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Chronic Cough: A Gastroenterology Perspective

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Abstract

Purpose of review—The purpose of this review is to highlight recent work and provide recommendations on the approach for diagnosis and management of chronic cough in a gastroenterology clinic.

Recent findings—Chronic cough is a burdensome symptom affecting a large number of patients and contributes significant cost to the healthcare system. Recent work has shown that select patients may benefit from acid suppressive therapy and even surgery when there is true pathologic evidence of reflux disease with cough. However, judicious use and proper interpretation of diagnostic testing for gastroesophageal reflux in the setting of cough is important to avoid unnecessary or inappropriate therapy.

Summary—Chronic cough remains a vexing problem for many physicians, including gastroenterologists. It is important that physicians approach refractory cough in a multi-disciplinary manner. Future research is needed to better understand the likely central hypersensitivity response mediating reflux related cough and potential alternative approaches to therapy.

Keywords

gastroesophageal reflux disease; extra-esophageal symptoms; multi-channel intraluminal pH impedance

Introduction

Chronic cough, defined as cough lasting for more than 8 weeks, affects 11–20% of patients presenting to ambulatory care.¹ The incidence is likely lower in Asian countries as one recent study estimated that 4.6% of cases were due to gastroesophageal reflux disease (GERD).² Interestingly, patients with cough attributed to GERD had the longest duration of symptoms prior to diagnosis (median of 48 months compared to 12 for all other causes).

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Although prevalence estimates overall are lower than those of traditional GERD, a recent single center study of 281 patients with extra-esophageal manifestations of GERD, of which 50% had cough, estimated that the direct cost of treating patients was 5.6 times higher than patients with typical GERD symptoms.³ The authors further estimated that the US national annual economic burden of extraesophageal reflux was ~\$50 billion compared to \$9 billion for “typical” GERD, mainly attributable to inappropriate overuse of proton pump inhibitor therapy.³

Many patients with chronic cough will have seen multiple physicians including primary care, allergy, otolaryngology, and pulmonary specialists prior to referral to gastroenterology. The gastroenterologist is then faced with challenging diagnostic and management issues for a chronic symptom in which multiple other causes have (or should have) been ruled out. The purpose of this review is to highlight recent work and provide recommendations on the approach for diagnosis and management of chronic cough in a gastroenterology clinic.

Pathophysiology of reflux related cough

One traditional view is that reflux related cough occurs via micro-aspiration events from the esophagus into the bronchial tree. This view has been challenged with work evaluating the temporal association of cough and reflux, using both multichannel intraluminal impedance pH monitoring (MII-pH) and acoustic monitoring of cough events.⁴ Smith and colleagues elegantly showed that cough was temporally associated with preceding reflux but that there was no difference in reflux events or esophagitis in patients with positive and negative symptom association probabilities (SAP).⁴ In addition, there were a similar number of patients with cough preceding reflux, suggesting a “perpetuating” cycle of cough-reflux events. This study provided some of the strongest data to date that chronic cough attributed to reflux disease is likely a centrally mediated process, in which the cough reflux becomes “hypersensitive” to stimuli such as esophageal reflux. Of note, esophageal reflux monitoring did not record many cough events identified by acoustic monitoring.

Grabowski et al. recently evaluated airway inflammatory markers from induced sputum in patients with chronic cough attributed to GERD.⁵ Of note, patients were allowed to be on a PPI at time of initial sputum collection and patients not on an initial PPI were then treated with omeprazole 40mg daily for 4 weeks. There was ultimately no difference in sputum differential cell counts of the 41 patients enrolled (21 cases, 20 controls). However they did find higher sputum MCP-1 levels in patients with chronic cough and increased sputum TSLP levels, most likely produced by airway epithelial cells, as a consequence of direct mechanical stress or reflex-induced epithelial nerve stimulation. They also concluded that T cell cytokines probably do not play a major role in airway inflammation (via microaspiration) which indirectly supports the hypothesis that the majority of chronic cough associated with GERD is likely mediated by a central process.

Approach to diagnosis in gastroenterology

Before cough can be attributed to GERD, other cardiopulmonary, infectious, and allergic causes should be ruled out. Patients should undergo spirometry, a bronchial provocation test, imaging, and bronchoscopy prior to referral to gastroenterology. If there are seasonal or

other suspected allergic triggers, treatment with anti-histamine and/or nasal steroids may be appropriate in concert with an allergy evaluation. If these measures do not help, the gastroenterologist is faced with the choice of empirical treatment with acid suppressive therapy or further diagnostic testing for GERD. Our proposed clinical algorithm is shown in Figure 1. A careful history is obviously important and it may be useful to incorporate validated questionnaires at the initial evaluation. Morice and colleagues developed the Hull Airway Reflux Questionnaire (HARQ) for the diagnosis of cough hypersensitivity syndrome,⁶ although it does not differentiate reflux related cough from other causes.⁷ A Japanese group evaluated the association of patient reported triggers with cough, including GERD induced symptoms.⁸ Of 194 patients, only 19 had GERD as defined by questionnaire scores (Frequency Scale for Symptoms of GERD and QUEST – questionnaire for the diagnosis of reflux disease). These patients were more likely to report “spices” and “meals” as triggering cough and higher questionnaire scores were independently associated with cough symptoms.

Research suggests that patients with chronic cough may be effectively managed using a simple clinical algorithm relying on few diagnostic tests (CXR and spirometry) and empiric therapy based on related symptoms (bronchodilators vs. anti-histamine vs. proton pump inhibitor).⁹ Of 112 consecutive patients, 81 (72%) were effectively managed using only a clinical protocol including 19 (37.3%) with proton pump inhibitor therapy. The authors argue that this approach would obviate the need for most specialist referrals and advanced diagnostic testing.⁹

A Japanese group also evaluated a systematic approach to chronic cough using response to medical therapy to classify patients.¹⁰ They classified GERD related cough as cough responding to 14 days of rabeprazole therapy after not responding to an initial course of inhaled corticosteroid, followed by clarithromycin and carbocysteine if there was lack of response. Further non-responders were treated with a rabeprazole and ultimately a total of 12 of 184 patients were found to have GERD related cough. This data reiterates that the vast majority of patients with cough do not likely have GERD, which is important to keep in mind before interpreting diagnostic testing results, as discussed below.¹⁰

Acid suppressive therapy to control chronic cough

Approximately 30–50% of patients with cough secondary to GERD will not respond to PPI therapy and this may not necessarily correlate with diagnostic testing results. Kawamura et al. recently studied 10 patients with cough symptoms responsive to PPI therapy and compared MII-pH testing results to 10 normal controls and 10 patients with GERD without aerodigestive symptoms.¹¹ They evaluated pharyngeal reflux events in all patients and found no difference in the number events; also no liquid events were observed in any patients. They did observe a greater number of weakly acidic gas pharyngeal reflux events in patients with cough.

In a recent systematic analysis of published data, Kahrilas and co-authors identified 9 studies that rigorously evaluated the effect of acid suppressive therapy on chronic cough symptoms (8 with proton pump inhibitors and 1 with histamine type-2 receptor

antagonists).¹² They found that there was evidence of therapeutic response (for proton pump inhibitors only) in 2 trials, although only in the first period of crossover study designs. Also, the overall therapeutic gain from 5 datasets was 24.1%, but this was mainly seen in patients with pathologic evidence of esophageal acid exposure.¹² This data is shown in Figure 2 (with permission) and suggests that there may be a small therapeutic benefit of acid suppression in patients with chronic cough. However, practitioners should likely select patients based on physiologic evidence of esophageal reflux for the best chance of improving patient outcomes.

Diagnostic testing for cough associated with GERD

As most patients will have likely been started on a proton pump inhibitor prior to gastroenterology consultation, we would recommend diagnostic testing, albeit with a limited systematic approach in assessing chronic cough (Figure 1). We have recently reviewed the appropriate use of ambulatory reflux monitoring in diagnosing GERD.¹³ In the case of chronic cough, it is important to ensure that other causes have been ruled out and that laryngoscopy is performed to rule out oropharyngeal and laryngeal structural causes. At this point, the gastroenterologist should decide if an upper endoscopy is warranted based on the presence of warning signs or symptoms.¹⁴ If endoscopy is normal or not indicated, it is then reasonable to empirically treat and evaluate for true PPI non-response for a limited time period. However, PPIs should not be continued indefinitely¹⁵ and ultimately stopped if the cough does not improve, especially in the absence of any classic reflux symptoms such as heartburn, acid taste in the mouth, or regurgitation.

Ambulatory reflux monitoring

A recent Chinese study evaluated the use of MII-pH monitoring in patients with typical and atypical symptoms attributed to reflux, including cough.¹⁶ They concluded that chronic cough patients had a higher De-Meester score, percentage of acid exposure time, acid bolus exposure % time, distal acid reflux episodes, and proximal acid reflux episodes ($p=0.030$) than subjects without chronic cough. However, a major limitation of their study is that they did not report symptom association probabilities or symptom indices, thus the grouping of patients was only based on an initial symptom survey. Also, the population was heterogeneous and it is difficult to draw conclusions on the utility of pH monitoring for only chronic cough patients.

Oropharyngeal pH monitoring using a Restech® Dx-pH catheter has been developed to aid in the diagnosis of extra-esophageal symptoms such as cough, although there is lack of strong evidence that physiologic parameters correlate with symptoms. Ummarino et al. recently determined and compared oropharyngeal pH measurements using the Restech device and upper esophageal sphincter reflux events with MII-pH monitoring in 10 patients off acid suppressive therapy.¹⁷ They found that of 515 total reflux episodes identified by MII-pH, only 3 were recorded simultaneously by the Restech Dx-pH probe. Symptom association was very poor and 17 of 39 total events (43.5%) detected by the Dx-pH probe were actually swallow events as determined by MII-pH. Overall, the authors conclude (and we agree) that transnasal pH monitoring cannot be recommended for diagnosing cough related reflux.

Based on existing data, we do believe that limited ambulatory reflux monitoring is reasonable in patients who have not responded to a short trial of PPI for chronic cough (Figure 1). Most patients with cough will not have GERD, and thus the pre-test probability is low especially with lack of classic GERD symptoms. Thus, pH testing should be performed off PPI therapy.¹³ A normal test in this setting effectively rules out GERD and should limit further empiric use of medical and surgical GERD treatment which is unlikely to benefit the patient.

High resolution manometry

Vardar and colleagues retrospectively evaluated pharyngeal and esophageal motility using high-resolution manometry in patients with chronic cough.¹⁸ A total of 34 patients were included with both negative and positive symptom association probabilities as determined by pH testing. Ultimately, manometric parameters were highly variable across their patient sample and a minority of patients had pathologic upper esophageal sphincter dysfunction (n=9); only one patient had esophageal dysmotility. Based on this data, manometry should not be a first-line test but could be considered for very refractory cases in which an etiology remains elusive.

Biomarkers

There is growing interest in the use of alternative biomarkers for reflux associated cough such as pepsin levels and lipid-laden alveolar macrophages.^{19–21} However, a recent study in children determined that pepsin levels in the lung for predicting reflux disease (by pH or pH-MII) had a PPV of only 50% and NPV of 71%.²¹ Pepsin levels in the lung only weakly correlated with non-acid reflux burden and did not correlate with any other reflux parameters.²¹ Another recent study found that pepsin levels were similar in patients with and without cough.²⁰ At this time, the routine use of pepsin levels to diagnose cough related reflux cannot be recommended and the search for biomarkers with adequate sensitivity and specificity remains elusive.

Other therapeutic options

As hypersensitivity to stimuli (reflux) is thought to contribute to chronic cough, neuromodulating agents (e.g. amitriptyline, gabapentin, baclofen) have been investigated as treatment agents. Canning et al. recently evaluated the effect of lesogabaran, a GABA_B receptor agonist, in guinea pigs with citric acid induced cough.²² They reported that both lesogabaran and baclofen reduced coughing in a dose dependant fashion, but lesogabaran did not affect the respiratory rate. In humans, Xu et al. recently reported a small case series of 3 patients with chronic cough who responded to baclofen.²³ However, the data to date supporting neuromodulator agents for chronic cough was systematically analyzed with data from 8 studies (2 randomized controlled trials) that had significant methodological limitations. The studies did report varying levels of response, but the current evidence is mainly hypothesis generating and should be used to design more rigorous trials with strict patient inclusion criteria.

If baclofen is used off label for refractory cough symptoms we would recommend starting at the lowest possible dose (5mg) daily then increasing to three times daily over 3 days. If no response is seen, another increase over 3 days up to 10mg TID is reasonable. We would then recommend assessing the patient via telephone or in person at this time (after 1 week) for response to treatment. Similarly, if gabapentin is prescribed we would also recommend starting at the lowest available dose and assessing response in a timely manner (within 1–2 weeks).

Surgical therapy

If a patient is deemed to truly have refractory cough related to reflux disease, surgical therapy may be an option. Faruqi et al. recently reviewed outcomes of patients who underwent fundoplication for a diagnosis of reflux related cough.²⁴ Over 6 years, they identified 47 patients who had a Nissen fundoplication and mailed a survey regarding symptoms. Short term improvement of cough was seen in 30 patients (30%) and complete response in 21 patients (45%). Similar data was seen in a recent single US center review of patients who had pH-impedance testing.²⁵ A total of 49 out of 314 patients (15.6%) with testing had chronic cough; 36 of the 49 were identified as having abnormal proximal acid exposure. Ultimately, 16 of these patients had anti-reflux surgery with 13 (81%) having resolution of the cough. These studies should not be taken as direct evidence that cough responds to fundoplication. Rather, similar to PPI responsiveness, in a select group of patients where fundoplication is deemed appropriate for reflux disease, chronic cough may also show improvement. There does not appear to be difference in surgery as the proportion of patients with chronic cough improvement did not differ in a study comparing outcomes of laparoscopic Nissen fundoplication and Toupet fundoplication.²⁶

Conclusions

Chronic cough remains a burdensome symptom both at the patient and healthcare system level. Select patients may benefit from acid suppressive therapy and even surgery when there is pathologic evidence of reflux disease. However, the value of a negative diagnostic test for gastroesophageal reflux should not be underestimated as this could provide reassurance and avoidance of long term PPI use and repeated unnecessary diagnostic testing. Future research is needed to better understand the likely central hypersensitivity response mediating reflux related cough and alternative approaches to therapy that may modulate this process. Trials assessing behavioral and psychologic therapies (cognitive behavioral therapy and hypnosis) to treat cough hypersensitivity are needed as these approaches have recently been shown to be effective in other GI disorders with suspected components of central pathophysiology.^{27–32} Ultimately, the gastroenterologist can play a key role in supporting a systematic, multi-disciplinary approach to refractory cough that judiciously utilizes diagnostic testing and treatment strategies.

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Abbreviations

GERD	gastroesophageal reflux disease
PPI	proton pump inhibitor
H2RA	Histamine-2 Receptor Antagonists
MII-pH	multichannel intraluminal impedance pH monitoring

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patients with chronic cough do not respond to acid suppressive therapy. However, clinicians should be mindful that the most likely benefit will be seen in those patients with pathologic evidence of reflux disease. This fits well with our proposed clinical algorithm that advocates for the systematic use of pH monitoring for GERD.

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Summary points

1. Chronic refractory cough is likely a central mediated process, in which the cough reflex becomes “hypersensitive” to a variety of stimuli such as esophageal reflux.
2. For chronic cough, it is reasonable to empirically treat and evaluate for true PPI response for a limited time period, but PPIs should not be continued indefinitely without follow-up.
3. Expedited diagnostic testing (ambulatory pH and pH-impedance monitoring) may help rule out reflux disease, especially in those patients without classic reflux symptoms.
4. It is critical that gastroenterologists and other physicians approach refractory cough communicate in a multi-disciplinary manner as this will limit unnecessary testing and expedite therapeutic approaches.

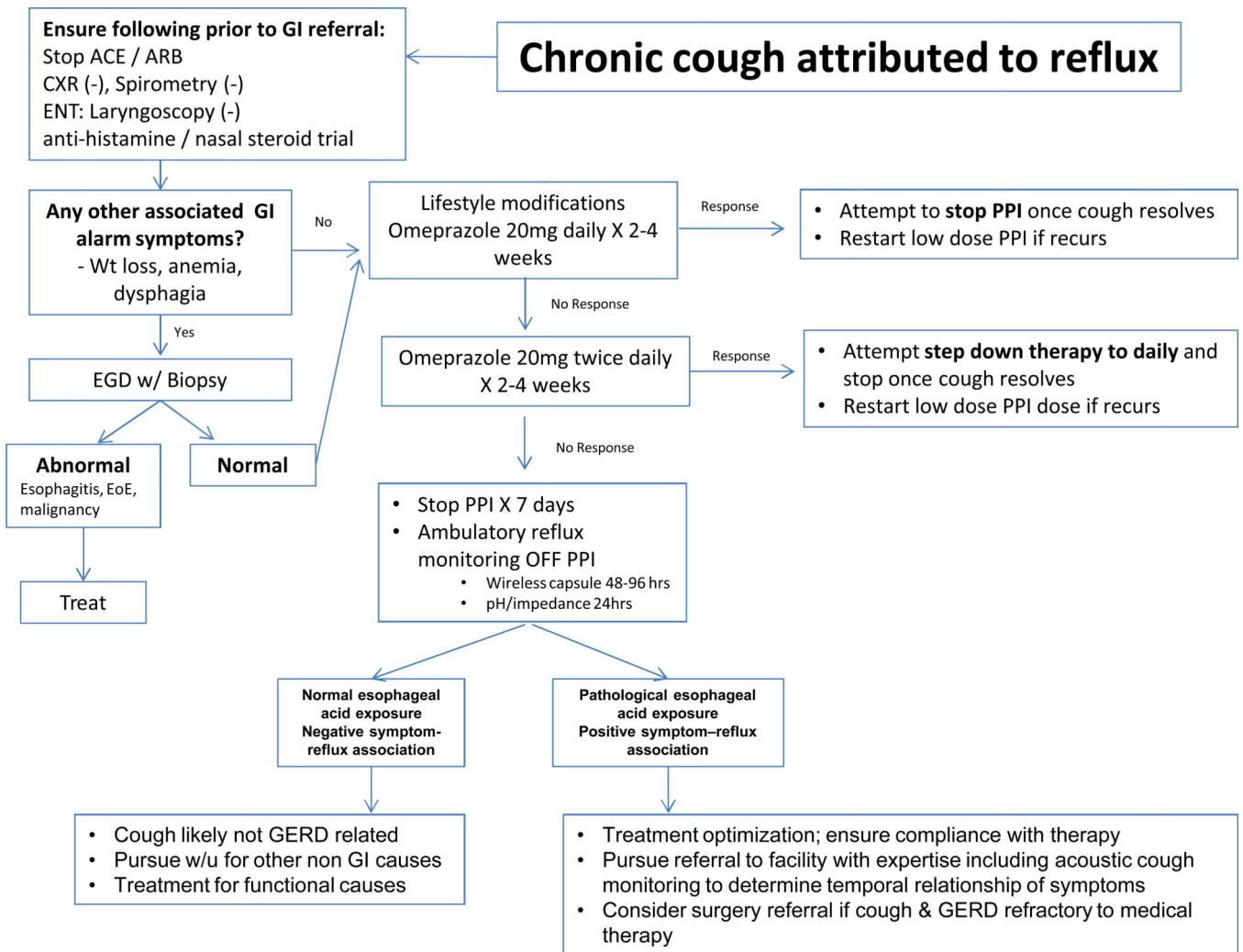


Figure 1.
 Diagnostic algorithm for chronic cough attributed to gastroesophageal reflux disease

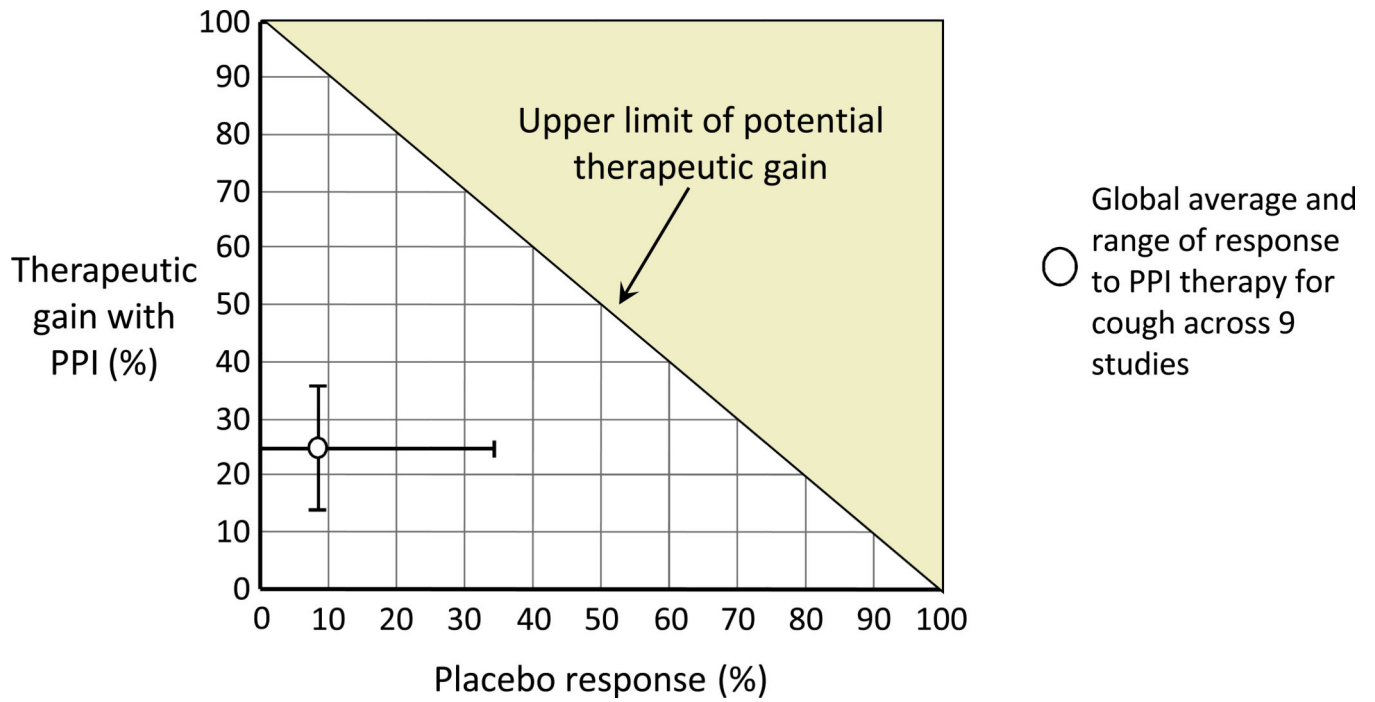


Figure 2. Overall average and range of therapeutic gain in cough patients treated with PPI therapy based on datasets from 9 studies (Reproduced with permission from [12])