

Diagnosis and Treatment of the Extraesophageal Manifestations of Gastroesophageal Reflux Disease

Feroze Sidhwa, MD, MPH, Alessandra Moore, MD, Elaine Alligood, MLS, and Piero Marco Fisichella, MD, MBA

Objective: To review the clinical presentation, diagnosis, and treatment options available for management of extraesophageal manifestations of gastroesophageal reflux disease (GERD) and to compare the most recent technological advances to the existing guidelines.

Summary Background Data: Extraesophageal manifestations of GERD include cough, laryngopharyngeal reflux (LPR), and asthma. Recent advances in diagnostic modalities may have outpaced the existing diagnostic and therapeutic clinical guidelines.

Methods: We searched the MEDLINE, Cochrane, and Embase databases for articles pertaining to the presentation, diagnosis, and treatment of extraesophageal manifestations of reflux, specifically cough due to reflux, LPR, and asthma due to reflux. Search terms applied to 3 thematic topics: diagnosis, medical treatment, and surgical treatment. We had searched the bibliographies of included studies, yielding a total of 271 articles for full review. We graded the level of evidence and classified recommendations by size of treatment effect, according to the guidelines from the American Heart Association Task Force on Practice Guidelines.

Results: One hundred twenty-eight articles met criteria for analysis. Our findings show that the diagnosis of cough, LPR, or asthma due to gastroesophageal reflux is difficult, as no criterion standard test exists. Also, patients often present without heartburn or regurgitation typical of GERD. Combined multichannel intraluminal impedance, the pH (MII-pH) monitoring system, and the symptom association probability (SAP) test might distinguish extraesophageal manifestations of reflux from idiopathic chronic cough, laryngitis due to other causes, and atopic asthma. In addition, extraesophageal manifestations of reflux are most effectively diagnosed with a stepwise approach incorporating empiric treatment and antisecretory therapy, combined MII-pH monitoring, and surgical intervention in few selected cases.

Conclusions: Recent studies demonstrate the potential diagnostic role of MII-pH monitoring. Surgical intervention provides resolution of extraesophageal symptoms less reliably than typical symptoms when the patient has GERD.

Keywords: asthma, cough, gastroesophageal reflux disease, laryngopharyngeal reflux

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Extraesophageal manifestations of gastroesophageal reflux disease (GERD) include cough, laryngopharyngeal reflux (LPR), and asthma. Both GERD and its extraesophageal manifestations are

prevalent in clinical practice. In population-based studies, 19.8% of North Americans complain of typical symptoms of GERD (heartburn and regurgitation) at least weekly.^{1,2} Also in the late 1990s, GERD accounted for \$9.3 to \$12.1 billion in direct annual healthcare costs in the United States, higher than any other digestive disease. As a result, acid-suppressive agents were the leading pharmaceutical expenditure in the United States. The prevalence of GERD in the primary care setting becomes even more evident when one considers that, in the United States, 4.6 million office encounters annually are primarily for GERD, whereas 9.1 million encounters include GERD in the top 3 diagnoses for the encounter. GERD is also the most frequently first-listed gastrointestinal diagnosis in ambulatory care visits.^{1,2}

Extraesophageal manifestations of reflux have been estimated to cost \$5438 per patient in direct medical expenses in the first year after presentation and \$13,700 for 5 years. Estimates of the economic burden of extraesophageal reflux have shown that expenditures for extraesophageal manifestations of reflux could surpass \$50 billion, 86% of which could be attributable to pharmaceutical costs.² In addition, the National Health Care Survey carried out by the Center for Disease Control and Prevention has demonstrated that the chief complaint for primary care patient visits was cough in 6.1%, throat symptoms in 4%, and asthma in 2.8%.³ Within these visits for cough, asthma, and throat symptoms are contained the hidden prevalence of extraesophageal manifestations of GERD, which to date have not been adequately addressed from a medical or surgical perspective due to their obscurity.

Distinguishing whether cough, LPR, and asthma are caused by GERD remains challenging for both the primary care physician and the specialist. This distinction is important because treatment of GERD with the intent of improving or curing extraesophageal manifestation can be ineffective. This review summarizes the current literature on extraesophageal manifestations of reflux to assist in clinical decision making.

METHODS

We addressed 3 key questions: (1) How are extraesophageal manifestations of reflux diagnosed? (2) What is the effect of medical therapy? and (3) What is the effect of surgical therapy? We performed a systematic review of the MEDLINE, Cochran, and Embase databases, using separate search items for each of the 3 key questions (eAppendix, <http://links.lww.com/SLA/B57>). We limited searches to English-language articles reporting results from adults. We combined all articles into a single list and we excluded duplicates, resulting in 1411 abstracts for review. We reviewed abstracts and excluded commentary or opinion pieces, review articles that reported data included in other selected references, and articles containing primary data duplicated in other works. We supplemented our automated search by manually searching for additional references from the bibliographies of included studies, yielding 271 articles for review. We reviewed the studies selected for inclusion according to guidelines from Preferred Reporting Items for Systematic Reviews and Meta-Analyses.⁴ We graded the level of evidence and classified

From the VA Boston Healthcare System, Boston, MA; Brigham and Women's Hospital, Harvard Medical School, Boston MA; and Boston University Medical Center, Boston, MA.

Reprints: Piero Marco Fisichella, MD, MBA, FACS, VA Boston Healthcare System, Brigham and Women's Hospital, Harvard Medical School, Boston MA 1400 Veterans of Foreign Wars Pkwy, West Roxbury, MA 02132. E-mail: piero.fisichella@va.gov.

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recommendations by size of treatment effect, according to the guidelines from the American Heart Association Task Force on Practice Guidelines.⁵ We compared the resulting recommendations with those of the most comprehensive recent clinical practice guidelines on the management of extraesophageal manifestations of reflux. Ultimately, we selected 128 articles.

Clinical Presentation

Extraesophageal manifestations of GERD include cough, LPR, and asthma. Chronic cough due to reflux is caused by gastric refluxate irritating the larynx and activating the afferent limb of the cough reflex. This is typically caused by direct irritation of the tracheobronchial tree after aspiration of gastric contents into the airway, or by stimulating an esophageal-bronchial neural cough reflex. Most studies define chronic a cough lasting more than 8 weeks.⁶

LPR results from reflux of gastric contents beyond the upper esophageal sphincter and onto the tissues of the laryngopharynx, triggering chronic laryngitis, or laryngopharyngitis. As in chronic laryngopharyngitis caused by other insults, patients often complain of chronic throat clearing, globus sensation, cough, throat pain, and/or vocal changes, especially hoarseness.⁷

Asthma due to reflux might be induced by reflux of gastric contents into the tracheobronchial tree, causing direct irritation and bronchoconstriction. Alternatively, it might be caused by reflux of gastric contents into the esophagus, activating a neural reflex arc through the vagus nerve that leads to bronchoconstriction. As with asthma due to other causes, patients typically complain of wheezing and/or shortness of breath.⁸

Patients presenting with extraesophageal manifestations of GERD often present without typical GERD symptoms (heartburn and regurgitation), which challenges the clinician's ability to identify the cause of the patient's complaint and risks misdiagnosis.

DIAGNOSIS

Cough

There is no criterion standard for diagnosing cough due to reflux.⁹ Investigators have, however, used different methods to link chronic cough to reflux. Empiric therapy with antisecretory drugs over 8 to 16 weeks has been the traditional method used to distinguish cough due to reflux.^{10,11} Recurrence of cough upon discontinuation of therapy has also been used for diagnosis.¹² These diagnostic modalities have some drawbacks. First, antisecretory therapy may allow pharyngolaryngeal tissues to heal and resist activation of the cough reflex despite ongoing reflux. Second, the placebo effect in all related trials is large and variable. In fact, in RCTs that included a placebo arm, outcomes improved 1% to 34% in the placebo groups, and these improvements often met statistical significance.^{13,14} Other diagnostic have included pathological reflux discovered with esophageal pH-monitoring or combined multi-channel intraluminal impedance and pH (MII-pH) monitoring, esophageal dysmotility on esophageal manometry, or erosive esophagitis on esophagoscopy in patients with chronic cough.^{10,15,16} The finding of abnormal esophageal acid exposure in a patient with chronic cough, however, does not necessarily indicate that the cough is due to reflux. Therefore, to study the association and draw inferences on causality between chronic cough and reflux, investigators have evaluated combining esophageal (or pharyngoesophageal) pH-monitoring and MII-pH monitoring—a technique that can detect non-acid reflux—with a method of statistical analysis known as symptom association probability (SAP). SAP analysis consists in conducting a Fisher exact test of association between reflux events

(measured by the intraluminal pH or MII-pH monitor) and cough (which is usually self-reported). If a cough event is recorded within 2 minutes of a reflux event, then the 2 are considered associated and the Fisher exact test for association between cough and reflux may confirm their association. SAP has been shown to be more sensitive to detect cough due to reflux than other indexes, such as the symptom index and symptom sensitivity index.^{16,17} Positive SAP on esophageal pH monitoring showed in 1 study to be the only statistically significant predictor of response to antisecretory therapy, with a sensitivity, specificity, positive predictive value, and negative predictive value of 0.47, 0.82, 0.28, and 0.72, respectively.¹⁸ Using MII-pH monitoring, another study showed that those with chronic cough without typical GERD symptoms and normal pH monitoring were SAP positive 44% of the time, 75% of which from non-acidic or weakly acidic reflux.⁹

Attempts to prove a statistical association between cough episodes and esophageal reflux episodes to distinguish cough due to reflux has been complicated by the way cough is recorded. Patients record their symptoms using a symptom button on a monitoring device and/or in a symptom diary, so recording delays might be substantial. In fact, when patient reporting and concurrent recording of cough bursts on esophageal manometry are examined concurrently, Sifrim et al⁹ demonstrated that only 39% of cough bursts recorded by manometry were reported by patients, and with an average delay of 28 seconds. These delays and lost data might increase the false-negative rate of SAP testing.

Laryngopharyngeal Reflux

The diagnosis of LPR is equally challenging. Patients who present with symptoms of laryngitis, in whom other common causes, such as smoking, alcohol, industrial exposures, or chronic cough, have been ruled out, are usually started on an empiric trial of proton-pump inhibitors (PPIs). If symptoms fail to resolve after 8 to 12 weeks, one might consider the possibility of LPR caused by non- or weakly acidic reflux, or other organic or functional disorders.

As for cough, there is no criterion standard for diagnosing LPR. Diagnostic test include the response to antisecretory therapy, which is limited by a 40% placebo effect. Nevertheless, introducing the Reflux Symptom Index and the Reflux Finding Score (which incorporate symptoms of LPR and GERD) into clinical diagnosis has improved the diagnostic yield by 16% to 32% in the placebo arms of randomized controlled trials.^{19–21} Esophageal and oropharyngeal pH monitoring have also been used as a diagnostic tool. Their use is, however, problematic because of the unclear role of non-acid or weakly acidic refluxate on pharyngolaryngeal tissues.^{22–24} In addition to these methods, symptoms suggesting LPR, the finding of laryngitis on laryngoscopy, and the presence of esophagitis on endoscopy or in esophageal mucosal biopsies have been used to diagnose LPR.^{23,25} This methodology is potentially too restrictive, as patients without esophagitis may still have laryngitis caused by reflux as the tissues of the larynx may not be as resilient as the esophagus to exposure to gastric contents. By using these reference standards, many patients with LPR would be classified as not having LPR and the negative effects on the specificity and the positive predictive value of the diagnostic tests might be significant.

Asthma

The diagnosis of asthma due to reflux is complicated by the nonspecific nature of the presenting complaints and the lack of a standard diagnostic test. Two methods have been used to link asthma to reflux: the presence of symptoms of asthma in those with GERD on esophageal pH monitoring,²⁶ and the response of symptoms of asthma and/or pulmonary function tests to antisecretory therapy.²⁷

These reference standards might have excluded those with non- or weakly acid reflux as not having asthma due to reflux.

TREATMENT

Cough

Four randomized controlled trials have found no significant difference between PPIs and placebo groups in relieving cough due to reflux^{13,14,28,29} (Table 1; eAppendix, <http://links.lww.com/SLA/B57>). We, however, point out that a large numbers of patients who might not have had cough due to reflux might have been enrolled in these trials, biasing the trials toward type II error. In addition, inclusion and exclusion criteria and outcomes varied between studies, making comparisons and meta-analysis difficult and inconclusive.

The surgical treatment of cough due to reflux is hampered by many of the same problems discussed for medical therapy and the difficulty of performing blinded, placebo-controlled trials. Observational studies varied in patient selection and the definition of outcomes measured.^{30–38} With these limitations, most studies reported success rates of 65% to 74%.^{32,34,39,40} Patients who are more likely to report resolution of symptoms are those with concomitant typical GERD symptoms or positive esophageal pH monitoring.⁴¹ The use of MII-pH monitoring in patients on bid PPI therapy has been limited but has shown that in patients with a positive non-acid symptom index for cough, antireflux surgery can achieve complete resolution of cough.⁴²

Laryngopharyngeal Reflux

Nine randomized trials have evaluated the efficacy of antisecretory therapy, primarily twice-daily PPIs, on LPR. These studies were relatively small, ranging in sample size from 14 to 145 subjects, and enrolled patients based on a varied combination of symptoms and laryngoscopic findings (Table 1; eAppendix, <http://links.lww.com/SLA/B57>). Six trials found no difference between treatment and placebo groups,^{19,21,43–46} whereas 3 trials reported statistically significant results.^{20,47,48} Again, the difference in results might be explained by the placebo effect and the varied patient inclusion criteria.

No randomized controlled trials have compared medical and surgical intervention for LPR and only few small observational studies have been published.^{33,49} It is important to note that, as with other extraesophageal manifestation of GERD, patients who are more likely to report resolution of symptoms (up to 72% of cases) are those with concomitant typical GERD symptoms and positive esophageal pH monitoring.^{49,50}

Asthma

Nine randomized trials evaluated the effect of medical treatment of GERD on asthma due to reflux. Six randomized trials enrolled patients based on some combination of asthma and GERD.^{51–56} Most studies reported changes in self-reported asthma symptoms and/or asthma-related quality of life indexes,^{51–55,57,58} and some reported differences in rescue bronchodilator use^{51,52,54,55} or in unscheduled healthcare visits for asthma^{52,58} (Table 1; eAppendix, <http://links.lww.com/SLA/B57>).

Among the 3 randomized trials that enrolled patients with both asthma and GERD, all reported greater improvement in the treatment than the placebo (or no treatment) groups. The differences in outcomes, however, varied. Kiljander et al found significant improvement in morning peak expiratory flow (PEF), forced expiratory volume in 1 second (FEV₁), and the Asthma Quality of Life Questionnaire in subjects treated with esomeprazole 40 mg QD or BID compared with placebo. They, however, found no difference in

changes in evening PEF, time to asthma exacerbation, number of severe asthma exacerbations, use of rescue inhalers, or asthma-free days.⁵¹ Sharma et al⁵² found greater improvement in mean daytime asthma symptom scores, mean nighttime asthma symptom scores, rescue inhaler use, morning PEF, evening PEF, FEV₁, and forced vital capacity (FVC) in subjects treated with omeprazole 20 mg BID and domperidone 10 mg TID for 16 weeks compared with placebo. Littner et al found no significant differences in changes in diary-recorded asthma symptoms, rescue inhaler use, morning or evening PEF, FEV₁, FVC, or the Standardized Asthma Quality of Life Questionnaire score. They, however, found significantly fewer patients in the treatment group experienced an asthma exacerbation or a moderate-severe asthma exacerbation.⁵⁴

The differences in outcomes between these trials may be explained by patient selection, both in terms of the severity of asthma and the severity of reflux in the study subjects. None of these trials used MII-pH monitoring to assess for non-acid esophageal reflux, and only 1 study enrolled patients with clinically silent GERD discovered on esophageal pH monitoring.

Only 1 trial randomized patients with both asthma and GERD (on pH monitoring and esophagitis on endoscopy) to medical or surgical treatment. After 2 years of follow-up, mean asthma symptom scores decreased more in the surgical group than in the medical group. Furthermore, 75% of surgical patients improved, markedly improved, or were cured of asthma when compared to 9% of the medical group. Changes in mean PEF, mean PEF percentage variation, PFTs, or asthma medication requirements were, however, not significantly different.⁵⁵

Current Guidelines

Cough

The American College of Chest Physicians (ACCP) guidelines define chronic a cough lasting 8 weeks or longer. In patients who do not smoke and do not take an ACE inhibitor, ACCP recommends to evaluate for upper airway cough syndrome (also known as postnasal drip syndrome), asthma, nonasthmatic eosinophilic bronchitis, and GERD—the most common causes of chronic cough. Patients with chronic cough and typical symptoms of GERD, or patients whose chronic cough persists after ruling out or treating upper airway cough syndrome, asthma, and nonasthmatic eosinophilic bronchitis should undergo medical treatment for GERD—dietary and lifestyle modifications with acid suppression therapy, and prokinetic therapy if there is no response to the initial therapy. Response should be assessed 1 to 3 months after initiation of therapy. Patients with typical symptoms of GERD whose cough does not resolve with antisecretory therapy should undergo esophageal pH monitoring while on therapy to determine whether antisecretory therapy has failed. Maximal medical therapy includes an antireflux diet (<45 g of fat per day, elimination of coffee, tea, soda, chocolate, mints, citrus, and alcohol), eliminating smoking, and limiting activities that increase intra-abdominal pressure, maximal PPI therapy, and prokinetic therapy. Antireflux surgery is recommended in patients who have positive esophageal pH monitoring, in whom cough has not improved after a minimum of 3 months of maximal medical therapy, and in whom reflux is present while on maximal medical therapy. The ACCP guidelines do not address the diagnostic role of MII-pH monitoring or association tests, and they state that esophageal pH monitoring is the most sensitive and specific test for cough due to reflux.^{6,59,60} More recent data, however, support using combined MII-pH monitoring with SAP analysis while continuing medical therapy when patients fail to respond to antisecretory therapy, instead of using pH monitoring alone. Furthermore, more recent data might support using in selected patients concomitant esophageal

manometry to objectively record cough episodes instead of less reliable patient recordings. Finally, patients who have been ruled out or treated for the 3 other most common causes of chronic cough and in whom MII-pH monitoring shows acid or non-acid reflux while on maximal antiseecretory therapy, might be considered for evaluation for antireflux surgery (Table 2 eAppendix, <http://links.lww.com/SLA/B57>).

Laryngopharyngeal Reflux

The American Academy of Otolaryngology published guidelines on hoarseness in 2009.⁶¹ Ford published a review of the available evidence in 2005. He recommended evaluating patients with suspected LPR with both the Reflux Symptom Index and the Reflux Finding Score. If greater than 13 and 7, respectively, he recommended proceeding to treatment with 3 to 6 months of an antireflux diet, lifestyle modifications (quitting smoking and alcohol intake), and twice daily PPI therapy. He recommended titrating medications off in patients whose symptoms resolved after 3 or 6 months. If symptoms improved but did not resolve after 6 months, or if symptoms did not improve at all after 3 months, Ford recommended evaluation with MII-pH monitoring to demonstrate reflux, and esophageal manometry and endoscopy to guide possible operative planning.⁷ More recent data support prescribing 8 to 12 weeks of twice-daily PPIs and re-evaluation in patients in whom LPR is suspected and in whom other common causes of chronic laryngitis have been ruled out. Similarly, evaluation for antireflux surgery should include extensive counseling about the uncertainty of outcomes, and patients with objective evidence of GERD should be offered surgery with the understanding that resolution of extraesophageal symptoms is less reliable than those of typical symptoms.

Asthma

The National Heart, Lung, and Blood Institute of the National Institutes of Health released its Expert Panel Report 3 in 2007, with guidelines for the diagnosis and management of asthma.⁸ These guidelines recommend that clinicians should evaluate patients with asthma for GERD when asthma is poorly controlled on maximal medical therapy. The panel recommended that patients with concomitant GERD symptoms should be treated for GERD, whereas patients with poorly controlled asthma despite maximal medical therapy should undergo evaluation for GERD even in the absence of typical GERD symptoms. The panel noted that antireflux surgery has been reported to reduce asthma symptoms and medication requirements, but did not explicitly endorse antireflux surgery as a means of controlling asthma due to reflux. The guidelines do not specifically address how to diagnose asthma due to reflux.

Recent evidence provides further support for the role of GERD in patients with uncontrolled asthma. Given the morbidity and mortality associated with uncontrolled asthma it is reasonable to initiate antiseecretory therapy on an empiric basis in patients with uncontrolled asthma without definitive proof of pathologic reflux. In patients who do not respond to maximal antiseecretory therapy and appropriate asthma therapy it might be reasonable to resort to MII-pH monitoring while on antiseecretory therapy. It may be reasonable to refer patients for antireflux surgery, however, as in the case of LPR, antireflux surgery is largely an unproven therapy for asthma due to reflux. Patients should be extensively counseled about the unknown likelihood of benefit before referral for surgery, and should only be offered an operation if their asthma is accompanied by objective evidence of GERD, an event that can increase the likelihood of a successful operation.

CONCLUSIONS

Extraesophageal manifestations of reflux are estimated to cost \$50 billion in healthcare expenditures annually and are responsible for 12.9% of all primary care provider encounters, yet they remain difficult to diagnose and treat. Extraesophageal manifestations of reflux may be most effectively diagnosed with a stepwise approach incorporating empiric treatment with antiseecretory therapy, combined MII-pH monitoring, and surgical intervention in highly selected cases.

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