

# Therapy Insight: treatment of gastroesophageal reflux in adults with chronic cough

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## SUMMARY

Gastroesophageal reflux (GER) is the second most common cause of chronic cough in immunocompetent patients who are nonsmokers, not on angiotensin-converting-enzyme inhibitors and have normal chest radiographs. Identification of GER in chronic cough patients can be difficult; most patients with GER-related cough have no esophageal symptoms and no esophageal test is adequate to make this diagnosis. *Post-hoc* analysis of four prospective intervention trials has identified a clinical patient profile that can predict the presence of GER-related cough 91% of the time. Clinical practice guidelines from the American College of Chest Physicians and the British Thoracic Society recommend initiating an initial empiric GER therapy trial, with esophageal testing being reserved for nonresponders. The empiric trial should include conservative measures and PPIs twice daily for 3 months. Selected patients who have dysphagia might benefit from the addition of a prokinetic agent. Esophageal manometry and pH testing with impedance monitoring (if available) should be performed in nonresponders while they are on therapy. It can take more than 50 days for cough to respond to medical GER therapy. Surgical fundoplication might be helpful in very carefully selected patients. Careful evaluation and treatment resolves cough in ~80% of patients with GER-related cough.

**KEYWORDS** chronic cough, esophageal manometry, gastroesophageal reflux, proton pump inhibitor, surgical fundoplication

## REVIEW CRITERIA

PubMed was searched with the following terms alone and in combination: "chronic cough", "treatment", "gastroesophageal reflux", and "nonacid reflux". The search included work published from 1980 through June 2007. Practice-based clinical guidelines published in 2006 that were developed by the American College of Chest Physicians and the British Thoracic Society, as well as the Cochrane Database reports on cough, were also accessed and reviewed.

## CME

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## Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Recognize the proportion of patients with gastroesophageal reflux (GER)-related cough who have no identifying symptoms.
- 2 List the 5 most common causes of cough in immunocompetent nonsmoking adults not on angiotensin-converting enzyme inhibitors.
- 3 Describe the symptoms most likely to be associated with GER-related cough.
- 4 Identify the best test for identifying GER as the etiology of chronic cough.
- 5 Describe the management of GER-related cough after empirical treatment fails.

## INTRODUCTION

Cough is the most common symptom that patients present with to their general practitioner and it is considered chronic if it persists for more than 8 weeks.<sup>1-4</sup> Chronic cough has more than 30 etiologies and many patients have more than one etiology present.<sup>5</sup> Gastroesophageal reflux (GER) is the second most common cause of chronic cough.<sup>6-8</sup> In Japan, the overall prevalence of endoscopic/symptomatic GER in patients with chronic cough is 18%, whereas in western populations it is 21-59%.<sup>9-11</sup> The prevalence of GER-related cough is, therefore, lower (2-7%) in Japan.<sup>9-14</sup>

Guidelines from the American College of Chest Physicians (ACCP) define GER-related cough as a cough that is improved or eliminated by GER-specific therapy.<sup>15</sup> As acid, weakly acidic, and nonacid GER can all elicit cough, therapy

directed at acid suppression might not improve GER-related cough.<sup>16,17</sup> Up to 75% of patients who have GER-related cough do not have heartburn or other esophageal symptoms, which makes identification of GER difficult.<sup>18–20</sup>

Even if GER is present, it might not be the cause of cough. Cough threshold to the tussive effect of capsaicin might not be affected by esophageal acid in all GER patients. This finding might explain why many GER patients do not have chronic cough.<sup>21</sup> In addition, the act of coughing itself can elicit GER, so there might be a self-perpetuating positive feedback cycle between cough and GER.<sup>22</sup>

Another complicating factor is that there is no diagnostic test that can accurately identify GER as a cause of cough.<sup>15</sup> Esophageal pH testing with cough correlation is the best method to link GER and cough in a causal relationship; however, this method has inherent limitations.<sup>15–23</sup> Although esophageal pH testing has a sensitivity of approximately 90% for the evaluation of chronic cough, its specificity ranges from 66% to 100%.<sup>24,25</sup> These pitfalls in our ability to diagnose GER-related cough accurately led two professional societies (the ACCP and the British Thoracic Society [BTS]) to publish clinical practice guidelines in 2006 that recommend the initiation of empiric GER therapy to identify and treat GER-related cough.<sup>15,26,27</sup> This empiric approach was shown to be effective (i.e. cough was improved or resolved) in a community-based cough population in the US.<sup>28</sup>

The remainder of this Review focuses on the evaluation of chronic cough patients and the identification of those with GER-related cough, and discusses management and treatment options for these patients. To do this, we review the most common causes of chronic cough and discuss the clinical features of GER-related cough. We also consider the usefulness of an empiric trial to identify and treat patients with GER-related cough and how to proceed when patients do not improve with an empiric therapy trial. Finally, we discuss clinical outcomes of GER-related cough, long-term GER therapy for GER-related cough, and potential pitfalls of the treatment of GER-related cough.

### COMMON CAUSES OF CHRONIC COUGH

Cough is caused by numerous entities that require careful evaluation. The key to successful treatment of chronic cough is to determine

the underlying cause or causes of the cough. Diagnostic protocols allow the cause or causes of chronic cough to be determined in 80–98% of cases.<sup>14,15</sup> In a study by Kastelik, the etiology of chronic cough was identified in 93% of patients.<sup>8</sup> Furthermore, specific therapy targeted at the cause leads to cough resolution in 84–98% of cases.<sup>5</sup>

Complicating the successful management of chronic cough is the fact that chronic cough can be caused by more than one condition in the same patient. In a community study, where cough cause was defined by cough response to therapy, 52% of patients had cough caused by GER plus another cause, and 5% had cough caused by GER plus two other causes.<sup>28</sup> Kastelik and colleagues noted that only 8% of patients had multiple cough etiologies;<sup>8</sup> by contrast, other studies report more than one cough cause in 25–61% of patients.<sup>29–32</sup> GER therapy will, therefore, not be effective if other cough causes are not identified and treated.

In nonsmokers who are immunocompetent, have a normal chest radiograph and are not taking angiotensin-converting enzyme (ACE) inhibitors, the five most common causes of cough are upper airway cough syndrome (UACS; also referred to as postnasal drip syndrome [PNDS] caused by various rhinosinus conditions), GER, asthma, nonasthmatic eosinophilic bronchitis, and postinfectious cough. If evaluation and therapy for the most common causes of cough do not result in cough resolution, then other potential causes should be considered (Table 1).<sup>8,11,15,28,32</sup> Vigilance is required to carefully evaluate for these causes, especially if empiric therapy fails.

In general, esophageal GER symptoms are present in 6–10% of chronic cough patients; however, GER is clinically silent in up to 75% of patients who have GER-related cough.<sup>20</sup> GER has a role in many cases of chronic cough.<sup>15</sup>

### CLINICAL FEATURES OF GER-RELATED COUGH

The clinical features of GER-related cough include heartburn, regurgitation, and/or worsening of cough after ingestion of foods or medications that decrease lower esophageal sphincter pressure. Other extra-esophageal manifestations of GER can be present, including hoarseness, chest pain, wheezing, sore throat, globus and dysphonia.<sup>32–34</sup> Everett and Morice have described GER cough symptomatology in 47 patients.<sup>35</sup> They found that cough on phonation, rising from bed, or associated

**Table 1** Causes of chronic cough.<sup>a</sup>

Cause	Patients affected (%) <sup>b</sup>
<b>Most common</b>	
Upper airway cough syndrome/ post nasal drip syndrome	10–58
Asthma	24–59
Gastroesophageal reflux	21–41
Nonasthmatic eosinophilic bronchitis	0–13
Postinfectious cough (including <i>Bordetella pertussis</i> and postviral)	0–25
<b>Less common</b>	
Bronchiolitis	Variable
Bronchiectasis	Variable
Bronchitis	Variable
Lung tumors	Variable
Aspiration (oral–pharyngeal dysphagia)	Variable
Interstitial lung disease	Variable
Habit, tic cough, psychogenic cough	Variable
Occupational and environmental (irritant) cough	Variable
Unexplained (idiopathic) cough	Variable

<sup>a</sup>Chronic cough is defined as cough lasting >8 weeks in patients who have a normal chest radiograph, are nonsmokers, immunocompetent and are not on an angiotensin-converting enzyme (ACE) inhibitor. <sup>b</sup>Data obtained from references 8,11,15,28,32.

**Box 1** Clinical profile of patients with GER-related cough.<sup>15</sup>

- Not exposed to environmental irritants
- Not a present smoker
- Not on an ACE inhibitor
- Normal or stable chest radiograph
- Symptomatic asthma ruled out (i.e. cough not improved on therapy, or negative methacholine inhalation challenge test)
- Upper airway cough syndrome due to rhinosinus diseases ruled out (i.e. cough not improved by first generation H<sub>1</sub>-receptor antagonists and 'silent' sinusitis ruled out)
- Non-asthmatic eosinophilic bronchitis ruled out (i.e. sputum studies negative or cough not improved by inhaled/systemic corticosteroids)

Abbreviation: ACE, angiotensin-converting enzyme. Adapted with permission from The American College of Chest Physicians © Irwin RS (2006) *Chest* 129: 80S–94S<sup>15</sup>

with certain foods or with eating in general was more common than heartburn, indigestion or acid reflux, which was found only in 63% of their patients.<sup>35</sup> Aspiration syndrome is another presentation of GER-related cough.<sup>5</sup>

As up to 75% patients with GER-related cough might not have the classic esophageal symptoms of GER, Irwin's group identified a clinical profile (Box 1) that predicts (~91% of the time) when a patient's cough will respond to GER therapy, even when they have no esophageal symptoms.<sup>15</sup> This clinical profile, which is based on a *post-hoc* analysis of four prospective before-and-after intervention studies,<sup>15,18,29,31,34</sup> allows the identification of patients who have a high likelihood of improving on empiric GER therapy without the need for diagnostic testing.

**EMPIRIC GER THERAPY TRIAL AND DIAGNOSTIC WORK-UP**

As no currently available esophageal test identifies patients whose cough will respond to GER therapy, guidelines from the ACCP and the BTS recommend an empiric GER therapy trial to diagnose and treat GER-related cough.<sup>15,26,27</sup> An empiric trial should be considered in chronic cough patients who have esophageal-related symptoms and in those patients who fit the clinical profile outlined in Box 1.<sup>15</sup> The rationale for beginning an empiric trial includes the lack of a specific and sensitive test for the identification of GER-related cough and the high frequency of 'clinically silent' GER.

Diagnostic tests (including inhaled tussigenic challenges, endoscopy, examining bronchoalveolar lavage fluid and/or sputum for lipid laden macrophages, Bernstein test, barium swallow, radioisotope scintiscan, and radionuclide gastric emptying studies with solids) all have inadequate sensitivities and specificities for GER-related cough.<sup>15,33</sup> Even esophageal pH testing, which has a sensitivity of approximately 90%, has limitations in the chronic cough population and has a specificity as low as 66%.<sup>20,29,36</sup>

The single best test to link cough to GER in a cause-and-effect relationship is esophageal pH testing; however, conventionally used diagnostic criteria (percentage time at pH <4) can be misleading. Acid-cough correlation is more important than the total esophageal acid contact time.<sup>15,33</sup> Even temporal correlation of acid with the cough in patients with GER-related cough has positive and negative predictive values of

83% and 90%.<sup>5</sup> The symptom index (SI) and/or the symptom association probability index (SAP) might be more helpful, but further research is needed to determine whether this is the case.<sup>25</sup> Furthermore, weakly acidic and nonacid GER can precipitate cough, and combined esophageal pH and impedance monitoring is required to identify these events.<sup>16,17,37</sup> Esophageal manometry identifies esophageal dysmotility and a hypotensive lower esophageal sphincter. Esophageal pH testing and/or impedance monitoring are very helpful for diagnosis in patients who fail empiric GER therapy.<sup>15</sup>

Compelling evidence for beginning an empiric GER therapy trial before objective esophageal testing comes from Poe and colleagues, who noted that empiric GER therapy successfully diagnosed GER-related cough in 79% of patients in the US.<sup>28</sup> Cough resolution occurred in 86% of patients within 4 weeks of beginning empiric therapy.<sup>28</sup> Furthermore, according to two reports, this initial empiric approach is more cost effective than esophageal testing.<sup>38,39</sup>

Potential candidates for empiric GER therapy include patients who have GER symptoms and cough, and patients who do not have esophageal GER symptoms but who fit the clinical profile described in Box 1. Furthermore, if esophageal testing is performed, patients found to have esophageal dysmotility, those with abnormal esophageal pH test results, or those with cough–esophageal acid correlation on pH testing, should be considered for medical GER therapy.

An empiric trial strategy for GER-related cough is shown in Box 2.<sup>15,23,32,33</sup> The strategy includes both conservative lifestyle modifications and acid suppression with PPIs twice daily. Selected patients with dysphagia or esophageal dysmotility might benefit from taking a prokinetic agent; however, there are no outcomes data for the sole use of these agents in GER-related cough. Cough outcomes should be evaluated at 1 and 3 months. PPIs are recommended for gastric acid suppression, because in trials not using PPIs cough resolution was prolonged—taking up to 179 days.<sup>29</sup> Cough resolution often occurs within 2 weeks of using PPIs, although it can take as long as 53 days in some patients.<sup>40,41</sup> Even if empiric therapy fails, it should not be assumed that GER has been ruled out as a cause of chronic cough.

There are many ways to assess cough outcomes, including visual analog scales, quality of

**Box 2** Possible empiric medical trial for GER-related cough.<sup>15,23,32,33</sup>

#### GER lifestyle modifications

- Weight loss if obese
- Smoking cessation
- Elevate head of bed by 15 cm (6 inches)
- Refrain from eating 2 hours before bedtime
- Avoid a high-fat diet
- Avoid foods that worsen GER (caffeine, carbonated beverages, chocolate, mint, citrus products, alcohol)
- Avoid (if possible) medications that worsen GER (anticholinergics, beta-agonists, bisphosphonates, calcium-channel blockers, corticosteroids, benzodiazepines, estrogens, opiates, progesterone, prostaglandins, theophylline)
- Nasal CPAP if obstructive sleep apnea is present
- Avoid exercise that may increase intra-abdominal pressure

#### Plus

- Twice daily PPIs 30–60 minutes before breakfast and dinner
- Consider adding a prokinetic agent initially if dysphagia is present or if cough does not improve with PPI
- Assess response to therapy within 1–3 months
- Use esophageal testing in nonresponders

Abbreviations: CPAP, continuous positive airway pressure; GER, gastroesophageal reflux.

life scales, cough monitors, or even inhalation cough challenges. The European Respiratory Society has published guidelines for cough assessment.<sup>42</sup> We recommend using a visual analog scale plus a quality of life scale. At least a 50% improvement in cough is considered significant in our experience; however, in some research studies, cough improvement is defined as cough resolution.

There are many reasons why empiric GER therapy might not lead to cough resolution. It is possible that acid GER is not adequately controlled, nonacid GER events are triggering cough, GER treatment duration is inadequate, or coexisting cough causes are not adequately treated, thereby perpetuating the cough–GER cycle.<sup>15,29,32</sup> Furthermore, there

**Table 2** Treatment outcomes with PPIs in GER-related cough.

Investigators	Study design	Number of patients	Intervention	Response rate	Time to cough resolution
Ours <i>et al.</i> <sup>40</sup>	Prospective, double-blind, placebo-controlled	17	Omeprazole 40 mg twice a day for 12 weeks	35%	14 days
Kiljander <i>et al.</i> <sup>19</sup>	Prospective, double-blind, placebo-controlled, crossover	29	Omeprazole 40 mg once a day for 8 weeks	Unknown, cough improved ( $P=0.02$ )	Analyzed at 8 weeks

are case reports showing that omeprazole can itself induce cough:<sup>43</sup> the package insert for Prilosec® (Procter & Gamble, Cincinnati, OH), for example, notes that 1.1% of patients taking omeprazole report cough.<sup>44</sup>

If the empiric GER therapy trial fails and the patient's cough is not improved, then esophageal manometry and pH testing are recommended while the patient remains on GER therapy.<sup>5,15,16,32,33</sup> Monitoring the temporal association between acid and cough events is very important.<sup>5,15,16,32,33</sup> If combined multi-channel esophageal intraluminal impedance and pH testing is available, then this modality is superior to esophageal pH testing alone because it can also evaluate weakly acidic and nonacid GER.<sup>16,17</sup> Again, it is important to correlate cough with esophageal acid and nonacid events.<sup>16,17,37</sup> Esophageal manometry is useful for ensuring the proper placement of ambulatory probes and to identify esophageal dysmotility, especially before considering anti-reflux surgery. It has been suggested that patients who have ineffective peristalsis should avoid surgery.<sup>45</sup> Combined impedance–manometry also has the potential to identify ineffective peristalsis and thereby detect which patients have significant motility problems.<sup>46,47</sup> Reports have, however, found that patients undergoing fundoplication who had esophageal dysmotility had adequate reflux control: dysphagia was no more common than in patients who didn't have esophageal dysmotility.<sup>46,48</sup>

### OTHER THERAPY OUTCOMES

Appropriate GER therapy results in cough improvement or resolution in most patients if the appropriate diagnostic/therapeutic protocol is followed. Many uncontrolled studies report treatment success rates of approximately 75%.<sup>1,2,5</sup>

### Medical trials

So far, there have been only two prospective, double-blind, placebo-controlled trials of PPIs in

patients with GER-related cough (Table 2).<sup>19,40</sup> Although there is significant selection bias present in these studies, cough response was noted in approximately 35% of participants. Ours and colleagues<sup>40</sup> noted that cough resolution took approximately 14 days using omeprazole 40 mg twice daily for 12 weeks. Kiljander and colleagues performed a crossover, placebo-controlled trial<sup>19</sup> and reported cough improvement after 8 weeks of omeprazole 40 mg per day. When interpreting these findings, it is worth noting that there has been some criticism of how the crossover design trial was evaluated (i.e. the statistical analysis).<sup>49,50</sup> Putting that aside, cough improved in 35–57% of patients who received GER therapy.

Chang and colleagues examined the Cochrane Database and noted that GER was a causative factor of cough in up to 41% of patients.<sup>1,2</sup> They performed a meta-analysis of six studies in adults who used a PPI for 2–3 months. There was no difference in cough resolution for patients who received placebo versus a PPI. There was, however, a significant improvement in cough scores for patients who received PPI therapy, with a mean difference of  $-0.41$  [95% CI  $-0.75, -0.07$ ] in crossover trials. The authors noted that there was significant heterogeneity in the study populations included in the six trials and they had insufficient evidence to make any general recommendations, including treatment duration for GER-related cough. It is of note that of the six studies examined, only two (Ours *et al.* and Kiljander *et al.*) included adult patients with cough.<sup>19,40</sup> The other four studies included patients who also had “laryngitis, posterior pharyngolaryngitis, and/or laryngopharyngeal reflux.”<sup>1,2</sup> Furthermore, other common potential causes for chronic cough were not evaluated in these patients. Chang and colleagues concluded that further randomized, controlled, parallel design trials are needed that have a treatment duration of at least 2 months before firm recommendations can be made. It is

**Table 3** Surgical treatment outcomes in GER-related cough.

Investigators	Study design	Number of patients	Response rate
Irwin <i>et al.</i> <sup>51</sup>	Prospective	8	Cough improvement in 100% of patients at 1 year follow-up (medical nonresponders)
Pellegrini <i>et al.</i> <sup>52</sup>	Prospective	5	Cough resolution in 100% of patients (highly selective patients who were thought to be aspirators)
DeMeester <i>et al.</i> <sup>53</sup>	Prospective	17	Cough resolution in 100% of patients with normal esophageal manometry
Giudicelli <i>et al.</i> <sup>54</sup>	Prospective	13	Cough resolution in 85% of patients (highly selected)
Johnson <i>et al.</i> <sup>55</sup>	Prospective	50	Cough resolution in 76% at 3 years
Allen <i>et al.</i> <sup>56</sup>	Prospective	354	Cough improvement based on cough score in 81% of patients at 6 months
So <i>et al.</i> <sup>57</sup>	Prospective	16	Cough resolution or improvement at 1 year in 56% (medical responders might have been included)
Novitsky <i>et al.</i> <sup>58</sup>	Prospective	21	Cough improvement in 86% and complete resolution in 62% of patients at 1 year (medical nonresponders)
Allen <i>et al.</i> <sup>59</sup>	Prospective	528	Cough improvement in 83% at 6 months, 74% at 2 years and 71% of patients at 5 years

also possible that the placebo and time-period effect might influence the favorable response of GER-related cough. For instance, the cough could resolve spontaneously over time because of factors unrelated to GER. Taking the above limitations into consideration, practitioners are encouraged to start empiric treatment as suggested by the ACCP and BTS clinical practice guidelines.<sup>15,26</sup>

### Surgical trials

Until better medical GER therapies become available, surgical fundoplication can also be used to treat patients with GER-related cough, including those who have nonacid reflux.<sup>6,51</sup> The outcomes of prospective trials evaluating surgical treatment for GER-related cough are outlined in Table 3.<sup>51-59</sup>

There is evidence that patients with GER-related cough who respond to GER surgery have heightened cough sensitivity. In nine prospective studies, 586 out of 689 surgically-treated patients (85%) had a significant cough response.<sup>51-59</sup> These studies have design weaknesses, including lack of blinding, lack of controls, use of highly selected patient populations, and different postoperative follow-up evaluations.

Allen and Anvari examined long-term (5-year) cough outcomes in 528 patients who had chronic cough by using a validated cough scale.<sup>59</sup> They noted that at 6 months, 83% of patients had a cough response: 52% had cough

resolution and 31% had cough improvement. At 2 years, 74% of patients had a cough response: 43% had cough resolution and 31% had cough improvement. At 5 years, 71% of patients had a cough response: 36% were cured and 35% improved. This study shows that over a 5-year period there is a decrease in the cough response with GER surgery.

In a report published in 2006, Kaufman and colleagues noted that laparoscopic GER surgery improves airway symptoms in 70% of patients, and typical GER symptoms in 90% of patients.<sup>60</sup> It is important to point out that in the hands of highly experienced surgeons, overall outcomes will be better than in the hands of less experienced surgeons, and that there will be fewer surgical complications.<sup>61</sup>

### LONG-TERM THERAPEUTIC OPTIONS

#### Medical therapy

Although there are outcome data showing that short-term treatment for GER-related cough is efficacious, there are no data examining long-term efficacy.<sup>1,2,5,33</sup> Patients should continue conservative GER therapy on a long-term basis. After cough resolution, the PPI dosing could be reduced from twice daily to once daily, 30 minutes to 1 hour before breakfast.

The superiority of one PPI over another has not been adequately evaluated in patients with GER-related cough. All available PPIs are efficacious, although some have minor physiological

**Table 4** Oral medications for GER-related cough.<sup>69–71</sup>

Medication	Dose (mg)
<b>PPIs</b>	
Omeprazole	20
Omeprazole plus HCO <sub>3</sub>	20 or 40
Esomeprazole	20 or 40
Lansoprazole	30
Pantoprazole	40
Rabeprazole	20
Tenatoprazole <sup>a</sup>	40
<b>H<sub>2</sub>-receptor antagonists</b>	
Cimetidine	400 or 800
Ranitidine	150
Nizatadine	150
Famotidine	20
<b>Prokinetic agents</b>	
Metoclopramide	5 and 10
Baclofen <sup>a</sup>	10 or 20
<b>Potential future agents</b>	
GABA-beta agonists <sup>a</sup>	–
ABT-229 motilin agonist <sup>a</sup>	–
Mosapride (5-HT <sub>4</sub> agonist and 5-HT <sub>3</sub> antagonist) <sup>a</sup>	–
Antigastrin vaccine <sup>a</sup>	–
Soraprazan (potassium-competitive acid blockers) <sup>a</sup>	–
Cholecystokinin-2 receptor antagonists <sup>a</sup>	–

<sup>a</sup>Does not have an FDA indication for GER. Abbreviations: 5-HT<sub>3</sub>, 5-HT<sub>4</sub>; 5-hydroxytryptamine (serotonin) receptors.

advantages. Rabeprazole, for example, has a slightly faster onset, and pantoprazole has the lowest potential for drug interactions. Lansoprazole has the potential for interaction with theophylline, and omeprazole has the highest potential for drug interactions with warfarin, diazepam, and phenytoin.<sup>62</sup>

Although PPIs have been used for almost 20 years, the overall risk–benefit ratio for long-term use is generally good. Long-term PPI use is, however, associated with an increased risk of community-acquired pneumonia and hip fracture.<sup>63,64</sup> Future research will further define these risks. Despite aggressive inhibition of proton pumps, nocturnal gastric acid breakthrough does occur while patients are on PPIs.<sup>65</sup>

The significance of this effect for patients with GER-related cough is unknown.

Some patients can be switched to an H<sub>2</sub>-receptor antagonist; many of these agents are available over the counter. Patients who are taking an H<sub>2</sub>-receptor antagonist also have a 1.63-fold increased risk of pneumonia compared to with patients not taking them.<sup>66</sup> There are no data available on how long medical therapy should continue after cough resolution. Therapy duration should, therefore, be decided on an individual case-by-case basis.

GER is a motility disorder and, interestingly, a large community-based cross-sectional survey published in 2006 reported that there was a significant association, which might be of etiological significance, between chronic cough and irritable bowel syndrome.<sup>4</sup> Currently available prokinetic agents for the treatment of motility disorders unfortunately have significant adverse effects. In GER-related cough, prokinetic agents are used in patients who have dysphagia, esophageal dysmotility and in patients whose cough continues despite treatment with a high-dose (twice daily) PPI.<sup>28,33,34</sup> Prokinetic agents include metoclopramide, erythromycin, domperidone and, previously, cisapride. To date, no clinical study has reported the individual efficacy of any of the prokinetic agents for the treatment of GER-related cough in adults. Metoclopramide, which is usually taken at mealtime and bedtime, has significant nervous system adverse effects, including drowsiness, irritability and extra-pyramidal effects; such extra-pyramidal effects occur in 20–50% of patients.

There are minimal data available on the use of baclofen, a GABA ( $\gamma$ -aminobutyric acid) agonist, in patients with GER-related cough. This drug has the potential to decrease nonacid GER, but also has significant adverse effects, including drowsiness, confusion, dizziness, and fatigue.<sup>67,68</sup> Baclofen dosing should begin at 5 mg three times daily. It should also be noted that baclofen does not have an FDA indication for GER.<sup>69</sup> The medications and potential new agents used for the treatment of GER are shown in Table 4.<sup>69–71</sup>

### Surgical therapy

Surgical fundoplication, performed using open or laparoscopic techniques, can control GER-related cough over a long period of time. Careful cough and esophageal evaluation is

required in patients who have a cough response when given medical GER therapy and who are considering surgery. Allen and colleagues identified predictors of cough response in 354 cough patients.<sup>56</sup> All patients underwent endoscopy, Bernstein test, esophageal manometry with pH testing (pre-operatively), and had to complete a quality of life survey. Predictors of a good cough response included a positive Bernstein test, a higher pre-operative cough symptom score, and a good cough response on PPI therapy.<sup>56</sup> As noted previously, however, the cough response decreases with time over a 5 year period.<sup>59</sup>

At present, fundoplication is the optimal way to control nonacid GER.<sup>16</sup> Esophageal impedance testing, preferably combined with pH testing, is the optimal way to identify patients for whom weakly acidic or nonacid GER is responsible for their cough nonresolution despite aggressive medical GER therapy.<sup>16,17,68</sup> Patients who do not have cough resolution despite aggressive medical GER therapy should be evaluated extensively by a gastroenterologist and a pulmonologist (allergist/respirologist) before considering fundoplication.

### Endoscopic therapy

There are minimal data evaluating endoscopic endoluminal techniques in chronic cough patients.<sup>72</sup> Liu and colleagues evaluated 19 chronic cough patients who had cough despite a minimum of 3 months' acid-suppression therapy.<sup>73</sup> No other causes of cough were identified in these patients. Endoluminal gastroplication (reversible suturing of the gastroesophageal junction) resulted in short-term (within 6 months) cough resolution in 17 patients. Long-term success was less favorable—seven patients who had short-term cough resolution developed recurrent symptoms 1–3 years after the procedure. Endoscopic therapy for GER-related cough is considered experimental and is, therefore, not recommended at this time.<sup>33,73</sup>

### POTENTIAL PITFALLS WHEN TREATING GER-RELATED COUGH

Management of chronic cough patients is difficult and requires an integrative diagnostic approach. Even with careful assessment and appropriate management, vigilance is required to avoid the potential pitfalls in treating GER-related cough, such as the failure to recognize and treat coexisting causes of cough or the

#### Box 3 Potential pitfalls in therapy of GER-related cough.<sup>32,33,74</sup>

- Failure to recognize and treat coexisting causes of cough
- Failure to recognize that GER can be 'clinically silent'
- Inadequate duration of GER treatment
- Failure to recognize GER treatment failures
  - Inadequate control of acid GER
  - Presence of nonacid GER
- Inadequate esophageal investigation if empiric medical GER-therapy trial fails
- PPIs may induce cough

failure to treat patients with GER therapy for an adequate length of time. All of the known potential pitfalls are noted in Box 3;<sup>32,33,74</sup> avoiding them is crucial for the long-term management of GER-related cough.<sup>32,33,74</sup>

### CONCLUSIONS

Long-term medical therapy with lifestyle modifications remains the primary therapy for patients with GER-related cough. Most patients require long-term PPI therapy, although the PPI dosing can often be tapered to once daily. Some patients' symptoms can be controlled with H<sub>2</sub>-receptor antagonists. As they have significant adverse effects, prokinetic agents are used only in combination with PPIs in difficult-to-treat patients, especially those who have esophageal dysmotility.

Surgical fundoplication is reserved for patients who desire surgical therapy after extensive evaluation or patients who have continued cough and acid and/or weakly acidic and/or nonacid reflux despite receiving the maximum medical GER therapy. Careful evaluation of GER, esophageal function, and identification and treatment of other potential cough causes are recommended before considering surgery in GER-therapy nonresponders. Endoscopic GER therapies are considered experimental for the treatment of GER-related cough.

Although GER-related cough generally has a good outcome in most patients, GER is a chronic disease and cough might return when GER medications are decreased or stopped. Episodic and prolonged GER therapy, including surgical interventions, might, therefore, be required.

## KEY POINTS

- There are more than 30 causes of chronic cough (cough lasting for >8 weeks), and more than one cause is present in 8–75% of cases
- GER is the second most common cause of chronic cough when GER-related cough is defined as a cough that is improved or resolved by GER therapy; nonacid or weakly acidic GER can elicit cough
- Up to 75% of patients with GER-related cough have no esophageal GER symptoms, but it is still possible to predict the presence of GER-related cough. An empiric trial of conservative measures plus twice-daily PPIs for 3 months can successfully identify and treat GER-related cough in approximately 80% of patients; GER-related cough can take more than 3 months to improve even with aggressive medical GER therapy
- Esophageal diagnostic testing is recommended if an empiric therapy trial fails and should include esophageal manometry, pH monitoring and impedance monitoring, if available, while maintaining GER therapy
- Surgical fundoplication can be considered in selected patients who desire surgical therapy and who respond to medical therapy after a comprehensive evaluation, or in patients with documented nonacid reflux who do not respond to medical therapy

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SM Harding has declared associations with the following companies/organizations: AstraZeneca LP, National Institutes of Health (NHLBI). See the article online for full details of the relationship. KMD Chandra declared no competing interests.