. There have been new prescription products approved by the US Food and Drug Administration (FDA) for the treatment of cough; however, these are primarily new combinations of previously approved products. In addition, concerns about medication safety have led to recommendations regarding the use of some products in specific populations.

The first hydrocodone and guaifenesin combination product (Vituz; Hawthorn Pharmaceuticals)³⁰ was marketed in 2013. No new clinical studies were required by the FDA for approval of this combination product; efficacy was based on the demonstrated bioequivalence of the active ingredients to their respective reference products. The same pathway of approval has been used for several other cough and cold preparations over the past 3 years; hydrocodone bitartrate and guaifenesin oral solution (Obredon; Sovereign Pharmaceuticals),³¹ (Flowtuss; Mission Pharmacal)³² extended-release codeine and chlorpheniramine (Tuzistra XR; Vernalis Therapeutics, Inc.),³³ and hydrocodone bitartrate, pseudoephedrine hydrochloride, and guaifenesin oral solution (Hycufenix; Mission Pharmacal).³⁴ This guideline will be updated when additional studies are reported regarding the efficacy of these or other therapies for CACC.

In January 2008, the FDA released a consumer update strongly recommending that “over-the-counter (OTC) cough and cold products should not be used for infants and children under 2 years of age because serious and potentially life-threatening side effects could occur.”³⁵

In March 2011, the FDA took action against unapproved prescription oral cough, cold, and allergy products secondary to a concern about potential risks with extended-release formulations and irrational combinations of active ingredients.³⁶

In July 2015, the FDA issued a news release warning that caregivers should not use codeine-containing medications to treat coughs and colds in children < 18 years of age because of the potential for serious side effects, including slowed or difficult breathing.³⁷

In August 2016, the FDA issued a news release warning that the combination of opioids (those prescribed for pain and found in cough medicines) should not be combined with benzodiazepines or other central nervous

depressants.³⁸ Prescribers are advised to stay abreast of FDA communications and warning statements.

Both prescription and OTC products contain active ingredients that may be abused. For example, high doses of dextromethorphan can produce euphoria and dissociative effects. The ingestion of large doses of dextromethorphan (Robitussin) cough syrup is referred to as “robo-tripping.”³⁹ “Purple drank” is a cocktail used by teens or young adults in which promethazine with codeine syrup is combined with soda, fruit candy, or even alcohol. This mixture produces a sensation of relaxation, euphoria, and intoxication.⁴⁰ These medication misadventures can lead to serious complications and even death.

4. In pediatric patients (aged < 18 years) with cough due to the common cold, we suggest avoiding use of codeine-containing medications because of the potential for serious side effects including respiratory distress (Ungraded Consensus-Based Statement).

Areas for Future Research

To improve therapeutic options for treatment of cough due to common cold, potential research endeavors include the following:

- Development of validated models to demonstrate that mucoactive drug efficacy can accelerate the clinical development of mucoactive drugs for symptomatic respiratory tract infections⁴¹
- Development of clinical studies to validate the use of multi-ingredient prescription and nonprescription cough therapies⁴²
- Development of effective antitussive medications that are safe for children and adults
- RCTs with appropriate comparators

Conclusions

Unfortunately, there has been little change in the treatment choices for cough due to the common cold since publication of the 2006 CHEST cough guidelines. Many of the published studies are small and have significant limitations and potential biases. Data pooling was generally not possible, making it difficult to provide definitive recommendations. Cold symptoms are one of the most common reasons for seeking medical attention, and cough is one of the most irritating and persistent cold symptoms. We have reviewed the available literature and, when possible, provided treatment recommendations. This article also identified knowledge gaps and suggests areas for future research.

Acknowledgments

Author contributions: M. A. M. and P. C.-L. were the topic editors for this article and developed the key question using the Population, Intervention, Comparator, Outcome (PICO) format in collaboration with R. S. I. B. I. was the appointed methodologist and was among the investigators who conducted the systematic review that formed the basis for the suggestions. M.A.M. wrote the first draft; P. C.-L., B. I., and R. S. I. reviewed and contributed to subsequent versions.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following: R. S. I. reports that he has no financial or intellectual conflicts of interest regarding the content of this manuscript. Although R. S. I. is the Editor in Chief of *CHEST*, he discloses that he had nothing to do with the review of this manuscript and all decisions regarding the review process and acceptance of this manuscript were independently made by others. None declared (M. A. M., P. C. L., B. I.).

Collaborators: Todd M. Adams, MD (Webhannet Internal Medicine Associates of York Hospital, York, ME), Kenneth W. Altman, MD, PhD (Baylor College of Medicine, Houston, TX), Elie Azoulay, MD, PhD (University of Paris, Paris, France), Alan F. Barker, MD (Oregon Health & Science University, Portland, OR), Surinder S. Biring, MBChB, MD (Division of Asthma, Allergy and Lung Biology, King's College London, Denmark Hill, London, England), Fiona Blackhall, MD, PhD (Department of Medical Oncology, University of Manchester, Manchester, England), Donald C. Bolser, PhD (College of Veterinary Medicine, University of Florida, Gainesville, FL), Louis-Philippe Boulet, MD, FCCP (Institut universitaire de cardiologie et de pneumologie de Québec, Québec, [IUCPQ], QC, Canada), Sidney S. Braman, MD, FCCP (Mount Sinai Hospital, New York, NY), Christopher Brightling, MBBS, PhD, FCCP (University of Leicester, Glenfield Hospital, Leicester, United Kingdom), Priscilla Callahan-Lyon, MD (Adamstown, MD), Anne B. Chang, MBBS, PhD, MPH (Royal Children's Hospital, Queensland, Australia), Andréanne Côté, MD (Institut universitaire de cardiologie et de pneumologie de Québec [IUCPQ], Québec, QC, Canada), Terrie Cowley (The TMJ Association, Milwaukee, WI), Paul Davenport, PhD (Department of Physiological Sciences, University of Florida, Gainesville, FL), Satoru Ebihara, MD, PhD (Department of Rehabilitation Medicine, Toho University School of Medicine, Tokyo, Japan), Ali A. El Solh, MD, MPH (University at Buffalo, State University of New York, Buffalo, NY), Patricio Escalante, MD, MSc, FCCP (Mayo Clinic, Rochester, MN), Stephen K. Field, MD (University of Calgary, Calgary, AB, Canada), Dina Fisher, MD, MSc (University of Calgary, Respiratory Medicine, Calgary, AB, Canada), Cynthia T. French, PhD, FCCP (UMass Memorial Medical Center, Worcester, MA), Cameron Grant, MBChB, PhD (University of Auckland, Auckland, New Zealand), Peter Gibson, MBBS (Hunter Medical Research Institute, New South Wales, Australia), Philip Gold, MD, MACP, FCCP (Loma Linda University, Loma Linda, CA), Susan M. Harding, MD, FCCP (Division of Pulmonary, Allergy and Critical Care Medicine University of Alabama at Birmingham, Birmingham, AL), Anthony Harnden, MBChB, MSc (University of Oxford, Oxford, England), Adam T. Hill, MBChB, MD (Royal Infirmary and University of Edinburgh, Edinburgh, Scotland), Richard S. Irwin, MD, Master FCCP (UMass Memorial Medical Center, Worcester, MA), Peter J. Kahrilas, MD (Feinberg School of Medicine, Northwestern University, Chicago, IL), Joanne Kavanagh, MBChB, (Division of Asthma, Allergy and Lung Biology, King's College London, Denmark Hill, London, England), Karina A. Keogh, MD (Mayo Clinic, Rochester, MN), Kefang Lai, MD, PhD (First Affiliated Hospital of Guangzhou Medical College, Guangzhou, China), Andrew P. Lane, MD (Johns Hopkins University School of Medicine, Baltimore, MD), Kaiser Lim, MD (Mayo Clinic, Rochester, MN), J. Mark Madison, MD, FCCP, (UMass Memorial Medical Center, Worcester, MA), Mark A. Malesker, PharmD, FCCP (Creighton University School of Pharmacy and Health Professions, Omaha, NE), Stuart Mazzone, PhD, FCCP (University of Queensland, Queensland, Australia), Lorcan McGarvey, MD (The Queens University Belfast, Belfast, Ireland), Alex Molassiotis, PhD, MSc, RN (Hong Kong Polytechnic University, Hong Kong, China), M. Hassan Murad, MD, MPH (Mayo Clinic, Rochester, MN), Mangala Narasimhan, DO, FCCP (Hofstra-Northwell Health, Manhasset, NY), Peter Newcombe, PhD (School of Psychology University of

Queensland, Queensland, Australia), Huong Q. Nguyen, PhD, RN (Kaiser Permanente, Pasadena, CA), John Oppenheimer, MD (University of Medicine and Dentistry of New Jersey -Rutgers University), Marcos I. Restrepo, MD, MSc, FCCP (South Texas Veterans Health Care System, San Antonio), Mark Rosen, MD, Master FCCP (Icahn School of Medicine at Mount Sinai, New York, NY), Bruce Rubin, MEng, MD, MBA (Virginia Commonwealth University, Richmond, VA), Jay H. Ryu, MD, FCCP (Mayo Clinic, Rochester, MN), Jaelyn Smith, MB ChB, PhD (University of Manchester, Manchester, England), Susan M. Tarlo, MBBS, FCCP (Toronto Western Hospital, Toronto, ON, Canada), Julie Turmel, PhD (Quebec Heart and Lung Institute, Laval University, Quebec City, QC, Canada), Anne E. Vertigan, PhD, MBA, BAppSc (SpPath) (John Hunter Hospital, New South Wales, Australia), Gang Wang, MD, PhD (Sichuan University, West China Hospital, Chengdu, China), Miles Weinberger, MD, FCCP (University of Iowa Hospitals and Clinics, Iowa City, IA), Kelly Weir, BSpThy, MspPath, PhD, CPSP (Menzies Health Institute Queensland/Griffith and Gold Coast, Australia).

Other contributions: The authors thank Nancy Harger, MLS, and Judy Nordberg, MLS, Education and Clinical Service Librarians working at in the University of Massachusetts Medical Library who undertook all the searches for this systematic review. The authors also thank Tamara Pringsheim, MD, and Rebecca L. Diekemper, MPH, for methodology support.

Endorsements: This guideline has been endorsed by the American Association for Respiratory Care (AARC), American Bronchoesophological Association (ABEA), American College of Allergy, Asthma, and Immunology (ACAAI), Asian Pacific Society for Respiriology (APSR), and Irish Thoracic Society (ITS).

Role of Sponsors: The American College of Chest Physicians was the sole supporter of these guidelines, this article, and the innovations addressed within.

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