Chronic Cough Due to Gastroesophageal Reflux Disease

ACCP Evidence-Based Clinical Practice Guidelines

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Objectives: To critically review and summarize the literature on cough and gastroesophageal reflux disease (GERD), and to make evidence-based recommendations regarding the diagnosis and treatment of chronic cough due to GERD.

Design/methodology: Ovid MEDLINE literature review (through March 2004) for all studies published in the English language and selected articles published in other languages such as French since 1963 using the medical subject heading terms “cough,” “gastroesophageal reflux,” and “gastroesophageal reflux disease.”

Results: GERD, singly or in combination with other conditions, is one of the most common causes of chronic cough. In patients with normal chest radiographic findings, GERD most likely causes cough by stimulation of an esophageal-bronchial reflex. When GERD causes cough, there may be no GI symptoms up to 75% of the time. While 24-h esophageal pH monitoring is the most sensitive and specific test in linking GERD and cough in a cause-effect relationship, it has its limitations. In addition, there is no general agreement on how to best interpret the test, and it cannot detect non-acid reflux events. Therefore, when patients fit the clinical profile that has a high likelihood of predicting that GERD is the cause of cough, antireflux medical therapy should be empirically instituted. While some patients improve with minimal medical therapy, others require more intensive regimens. When empiric treatment fails, it cannot be assumed that GERD has been ruled out as a cause of chronic cough. Rather, an objective investigation for GERD is then recommended because the empiric therapy may not have been intensive enough or medical therapy may have failed. Surgery may be efficacious when intensive medical therapy has failed in selected patients who have undergone an extensive objective GERD evaluation.

Conclusions: Accurately diagnosing and successfully treating chronic cough due to GERD can be a major challenge.

(CHEST 2006; 129:80S–94S)

Key words: acid reflux disease; clinical profile of cough due to gastroesophageal reflux disease; cough due to gastroesophageal reflux disease; esophageal-bronchial cough reflex; gastroesophageal reflux; gastroesophageal reflux disease; macroaspiration; microaspiration; nonacid reflux disease; silent reflux disease

Abbreviations: GER = gastroesophageal reflux; GERD = gastroesophageal reflux disease; PPI = proton pump inhibitor; BAL = bronchoalveolar lavage

The origin of the terms gastrolesophageal reflux (GER) and gastroesophageal reflux disease (GERD) is Latin.1 Reflux literally means backflow, coming from the two Latin words (re meaning “back,” plus fluere meaning “to flow”). It follows that GERD is a term that refers to the backflow of stomach contents into the esophagus. Because GER episodes can occur up to 50 times a day, usually during meals and the postprandial state in healthy individuals, and not produce any symptoms, GER events can be physiologic in nature.2 On the other hand, GERD is a term that refers to a disease that is caused by GER manifested by either symptoms and/or tissue damage.

GERD is a term that encompasses a spectrum of common clinical manifestations from localized...
esophageal manifestations, such as heartburn and regurgitation, to extraesophageal problems, such as cough or hoarseness, without any GI complaints. For example, in a population-based study in Olmsted County, MN, Locke et al., using a validated GER questionnaire, identified a prevalence rate of 59% for occasional episodes of GER-related symptoms such as heartburn, regurgitation, and dysphagia; 20% of the respondents reported weekly symptoms. In a prospective before-and-after intervention trial, Irwin et al.4 found that when GERD was the cause of chronic cough, it could be silent from a GI standpoint up to 75% of the time. In a study in which the symptoms and findings of GERD were specifically sought and prospectively compared in otolaryngology and gastroenterology patients, Ossakow et al.5 found that hoarseness was present in 100% of the otolaryngology patients and 0% of the gastroenterology patients, while heartburn was present in 89% of the gastroenterology patients, while heartburn was present in 89% of the gastroenterology patients and in only 6% of the otolaryngology patients. When otolaryngologists diagnose laryngeal or pharyngeal disease due to the backflow of stomach contents into the laryngopharynx, they refer to it as laryngopharyngeal reflux disease.1

It is now clear that the spectrum of clinical manifestations of GERD as evaluated by different specialists can vary.1,4,6 It is also becoming increasingly more likely that the management of a variety of extraesophageal manifestations of GERD cannot only differ in clinical and diagnostic ways from the classic GERD seen by gastroenterologists, but also perhaps in pathogenetic and therapeutic aspects as well. Physicians who manage patients with cough should be aware of these differences. While there is much that has been learned about a variety of esophageal and extraesophageal manifestations of GERD, this section will focus solely on chronic cough. Literature on screening for and managing complications of esophageal GERD, such as Barrett epithelium and esophageal cancer, can be found elsewhere.7,8 This section reflects an Ovid MEDLINE literature review (through March 2004) for all studies published in the English language and selected articles published in other languages such as French since 1963 using the medical subject heading terms “cough,” “gastroesophageal reflux,” and “gastroesophageal reflux disease.”

Prevalence of GERD as a Cause of Cough

When the diagnosis of chronic cough due to GERD is based on a favorable response (e.g., elimination of or improvement in cough) to specific GERD treatment, prospective before-and-after intervention studies9–14 have revealed that GERD, singly or in combination with other conditions, is one of the most common causes of chronic cough in adults in the world. The prevalence in these studies ranged from 5 to 41%. While it is not clear what accounts for the variation in prevalence, multiple factors likely contribute to it, such as differences in the populations referred and studied. For example, in three prospective studies published by Irwin et al.9,15,16 over a period of 17 years, the prevalence and relative commonness of GERD as the cause of chronic cough increased from a low of 10% and being the fourth most common cause in 1981,15 to 21% and the third most common cause in 1990,9 to 36% and the second most common cause in 1998.16

Pathophysiology

Knowledge of what is known about where and how GERD can cause cough provides a framework for understanding what has been learned about diagnosis and treatment.17 Although GERD can stimulate the afferent limb of the cough reflex by irritating the upper respiratory tract without aspiration (e.g., the larynx) and by irritating the lower respiratory tract by microaspiration or macroaspiration, there is evidence from a randomized and controlled study by Ing and colleagues18 that strongly suggests that GERD also can cause chronic cough by stimulating an esophageal-bronchial cough reflex. By this neural reflex mechanism, refluxate into the distal esophagus alone is thought to be a sufficient stimulus to cause cough.19

When GERD causes cough by irritating the larynx, laryngoscopy has the potential to demonstrate signs consistent with “reflux laryngitis” (e.g., posterior laryngitis with red arytenoids and paled-up interarytenoid mucosa).20 Bronchoscopy and chest-imaging studies have the potential to detect abnormalities consistent with aspiration. Bronchoscopy may reveal airway signs consistent with aspiration (e.g., subglottic stenosis, hemorrhagic tracheobronchitis, and erythema of subsegmental bronchi).21 Chest-imaging studies may demonstrate a wide spectrum of parenchymal abnormalities.22 While laryngoscopic and bronchoscopic signs are consistent with reflux-induced injury, one must be cautious and not assume that merely observing changes consistent with inflammation and edema of the larynx and lower Airways is specific for GERD because they may also potentially be due to the act of coughing itself that is provoked by other diseases.23 When laryngoscopy, bronchoscopy, and chest-imaging studies are normal, it is assumed that GERD has caused cough by stimulating the esophageal-bronchial reflex. Multiple
Evidence is mounting (eg, prospective before-and-after, successful antireflux surgery intervention trial in patients who had previously failed to improve despite total/near-total elimination of esophageal acid\textsuperscript{24}; prospective, randomized, controlled pharmacologic studies\textsuperscript{18}; and randomized, controlled intravesophageal acid/saline solution challenge studies\textsuperscript{4,18}) that there are likely to be multiple potential triggers of cough including, but not limited to, acid in the gastric refluxate, and the triggers of cough may differ among patients. While it is not known what the nonacid factors are, they may include\textsuperscript{4,24} alkaline pH, pancreatic enzymes, bile, and esophageal dysmotility.\textsuperscript{25,26} Because esophageal dysmotility can be commonly demonstrated in patients with GERD, it is not clear whether or when esophageal dysmotility is an adverse occurrence due to GERD or contributing to GERD. Because the term \textit{acid reflux disease} when applied to chronic cough due to GERD can be a misnomer and may mislead clinicians into thinking that all patients with cough due to GERD should improve with acid-suppression therapy, it is recommended that the term \textit{acid reflux disease} no longer be used in the context of cough unless it can be definitively shown to apply. Unless acid reflux disease can be definitively proven, the more general term \textit{reflux disease} should be used.

Because coughing can induce GER episodes,\textsuperscript{27} a cough-GER self-perpetuating cycle may be involved in the pathophysiology of a patient’s chronic cough.\textsuperscript{18,28} While cough-induced GER episodes are often observed in 24-h esophageal pH-monitoring tracings, the mechanisms by which these GER episodes are triggered by coughing is unknown.

Based on inhaled tussigenic cough challenges, there is little evidence to support the theory that an increased sensitivity of the cough reflex is the sole explanation why some patients with GERD complain only or predominantly of cough, while others primarily have GI complaints. An increased sensitivity has been observed in patients with GERD who do not cough\textsuperscript{29} as well as in those who do cough.\textsuperscript{30}

Recommendation

1. In patients with chronic cough due to GERD, the term \textit{acid reflux disease}, unless it can be definitively shown to apply, should be replaced by the more general term \textit{reflux disease} so as not to mislead the clinicians into thinking that all patients with cough due to GERD should improve with acid-suppression therapy. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

Diagnosis

Clinical Presentation

There is nothing about the character and timing of the cough due to GERD that distinguishes it from other causes of cough.\textsuperscript{31} It can present as a cough-phlegm (ie, productive cough) syndrome, just like chronic bronchitis from cigarette smoking, as well as a dry cough. It occurs nocturnally in only a minority of patients,\textsuperscript{31} and it can be “silent” from a GI standpoint up to 75% of the time.\textsuperscript{4}

On the other hand, GERD should always be considered as a possible cause of chronic cough when patients also complain of typical and frequent GI symptoms such as daily heartburn and regurgitation, especially when the chest-imaging studies and/or clinical syndrome are consistent with an aspiration syndrome.\textsuperscript{22} Aspiration syndromes associated with cough due to GERD include Mendelson syndrome, bacterial pneumonia and lung abscesses, chemical pneumonitis, exogenous lipid pneumonia, recurrent bacterial pneumonias, chronic interstitial fibrosis, bronchiectasis, \textit{Mycobacterium fortuitum} or \textit{Mycobacterium chelonel} pneumonia, diffuse aspiration bronchiolitis, and tracheobronchitis.\textsuperscript{22}

While the character and timing of cough are not predictive of when GERD is likely to be the cause of chronic cough, there is a clinical profile that has been highly predictive (approximately 91%) that the patient’s cough will respond to antireflux treatment, even when there are no GI complaints. This clinical profile, which appears in Table 1, was initially sug-

Table 1—Clinical Profile That Predicts That Chronic Cough Is Likely Due to GERD

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prediction</th>
<th>Benefit</th>
<th>Highest Grade of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic cough</strong></td>
<td></td>
<td></td>
<td>E/A</td>
</tr>
<tr>
<td>Not exposed to environmental irritants nor a present smoker</td>
<td></td>
<td></td>
<td>E/A</td>
</tr>
<tr>
<td>Not taking an angiotensin-converting enzyme inhibitor</td>
<td></td>
<td></td>
<td>E/A</td>
</tr>
<tr>
<td>Chest radiograph normal or shows nothing more than stable, inconsequential scarring</td>
<td></td>
<td></td>
<td>E/A</td>
</tr>
<tr>
<td>Symptomatic asthma has been ruled out</td>
<td></td>
<td></td>
<td>E/A</td>
</tr>
<tr>
<td>Cough has not improved with asthma therapy, or</td>
<td></td>
<td></td>
<td>E/A</td>
</tr>
<tr>
<td>Methacholine inhalation challenge is negative</td>
<td></td>
<td></td>
<td>E/A</td>
</tr>
<tr>
<td>Upper airway cough syndrome due to rhinosinus diseases has been ruled out</td>
<td></td>
<td></td>
<td>E/A</td>
</tr>
<tr>
<td>First-generation H\textsubscript{1}-antagonist has been used and cough failed to improve, and</td>
<td></td>
<td></td>
<td>E/A</td>
</tr>
<tr>
<td>“Silent” sinusitis has been ruled out</td>
<td></td>
<td></td>
<td>E/A</td>
</tr>
<tr>
<td>Nonasthmatic eosinophilic bronchitis has been ruled out</td>
<td></td>
<td></td>
<td>E/A</td>
</tr>
<tr>
<td>Properly performed sputum studies are negative, or</td>
<td></td>
<td></td>
<td>E/A</td>
</tr>
<tr>
<td>Cough has not improved with inhaled/systemic corticosteroids</td>
<td></td>
<td></td>
<td>E/A</td>
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gested by post hoc analyses of four prospective, before-and-after intervention studies\textsuperscript{9,15,31,32} of patients with chronic cough due to a variety of diseases, and was prospectively assessed in two small, before-and-after intervention studies\textsuperscript{4,33} of patients with chronic cough due to GERD. In one of these prospective studies,\textsuperscript{4} cough disappeared in 12 of 12 patients receiving intensive medical therapy; in the other study,\textsuperscript{33} cough disappeared or significantly improved in 18 of 21 patients who had undergone antireflux surgery after they had not responded to intensive medical therapy.

The results of a prospective, before-and-after intervention trial\textsuperscript{24} have suggested that GERD cannot be excluded on clinical grounds as the potential cause of cough. This study suggested that there can be a dissociation in improvement in cough and GI complaints. Chronic cough due to GERD in some patients remained unchanged, while GI symptoms improved or disappeared with medical antireflux therapy. Moreover, because prior antireflux surgery failed to control GERD in some of the patients, perhaps for technical reasons, this study also suggested that it cannot be assumed that GERD has been definitively ruled out as a cause of cough because there is a history of prior antireflux surgery.

A number of potential risk factors for GERD have been identified. These include the following: drugs such as alendronate,\textsuperscript{34} oral corticosteroids,\textsuperscript{35} bronchodilators such as inhaled β\textsubscript{2}-adrenergic agonists\textsuperscript{36} and theophylline in some studies,\textsuperscript{37} progesterone,\textsuperscript{37} calcium channel-blocking agents,\textsuperscript{37} anticholinergic agents,\textsuperscript{37} morphine,\textsuperscript{37} and meperidine\textsuperscript{37}; obesity\textsuperscript{38}; smoking\textsuperscript{37}; vigorous exercise\textsuperscript{39,40}; alcohol\textsuperscript{41}; caffeine in some studies\textsuperscript{37}; fatty foods, chocolate, carminatives, and irritating foods such as citrus juices and tomato products\textsuperscript{37}; prolonged gastric intubation\textsuperscript{42,43}; lung transplantation\textsuperscript{44}; following pneumonectomy\textsuperscript{45} and peritoneal dialysis\textsuperscript{46,47}; and a variety of respiratory diseases such as asthma\textsuperscript{48} and obstructive sleep apnea.\textsuperscript{49–51}

While it is not known what their presence means from a diagnostic standpoint in the evaluation of cough, the failure to correct or eliminate risk factors may assume importance during treatment. This will be discussed in the "Treatment" section. Based on a small genome-wide scan\textsuperscript{52} of families affected by severe pediatric GERD, followed by haplotyping and by pairwise and multipoint linkage analyses based on epidemiologic studies, it is possible that GERD, in the future, may one day be found to be a genetically determined disease, and that genetic testing may be able to predict who is at risk for GERD and its varied presentations.\textsuperscript{52}

### Laboratory Testing

Depending on the information that is sought, there are a variety of laboratory tests from which to choose. For example, the results of esophageal manometry to assess for a hypotensive lower esophageal sphincter and barium esophagography to assess for the presence of a hiatus hernia may suggest that there is the potential for GERD. While barium esophagography results may suggest that there is mucosal injury, esophagoscopy with mucosal biopsy can confirm it. Intraesophageal hydrochloric acid infusion while monitoring symptoms (ie, the Bernstein test) may reveal esophageal mucosal acid sensitivity. Barium esophagography, radionuclide esophageal scintigraphy, and esophageal pH monitoring can assess for GER events. Dual esophageal and pharyngeal simultaneous pH monitoring can evaluate for gastropharyngeal GER events and their potential to cause laryngopharyngeal injury, and the risk of aspiration. A radionuclide gastric-emptying study with solids has the potential to assess for GERD that may be contributed to by delayed gastric emptying. Last, 24-h esophageal pH monitoring, lung scintiscanning after intragastric \textsuperscript{99m}Tc-sulfur colloid infusion, investigating for lipid-laden alveolar macrophages in induced sputum or BAL fluid and observing the gross appearance of airway mucosal surfaces during laryngoscopy and bronchoscopy, and lung biopsy have been utilized to link GER with a variety of pulmonary diseases as well as cough.

While tests that link GER with cough suggest a potential cause-effect relationship, a definitive diagnosis of cough due to GERD requires that cough nearly or completely disappear with antireflux treatment.\textsuperscript{28} Utilizing a favorable response to specific antitussive therapy as the "gold standard" test for comparison, and following previously published evidence-based guidelines for interpreting 24-h esophageal pH monitoring and treating GERD in the context of chronic cough,\textsuperscript{28} three prospective before-and-after intervention trials\textsuperscript{4,9,32} have revealed the following.\textsuperscript{17} Although the standard catheter-based 24-h esophageal pH monitoring has been shown to be the single best test to link GERD and cough in a cause-effect relationship, because it is the most sensitive and specific test, it is important to be aware that conventionally utilized diagnostic indexes of GERD (eg, percentage of time that pH is < 4) can be misleadingly normal and that observing GER-induced coughs can more often be helpful. Consequently, the sensitivity of the test can depend on how it is interpreted. Until future studies provide better guidelines, it is recommended that the test be interpreted as normal only when conventional indexes for acid reflux are within the normal range and no
Reflux-induced coughs appear during the monitoring study. For example, in three prospective studies, a cough was considered to be induced by acid reflux only when cough occurred simultaneously with or within 3 min following a drop in pH to < 4. These criteria were empirically established and will need to be validated by future prospective studies. When cough is due to GERD, it should not be expected that there will necessarily be a high percentage of coughs that appear to be induced by GER events in the 24-h esophageal pH tracing. In two prospective, before-and-after intervention trials in which it was determined that chronic cough was due to GERD, GER events in the distal esophagus appeared to induce an average of 29% of the patients’ coughs (range, 0 to 100 coughs) and 35% of the patients’ coughs (range, 0 to 89 coughs). It is also important to stress that the degree of abnormality noted in the esophageal pH-monitoring variables does not directly correlate with the severity of the patients’ cough.

The standard, catheter-based 24-h esophageal pH-monitoring study has its own inherent limitations. For example, because it cannot detect reflux events with a pH similar to that of the normal esophagus, the monitoring study can be entirely normal at a time when nonacid GERD is the cause of cough. In this situation, barium esophagography may be the only available test to reveal GER of potential pathologic significance (see the discussion below regarding esophageal impedance monitoring). Barium esophagography has revealed reflux to the mid-esophagus or higher when refluxate from the stomach had a pH value similar to that of the normal esophagus. Because the majority of patients with cough due to GERD do not have esophagitis or Barrett epithelium, a normal esophagoscopy finding does not rule out GERD as the cause of cough. While pilot studies have shown that ambulatory esophageal pH monitoring using a wireless recording system is a viable option for patients who are unwilling or unable to undergo conventional ambulatory pH-monitoring studies using a transnasally positioned pH catheter, it is likely that future studies will show that the wireless system will have the same limitations as the standard catheter-based systems, which were summarized above.

Because 24-h esophageal pH monitoring in the context of prospectively evaluating chronic cough has a sensitivity of < 100% (approximately 90%) and its specificity has ranged between 66% and 100%, even when interpreted according to the guidelines described above, and because these ranges have been confirmed in a retrospective study, it is recommended that treatment be initially started in lieu of testing for patients who fit the clinical profile for cough due to GERD (Table 1). This recommendation is supported by a retrospective, before-and-after intervention study in which GERD was diagnosed as the cause of chronic cough in 79% of patients (44 of 56 patients) by the empiric trial of therapy, thus obviating the need to perform 24-h esophageal pH monitoring. The performance of 24-h esophageal pH monitoring is recommended during therapy when cough does not improve or resolve to assist in determining whether the therapy needs to be intensified or medical therapy has failed. The usefulness of this recommendation was shown in a small prospective before-and-after intervention trial. Hopefully, in the near future, it will be determined whether simultaneous 24-h monitoring of intraesophageal impedance and pH will allow us to more easily determine when acid reflux disease and/or nonacid reflux disease are the causes of chronic cough.

While impedance monitoring allows for the detection of air and liquid reflux without requiring a pH shift to detect the liquid reflux, the simultaneous monitoring of pH helps to determine whether the liquid reflux observed by impedance was acidic in nature. Dual-impedance pH monitoring may also help to determine the roles of esophageal manometry in diagnosing cough and esophageal dysmotility in causing cough due to GERD. While a high prevalence of abnormal esophageal manometric measurements have been reported in a group of patients with chronic cough thought to be due to GERD, and manometry was the only abnormal test result in 32% of patients, a randomized, prospective study utilizing a control group of patients with cough due to conditions other than GERD will be required to determine whether manometry is a useful diagnostic test for distinguishing cough due to GERD from cough due to other diseases. Moreover, a randomized, prospective, double-blind, placebo-controlled trial will be required to determine whether esophageal dysmotility is pathogenetically linked to cough due to GERD.

As stated above, the findings of chest-imaging studies, laryngoscopy, and bronchoscopy can be entirely normal when GERD is the cause of cough. In this context, GERD most likely has caused cough via stimulation of an esophageal-bronchial reflex pathway. While laryngoscopic findings and bronchoscopic findings putatively due to GERD, have been published, it is not known how specific any of the findings are for injury due to GERD because they may also be potentially caused by the trauma of coughing itself (also see the “Complications” section elsewhere in this Supplement).

Lipid-laden alveolar macrophages have been prospectively evaluated as a marker of aspiration by...
BAL in patients with pulmonary parenchymal lung diseases\textsuperscript{62} and by induced sputum in patients with either GI symptoms without respiratory complaints or patients with mild asthma in the context of normal chest radiographs.\textsuperscript{63} In the first study,\textsuperscript{62} the mere presence of lipid-laden alveolar macrophages in lower respiratory tract secretions was found to be a nonspecific marker of parenchymal lung disease because the presence and/or appearance of intracellular lipid in these cells was not helpful in differentiating aspiration from nonaspiration as the cause of the lung disease. A post hoc analysis of the data revealed that observing few or no lipid-laden alveolar macrophages might be helpful in ruling out aspiration as the cause of the parenchymal lung disease. This conclusion was reached on the basis of the following information: a lipid cellular index of \( \geq 100 \), which was computed by multiplying the observed amount of intracellular lipid in 100 cells, graded from 0 to 4, had a specificity of 57\%, and sensitivity and negative predictive values of 100\%. In the second study,\textsuperscript{63} while it was found that the presence of an increased number of lipid-laden macrophages in induced sputum predicted the presence of oropharyngeal reflux by dual-channel 24-h esophageal and pharyngeal pH monitoring, it was not determined that these same patients actually had aspirated. Most relevant to the discussion in this section, the diagnostic usefulness of the presence of lipid-laden macrophages in induced sputum was not assessed in patients with chronic cough. On the basis of these studies, assessing for lipid-laden macrophages in BAL fluid and induced sputum does not appear, at this time, to have a role to play in diagnosing cough due to GERD.

Because inhaled tussigenic challenges with capsaicin have revealed the increased sensitivity of the cough reflex in a variety of diseases (eg, asthma, viral upper respiratory tract infections, and angiotensin-converting enzyme inhibitors) in addition to GERD\textsuperscript{30} and even in patients with GERD without cough,\textsuperscript{29} inhaled tussigenic challenges with capsaicin at this time do not appear to have a role to play in diagnosing cough due to GERD. Because exhaled nitric oxide can be a marker of airway inflammation in patients with asthma, its measurement may be of potential benefit in diagnosing the cause of chronic cough. However, preliminary studies\textsuperscript{64,65} to date have not shown exhaled nitric oxide measurements to be particularly helpful in diagnosing cough due to GERD. In a cross-sectional prospective study,\textsuperscript{66} utilizing exhaled nitric oxide as well as induced sputum, it was determined that GERD, when associated with cough or mildly symptomatic asthma, did not cause or aggravate existing airway inflammation as measured by exhaled nitric oxide or other indexes of airway inflammation (eg, cell counts and fibrinogen level).

Because two prospective studies\textsuperscript{4,18} in subjects with chronic cough due to GERD have produced divergent results during intravesophageal infusions of hydrochloric acid to provoke cough, a negative Bernstein test cannot be used to exclude the diagnosis of cough due to GERD. While a radioisotope scintiscan that documents pulmonary aspiration of gastric contents is definitive, it is not routinely performed because it may be positive in not \( > 50\% \) of subjects with suspected aspiration, and it has a much lower sensitivity.

Empiric Trial of Therapy

The first consensus panel report\textsuperscript{28} in 1998 recommended that, when 24-h esophageal pH monitoring cannot be performed or is not available, a diagnostic, empiric trial of medical antireflux therapy be performed in patients who meet the clinical profile (Table 1) predicting that silent GERD is the likely cause of chronic cough or in patients with chronic cough who also have prominent upper GI symptoms that are consistent with GERD. The first consensus panel report\textsuperscript{28} also recommended that if empiric treatment fails, it cannot be assumed that GERD has been ruled out as a cause of chronic cough; rather, objective investigation for GERD is then recommended because the empiric therapy may not have been intensive enough or medical therapy may have failed.

Since 1998, a number of articles have been published that support the above two recommendations. Poe and Kallay,\textsuperscript{57} in a retrospective before-and-after empirical medical intervention trial, provided data suggesting that an empiric trial of therapy can be successful; they were able to avoid the performance of 24-h esophageal pH monitoring in 44 of 56 patients in whom cough due to GERD had been determined. Others have provided data that support the contention that a negative finding in an empiric trial of therapy does not rule out GERD as a cause of cough. Peghini et al,\textsuperscript{66} in a controlled investigation that assessed for nocturnal acid breakthrough in patients with GI complaints who were receiving omeprazole (20 mg bid) or lansoprazole (30 mg bid) and in healthy volunteers, showed that nocturnal acid breakthrough occurred in the majority of all subjects. This study underscores the importance of being aware that a fixed dose of medication may not be adequate in all patients. Allen and Anvari,\textsuperscript{67} in a prospective before-and-after antireflux surgery intervention trial in patients who had failed to improve with intensive medical therapy, showed that laparo-
scopic reflux surgery had improved or cured cough in 85% of chronic coughers 6 months after surgery. Novitsky et al, in a prospective before-and-after antireflux surgery intervention trial in patients with chronic cough who had failed to respond to intensive medical therapy, reported an 86% improvement of chronic cough 12 months following surgery. Irwin et al, in a small, prospective, before-and-after intervention trial in patients with chronic cough who had failed to respond to very intensive medical therapy, reported the improvement or elimination of cough in all subjects 12 months following surgery. In this study, cough persisted prior to surgery even though the antireflux medical regimen was serially intensified until there was total or near-total elimination of esophageal acid on repeated 24-h esophageal pH monitoring. This finding supported the diagnosis of nonacid reflux disease.

The results of a metaanalysis of 15 trials (open-label, 2 trials; randomized, controlled, 10 trials; randomized, controlled, crossover, 3 trials) that did not involve extragastric symptoms such as cough showed that the short-term treatment (ie, 1 to 4 weeks) of GERD with normal-dose or high-dose proton pump inhibition (ie, the so-called PPI test) in patients who were suspected of having GERD did not confidently establish or exclude the diagnosis when GERD was defined by objective reference standards. In patients with GI symptoms suggestive of GERD in which the clinical response to a short course of proton pump inhibition was compared with 24-h esophageal pH monitoring, the positive likelihood of a symptomatic response detecting GERD ranged from 1.63 to 1.87. The sensitivity was 0.78 (95% confidence interval, 0.66 to 0.86) and specificity 0.54 (95% confidence interval, 0.44 to 0.65).

While Oura et al concluded from their prospective, double-blind, randomized, placebo-controlled study that the best diagnostic and therapeutic approach to chronic cough is a fixed dose of omeprazole, 40 mg bid for 2 weeks, there are many methodological concerns about this study that make the results uninterpretable. With respect to concerns about GERD, there were 17 patients with chronic cough who had abnormal findings of 24-h esophageal pH-monitoring studies, and only 6 patients improved with omeprazole therapy for a response rate of 35%. Because the authors assumed that the dose and duration of omeprazole therapy that they used would cure all patients with cough due to GERD, they reasoned that the other patients with abnormal findings of 24-h esophageal pH-monitoring studies could not have GERD. In the patients who did not respond, the authors did not (1) determine whether their medical therapy was maximal, (2) consider that their subjects might have had nonacid reflux disease and therefore required more than acid suppression therapy, and (3) did not find another cause for the chronic coughs of the patients.

On the basis of the above considerations, the panel recommends that an empiric trial of medical antireflux therapy be performed in patients who meet the clinical profile (Table 1) predicting that silent GERD is the most likely cause of chronic cough, or in patients with chronic cough who also have prominent upper GI symptoms (eg, heartburn, sour taste, and regurgitation) that are consistent with GERD. The panel does not think that it is necessary to order tests to assess for the potential of GERD before observing the response to empiric therapy. While it is not known what constitutes the minimum effective medical therapy for treating the majority of patients with chronic cough due to GERD, the panel, by expert opinion, recommends (1) dietary and lifestyle modifications, (2) acid suppression therapy, (3) the addition of prokinetic therapy (ie, to enhance gut motility) either initially or if there is no response to the therapy stated in steps 1 and 2 (see section on Treatment), and (4) that the response to therapy be assessed within 1 to 3 months. In some patients, there can be a delay of 2 to 3 months in improvement with therapy that will eventually eliminate the cough. If empiric treatment fails, it cannot be assumed that GERD has been ruled out as a cause of chronic cough; rather, the objective investigation for GERD is then recommended because the empiric therapy may not have been intensive enough or medical therapy may have failed.

**Recommendations**

2. **In patients with chronic cough who also complain of typical and frequent GI complaints such as daily heartburn and regurgitation, especially when the findings of chest-imaging studies and/or clinical syndrome are consistent with an aspiration syndrome,** the diagnostic evaluation should always include GERD as a possible cause. Level of evidence, low; benefit, substantial; grade of recommendation, B

3. **Patients with chronic cough who have GI symptoms that are consistent with GERD or who fit the clinical profile described in Table 1,** should be considered to have a high likelihood of having GERD and should be prescribed antireflux treatment even when they have no GI symptoms. Level of evidence, low; benefit, substantial; grade of recommendation, B

4. **In patients with chronic cough, it should not be assumed that GERD has been definitively ruled out as a cause of cough simply**
because there is a history of antireflux surgery. Level of evidence, low; benefit, substantial; grade of recommendation, B

5. In patients with chronic cough, while tests that link GERD with cough suggest a potential cause-effect relationship, a definitive diagnosis of cough due to GERD requires that cough nearly or completely disappear with antireflux treatment. Level of evidence, low; benefit, substantial; grade of recommendation, B

6. In patients with chronic cough being evaluated for GERD, the 24-h esophageal pH-monitoring test is the most sensitive and specific test; however, it is recommended that the test results be interpreted as normal only when conventional indexes for acid reflux are within the normal range and no reflux-induced coughs appear during the monitoring study. Level of evidence, low; benefit, substantial; grade of recommendation, B

7. In patients with cough who are undergoing 24-h monitoring, a low percentage of coughs associated with (or induced by) reflux does not exclude a diagnosis of cough due to GERD. Level of evidence, low; benefit, substantial; grade of recommendation, B

8. In patients with cough due to GERD, the degree of abnormality noted in the esophageal pH-monitoring variables, such as the frequency and duration of reflux events, does not directly correlate with the severity of the patients’ cough. Level of evidence, low; benefit, substantial; grade of recommendation, B

9. In diagnosing nonacid GERD as the cause of cough, barium esophagography may be the only available test to reveal GER of potential pathologic significance in this setting (see the discussion regarding esophageal impedance monitoring in the “Laboratory Testing” section). When this is the case, barium esophagography is the test of choice to reveal GER of potential pathologic significance. Level of evidence, low; benefit, substantial; grade of recommendation, B

10. In patients with cough due to GERD, normal esophagoscopy findings do not rule out GERD as the cause of cough. Level of evidence, low; benefit, substantial; grade of recommendation, B

11. For patients fitting the clinical profile for cough due to GERD, it is recommended that treatment be initially started in lieu of testing. Level of evidence, low; benefit, substantial; grade of recommendation, B

12. For patients fitting the clinical profile for cough due to GERD, the performance of 24-h esophageal pH monitoring is recommended on therapy when cough does not improve or resolve to assist in determining whether the therapy needs to be intensified or if medical therapy has failed. Level of evidence, low; benefit, substantial; grade of recommendation, B

13. For patients with chronic cough, the following tests are not routinely recommended to link cough with GERD: (a) assessing for lipid-laden macrophages in BAL fluid and induced sputum, because this test has not been studied in patients with chronic cough and because a positive test result is not specific for aspiration; (b) exhaled nitric oxide measurements, because they do not appear to be helpful in diagnosing cough due to GERD; (c) a Bernstein test, because a negative Bernstein test result cannot be used to exclude the diagnosis of cough due to GERD; and (d) inhaled tussigenic challenges with capsaicin, because they are not specific for coughs due to GERD and because the test result can be positive in patients with GERD without cough. Level of evidence, low; benefit, conflicting; grade of recommendation, I

**TREATMENT**

Based on the apparent heterogeneity of patient populations with differing pathogenetic mechanisms and differing risk factors that can adversely affect GERD, it is not likely that all patients will theoretically respond to the same treatment. A review of the literature on the treatment of cough due to GERD, which is summarized in Table 2, supports this statement. The review suggests the following: that when medical therapy is effective, some patients with cough due to GERD will favorably respond to acid suppression therapy alone; that proton pump inhibition may be effective when H2-antagonism alone has failed to improve with maximal medical therapy and that cough in other patients will only improve or be eliminated with antireflux surgery; after cough in these patients has failed to improve with maximal medical therapy that includes an intensive antireflux diet, maximum acid suppression, and prokinetic therapy. These findings have come from prospective and retrospective before-and-after intervention trials, and from two imperfectly designed (see Table 2), prospective,
### Table 2—Evidence for the Treatment of Chronic Cough Due to GERD*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosing</th>
<th>Study ID</th>
<th>Patients, No.</th>
<th>Age</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet + LS, antacids, cimetidine</td>
<td>qid 300 mg hs</td>
<td>Prospective, before/after intervention, uncontrolled, unblinded</td>
<td>5</td>
<td>67.2 yr</td>
<td>Cough cured 100%</td>
</tr>
<tr>
<td>Diet + LS, metoclopramide and/or H2-blockers</td>
<td>Not stated</td>
<td>Prospective, before/after intervention, uncontrolled, unblinded</td>
<td>9</td>
<td>52 ± 11 yr</td>
<td>Cough cured 100%; time to cure, 161 ± 74 d</td>
</tr>
<tr>
<td>Diet + LS, metoclopramide and/or H2-blockers</td>
<td>Not stated</td>
<td>Prospective, before/after intervention, uncontrolled, unblinded</td>
<td>28</td>
<td>56 ± 12 yr</td>
<td>Cough cured 100%; time to cure, 179 ± 205 d</td>
</tr>
<tr>
<td>Diet + LS, antacids, cimetidine, surgery</td>
<td>10 mg tid, 300 mg qid, 20–40 mg/d</td>
<td>Prospective, before/after intervention, uncontrolled, unblinded</td>
<td>20</td>
<td>Adult</td>
<td>Cough cured 90%; 70% cured with medication in 3 mo, 20% with surgery</td>
</tr>
<tr>
<td>Diet + LS, omeprazole or surgery</td>
<td>0.2 mg/kg qid divided qid</td>
<td>Prospective, before/after intervention, uncontrolled, unblinded</td>
<td>55</td>
<td>Infants</td>
<td>Cough improved 64.5%; no significant difference between drugs</td>
</tr>
<tr>
<td>Cisapride, domperidone</td>
<td>0.2 mg/kg tid</td>
<td>Prospective, before/after intervention, uncontrolled, unblinded</td>
<td>18</td>
<td>1 mo to 12.7 yr</td>
<td>Cough improved 100% (p &lt; 0.05)</td>
</tr>
<tr>
<td>Diet Prokinetic and/or H2-blockers</td>
<td>Not stated</td>
<td>Prospective, before/after intervention, uncontrolled, unblinded</td>
<td>20</td>
<td>58 ± 17 yr</td>
<td>Cough cured in 97%; productive coughs in all patients</td>
</tr>
<tr>
<td>Surgery</td>
<td>Not stated</td>
<td>Prospective, before/after intervention, uncontrolled, unblinded</td>
<td>17</td>
<td>Adult</td>
<td>100% cure if esophageal motility was normal</td>
</tr>
<tr>
<td>Surgery</td>
<td>Prospective, before/after intervention, uncontrolled, unblinded</td>
<td>5</td>
<td>Adult</td>
<td>100% cured in highly selected patients who were thought to be aspirators; only 5/100 patients were suitable</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>Prospective, before/after intervention, uncontrolled, unblinded</td>
<td>13</td>
<td>Adult</td>
<td>Cough cured in 84%; only 13/140 patients considered suitable</td>
<td></td>
</tr>
<tr>
<td>Diet, prokinetics and/or PPIs</td>
<td>Cisapride or metoclopramide 10 mg qid, omeprazole up to 40 mg and lasoaprazole, 30 mg bid</td>
<td>Retrospective, before/after intervention, uncontrolled, unblinded</td>
<td>56</td>
<td>57 yr</td>
<td>Cough cured or improved in 86%; 17/56 had not responded to H2-blockers; 3/56 required up to 8 weeks to improve, and 1/55 up to 12 weeks; 24/56 only required PPIs, 18/56 required PPIs plus prokinetics</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>Omeprazole, 40 mg/d, or placebo for 8 wk</td>
<td>Prospective, double-blind, randomized, placebo-controlled, cross-over trial</td>
<td>29</td>
<td>Adults</td>
<td>Cough improved (p = 0.02) with omeprazole compared to placebo, proper statistics were not utilized to analyze crossover design</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>Omeprazole, 40 mg bid, or placebo for 12 wk</td>
<td>Prospective, double-blind, randomized, placebo-controlled trial</td>
<td>23</td>
<td>Adults</td>
<td>Of 17 patients with abnormal findings of 24-h esophageal pH monitoring studies, 6 significantly improved after drug therapy compared to placebo; it is not known whether the remaining patients also had GERD because no further testing was performed and treatment was not intensified</td>
</tr>
<tr>
<td>Surgery</td>
<td>Prospective, before/after intervention, uncontrolled, unblinded</td>
<td>119</td>
<td>Adults</td>
<td>Of 119 patients with inadequate control of respiratory symptoms with medical therapy, 42 had chronic cough as chief complaint; surgery cured or improved cough in 85% at 6 mo after surgery</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>Prospective before/after intervention, uncontrolled, unblinded</td>
<td>35</td>
<td>Adults</td>
<td>Of 35 patients with chronic cough, cough improved or was cured in 56% at 12 mo; patients did not appear to have been selected based upon lack of response to medical treatment</td>
<td></td>
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<tr>
<td>Surgery</td>
<td>Prospective before/after intervention, uncontrolled, unblinded</td>
<td>21</td>
<td>Adults</td>
<td>At 1 yr following surgery, cough had significantly improved (p &lt; 0.01); improvement was reported by 86% of patients, with complete resolution in 62%; prior to surgery, cough had failed to improve with intensive medical therapy</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>Prospective before/after intervention, uncontrolled, unblinded</td>
<td>8</td>
<td>54.2 ± 10.8 yr</td>
<td>At 1 yr following surgery, cough had significantly improved (p &lt; 0.001), all patients reported improvement in cough; prior to surgery, patients had failed to respond to maximal medical therapy even though there was total/near-total elimination of esophageal acid</td>
<td></td>
</tr>
</tbody>
</table>

*LS = lifestyle changes (such as not wearing constricting clothing and head of bed elevation). Diets were not well-described in any study and were not consistently described between studies.
†Cisapride is off the market in the United States but is available in other countries.
double-blind, randomized placebo-controlled trials\textsuperscript{59,71} that have compared the effects of omeprazole with placebo.

While the optimal way to treat all patients with cough due to GERD has yet to be determined, medical therapy in adults, based on the results of prospective and retrospective before-and-after intervention trials, when not limited to acid suppression therapy alone, has improved cough in 70 to 100\% of patients. When cough in adults has not improved with medical therapy, surgery has improved cough 6 to 12 months following surgery in prospective, before-and-after intervention trials\textsuperscript{33,67} in approximately 85\% of patients.

Until multiple randomized controlled clinical trials provide guidance on which treatment regimens will be successful in which groups of subjects, the panel by consensus recommends that clinicians must be aware of the spectrum of treatment options that may favorably affect GERD (Table 3) and that an intensive medical treatment regimen that includes all medical therapeutic options listed in Table 3 be instituted before considering antireflux surgery.\textsuperscript{17} While there has been an anecdotal report\textsuperscript{72} suggesting that one patient may have developed an intractable cough due to receiving omeprazole therapy, the patient was not rechallenged with the drug to solidify the association. Nevertheless, if drug-induced cough is considered to be a clinical possibility, the agent should be discontinued to determine whether it might be playing a role before recommending surgery.

An intensive medical treatment regimen includes the following: (1) an antireflux diet that includes no > 45 g of fat in 24 h and no coffee, tea, soda, chocolate, mints, citrus products, including tomatoes\textsuperscript{37,73} or alcohol,\textsuperscript{41} no smoking,\textsuperscript{37} and limiting vigorous exercise that will increase intraabdominal pressure\textsuperscript{38,40}; (2) acid suppression with a proton pump inhibitor (PPI); and (3) prokinetic therapy. Even though nocturnal breakthrough gastric acid production has been noted in healthy control subjects and patients with GERD who are receiving PPIs, the addition of a nocturnal H\textsubscript{2}-antagonist has not been shown to improve clinical outcomes.\textsuperscript{66,74,75} Because comorbid diseases such as obstructive sleep apnea\textsuperscript{35,76} or therapy for comorbid conditions (eg, nitrates, progesterone, and calcium channel blockers)\textsuperscript{37,77} can potentially make GERD more difficult to control, routinely consider trying to mitigate the influences of these factors whenever possible. Because coughing can induce GER events, it should be appreciated that less than optimal results may occur due to a cough-GER self-perpetuating cycle unless all causes of cough are adequately treated.\textsuperscript{29} Reliance on acid suppression alone may not fail to adequately control the cough but also potentially place the patient at increased risk of community-acquired pneumonia. According to a retrospective case-control analysis, which was nested in a cohort of incident users of acid-suppressive drugs for at least 1 year,\textsuperscript{78} the adjusted risk for pneumonia among persons currently using PPIs compared with those who stopped receiving the PPIs was 1.89. Current users of histamine-2 receptor antagonists had a 1.63-fold increased risk of pneumonia compared with those patients who had stopped using them. These data translated into approximately one case of pneumonia for every 100 years of patient exposure.\textsuperscript{79} A prospective, randomized, controlled clinical trial will be necessary to confirm the accuracy of these results.

While the role of antireflux surgery has not been clearly defined, it appears that antireflux surgery has been able to effectively eliminate or significantly improve cough that is unresponsive to intensive antireflux medical therapy. The panel by consensus recommends that antireflux surgery be considered in patients who meet the following criteria: (1) the findings of a 24-h esophageal pH-monitoring study before treatment are positive, as defined above; (2) patients fit the clinical profile suggesting that GERD is the likely cause of their cough (Table 1); (3) cough has not improved after a minimum of 3 months of intensive therapy (Table 3), and serial esophageal pH-monitoring studies or other objective studies (eg, barium esophagography, esophagoscopy, or gastric-emptying study with solids) performed on therapy show that intensive medical therapy has failed to control the reflux disease and GERD is still the likely cause of cough; and (4) patients express the opinion that their persisting cough does not allow them a satisfactory quality of life. While one small prospec-

<table>
<thead>
<tr>
<th>Table 3—Spectrum of Options for Treating Chronic Cough Due to GERD</th>
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<tbody>
<tr>
<td><strong>Treatment</strong></td>
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<tr>
<td>Antireflux medical therapy</td>
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<td></td>
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<td>Medications</td>
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<tr>
<td>Antireflux surgery</td>
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tive, uncontrolled and unblinded, descriptive study suggested that an assessment of gastric emptying would not assist in patient management, another small, prospective, before-and-after intervention trial found that a gastric-emptying study with solids provided the only insight as to why prior antireflux surgery had failed to control cough. Redo antireflux surgery that included a gastric-emptying procedure in three of four patients was successful. While a variety of endoscopically assisted interventional techniques have been developed and performed in patients with classic GI GERD symptoms, these procedures should be considered experimental at this time in the population of patients with cough.

Recommendations

14. In patients who meet the clinical profile predicting that silent GERD is the likely cause of chronic cough or in patients with chronic cough who also have prominent upper GI symptoms consistent with GERD, an empiric trial of medical antireflux therapy is recommended. Level of evidence, low; benefit, substantial; grade of recommendation, B

15. For treating the majority of patients with chronic cough due to GERD, the following medical therapies are recommended: (a) dietary and lifestyle modifications; (b) acid suppression therapy; and (c) the addition of prokinetic therapy either initially or if there is no response to the first two therapies. The response to these therapies should be assessed within 1 to 3 months. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

16. In patients in which this empiric treatment fails, it cannot be assumed that GERD has been ruled out as a cause of chronic cough; rather, the objective investigation for GERD is then recommended because the empiric therapy may not have been intensive enough or medical therapy may have failed. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

17. In some patients, cough due to GERD will favorably respond to acid suppression therapy alone; proton pump inhibition may be effective when H2-antagonism has been ineffective; prokinetic therapy and diet, when added to proton pump inhibition, may be effective when proton pump inhibition alone has been ineffective. Level of evidence, low; benefit, substantial; grade of recommendation, B

18. Patients requiring an intensive medical treatment regimen should be treated with the following: (a) antireflux diet that includes no > 45 g of fat in 24 h and no coffee, tea, soda, chocolate, mints, citrus products, including tomatoes, or alcohol, no smoking, and limiting vigorous exercise that will increase intra-abdominal pressure; (b) acid suppression with a PPI; (c) prokinetic therapy; and (d) efforts to mitigate the influences of comorbid diseases such as obstructive sleep apnea or therapy for comorbid conditions (eg, nitrates, progesterone, and calcium channel blockers) whenever possible. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

19. In patients with chronic cough due to GERD that has failed to improve with the most maximal medical therapy, which includes an intensive antireflux diet and lifestyle modification, maximum acid suppression, and prokinetic therapy, and the rest of the spectrum of treatment options in Table 3, cough may only improve or be eliminated with antireflux surgery. Level of evidence, low; benefit, substantial; grade of recommendation, B

20. In patients who meet the following criteria, antireflux surgery is the recommended treatment: (a) findings of a 24-h esophageal pH-monitoring study before treatment is positive, as defined above; (b) patients fit the clinical profile suggesting that GERD is the likely cause of their cough (Table 1); (c) cough has not improved after a minimum of 3 months of intensive therapy (Table 3), and serial esophageal pH-monitoring studies or other objective studies (eg, barium esophagography, esophagoscopy, and gastric-emptying study with solids) performed while the patient receives therapy show that intensive medical therapy has failed to control the reflux disease and that GERD is still the likely cause of cough; and (d) patients express the opinion that their persisting cough does not allow them a satisfactory quality of life. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

Summary of Recommendations

1. In patients with chronic cough due to GERD, the term acid reflux disease, unless it can be definitively shown to apply, should be replaced by the more general term reflux disease so as not to mislead the clinicians into thinking that all patients with cough due to GERD should improve with acid-
suppression therapy. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

2. In patients with chronic cough who also complain of typical and frequent GI complaints such as daily heartburn and regurgitation, especially when the findings of chest-imaging studies and/or clinical syndrome are consistent with an aspiration syndrome, the diagnostic evaluation should always include GERD as a possible cause. Level of evidence, low; benefit, substantial; grade of recommendation, B

3. Patients with chronic cough who have GI symptoms that are consistent with GERD or who fit the clinical profile described in Table 1, should be considered to have a high likelihood of having GERD and should be prescribed antireflux treatment even when they have no GI symptoms. Level of evidence, low; benefit, substantial; grade of recommendation, B

4. In patients with chronic cough, it should not be assumed that GERD has been definitively ruled out as a cause of cough simply because there is a history of antireflux surgery. Level of evidence, low; benefit, substantial; grade of recommendation, B

5. In patients with chronic cough, while tests that link GERD with cough suggest a potential cause-effect relationship, a definitive diagnosis of cough due to GERD requires that cough nearly or completely disappear with antireflux treatment. Level of evidence, low; benefit, substantial; grade of recommendation, B

6. In patients with chronic cough being evaluated for GERD, the 24-h esophageal pH-monitoring test is the most sensitive and specific test; however, it is recommended that the test results be interpreted as normal only when conventional indexes for acid reflux are within the normal range and no reflux-induced coughs appear during the monitoring study. Level of evidence, low; benefit, substantial; grade of recommendation, B

7. In patients with cough who are undergoing 24-h monitoring, a low percentage of coughs associated with (or induced by) reflux does not exclude a diagnosis of cough due to GERD. Level of evidence, low; benefit, substantial; grade of recommendation, B

8. In patients with cough due to GERD, the degree of abnormality noted in the esophageal pH-monitoring variables, such as the frequency and duration of reflux events, does not directly correlate with the severity of the patients’ cough. Level of evidence, low; benefit, substantial; grade of recommendation, B

9. In diagnosing nonacid GERD as the cause of cough, barium esophagography may be the only available test to reveal GER of potential pathologic significance in this setting (see the discussion regarding esophageal impedance monitoring in the “Laboratory Testing” section). When this is the case, barium esophagography is the test of choice to reveal GER of potential pathologic significance. Level of evidence, low; benefit, substantial; grade of recommendation, B

10. In patients with cough due to GERD, normal esophagoscopy findings do not rule out GERD as the cause of cough. Level of evidence, low; benefit, substantial; grade of recommendation, B

11. For patients fitting the clinical profile for cough due to GERD, it is recommended that treatment be initially started in lieu of testing. Level of evidence, low; benefit, substantial; grade of recommendation, B

12. For patients fitting the clinical profile for cough due to GERD, the performance of 24-h esophageal pH monitoring is recommended on therapy when cough does not improve or resolve to assist in determining whether the therapy needs to be intensified or if medical therapy has failed. Level of evidence, low; benefit, substantial; grade of recommendation, B

13. For patients with chronic cough, the following tests are not routinely recommended to link cough with GERD: (a) assessing for lipid-laden macrophages in BAL fluid and induced sputum, because this test has not been studied in patients with chronic cough and because a positive test result is not specific for aspiration; (b) exhaled nitric oxide measurements, because they do not appear to be helpful in diagnosing cough due to GERD; (c) a Bernstein test, because a negative Bernstein test result cannot be used to exclude the diagnosis of cough due to GERD; and (d) inhaled tussigenic challenges with capsaicin, because they are not specific for coughs due to GERD and because the test result can be positive in patients with GERD without...
14. In patients who meet the clinical profile predicting that silent GERD is the likely cause of chronic cough or in patients with chronic cough who also have prominent upper GI symptoms consistent with GERD, an empiric trial of medical antireflux therapy is recommended. Level of evidence, low; benefit, conflicting; grade of recommendation, I

15. For treating the majority of patients with chronic cough due to GERD, the following medical therapies are recommended: (a) dietary and lifestyle modifications; (b) acid suppression therapy; and (c) the addition of prokinetic therapy either initially or if there is no response to the first two therapies. The response to these therapies should be assessed within 1 to 3 months. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, B

16. In patients in which this empiric treatment fails, it cannot be assumed that GERD has been ruled out as a cause of chronic cough; rather, the objective investigation for GERD is then recommended because the empiric therapy may not have been intensive enough or medical therapy may have failed. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

17. In some patients, cough due to GERD will favorably respond to acid suppression therapy alone; proton pump inhibition may be effective when H₂-antagonism has been ineffective; prokinetic therapy and diet, when added to proton pump inhibition, may be effective when proton pump inhibition alone has been ineffective. Level of evidence, low; benefit, substantial; grade of recommendation, B

18. Patients requiring an intensive medical treatment regimen should be treated with the following: (a) antireflux diet that includes no > 45 g of fat in 24 h and no coffee, tea, soda, chocolate, mints, citrus products, including tomatoes, or alcohol, no smoking, and limiting vigorous exercise that will increase intraabdominal pressure; (b) acid suppression with a PPI; (c) prokinetic therapy; and (d) efforts to mitigate the influences of comorbid diseases such as obstructive sleep apnea or therapy for comorbid conditions (e.g., nitrates, progesterone, and calcium channel blockers) whenever possible. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

19. In patients with chronic cough due to GERD that has failed to improve with the most maximal medical therapy, which includes an intensive antireflux diet and lifestyle modification, maximum acid suppression, and prokinetic therapy, and the rest of the spectrum of treatment options in Table 3, cough may only improve or be eliminated with antireflux surgery. Level of evidence, low; benefit, substantial; grade of recommendation, B

20. In patients who meet the following criteria, antireflux surgery is the recommended treatment: (a) findings of a 24-h esophageal pH-monitoring study before treatment is positive, as defined above; (b) patients fit the clinical profile suggesting that GERD is the likely cause of their cough (Table 1); (c) cough has not improved after a minimum of 3 months of intensive therapy (Table 3), and serial esophageal pH-monitoring studies or other objective studies (e.g., barium esophagography, esophagoscopy, and gastric-emptying study with solids) performed while the patient receives therapy show that intensive medical therapy has failed to control the reflux disease and that GERD is still the likely cause of cough; and (d) patients express the opinion that their persisting cough does not allow them a satisfactory quality of life. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

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