Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Treatment of unexplained chronic cough: CHEST guideline and Expert Panel report.

Bibliographic Source(s)

Gibson P, Wang G, McGarvey L, Vertigan AE, Altman KW, Birring SS, CHEST Expert Cough Panel. Treatment of unexplained chronic cough: CHEST guideline and Expert Panel report. Chest. 2016 Jan;149(1):27-44. [44 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Pratter MR. Unexplained (idiopathic) cough: ACCP evidence-based clinical practice guidelines. Chest. 2006 Jan;129(1 Suppl):220S-1S. [10 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

The grades of recommendation (1A–2C, consensus-based [CB]) and the approach to rating the quality of evidence are defined at the end of the "Major Recommendations" field.

1. In adult patients with chronic cough, the Expert Panel suggests that unexplained chronic cough be defined as a cough that persists longer than 8 weeks, and remains unexplained after investigation, and supervised therapeutic trial(s) conducted according to published best-practice guidelines (CB).
2. In adult patients with chronic cough, the Expert Panel suggests that patients with chronic cough undergo a guideline/protocol based assessment process that includes objective testing for bronchial hyperresponsiveness and eosinophilic bronchitis, or a therapeutic corticosteroid trial (CB).
3. In adult patients with unexplained chronic cough, the Expert Panel suggests a therapeutic trial of multimodality speech pathology therapy (Grade 2C).
4. In adult patients with unexplained chronic cough and negative tests for bronchial hyperresponsiveness and eosinophilia (sputum eosinophils, exhaled nitric oxide), the Expert Panel suggests that inhaled corticosteroids not be prescribed (Grade 2B).
5. In adult patients with unexplained chronic cough, the Expert Panel suggests a therapeutic trial of gabapentin as long as the potential side effects and the risk-benefit profile are discussed with patients before use of the medication, and there is a reassessment of the risk-benefit profile at 6 months before continuing the drug (Grade 2C).

Remarks: Because health-related quality of life of some patients can be so adversely impacted by their unexplained chronic cough, and because gabapentin has been associated with improvement in quality of life in a randomized controlled clinical trial, the American College of Chest Physicians (CHEST) Cough Expert Panel believes that the potential benefits in some patients outweigh the potential side effects. With respect to dosing, patients without contraindications to gabapentin can be prescribed a dose escalation schedule beginning at 300 mg once a day with additional doses being added each day as tolerated up to a maximum tolerable daily dose of 1,800 mg a day in two divided doses.

6. In adult patients with unexplained chronic cough and a negative workup for acid gastroesophageal reflux disease, the Expert Panel suggests that proton pump inhibitor therapy not be prescribed (Grade 2C).

Definitions

American College of Chest Physicians (CHEST) Grading System

Grade of Recommendation	Balance of Benefit vs. Risk and Burdens (Strength of the Recommendation: Level 1 or 2)	Methodologic Strength of Supporting Evidence (Quality of Body of Evidence: A, B, C, or CB)	Implications
Graded evidence-based guideline recommendations			
Strong recommendation, high-quality evidence (1A)	Benefits clearly outweigh risk and burdens or vice versa	Consistent evidence from randomized controlled trials (RCTs) without important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change confidence in the estimate of effect.
Strong recommendation, moderate-quality evidence (1B)	Benefits clearly outweigh risk and burdens or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Higher-quality research may well have an important impact on confidence in the estimate of effect and may change the estimate.
Strong recommendation, low- or very-low-quality evidence (1C)	Benefits clearly outweigh risk and burdens or vice versa	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate.
Weak recommendation, high-quality evidence (2A)	Benefits closely balanced with risks and burden	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	The best action may differ depending on circumstances or patient's or societal values. Further research is very unlikely to change confidence in the estimate of effect.
Weak recommendation, moderate-quality evidence (2B)	Benefits closely balanced with risks and burden	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies	Best action may differ depending on circumstances or patient's or societal values. Higher-quality research may well have an important impact on confidence in the estimate of effect and may change the estimate.
Weak recommendation, low- or very-low-quality evidence (2C)	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Evidence for at least one critical outcome from observational studies, case series, or RCTs, with serious flaws or indirect evidence	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate.
Nongraded consensus-based suggestions			
Consensus-	Uncertainty due to lack	Insufficient evidence for a graded	Future research may well have an important impact

Grade of Recommendation	Balance of Benefit vs. Risk and Burdens (Strength of the Recommendation: Level 1 or 2)	Methodologic Strength of Supporting Evidence (Quality of Body of Evidence: A, B, C, or CB)	Implications
based (GB)	of evidence but expert opinion that benefits outweigh risk and burdens or vice versa	recommendation	on confidence in the estimate of effect and may change the estimate.

Clinical Algorithm(s)

An algorithm titled "A proposed algorithm detailing a management approach to the patient with 'difficult-to-treat' cough" is provided in the original guideline document.

Scope

Disease/Condition(s)

Unexplained chronic cough

Guideline Category

Evaluation

Management

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Pulmonary Medicine

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Respiratory Care Practitioners

Guideline Objective(s)

To make recommendations for treatment of unexplained chronic cough

Target Population

Patients with unexplained chronic cough

Interventions and Practices Considered

1. Guideline/protocol based assessment
    - Objective testing for bronchial hyperresponsiveness and eosinophilic bronchitis
    - Therapeutic corticosteroid trial
2. Therapeutic trial of multimodality speech pathology therapy
3. Therapeutic trial of gabapentin

Note: The following were considered but not recommended: inhaled steroids and proton pump inhibitors.

Major Outcomes Considered

- Efficacy of treatment compared with usual care for cough severity, cough frequency, and cough-related quality of life
- Potential side effects and the risk-benefit profile of medications used to treat unexplained chronic cough

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Systematic Review Question

The clinical question for this systematic review was generated by using the PICO (population, intervention, comparison, outcome) format. The review question was: What is the efficacy of treatment compared with usual care for cough severity, cough frequency, and cough-related quality of life in patients with unexplained chronic cough?

Literature Search

The methods used for this systematic review conformed with those outlined in the article "Methodologies for the development of CHEST guidelines and expert panel reports" (see the "Availability of Companion Documents" field). The

- National Guideline Clearinghouse (NGC) and the
- Guidelines International Network Library

were searched for existing guidelines on unexplained chronic cough. Systematic reviews and clinical trials were identified from searches of electronic databases (PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials [Cochrane Library]) 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: [Cough OR chronic cough] AND [Idiopathic OR refractory OR unexplained OR intractable]. An additional search for chronic cough and [clinical trial] was conducted in PubMed.

The titles and abstracts of the search results were independently evaluated by two reviewers 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 population (patients with chronic cough that was unexplained, refractory to treatment, or idiopathic; in adults or adolescents aged >12 years) (see Table 1 in the original guideline document). The full text of all potentially relevant articles was retrieved, and two reviewers independently evaluated all the retrieved studies against the criteria.

Number of Source Documents

Figure 2 in the original guideline document presents the results of the systematic review. Nineteen individual randomized controlled trials (RCTs) were identified; 11 met the inclusion criteria, and eight were excluded. Six potentially relevant systematic reviews were identified; five met the inclusion criteria, and one was excluded because it was a narrative review. No relevant guidelines were identified. This technique resulted in the inclusion of five systematic reviews and 11 RCTs, which assessed a variety of interventions for unexplained chronic cough, refractory cough, or idiopathic cough.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

The American College of Chest Physicians (CHEST) has adopted the GRADE framework (The Grading of Recommendations Assessment, Development and Evaluation). This framework separates the process of rating the quality of evidence from that of determining the strength of recommendation. The quality of evidence is based on the five domains of risk of bias, inconsistency, indirectness, reporting bias, and imprecision.

The quality of evidence (i.e., the confidence in estimates) is rated as high (A), moderate (B), or low or very low (C) (see the "Rating Scheme for the Strength of the Recommendations" field).

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Quality Assessment

Included articles underwent methodologic assessment. For randomized controlled trials (RCTs) and controlled clinical trials, quality assessment was conducted by using the Cochrane risk of bias tool. For systematic reviews, the Documentation and Appraisal Review Tool was used. Additional information is available in the "Methodologies for the Development of the Management of Cough" document (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

Description of Methods Used to Formulate the Recommendations

The methodology of the CHEST Guideline Oversight Committee was used to select the Expert Cough Panel chair and the international panel of experts to perform the systematic review, synthesis of the evidence, and development of the recommendations and suggestions (see the "Availability of Companion Documents" field for methodology documents).

Grading Recommendations

In addition to the quality of the evidence, the recommendation grading includes a strength of recommendation dimension, which is used for all CHEST guidelines. 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 (e.g., those provided in the present guideline), the Expert Panel intended for a strong recommendation (Grade 1) to imply that the Expert Panel recommends using intervention fidelity strategies in all studies in which patients with chronic cough are being diagnosed and managed. Intervention fidelity has been identified as an important aspect of chronic cough studies and is defined "as the extent to which an intervention was delivered as conceived and planned-to arrive

at valid conclusions concerning its effectiveness in achieving target outcomes." The strength of recommendation here is based on consideration of three factors: balance of benefits to harms, patient values and preferences, and resource considerations. Harms incorporate risks 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 statements because of their potential conflicts of interest (e-Table 1 [see the "Availability of Companion Documents" field]). Transparency of process was documented. Further details of the methods related to conflicts of interests and transparency have been published in the methodology and CHEST guideline development documents.

Rating Scheme for the Strength of the Recommendations

American College of Chest Physicians (CHEST) Grading System

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Strong recommendation, moderate-quality evidence (1B)	Benefits clearly outweigh risk and burdens or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Higher-quality research may well have an important impact on confidence in the estimate of effect and may change the estimate.
Strong recommendation, low- or very-low-quality evidence (1C)	Benefits clearly outweigh risk and burdens or vice versa	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate.
Weak recommendation, high-quality evidence (2A)	Benefits closely balanced with risks and burden	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	The best action may differ depending on circumstances or patients' or societal values. Further research is very unlikely to change confidence in the estimate of effect.
Weak recommendation, moderate-quality evidence (2B)	Benefits closely balanced with risks and burden	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies	Best action may differ depending on circumstances or patients' or societal values. Higher-quality research may well have an important impact on confidence in the estimate of effect and may change the estimate.
Weak recommendation, low- or very-low-quality	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and	Evidence for at least one critical outcome from observational studies, case series, or RCTs, with serious flaws or indirect evidence	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate.

Grade of Recommendation	Balance of Benefit vs. Risk and Burdens (Strength of the Recommendation; Level 1 or 2)	Methodological Strength of Supporting Evidence (Quality of Body of Evidence: A, B, C, or CB)	Implications
evidence (2C)	burden may be closely balanced		
Nongraded consensus-based suggestions			
Consensus-based (CB)	Uncertainty due to lack of evidence but expert opinion that benefits outweigh risk and burdens or vice versa	Insufficient evidence for a graded recommendation	Future research may well have an important impact on confidence in the estimate of effect and may change the estimate.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

After the Cough Executive Committee provided final approval, the NetWorks, Guideline Oversight Committee (GOC), and Board of Regents disseminated manuscripts and supporting documentation for review. The The American College of Chest Physicians (CHEST) NetWorks of interested members, in the areas of Airways Disorders, Allied Health, Clinical Pulmonary Medicine, Pediatric Chest Medicine, Pulmonary Physiology Function and Rehabilitation, and Respiratory Care, reviewed the content of the manuscripts. Members from the CHEST Board of Regents and GOC reviewed both content and methods, including consistency, accuracy, and completeness. The CHEST journal peer review process overlapped with the later rounds of these reviews. All ideas for modification were marked as mandatory or suggested, responded to or justified, and tracked through the multiple rounds of review. The CHEST Presidential line of succession provided the final approval allowing submission to the journal.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

In one systematic review of nonpharmacologic therapy for refractory chronic cough, the authors identified English-language reports that investigated nonpharmacologic treatment of refractory chronic cough in adults published between 1980 and 2012. This review identified one randomized controlled trial (RCT) and several observational studies. The intervention included two to four sessions of education, cough suppression techniques, breathing exercises, and counseling. The intervention resulted in a reduction in cough frequency (three studies), an improvement in cough severity (two studies), and a beneficial effect on cough-related quality of life (four studies).

Potential Harms

In one study, adverse events were reported in 31% of the gabapentin group and included confusion, dizziness, dry mouth, fatigue, and/or nausea; blurred vision, headache, and memory loss was reported in only one patient each. Adverse events were reported in 10% of the placebo group, and there was no statistically significant difference in adverse events between the gabapentin and placebo groups. In another study, morphine was well tolerated, and no patients dropped out because of adverse events. The most common adverse effects noted were constipation (40%) and drowsiness (25%).

Qualifying Statements

Qualifying Statements

American College of Chest Physician (CHEST) guidelines are intended for general information only, are not medical advice, and do not replace professional medical care and physician advice, which always should be sought for any medical condition. The complete disclaimer for this guideline can be accessed at http://www.chestnet.org/Guidelines-and-Resources/Guidelines-and-Consensus-Statements/CHEST-Guidelines .

Implementation of the Guideline

Description of Implementation Strategy

Dissemination

After publication, the guidelines were promoted to a wide audience of physicians, other health-care providers, and the public through multiple avenues. Press releases were prepared for both the lay and medical media, with major outreach efforts to all relevant print, broadcast, and Internet media. Panelists located in various large media markets were identified as potential spokespersons for interviews. Social media promotion was facilitated over Twitter, Facebook, American College of Chest Physicians (CHEST) e-Communities, internal and external blogs, and other communication routes. Blast communications were sent to CHEST members with links to the publication and postings on CHEST's Web site.

In addition to publication in *CHEST*, other derivative products were prepared to help with implementation, including slide sets, algorithms, and other clinical tools. These derivative products are posted on the CHEST Web site and will be made available in CHEST Guidelines. CHEST Guidelines will be the repository for the most current recommendations and suggestions from all CHEST guidelines, consensus statements, and hybrid documents. This online repository will also house a collection of related resources.

Associations that appointed representatives earlier in the process were asked to consider endorsing the approved guidelines for listing in the final publication. These organizations were requested to help promote the publication to their memberships through newsletters, Web sites, and other means.

Implementation Tools

Clinical Algorithm

Mobile Device Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Gibson P, Wang G, McGarvey L, Vertigan AE, Altman KW, Birring SS, CHEST Expert Cough Panel. Treatment of unexplained chronic cough: CHEST guideline and Expert Panel report. Chest. 2016 Jan;149(1):27-44. [44 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Jan

Guideline Developer(s)

American College of Chest Physicians - Medical Specialty Society

Source(s) of Funding

The American College of Chest Physicians (CHEST) was the sole supporter of these guidelines, this article, and the innovations addressed within.

Guideline Committee

Expert Cough Panel

Composition of Group That Authored the Guideline

Panel Members: Peter Gibson, MBBS; Gang Wang, MD, PhD; Lorcan McGarvey, MD; Anne E. Vertigan, PhD, MBA, BAppSc (SpPath); Kenneth W. Altman, MD, PhD; Surinder S. Birring, MB ChB, MD

Financial Disclosures/Conflicts of Interest

Financial/Nonfinancial Disclosures

The authors have reported to *CHEST* the following: L. M. previously served on advisory boards for Novartis and GlaxoSmithKline in relation to novel compounds with a potential role in treatment of cough; he also served as chairman for the Mortality Adjudication Committee for UPLIFT

and TIOSPIR, two Phase IV COPD clinical trials for Boehringer Ingelheim. None declared (P. G., G. W., A. E. V., K. W. A., S. S. B.).

Also see the methodology document (see the "Availability of Companion Documents" field) for a discussion of the American College of Chest Physicians' disclosure policies.

Guideline Endorser(s)

American Academy of Otolaryngology - Head and Neck Surgery Foundation - Medical Specialty Society

American Association for Respiratory Care - Professional Association

American College of Allergy, Asthma and Immunology - Medical Specialty Society

American Thoracic Society - Medical Specialty Society

Canadian Thoracic Society - Medical Specialty Society

Irish Thoracic Society - Medical Specialty Society

Lung Foundation Australia - Medical Specialty Society

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Pratter MR. Unexplained (idiopathic) cough: ACCP evidence-based clinical practice guidelines. Chest. 2006 Jan;129(1 Suppl):220S-1S. [10 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the CHEST Journal Web site . Also available to CHEST Journal subscribers through the CHEST app for iPhone, iPad, and iPod Touch.

Availability of Companion Documents

The following are available:

Methodology Documents

- Lewis SZ, Diekemper RL, French CT, Gold PM, Irwin RS. Methodologies for the development of the management of cough: CHEST guideline and Expert Panel report. Chest. 2014 Nov;146(5):1395-402. Available from the CHEST Journal Web site .
- Lewis SZ, Diekemper RL, Ornelas J, Casey KR. Methodologies for the development of CHEST guidelines and Expert Panel reports. Chest. 2014 Jul;146(1):182-92. Available from the CHEST Journal Web site .

Background Documents

- Gibson P, Wang G, McGarvey L, Vertigan AE, Altman KW, Birring SS, CHEST Expert Cough Panel. Treatment of unexplained chronic cough: CHEST guideline and Expert Panel report. Online supplement. Chest. 2016 Jan. 4 p. Available from the CHEST Journal Web site .
- Irwin RS, French CT, Lewis SZ, Diekemper RL, Gold PM. Overview of the management of cough: CHEST guideline and Expert Panel report. Chest. 2014 Oct;146(4):885-89. Available from the CHEST Journal Web site .
- Canning BJ, Chang AB, Bolser DC, Smith JA, Mazzone SB, McGarvey L. Anatomy and neurophysiology of cough: CHEST guideline and Expert Panel report. Chest. 2014 Dec;146(6):1633-48. Available from the CHEST Journal Web site .

- French CT, Diekemper RL, Irwin RS. Assessment of intervention fidelity and recommendations for researchers conducting studies on the diagnosis and treatment of chronic cough in the adult: CHEST guideline and Expert Panel report. Chest. 2015 Jul;148(1):32-54. Available from the CHEST Journal Web site .
- Boulet L, Coeytaux RR, McCrory DC, French CT, Chang AB, Birring SS, Smith J, Diekemper RL, Rubin B, Irwin R, CHEST Expert Cough Panel. Tools for assessing outcomes in studies of chronic cough: CHEST guideline and Expert Panel report. Chest. 2015 Mar;147(3):804-14. Available from the CHEST Journal Web site .
- Management of cough: overview of CHEST guideline and Expert Panel report. Podcast. 2014 Oct. Available from the CHEST Journal Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on May 4, 2006. The information was verified by the guideline developer on June 5, 2006. This summary was updated by ECRI Institute on May 20, 2016.

Copyright Statement

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