Future Directions in the Clinical Management of Cough

ACCP Evidence-Based Clinical Practice Guidelines

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Objectives: To impart a call for further research into the identified domains of particular interest in the etiology, management, and treatment of cough.

Design/methodology: A literature review was performed using the search term “cough” in PubMed between 1983 and 2004. The final draft of this guideline was reviewed, in addition to recent studies on cough, and suggestions provided by the authors were collated into a definitive inventory of specific areas in which the lack of quality evidence encumbered the development of clinically relevant evidence-based recommendations.

Results/conclusions: Although our understanding of the causes and optimal management of chronic cough have significantly increased over the past 25 years, further research remains to be done on this common symptom. This is reflected by the generally low level of evidence for many of the recommendations in these guidelines. Research is particularly needed on the optimal treatment of postinfectious cough, how to distinguish acute bronchitis from other conditions, how to reliably diagnose and treat cough due to gastroesophageal reflux disease, clearly identifying a role for nonpharmacologic protussive treatment modalities in diseases associated with an increased production of bronchial secretions, determining how often cough in patients with interstitial lung disease is due to conditions other than these, establishing the spectrum and frequency of causes of chronic cough in the immunocompromised hosts, and better characterizing psychogenic cough. Further studies are also needed on methods for the assessment of cough, in particular, noninvasive measures of airway inflammation, and pharmacotherapy. It should be determined how often unexplained cough (previously referred to as idiopathic cough) is due to the use of non-evidence-based guidelines or to environmental causes, and assessed whether an empiric, integrative approach of diagnosing chronic cough leads to better outcomes, including cost-effectiveness, than routine testing. While much work has been done on chronic cough, we need studies on the spectrum and frequency of acute and subacute coughs.

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Abbreviations: CEB = chronic eosinophilic bronchitis; GERD = gastroesophageal reflux disease

Chronic cough is one of the most common complaints in human beings, and although significant progress has occurred in the last 3 decades in regard to the optimal management of cough, further research needs to be done and the value of many therapeutic interventions should be evaluated.1

In regard to the main themes that require further addressing in the management of chronic cough, particular attention should be devoted to the role of noninvasive measures of airway inflammation, such as induced sputum analysis, in its evaluation and treatment. These measures may help to identify conditions such as nonasthmatic eosinophilic bronchitis and to better target therapy, but their value in
the global investigation of cough in various settings and populations remain to be addressed. Furthermore, additional studies are required on the optimal treatment of postinfectious cough, how to distinguish acute bronchitis from other conditions, as well as on the characteristics and management of psychogenic cough. Unexplained cough, previously referred to as idiopathic cough, remains a puzzling entity that may possibly result from use of non-evidence-based guidelines or environmental causes. Gastroesophageal reflux disease (GERD) is a common cause of chronic cough, but we need more data on how to reliably diagnose and treat cough due to this condition. The spectrum and frequency of the causes of cough in immunocompromised host patients or other with conditions such as interstitial lung diseases should also be documented. Finally, the spectrum and frequency of etiologies for acute and subacute coughs should be determined in various populations. In regard to therapeutics, the role of nonpharmacologic protussive treatment modalities should be better defined, and we should establish whether, compared to routine testing, an empiric, integrative approach to diagnosing chronic cough results in better outcomes, including cost-effectiveness.

These themes will be discussed more thoroughly, and some specific areas of interest in regard to future developments will be elaborated on, consisting mainly of the research that should be done and potential targets for therapy. Novel treatments will be addressed in another section of this guideline.

Cough Mechanisms

There has been a significant improvement in our understanding of the pathophysiology of cough from studies in animal models. These studies have suggested a major role of the vagus nerve through C-fibers and rapid-adapting receptors, although other neurogenic mechanisms may contribute to this symptom and remain to be explored. However, the relevance of the observations made in animals has to be determined for humans. Potential targets for therapy, such as afferent nerves, ion channel expression, and neurons of the CNS, such as the pre-Botzinger complex of the lower brainstem, which may modulate the cough reflex, should be researched.

Another useful area of research would also be to determine the mechanism of airway “hyperreactivity” that is associated with cough. Much of cough that is associated with the common cold appears to be associated with a hyperreactive cough reflex. Recent research on cough that is induced by airway vibration shows a clear differentiation between healthy subjects and those with colds. The method of inducing cough with airway vibration may be an entry into understanding this mechanism of hyperreactivity and in designing clinical trials to test new medicines that return the hyperreactive cough reflex back toward normal reactivity.

Complications of Cough

Although much remains to be studied, an influence of age, gender, and cultural background on the effects of cough on quality of life or interference with daily activities has been suggested, as well as some of the mechanisms by which cough may induce its numerous complications.

Upper Airways Cough Disorders, and Infectious and Postinfectious Cough

It is still unclear why some patients have upper airway symptoms, such as frequent throat clearing, that do not respond to medications. This may be due to inadequate adherence to the prescribed therapy, the need for another treatment, or environmental influences, or it may be a manifestation of another underappreciated disease such as GERD. The accuracy of a diagnosis of “acute bronchitis” or, in other words, how often other diseases such as the common cold, acute exacerbation of chronic bronchitis, and acute asthma are misdiagnosed as acute bronchitis should be determined.

The optimal method of assessment of and therapeutic approach for patients with postinfectious cough should be evaluated. The role of noninvasive measures of airway inflammation in this context needs to be explored. The relative frequency of the main conditions leading to chronic cough may change from one population to another, and epidemiologic studies should be instructive on how the proposed evaluation/treatment algorithms should be adapted to these findings.

The positive and negative predictive values of sinus CT scanning in the assessment of causes of cough remain to be determined. Furthermore, the role of the various corticosteroid preparations, combinations of inhaled corticosteroids and long-acting $\beta_2$ agonists, new anticholinergic agents, and other agents acting on airway inflammation and cough reflex remain to be evaluated in the context of a postinfectious cough. The influence of therapy with nasal corticosteroids on cough in the context of acute or chronic sinusitis should be explored, as well as the role of bacterial infection in chronic sinusitis and the criteria for the appropriate use of antibiotics.
Cough is a common symptom in most respiratory infections, and the possible causal microorganisms should be considered in regard to the population evaluated and epidemiologic factors. Further studies should help to predict the criteria for suspecting tuberculosis in populations at high risk of exposure and infection; this, in addition to an optimal diagnostic evaluation, could improve the use of resources and adherence to recommendations.

Asthma

The significance of “cough-variant asthma” and its optimal management require further evaluation. It would be of particular interest to determine why these subjects only or mostly have a cough as the clinical expression of asthma. Furthermore, the best treatment to offer to this subgroup of asthmatic subjects, not only for cough suppression but also for preventing the possible development of more severe asthma and long-term airway changes, is uncertain. Asthmatic patients who smoke, who account for about 25% of the asthmatic population, are another subgroup that requires more attention. In these patients, who often are without evidence of COPD, it may be difficult to determine whether asthma or smoking contributes the most to chronic cough. In regard to therapy, no study has specifically looked at the influence of asthma medications on cough in asthmatic patients who smoke. Chalmers et al have demonstrated that these last have a reduced response to agents such as corticosteroids; therefore, medications that are required to control asthma may differ compared to asthma in nonsmokers. The value of smoking-cessation therapies, particularly in this group of coughers, should be the object of further evaluations, and new strategies for therapy should be developed.

GERD

GERD is so common that this diagnosis should always be considered in the presence of a persisting cough. However, accurately diagnosing and successfully treating GERD is a difficult task. Although the causality relationship seems to be best established through a therapeutic trial, a diagnostic test to reliably diagnose GERD and to help to distinguish between acid and nonacid mediation of the cough would be a most valuable addition. In this regard, the determination of what items should be routinely included in the diagnostic regimen has not been determined. The minimum effective medical treatment needed to treat most GERD and the reasons why delays are often observed in improvements under therapy should also be explored.

Eosinophilic and Other Types of Bronchitis

Nonasthmatic chronic eosinophilic bronchitis (CEB) is a most intriguing condition. The discrepancies between reports on its prevalence suggest that this disease is often not recognized as such and is often confused with asthma, although it may be due to other host or environmental factors. We need more studies on the prevalence of this condition in various populations. The reasons why it does not translate into the full-blown picture of asthma and how to easily and reliably differentiate this condition from cough-variant asthma should be further evaluated. The long-term consequences of CEB on the structure and function of the airway are unknown.

Furthermore, an exploration of the possible etiologies of CEB is needed in order to develop preventive measures if the cause is environmental, such as common allergens or occupational substances, as in patients with asthma. Inhaled corticosteroids are generally an effective treatment for this condition. However, randomized controlled trials are required to define the optimal treatment of CEB, both in terms of therapeutic agent and in the duration and intensity of therapy. Noninvasive measures of airway inflammation such as induced sputum analysis are still infrequently used for clinical purposes, despite the fact that we have increasing evidence of their usefulness in the assessment of treatment needs in patients with asthma and for the diagnosis of CEB. Simpler methods for the assessment of airway inflammation should also be evaluated.

Chronic Bronchitis

Studies that specifically assess the effects of treatments on cough as an outcome in chronic bronchitis and acute exacerbations of this condition are needed.

Bronchiolitis and Bronchiectasis

In bronchiectasis, cough is a protective mechanism helping to eliminate the high volume of bronchial secretions produced. Better medical therapies to reduce the volume of secretions or to increase their elimination should be searched. The long-term benefits of treatments such as the association of corticosteroids and ibuprofen in patients with cystic fibrosis and the use of itraconazole in patients with allergic bronchopulmonary aspergillosis-related disease should also be explored.
bronchiectasis should be further studied; the optimal treatment of bronchial obstruction associated with these conditions should also be better defined. For these conditions, there is a need to determine whether or not nonpharmacologic protussive treatment modalities lead to favorable clinical outcomes, and to what extend. In regard to bronchiolitis, the prevalence and contribution of chronic cough as a manifestation of this condition should be further assessed.

**LUNG NEOPLASMS**

The influence of various modes of treatment for lung cancer on cough, particularly when it is a predominant complaint, remains to be studied. New treatments for cough suppression, particularly those such as nonopioid preparations that have fewer side effects in these patients, should be researched.

**ASPIRATION**

This frequent cause of cough is underdiagnosed, and there should be a high degree of suspicion in diseases that predispose the patient to swallowing dysfunction. The incidence and management of cough in these conditions should be further studied.

**DRUG-INDUCED COUGH**

The identification of cough related to drug therapy, especially new agents, should be routine to avoid unnecessary investigations. For each drug or category of drugs, we should try to identify the mechanisms and possible markers that predispose the patient to this type of complication. The optimal treatment for cough in patients in whom the cessation of therapy with those agents cannot be considered (e.g., angiotensin-converting enzyme inhibitors) should be studied.

**HABIT, UNEXPLAINED, AND PSYCHOGENIC COUGH**

The clinical characteristics of the profiles of habit cough and unexplained cough, previously referred to as psychogenic cough and idiopathic cough, respectively, remain to be defined, particularly in children and adolescents. The contribution of persistent cough to psychological problems should be differentiated from the contribution of psychological problems to cough. The various techniques for addressing psychogenic cough should be compared for efficacy.

It is suggested that a national or international registry be developed and collaborative research be initiated to better characterize patients with unexplained (idiopathic) cough and their long-term outcomes.

**CHRONIC INTERSTITIAL DISEASES AND UNCOMMON CAUSES**

It is generally assumed that when cough is associated with interstitial diseases, it is due to the same process. However, it is not known how often cough in patients with interstitial diseases such as idiopathic pulmonary fibrosis is due to this disease or to other etiologies, or what the spectrum and frequency of these other causes of cough are in these patients. The dissemination of this guideline hopefully will increase the awareness of peritoneal dialysis as a potential cause of chronic cough. The optimal investigation and treatment of cough in this setting remain to be studied.

**COUGH AND THE ENVIRONMENT**

The role of cough as a marker of sensitization to occupational agents is uncertain. Induced sputum analysis has been found to be useful in the investigation of occupational asthma, but its role in the detection of possible CEB induced by these agents when cough is the sole symptom should be explored further. The contribution of occupational upper airway disease, asthma, or other conditions, including CEB, and the respective contribution of these to the symptom of cough remain to be assessed.

Furthermore, as the outcome of many occupational causes of cough improves with an early diagnosis and a change in occupational exposure, research is needed to determine the most effective strategies for enabling the early recognition and contributions of occupational causes to cough. In this context, the role of submassive respiratory irritant exposures needs to be further understood and criteria developed for the diagnosis of these effects. Interactions between occupational sensitizers and irritants need also to be better understood to minimize morbidity from such exposures, taking into account host susceptibility factors. As a general recommendation to help prevent occupational asthma, methods for identifying new potential respiratory sensitizers prior to their use in the workplace need to be developed and alternative nonsensitizing materials developed.

The influence of various airborne contaminants in troublesome cases of cough must also be determined. In regard to problems that are more specific
to Nordic countries, the mechanisms and consequences of cold air-induced persistent cough and its optimal treatment should be studied, particularly in nonasthmatic subjects who cannot completely condition frigid air such as outdoor workers and cold-air athletes. Finally, we need more data on the role of allergic and nonallergic (endotoxins and mycotoxins) environmental factors in patients with unexplained cough.

**Cough in Immunocompromised Persons**

The relative contribution of cough to the diagnosis and clinical expression of specific conditions and complications in this population of patients requires more evaluation. To date, there appears to be only one retrospective study that has been conducted on the spectrum and frequency of chronic cough in such a population, which was performed in HIV-positive subjects. The contribution of medications that are used to treat complications associated with immunosuppression should also be defined.

**Assessment of Cough and Its Treatment**

Cough is often assessed only qualitatively and subjectively to determine the disease status and the patient’s response to treatment. In a pilot study in which subjective data were collected on a diary card and objective data were collected using home-based telemetry, strong correlations were found between subjective and objective data. However, more studies of this sort are needed to validate potential tools for assessing patients with cough and their response to therapy.

It could be beneficial to assess in a more formal or quantitative way the severity or frequency of cough, its pattern and time-course, and its interference with the performance of daily activities. Quality-of-life assessments and cough-recording devices have been proposed, and their relative contribution to cough management remains to be determined. How well empirical or empiric integrative diagnostic approaches perform compared to detailed diagnostic testing needs to be prospectively studied.

**Nonspecific Pharmacologic and Nonpharmacologic Cough Treatment**

The long-term effects of the various techniques to increase mucus clearance, particularly in patients with cystic fibrosis or bronchiectasis, on clinical status, health-care use, and pulmonary function remain to be documented. Although devices that are aimed at increasing sputum production have been shown to be helpful, their long-term benefits have not been assessed. There have been a limited number of studies on the beneficial effects of expiratory muscle training in patients with neuromuscular diseases.

**Cough in Children**

There are large gaps in our knowledge of pediatric cough, especially those relating to evidence-based management. Several suggested research goals for an evidence-based approach to cough in children are enumerated here.

**Etiology and Identification of Symptoms and Signs**

- Determine the ability of parents and clinicians in various settings to differentiate between dry and moist (productive) cough, and the specificity and sensitivity of dry vs moist (productive) cough for elucidating an underlying specific etiology of cough;
- Determine the optimal definitions of acute, subacute, and chronic cough based on diagnosis, treatment, and outcome criteria;
- Determine the criteria for children requiring further investigations based on large cohort studies that are inclusive of the primary care setting;
- Relationship (eg, temporal, severity, or type) between cough and both GERD and allergic rhinitis based on objective criteria; and
- Determine whether the adult anatomic protocol is relevant in children in various settings.

**Management and Treatment**

- Randomized clinical trials on the benefits and cost-effectiveness of the treatment of upper airway problems and GERD in children with isolated cough should be assessed;
- Understand how best to determine the etiology of cough in otherwise stable children with asthma who have a cough;
- Determine the natural history and outcomes of children with nonspecific cough; and
- Understand the role of therapy with antibiotics in children with chronic moist cough and in children with chronic cough after a viral infection.

**Dissemination and Implementation of Cough Guidelines**

An evaluation of the benefits of the recommendations made in this guideline on the populations...
treated and on health-care use should be performed. Although the dissemination of guidelines such as this one has been successful, the optimal way to implement and translate these recommendations into current practice should be assessed, as it should be the case for other guidelines. Not only it should be determined whether these documents influence the practices of health-care providers, but public education should also be considered. Chronic cough may affect everybody and is often associated with treatment delays, as well as, often, inappropriate self-treatment. Handouts for the general public have been occasionally produced and may be useful.

### Summary of Recommendations

1. As suggested in the various sections of this guideline, further research should be conducted to elucidate the mechanisms of the production of cough in various diseases and conditions, the optimal methods of assessment, and treatment, specific to the suspected cause. Level of evidence, expert opinion; benefit, substantial; strength of recommendation, E/A

2. Research is particularly needed in areas such as the treatment of postinfectious cough, the characterization of psychogenic cough, the methods of assessment of cough, and pharmacotherapy. Level of evidence, expert opinion; benefit, substantial; strength of recommendation, E/A

### References


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