

# An Empiric Integrative Approach to the Management of Cough

## ACCP Evidence-Based Clinical Practice Guidelines

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**Objective:** Review the literature to provide a comprehensive approach, including algorithms for the clinician to follow in evaluating and treating the patient with acute, subacute, and chronic cough.

**Methods:** We searched MEDLINE (through May 2004) for studies published in the English language since 1980 on human subjects using the medical subject heading terms “cough,” “treatment of cough,” and “empiric treatment of cough.” We selected case series and prospective descriptive clinical trials. We also obtained any references from these studies that were pertinent to the topic.

**Results:** The relative frequency of the disorders (alone and in combination) that can cause cough as well as the sensitivity and specificity of many but not all diagnostic tests in predicting the cause of cough are known. An effective approach to successfully manage chronic cough is to sequentially evaluate and treat for the common causes of cough using a combination of selected diagnostic tests and empiric therapy. Sequential and additive therapy is often crucial because more than one cause of cough is frequently present.

**Conclusion:** Algorithms that provide a “road map” that the clinician can follow are useful and are presented for acute, subacute, and chronic cough. (CHEST 2006; 129:222S–231S)

**Key words:** algorithmic approach; empiric therapy; sequential and additive therapy; systematic approach

**Abbreviations:** ACE = angiotensin-converting enzyme; A/D = antihistamine/decongestant; BPC = bronchoprovocation challenge; GERD = gastroesophageal reflux disease; HRCT = high-resolution CT; NAEB = nonasthmatic eosinophilic bronchitis; PPI = proton pump inhibitor; UACS = upper airway cough syndrome

The clinician faced with a patient with an unexplained cough needs a systematic, integrated approach to this problem. Fortunately, the information necessary to formulate such an approach exists. The relative frequency of the disorders (alone and in combination) that can cause cough, as well as the sensitivity and specificity of various findings on medical history, physical examination, and the pertinent diagnostic tests in predicting the cause of cough<sup>1–5</sup> are known from a number of clinical stud-

ies. A great deal is also known about specific treatments that work for the various conditions and the expected time frame of response.<sup>3,6–11</sup> The recommended approach delineated below and the schematic algorithms depicted reflect this composite body of knowledge. The “gold standard” for assessing the accuracy of diagnosis and the effectiveness of the physician’s management of a patient’s cough is the response to specific treatment.<sup>1</sup> Marked improvement or resolution of cough is the *sine qua non* for success. Based on this standard, it has been demonstrated that the use of empiric treatment, systematically directed at the common causes of cough (see below) works and is an important component of a successful approach to the diagnosis and treatment of cough.<sup>3</sup>

Based on duration, cough can be divided into the

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following three categories: acute, lasting < 3 weeks; subacute, lasting between 3 and 8 weeks; and chronic, lasting > 8 weeks.<sup>7</sup> Acute cough can persist and become a subacute or chronic problem.

We searched MEDLINE (through May 2004) for studies published in the English language since 1980 on human subjects using the medical subject heading terms “cough,” “treatment of cough,” and “empiric treatment of cough.” We selected case series and prospective descriptive clinical trials. We also obtained any references from these studies that were pertinent to the topic.

## ACUTE COUGH

Although there are no, large, prospective studies that have assessed the spectrum and frequency of causes of acute cough, acute cough is most commonly transient, as in the common cold, but it can occasionally be associated with life-threatening conditions such as pulmonary embolism, congestive heart failure, and pneumonia. The recommended approach to treating a patient with an acute cough is depicted in Figure 1. Clinically (*ie*, based on the findings of the medical history and physical examination), the most important first step is to decide whether the acute cough is potentially a reflection of a serious illness, as described above, or, as is usually the case, it is a manifestation of a non-life-threaten-

ing diagnosis such as an acute (upper) respiratory tract infection (*eg*, the common cold), a lower respiratory tract infection, exacerbation of a preexisting condition such as asthma, bronchiectasis, COPD, or upper airway cough syndrome (UACS), which was previously referred to as *postnasal drip syndrome*. When patients with acute cough present with a productive cough, acute bronchitis from a viral lower respiratory tract infection such as influenza A should be considered as well as other conditions that can mimic acute bronchitis. Conditions that can mimic acute bronchitis include acute asthma, acute exacerbation of chronic bronchitis, and the common cold.

If acute cough is thought to be due to the common cold, a first-generation antihistamine plus a decongestant has been shown in a double-blind placebo-controlled study<sup>12</sup> to decrease the severity of cough, and hasten the resolution of cough and postnasal drip associated with the common cold. Another double-blind, placebo-controlled prospective randomized study<sup>13</sup> showed that the nonsteroidal anti-inflammatory drug naproxen will favorably affect cough. A difficult issue is whether one can recognize the relatively infrequent acute infectious cough (*eg*, *Bordetella pertussis* or Chlamydia [*eg*, TWAR]) that will respond to antibiotic therapy if initiated early in the course of the disease. Potential acute irritant or allergic exposures should also be identified and, if possible, avoided or eliminated from the environment.

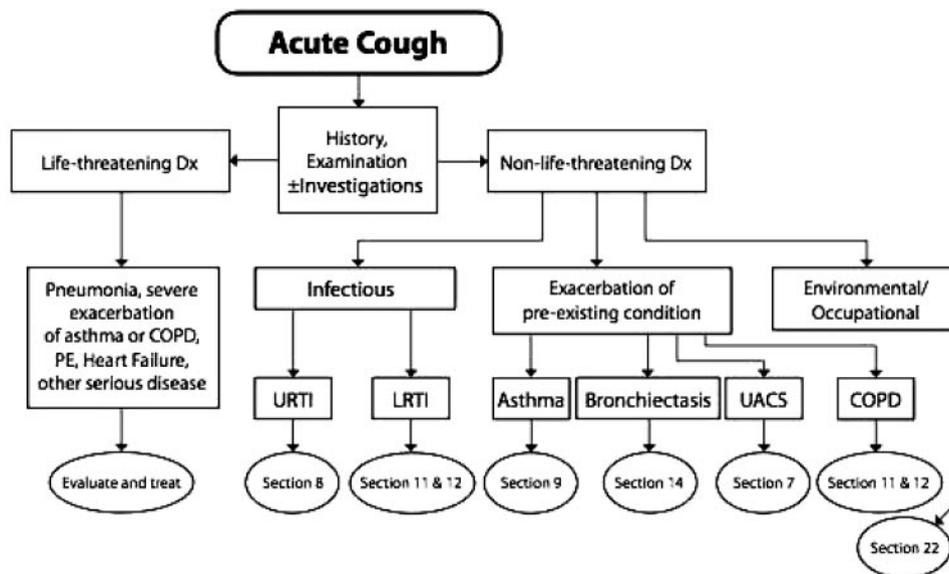


FIGURE 1. The acute cough algorithm for the management of patients aged  $\geq 15$  years with cough lasting < 3 weeks. For diagnosis and treatment recommendations refer to the section indicated in the algorithm. PE = pulmonary embolism; Dx = diagnosis; Rx = treatment; URTI = upper respiratory tract infection; LRTI = lower respiratory tract infection; Section 7-Irwin<sup>34</sup>; Section 8-Pratter<sup>35</sup>; Section 9-Pratter<sup>36</sup>; Section 11-Dicpinigaitis<sup>37</sup>; Section 12-Irwin<sup>38</sup>; Section 14-Braman<sup>39</sup>; Section 22-Irwin et al.<sup>40</sup>.

## SUBACUTE COUGH (PRESENT FOR 3 TO 8 WEEKS)

While there are no studies that have assessed the spectrum and frequency of causes of subacute cough, Figure 2 offers a conceptual approach based on “expert opinion” given the paucity of data on this topic. The committee recommends that in managing patients with subacute cough, the first step is to determine whether or not the cough has followed an obvious preceding respiratory infection. If the subacute cough does not appear to be postinfectious in nature, it should be evaluated and managed as if it were a chronic cough. On the other hand, subacute cough frequently starts with an acute upper respiratory tract infection, but lingers on and typically falls into the category of postinfectious cough. The mechanism of cough in many of these cases is probably persistent postnasal drip, upper airway irritation, mucous accumulation due to hypersecretion or decrease clearance, or a manifestation of bronchial hyperresponsiveness that may be transient or associated with asthma that has been exacerbated. Ongoing allergen or irritant exposure or the lingering effects of an infection such as that caused by *B pertussis* should also be considered as the diagnosis,

as well as pneumonia and an acute exacerbation of chronic bronchitis. In the case of allergen or irritant exposure, removing the patient from the environment or limiting contact is important. *B pertussis* during the initial phase, pneumonia, and acute exacerbation of chronic bronchitis should be treated with appropriate antibiotics if bacterial infection is thought to be present.

## CHRONIC COUGH

Chronic cough is a more complex problem because the differential diagnosis is broader than that for acute or subacute cough. It often is due to more than one condition being simultaneously present, the medical history often offers few clues as to the initiating event, and the characteristics of the cough have been shown to lack both diagnostic sensitivity and specificity.<sup>14</sup> Nevertheless, when approached in a systematic fashion, an accurate diagnosis and therapeutic success can usually be achieved. The recommended approach is depicted in Figure 3. In patients with chronic cough, the starting point is the medical history, physical examination, and chest roentgeno-

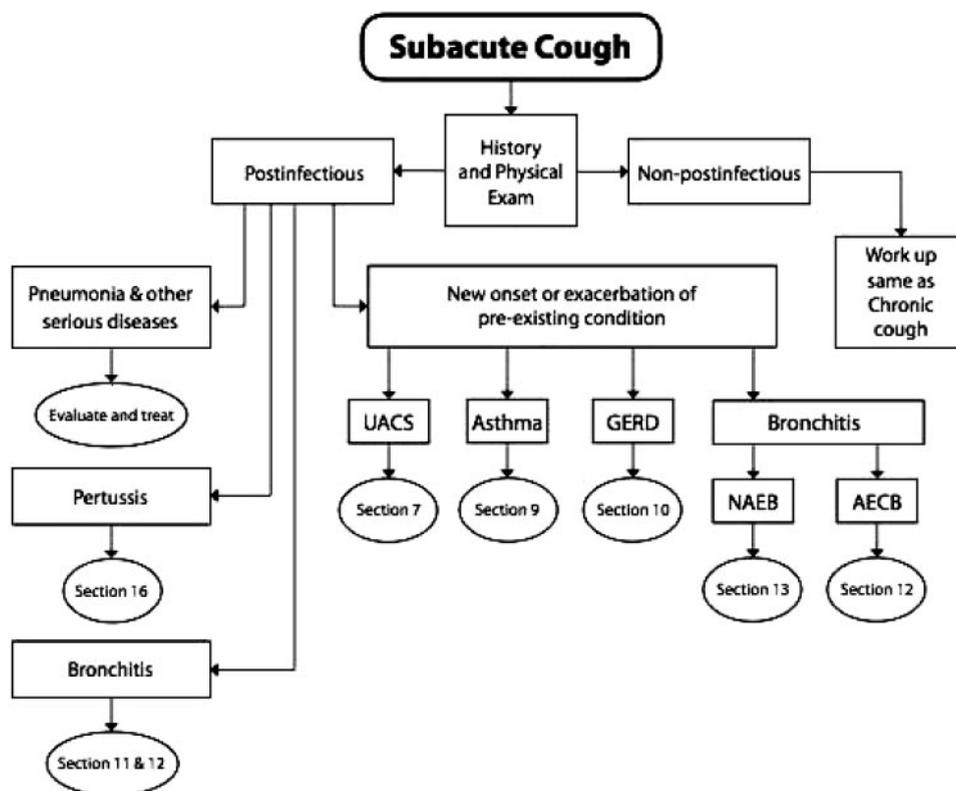


FIGURE 2. Subacute cough algorithm for the management of patients aged  $\geq 15$  years with cough lasting 3 to 8 weeks. For diagnosis and treatment recommendations refer to section indicated in algorithm. AECB = acute exacerbation of chronic bronchitis; Section 10-Pratter<sup>41</sup>; Section 13-Braman<sup>42</sup>; Section 16-Rosen.<sup>43</sup> See the legend of Figure 1 for other section references.

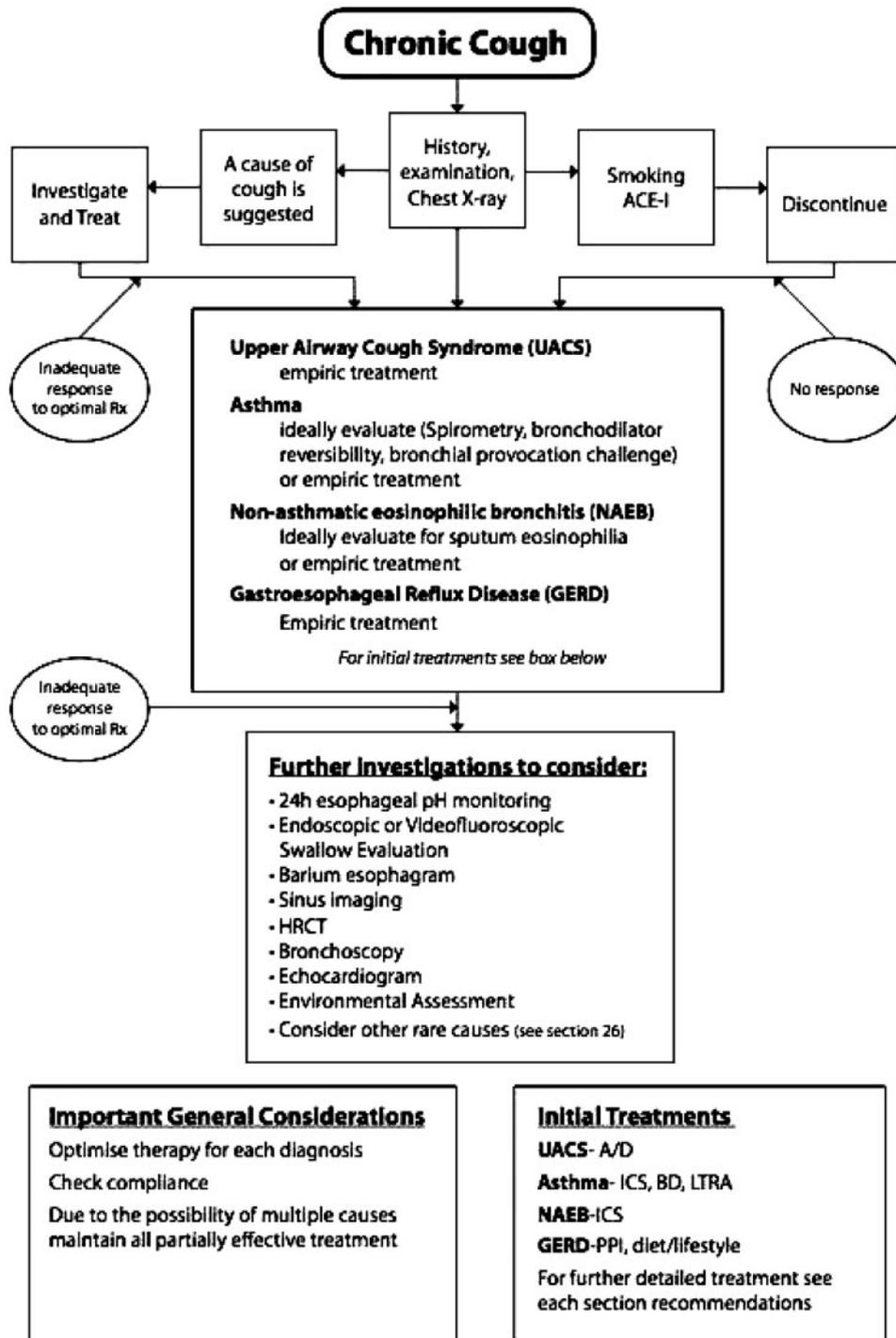


FIGURE 3. Chronic cough algorithm for the management of patients aged  $\geq 15$  years with cough lasting  $> 8$  weeks. ACE-I = ACE inhibitor; BD = bronchodilator; LTRA = leukotriene receptor antagonist; ICS = inhaled corticosteroid. See the legend of Figure 1 for abbreviation not used in the text.

gram. Although, as stated above, the timing and characteristics of the cough are of little diagnostic value, the medical history is important to determine whether the cough is acute (*ie*,  $< 3$  weeks), subacute (*ie*, 3 to 8 weeks), or chronic (*ie*,  $> 8$  weeks). The

medical history will also determine whether the patient is receiving an angiotensin-converting enzyme (ACE) inhibitor, particularly if the onset of the cough is temporally associated with starting to receive the medication within the past year. However,

in general, if the patient is receiving an ACE inhibitor, therapy should be stopped no matter what the temporal relationship. For example, cough may have preceded the use of the ACE inhibitor. However, the original cause of cough may have resolved and the persisting cough could be due to the drug. The resolution of cough usually will occur within a few days to 2 weeks of stopping use of the drug, but the median time is 26 days.<sup>7,15-17</sup> A second crucial piece of historical information is determining whether the patient is a current cigarette smoker. Cigarette smoking is commonly associated with cough that is usually productive in nature and typically meets the definition of chronic bronchitis. Smoking cessation is almost always effective.<sup>13</sup> The majority of patients will have cough resolution within 4 weeks, but in some cases it may take longer. However, in patients with severe COPD cough may persist and not completely resolve or may be perpetuated due to ever more frequent exacerbations of chronic bronchitis. If the patient has COPD, a clinical decision as to whether the cough is part of an exacerbation, as opposed to a chronic cough associated with stable COPD, needs to be made. If the former is the case, then therapy with antibiotics or corticosteroids needs to be considered. The medical history is also crucial to determine whether the patient is from an endemic area where certain diseases (*eg*, tuberculosis) that can cause cough are more prevalent. It is also important to determine whether there are any systemic signs of disease such as fever, sweats, or weight loss. A history of cancer, tuberculosis, or AIDS is also important to ascertain.

In most reported cases,<sup>1-5</sup> the typical patient with chronic cough is an immunocompetent nonsmoker who is otherwise healthy. A chest roentgenogram is commonly obtained, and in the vast majority of cases the findings are normal or insignificant.<sup>1-3</sup> (If a specific cause of cough is suggested from the chest radiograph [*eg*, a mass suggestive of lung cancer], this possibility should be directly investigated.) For most patients with essentially normal chest radiograph findings, it has been shown in repeated studies<sup>1-3,18</sup> that the three most common causes of cough are UACS due to a variety of rhinosinus conditions, asthma, and gastroesophageal reflux disease (GERD) in descending order of prevalence. Nonasthmatic eosinophilic bronchitis (NAEB) is frequent enough to warrant early consideration as well. This knowledge allows an algorithmic, sequential approach to chronic cough that will efficiently identify and treat patients with these common disorders while not delaying inordinately the identification of other potential causes of cough such as endobronchial tumor (rare in the presence of normal chest roentgenogram findings). The assumption is that if

the cough resolves, then the responsible factors have been identified. Thus, the approach is designed to start with the most common disorders and to investigate patients for less common conditions only after eliminating the presence of the usual causes of chronic cough.

A 2001 decision analysis<sup>19</sup> provides theoretical support for the strategy of treating chronic cough empirically. After assuming a prevalence of UACS of 44%, sequential empirical treatment starting with UACS (followed by asthma and GERD) or treating empirically for all three common causes was favored over extensive testing at the outset, depending on how much a patient is distressed by cough symptoms.

How to proceed if the chest roentgenogram findings are abnormal depends on the specific finding. A mass or other evidence consistent with bronchogenic carcinoma would lead directly to an evaluation for this diagnosis. A chest CT scan followed by bronchoscopy or a transthoracic fine-needle aspiration, or possibly a positron emission tomography scan, would typically be the next steps.<sup>20</sup> Evidence for interstitial lung disease might also lead to bronchoscopy with transbronchoscopic biopsy or possibly video-assisted thoracic surgery biopsy. A high-resolution CT (HRCT) scan of the chest is also likely to be of value. Chest roentgenographic findings of congestive heart failure would lead to a cardiovascular evaluation and perhaps an empiric attempt at diuresis. The presence of a mediastinal mass would lead to a biopsy to determine its etiology. Evidence of infection, especially tuberculosis, would focus attention on making a microbiological diagnosis either via expectorated sputum and/or via bronchoscopy.

The knowledge that chronic cough in many patients is multifactorial is essential to clinical success. For example, it is not uncommon to find that an individual has two (and occasionally all three) of the common diagnoses of UACS, asthma, and GERD.<sup>2,3,18</sup> The cough will not resolve until both (or all three) of these diagnoses have been effectively treated.

## UACS

Whereas UACS is the most common cause of chronic cough and its role in causing cough cannot be prospectively predicted, the approach to chronic cough should typically begin with a diagnostic/therapeutic trial of a first-generation antihistamine-decongestant (A/D), as noted in the section on UACS in this guideline.<sup>3</sup> If a patient has resolution or partial resolution of cough in response to A/D therapy, then UACS is considered to have been a cause of cough

and A/D therapy is continued. The typical time course of response to A/D therapy for UACS is at least some noticeable improvement in cough within days to 1 to 2 weeks of initiating therapy.<sup>3</sup> Marked improvement or resolution of cough may take several weeks and occasionally as long as a few months.<sup>3</sup>

If the resolution of cough with A/D therapy is only partial, then the next step in the evaluation can be guided by patient symptoms. If the patient no longer has signs or symptoms of UACS, it would be reasonable to proceed to the evaluation for asthma. If the patient has persistent nasal symptoms, then the addition of a topical nasal steroid, nasal anticholinergic agent, or nasal antihistamine may be effective. Persistent UACS symptoms after the addition of topical therapy would be an indication for sinus imaging to look for evidence of acute or chronic sinusitis. Air-fluid levels in the sinuses would be an indication for antibiotic therapy and perhaps short-term nasal topical vasoconstrictor therapy with an  $\alpha$ -agonist. Mucosal thickening is not as diagnostic of sinusitis, but in the setting of chronic cough that is unresponsive to treatment for UACS, patients with mucosal thickening should be treated presumptively for sinusitis. Until a prospective study is done comparing the diagnostic accuracy of "plain" sinus films vs a sinus CT scan, it will remain a clinical judgment as to which study to obtain. The lack of response to medical therapy for documented sinusitis should lead to a consultation with an ear, nose, and throat specialist and possibility measurement of serum Ig levels to see whether (acquired) hypogammaglobulinemia is present. It would also be appropriate to consider allergy testing as well as an evaluation of the patient's home and workplace if there is a potential environmental cause for persistent upper airway symptoms. The presence of nasal polyps in the presence of refractory chronic sinusitis warrants, in the absence of any contraindication, consideration of aspirin therapy. The patient should undergo a standard aspirin challenge. If the results of the challenge are positive, the patient should undergo desensitization, followed by the consideration of chronic aspirin therapy unless it is contraindicated. (See the section on UACS in this guideline for complete details on treatment).

### ASTHMA-INDUCED CHRONIC COUGH

The possibility that asthma is a causative factor in cough should be formally considered after the evaluation for UACS. The medical history is sometimes suggestive, but is not reliable in either ruling in or ruling out asthma.<sup>11,21</sup> Several studies<sup>1,3,22,23</sup> have documented the utility of bronchoprovocation chal-

lenge (BPC) in the evaluation for asthma as a cause of cough. The negative predictive value for a negative challenge is close to 100%. The positive predictive value of a positive challenge result is in the range of 60 to 88%. In most circumstances, a positive challenge result warrants a trial of treatment for asthma with clinical follow-up. The various treatment options for asthma have been described in the asthma section of this guideline. While the majority of patients with asthma will respond to therapy with inhaled corticosteroids (ICSs) and  $\beta$ -agonists with at least partial improvement within 1 week of therapy, complete resolution of cough may require up to 8 weeks of treatment,<sup>3</sup> and in some patients the response may be delayed or absent without a trial of oral corticosteroids. Therefore, in selected patients with a positive response to a methacholine challenge whose cough remains troublesome and who have not responded or cannot take inhaled medications, 5 to 10 days of treatment with oral corticosteroids (*eg*, prednisone, 40 mg/d) is a reasonable option in the absence of a significant contraindication. However, because treatment with oral leukotriene inhibitors may be effective in patients with asthmatic cough, consideration should be given for adding the leukotriene inhibitor to the treatment regimen before the oral corticosteroid.<sup>24</sup> The vast majority of patients with asthma causing cough will respond to treatment and then can be switched over to inhalational therapy.<sup>24</sup>

When BPC is not available and baseline spirometry findings are normal, then empiric treatment for asthma should follow treatment for UACS, with diagnostic conclusions based on the response. In this situation, the need for a definitive response makes the use of oral corticosteroid therapy desirable if inhaled  $\beta$ -agonists, ICSs, and leukotriene inhibitors are ineffective. (See the section on asthma in this guideline for complete details on treatment).

### NAEB

If the diagnostic/therapeutic evaluations listed above for UACS and asthma have failed to yield either a diagnosis or a resolution of the cough, then NAEB should be considered next. Although in most series GERD is a more common cause of cough than NAEB, because the diagnosis of NAEB diagnosis is relatively straightforward to make when there is access to laboratories set up to perform the rigorous analysis and the response to treatment is very predictable, it makes sense to consider this diagnosis next after UACS and asthma. A properly performed induced sputum test to determine whether there are an increased number of eosinophils present is the

diagnostic procedure of choice. Improvement within 4 weeks of initiating therapy with ICSs is typical, although some patients may require a course of oral corticosteroids. If the proper induced sputum technique is unavailable, an empiric trial of corticosteroids should be the next step.<sup>25–29</sup> (See the section on NAEB in this guideline for details of diagnosis and treatment.)

#### GERD-INDUCED CHRONIC COUGH

Patients whose cough responds only partially or not at all to the above interventions should next be evaluated for GERD. Because patients with the following clinical profile have been prospectively shown to have cough due to GERD in approximately 92% of cases, empiric therapy is recommended rather than testing: cough for > 2 months; normal chest roentgenogram findings; nonsmoking; not receiving ACE inhibitors; failed to get better with treatment for UACS; and asthma and NAEB with the use of systemic steroids. Patients with prominent upper GI GERD symptoms and persistent cough at this point should be treated with an antireflux diet and lifestyle modifications, and a proton pump inhibitor (PPI). Consideration should be given for adding prokinetic therapy if there is no or little response to treatment. (In patients with very prominent GERD symptoms, it could be argued that treatment for GERD should be part of the initial therapy.) Ideally, patients with persistent cough and no GERD symptoms at this point should undergo objective 24-h esophageal pH monitoring. However, esophageal pH monitoring can be problematic because of a lack of agreement in the literature on how to interpret the study. It has been recommended in the pulmonary literature<sup>30</sup> that the criteria to consider the test result as positive should be much more sensitive (*ie*, less evidence of reflux is required) than the standard published criteria typically recommended in the gastroenterology literature. Given some of the issues of interpretation as well as the limited availability of esophageal pH testing, this further supports the idea of an initial empiric trial of antireflux therapy.<sup>8,9,31</sup> It should be recognized, however, that the length of time from the initiation of therapy to an expected response is more variable for GERD than it is for UACS, asthma, or NAEB. Some patients will respond to high-dose PPI therapy within 2 weeks,<sup>32</sup> while in other cases it may take up to several months and only after prokinetic therapy has been added,<sup>2</sup> or there may be no response to medical therapy at all. Partial improvement or no improvement in cough with anti-GERD medical therapy leaves open the questions of whether the

therapeutic trial has been adequate, whether an additional cause of cough is present, whether more intensive therapy is required or whether the patient has medically refractory GERD.<sup>33</sup> An additional workup will be necessary at this point in the evaluation. See the section on GERD in this guideline as a cause of cough for recommendations for what to do at this point when patients have not responded to your treatment. For instance, the use of 24-h esophageal pH monitoring as well as the selected use of upper GI endoscopy or a barium swallow study should certainly be considered at this point. The addition to therapy of a prokinetic agent such as metoclopramide and rigorous adherence to dietary measures should be tried prior to labeling the patient as having medically refractory GERD or considering surgical fundoplication.<sup>33</sup> It should be recognized, however, that in some cases cough may persist due to nonacid reflux disease after the elimination of gastric acid and may respond to surgical intervention.<sup>33</sup> (See the section on GERD in this guideline for further details of management.)

If all of the diagnostic/therapeutic evaluations listed above have failed to yield either a diagnosis or the resolution of cough, in countries where tuberculosis remains a common problem, expectorated or induced sputum samples with acid-fast staining or bronchoscopy to detect occult endobronchial tuberculosis are reasonable considerations. In the United States, an HRCT scan to evaluate the patient for bronchiectasis or occult interstitial disease should probably be performed next. If the HRCT scan reveals bronchiectasis or interstitial lung disease, bronchoscopy should be performed next. Even if the HRCT scan findings are normal, bronchoscopy should be performed to look for occult airway disease (*eg*, endobronchial tumor, sarcoidosis, suppurative lower airway infection, eosinophilic, or lymphocytic bronchitis). Uncommon causes of cough such as nonacid reflux disease, a swallowing disorder, congestive heart failure, or habit cough should also be considered based on clinical findings. If a complete workup and appropriate therapeutic trials fail to identify the cause of cough, one is then left with the diagnosis of unexplained cough (previously referred to as *idiopathic cough*). However, before making this diagnosis, consideration of a referral to a cough specialist is appropriate.

#### SUMMARY

In summary, an effective approach to cough, whether acute, subacute, or chronic, is to sequentially evaluate and treat for the common causes of cough using a combination of selected diagnostic

tests and empiric therapy. It is important to realize that cough may be the only clinical manifestation of the common causes of cough, emphasizing the need for selective testing and adequate treatment (both in terms of the agents used and the duration of treatment) to see whether the cough responds. Sequential and additive therapy may be crucial because more than one cause of cough may be present. In patients with acute cough, the most important initial decision is on whether the cough is a manifestation of a serious, potentially life-threatening condition, such as pneumonia or pulmonary embolism, or, as is commonly the case, the result of the common cold, an acute bronchitis or asthma syndrome, or some environmental allergic or irritant exposure. In patients with subacute cough, the crucial initial distinction is whether it is a postinfectious cough or not. If it is postinfectious cough, rather than UACS, transient bronchial hyperresponsiveness, asthma, pertussis, or acute exacerbation of chronic bronchitis, need to be considered. If it is a noninfectious cough, it should be approached the same way as a chronic cough. The algorithm for chronic cough is based on the fact that an extensive amount of information exists about the different causes and their frequency, the value of selected diagnostic tests and empiric therapy, and the expected timeframe of response.

#### SUMMARY OF RECOMMENDATIONS

**1. In patients with cough, the starting point is the medical history and physical examination. Although the timing and characteristics of the cough are of little diagnostic value, the medical history is important to determine whether the patient is receiving an ACE inhibitor, is a smoker, or has evidence of a serious life-threatening or systemic disease.**

Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

**2. In patients with an acute cough, first determine whether the acute cough is a reflection of a serious illness such as pneumonia or pulmonary embolism, or, as is usually the case, a manifestation of a non-life-threatening disease such as a respiratory tract infection (eg, common cold or lower respiratory tract infection), an exacerbation of a preexisting condition (eg, COPD, UACS, asthma, or bronchiectasis), or an environmental or occupational exposure to some noxious or irritating agent (eg, allergic or irritant-induced rhinitis).** Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

**3. In patients with a subacute cough, first determine whether it is a postinfectious cough or not. If it is postinfectious, determine whether it is a result of UACS, transient bronchial hyperresponsiveness, asthma, pertussis, or an acute exacerbation of chronic bronchitis. If it is noninfectious, manage the cough the same way as chronic cough (see Fig 2).** Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

**4a. In patients with chronic cough, systematically direct empiric treatment at the most common causes of cough (ie, UACS, asthma, NAEB, and GERD).** Level of evidence, low; benefit, substantial; grade of recommendation, B

**4b. In patients with chronic cough, therapy should be given in sequential and additive steps because more than one cause of cough may be present.** Level of evidence, low; benefit, substantial; grade of recommendation, B

**5. Patients with a chronic cough who smoke should be counseled and assisted with smoking cessation.** Level of evidence, low; benefit, substantial; grade of recommendation, B

**6. In a patient with cough who is receiving an ACE inhibitor, therapy with the drug should be stopped and the drug should be replaced.** Level of evidence, low; benefit, substantial; grade of recommendation, B

**7. In patients with chronic cough, initial empiric treatment should begin with an oral first-generation A/D.** Level of evidence, low; benefit, substantial; grade of recommendation, B

**8a. In patients whose chronic cough persists after treatment for UACS, the possibility that asthma is the cause of cough should be worked up next. The medical history is sometimes suggestive, but is not reliable in either ruling in or ruling out asthma. Therefore, ideally, BPC, if spirometry does not indicate reversible airflow obstruction, should be performed in the evaluation for asthma as a cause of cough. In the absence of the availability of BPC, an empiric trial of antiasthma therapy should be administered (see section on the treatment of asthma in this guideline).** Level of evidence, low; benefit, substantial; grade of recommendation, B

**8b. In patients with chronic cough, in whom the diagnoses of UACS and asthma**

have been eliminated or treated without the elimination of cough, NAEB should be considered next with a properly performed induced sputum test for eosinophils. If a properly performed induced sputum test to determine whether eosinophilic bronchitis is present cannot be performed, an empiric trial of corticosteroids should be the next step. Level of evidence, low; benefit, substantial; grade of recommendation, B

**9. In the majority of patients with suspected cough due to asthma, ideally, before starting an oral corticosteroid regimen, a BPC should be performed and, if the result is positive, some combination therapy of ICSs, inhaled  $\beta$ -agonists, or oral leukotriene inhibitors should be administered. A limited trial of oral corticosteroids, however, should be administered in some patients who are suspected of having asthma-induced cough before eliminating the diagnosis from further consideration.** Level of evidence, low; benefit, substantial; grade of recommendation, B

**10. In patients whose cough responds only partially or not at all to interventions for UACS and asthma or NAEB, treatment for GERD should be instituted next.** Level of evidence, low; benefit, substantial; grade of recommendation, B

**11. In patients with cough whose condition remains undiagnosed after all of the above has been done, referral to a cough specialist is indicated.** Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

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