New Developments in Extraesophageal Reflux Disease

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Abstract: Gastroesophageal reflux disease (GERD) can present with a wide variety of extraesophageal symptoms that are usually difficult to diagnose because of the absence of typical GERD symptoms (ie, regurgitation or heartburn). The diagnostic process is further complicated by the lack of a definitive test for identifying GERD as the cause of extraesophageal reflux symptoms. Due to the low predictive value of upper endoscopy and pH testing—as well as the lack of reliability of the symptom index and symptom association probability—extraesophageal reflux disease is still an area of investigation. This paper discusses recent developments in this field, with special emphasis on new diagnostic modalities and treatment options.

Gastroesophageal reflux disease (GERD) is among the most common diseases encountered by primary care physicians and gastroenterologists in the Western world, and this condition is increasing in prevalence.[1] The predominant symptoms of GERD are heartburn and regurgitation; however, patients may also present with atypical symptoms such as chronic cough, asthma, and laryngitis, which are often referred to as extraesophageal manifestations of GERD (Figure 1). Extraesophageal reflux (EER) symptoms can occur with or without typical GERD symptoms, which, in the latter setting, may delay the diagnosis of reflux. The term “laryngopharyngeal reflux” (LPR) is often used by otolaryngologists to describe laryngeal findings of irritation in patients with chronic throat symptoms, including cough, hoarseness, throat clearing, dysphonia, and globus pharyngeus.[2,3]

Despite the use of different terminology, the same pathophysiologic factor is believed to be responsible for subjective patient symptom reports and objective findings. GERD contributes to extraesophageal syndromes via a direct mechanism (aspiration) or an indirect (vagally mediated) mechanism.[4-8] The extent of gastroduodenal reflux within the esophageal lumen may be classified as either high or distal.[9] High esophageal reflux is reflux that traverses the esophagus and induces cough or laryngeal irritation by direct pharyngeal or laryngeal stimulation or aspiration, causing a tracheal

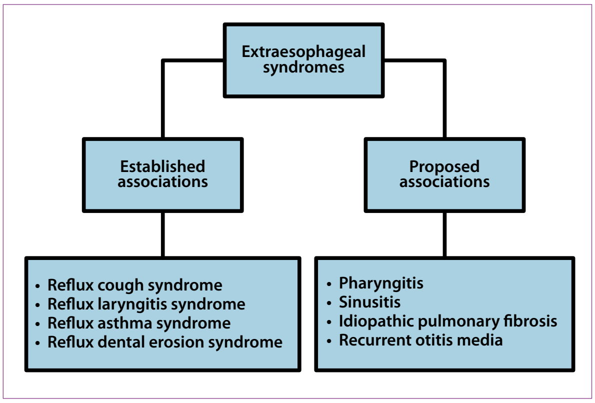

Figure 1. The Montreal definition of constituent syndromes of extraesophageal reflux.

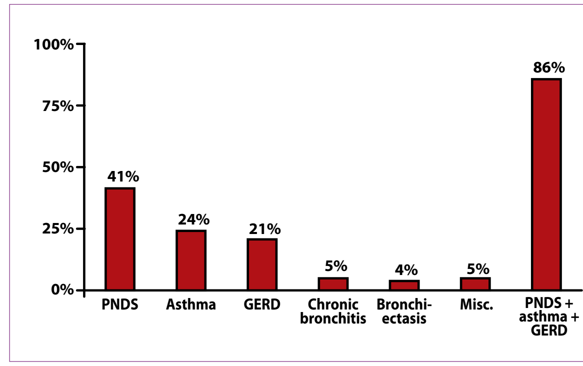

Figure 2. Gastroesophageal reflux disease (GERD) is the third most common cause of chronic cough (after postnasal drip syndrome [PNDS] and asthma). These 3 causes account for 86% of all cases of chronic cough, and there are often multiple causes for each case.

or bronchial response. In distal esophageal reflux, cough or throat symptoms may be produced by a vagally mediated, tracheal-bronchial reflex.[9,10] Embryologic studies have shown that the esophagus and bronchial tree share a common embryologic origin and neural innervation via the vagus nerve. Changes in the pressure gradient between the abdominal and thoracic cavities during the act of coughing may lead to a cycle of cough and reflux.[10,11] A disturbance in any of the normal protective mechanisms—such as a disruption of the mechanical barrier for reflux (ie, the lower esophageal sphincter [LES]) or the presence of esophageal dysmotility—may allow noxious gastroduodenal contents to come into direct contact with the larynx or airway.[12,13]

This paper will discuss recent developments in the field of EER, with special emphasis on new diagnostic modalities and treatment options.

Chronic Cough

Chronic cough, which is defined as cough lasting more than 8 weeks, is a condition commonly evaluated by physicians in the United States.[14,15] In nonsmoking patients who have normal chest radiograph findings and are not taking angiotensin-converting enzyme (ACE) inhibitors, the most common causes of chronic cough include postnasal drip syndrome (PNDS), asthma, GERD, and chronic bronchitis; these 4 conditions may account for up to 90% of chronic cough cases (Figure 2).[16] The diagnosis of GERD-associated chronic cough may be challenging, as many patients do not exhibit typical reflux symptoms. It has been estimated that up to 75% of patients with GERD-associated chronic cough do not display classic symptoms of reflux (ie, heartburn and regurgitation).[6,17,18] The diagnostic process is further complicated by the lack of a test that definitively identifies GERD as the cause of chronic cough. Esophagogastroduodenoscopy (EGD) and 24-hour esophageal pH monitoring have several inherent problems when used to evaluate reflux as a cause of chronic cough. It is difficult to use EGD as a diagnostic tool for reflux-associated cough because of the frequently poor correlation between esophagitis findings and cough. For example, in a study of 45 patients with chronic cough, Baldi and colleagues reported classic reflux symptoms in 55% of patients, but only 15% of the study population had EGD-confirmed esophagitis.[16] Therefore, EGD has a low sensitivity for establishing a link between chronic cough and esophageal findings. Most patients with chronic cough have normal endoscopy findings.

Although 24-hour esophageal pH monitoring has a 90% sensitivity for diagnosing abnormal esophageal acid exposure in patients with GERD, the use of this method is limited in patients with chronic cough, as its specificity in this population is as low as 66%.[9,11,19-22] An important advantage of pH monitoring in chronic cough patients may be its ability to correlate esophageal reflux episodes with cough symptoms via the 2 most commonly used indices: symptom index (SI) and symptom association probability (SAP). However, a recent study conducted by Slaughter and associates concluded that both the SI and SAP can be overinterpreted and are prone to misinterpretation.[23] The authors suggested that both the SI and SAP are essentially chance occurrences at best, except in patients with GERD that is refractory to proton pump inhibitor (PPI) therapy who have high rates of esophageal acid exposure.[23] A recent study using an acoustic cough monitoring device showed that cough temporally associates with reflux, irrespective of proposed diagnoses, and cough may be self-perpetuating in some patients, likely due to central processes and not just reflux.[24] Therefore, given the low predictive value of pH testing, the lack of reliability of the SI and SAP, and the lack of temporal association (which is not necessarily causal), the use of pH testing in patients with chronic cough may be problematic.

In patients with chronic cough suspected to be related to GERD, most experts recommend empiric PPI therapy, often via twice-daily dosing. This recommendation is solely based on open-label trials, as placebo-controlled studies have not shown a benefit with PPI therapy in this group. For example, Poe and Kallay found that 79% of patients with cough secondary to GERD experienced resolution of their symptoms following an empiric trial of PPI therapy.[10] A study conducted by Baldi and colleagues suggested that once-daily PPI therapy in these patients may yield results similar to those associated with twice-daily PPI therapy.[16] However, a meta-analysis of 5 placebo-controlled studies in adult patients with chronic cough found insufficient evidence in favor of PPI therapy.[25] In agreement with the conclusions of this meta-analysis, 2 other recent randomized controlled studies did not find any benefits with PPI therapy compared to placebo in adults with chronic cough.[26,27] Taken together, these studies show the uncertainty of the association between chronic cough and GERD, most likely due to poor diagnostic tests and, thus, inappropriate patient selection in controlled studies. In addition, we recently showed that the response to surgical intervention in patients with chronic cough may depend on the concomitant baseline presence of typical GERD symptoms (ie, heartburn and regurgitation).[28]

Recently, the term "sensory neuropathic cough" has been used to describe patients with recalcitrant cough in whom other causes, including GERD, have been excluded. This condition appears to result from a lowered stimuli response threshold (as with postherpetic neuralgic pain) and does not respond to usual therapies such as PPI therapy.[29] Sensory neuropathic cough is sudden, occurs in episodes, and may be triggered by eating, talking, or deep breathing. This condition can result in rhinorrhea, vomiting, laryngospasm, and syncope or near-syncope.[29] It has been estimated that up to 31% of patients with chronic cough may have sensory neuropathic cough.[30] Recent studies have suggested that gabapentin can cause symptomatic improvement of this type of cough.[31,32] Therefore, chronic cough patients in whom other causes have been excluded may experience some benefit with off-label use of a neuromodulator medication such as amitriptyline (10 mg/day), gabapentin (100–900 mg/day), or pregabalin (maximum dose of 150 mg twice daily). Amitriptyline is a tricyclic antidepressant. Pregabalin and gabapentin are very similar in structure, as they are both analogs of gamma-aminobutyric acid (GABA), although they do not bind to GABA A or GABA B; instead, they bind to subunits of presynaptic calcium channels and decrease the release of the neurotransmitters glutamate, noradrenaline, and substance P.[33]

In conclusion, the evaluation of chronic cough should begin by assessing causes such as PNDS or asthma in patients with normal chest radiograph findings and no history of ACE inhibitor use. After these causes have been ruled out, an empiric trial of acid suppression should be administered via once-daily or twice-daily PPI therapy for no more than 12–16 weeks, which will likely identify and treat the majority of patients with reflux-associated chronic cough. Patients who are unresponsive to this trial should undergo tests to exclude large mechanical defects such as hiatal hernia (which could cause volume regurgitation), or they should be evaluated for lung-related issues. In patients without an obvious cause of cough and poor clinical response to the usual therapies, including PPI therapy, a trial of neuromodulator medications may help to control chronic symptoms.

Asthma

Asthma has a strong correlation with GERD, and it has been proposed that the conditions may induce each other (Figure 3). GERD may induce asthma via the vagally mediated or microaspiration mechanisms mentioned above. It has been suggested that asthma may induce reflux via several mechanisms. Exacerbation of asthma results in negative intrathoracic pressure (which may cause reflux), and the medications used to treat asthma (theophylline, β-agonists, and steroids) may reduce the pressure of the LES. GERD should be suspected in patients with asthma whose symptoms are worse after meals and in patients who do not respond to traditional asthma medications. Patients who have heartburn and regurgitation before the onset of asthma symptoms may also be suspected of having reflux-induced asthma symptoms.

Epidemiologic studies, as well as physiologic testing with ambulatory 24-hour pH monitoring, have shown an association between asthma and GERD.[34,35] In a study that evaluated the prevalence of GERD in asthma patients, Kiljander and associates found that 35% of GERD patients did not have typical reflux symptoms but did have abnormal esophageal acid exposure according to pH monitoring.[34] Similarly, Leggett and coworkers conducted a study to assess GERD in patients with difficult-to-control asthma using 24-hour ambulatory pH monitoring with both distal probes (5 cm above the LES) and proximal probes (15 cm above the distal probes).[36] The distal probes detected reflux in 55% of patients, and the proximal probes detected reflux in 35% of patients. Thus, reflux is a common occurrence in patients with asthma.

As is the case for most EER conditions, there is controversy regarding the benefit of PPI therapy in patients suspected of having reflux-induced asthma. Studies have

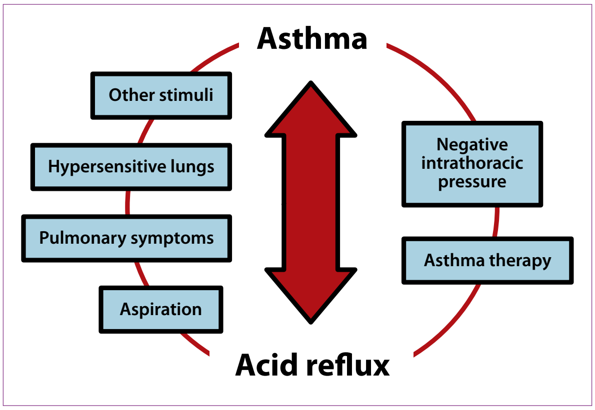

Figure 3. It has been proposed that asthma and gastroesophageal reflux disease (GERD) may exacerbate each other, as GERD may induce bronchospasm, and asthma may induce GERD. Treating both conditions may break this cycle and improve patients' symptoms.

used different endpoints to measure the efficacy of acid suppression therapy in this group: Some studies have employed objective measurements (such as improvement in forced expiratory volume [FEV1]), whereas other studies have relied on patient-reported questionnaires or a decrease in the need for asthma medications. Early trials reported improvements in pulmonary symptoms and function in patients treated with acid suppression therapy.[37] In 1994, Meier and colleagues conducted a double-blind, placebo-controlled, crossover study that evaluated the pulmonary function of asthma patients treated with omeprazole 20 mg twice daily for 6 weeks.[38] This study found that 27% of patients with reflux (4/15) had an increase in FEV1 of at least 20%.[38]

In another study, Sontag and associates divided 62 patients with GERD and asthma into 3 arms: control, medical treatment (ranitidine 150 mg 3 times daily), or surgical treatment (Nissen fundoplication).[37] After a 2-year follow-up period, 75% of patients who received surgical treatment experienced improvement in nocturnal asthma exacerbations, compared to 9.1% of patients who received medical therapy and 4.2% of patients in the control group. Additionally, there was a statistically significant improvement in mean asthma symptom score but no improvement in pulmonary function or reduction in the need for medication among the groups. In a different study, Littner and coworkers followed 207 patients who had symptomatic reflux and received either placebo or PPI therapy twice daily for 24 weeks.[39] The primary outcome of this study was daily asthma symptoms reported in patient diaries, and secondary outcomes were the need for rescue albuterol inhaler use, pulmonary function, asthma-associated quality of life, investigator-assessed asthma symptoms, and asthma exacerbations. The study showed that medical treatment of reflux did not reduce daily asthma symptoms or albuterol use and did not improve pulmonary function in asthma patients.[39] Similarly, a study conducted by the American Lung Association Asthma Clinical Research Center randomized 412 patients with poor asthma control to either esomeprazole 40 mg twice daily or placebo.[40] After 24 weeks of follow-up, the study found that PPI therapy had no treatment benefit for controlling asthma. Recently, a randomized controlled trial in children who had asthma, but not overt GERD, did not show an improvement in symptoms or lung function with lansoprazole therapy.[41] A Cochrane review of GERD treatment for patients with asthma found only minimal improvement of asthma symptoms with reflux therapy.[42] Nevertheless, a recent controlled trial in asthma patients suggested a therapeutic benefit with PPI therapy in the subgroup of asthma patients with both nocturnal respiratory symptoms and GERD symptoms.[43] Therefore, the effect of reflux treatment on asthma control in patients with both conditions is not yet clear.

The current recommendation in patients with asthma (with or without concomitant heartburn or regurgitation) is similar to that for patients with chronic cough: an initial empiric trial of once-daily or twice-daily PPI therapy for 2–3 months. In patients who are responsive to therapy for both heartburn and/or asthma symptoms, PPIs should be tapered to the minimal dose necessary to control symptoms. In unresponsive patients, it may be necessary to test for reflux via pH testing and/or impedance/pH monitoring in order to measure reflux of acidic or nonacidic material, which could still be responsible for asthma exacerbation.

Laryngitis

GERD is implicated as an important cause of laryngeal inflammation.[44] Common symptoms of this condition (which is referred to as LPR by otolaryngologists) include hoarseness, throat pain, the sensation of a lump in the throat, cough, repetitive throat clearing, excessive phlegm, difficulty swallowing, pain with swallowing, heartburn, and voice fatigue (Table 1). These symptoms are nonspecific and can also be seen in patients with PNDS or exposure to allergens, smoke, or other irritants.[45] However, reflux is often implicated in many of these patients, given the chronicity of their symptoms and the laryngeal findings of erythema and edema. The most common laryngeal signs associated with LPR are listed in Table 2.

Direct laryngeal exposure to injurious gastroduodenal contents is likely the pathophysiologic mechanism for the development of LPR. However, the relative importance of the specific agent(s) responsible is subject to debate. Earlier studies suggested that pepsin may be the main cause of LPR symptoms; however, later studies suggested the

Table 1. Symptoms That May Be Associated with Laryngopharyngeal Reflux

- Hoarseness
- Dysphonia
- Sore or burning throat
- Excessive throat clearing
- Chronic cough
- Globus pharyngeus
- Apnea
- Laryngospasm
- Dysphagia
- Postnasal drip
- Neoplasm

Table 2. Potential Laryngopharyngeal Signs Associated with Laryngopharyngeal Reflux

- Edema and hyperemia of the larynx
- Hyperemia and lymphoid hyperplasia of the posterior pharynx (cobblestoning)
- Contact ulcers
- Laryngeal polyps
- Granulomas
- Interarytenoid changes
- Subglottic stenosis
- Posterior glottic stenosis
- Reinke edema
- Tumors

co-importance of acid, pepsin, and bile acids.[3,7,46,47] There has recently been an increase in articles examining the role of pepsin in LPR patients. Some publications have suggested that an important contributor to LPR may be the reflux of pepsin into the larynx, with subsequent pepsin transfer into the cytoplasm of laryngeal cells and its later activation in cell organelles with lower pH than that of the lumen.[48] Dilation of intercellular spaces (DIS) has been reported to be an early morphologic marker in GERD, reflecting the alteration of esophageal mucosal integrity. However, recent studies assessing DIS in patients suspected of LPR and GERD have not shown a difference in epithelial space separation between patients and controls, thus questioning the uniform reflux-related epithelial presence of DIS.[49] E-cadherin may play an important role as a cellular adhesion molecule in mucosal integrity. There is some evidence that e-cadherin expression may be decreased in the laryngeal tissue of LPR patients.[50] However, it is not apparent whether the decrease is due to reflux or an inflammatory response to reflux.

Recent studies have suggested the importance of carbonic anhydrase (CA) isoenzymes (I, II, and III) in laryngeal protection and their role in LPR patients.[51,52] CA enables the esophagus or larynx to defend against acidic refluxate by producing bicarbonate. The expression of CA III has been demonstrated to vary in laryngeal biopsies obtained from different locations in LPR patients.[51] CA III expression is decreased in the vocal folds of LPR patients, but it is increased in the posterior commissure, with the degree of increase based on the severity of the patient's symptoms.[53,54] The difference may be attributed to the fact that the larynx contains both squamous and respiratory epithelium, which react differently to reflux.[3]

Laryngoscopy is an important tool for the diagnosis of reflux-associated laryngeal symptoms; however, the most common laryngoscopic findings of LPR patients are often highly subjective, nonspecific, and present in many individuals without GERD (Table 2).[55-58] For example, Milstein and coworkers highlighted the nonspecific nature of laryngeal evaluation in a study of 52 nonsmoking volunteers with no history of otolaryngology abnormalities or GERD.[57] This asymptomatic healthy group underwent both rigid and flexible video laryngoscopy. The authors found at least 1 sign of tissue irritation in 93% of patients via flexible video laryngoscopy and 83% of patients via rigid video laryngoscopy. Additionally, the findings were dependent on the technique. Laryngeal signs were more commonly reported via flexible transnasal laryngoscopy than via rigid transoral examination.[57] The high prevalence of laryngeal irritation in healthy volunteers—combined with the variability of the diagnosis based on the methods used—highlights the uncertainty associated with laryngeal signs in LPR patients.

Ambulatory pH monitoring is also commonly used in the diagnosis of LPR. However, this method lacks sensitivity and specificity for LPR. Hypopharyngeal and proximal esophageal pH monitoring have sensitivities of 40% and 55%, respectively.[59,60] Variability has been reported in the literature regarding placement of proximal and hypopharyngeal pH probes (eg, 15 cm above the LES, within the upper esophageal sphincter [UES], or above the UES). Also, gastroenterologists utilize manometry to guide placement, whereas otolaryngologists position pH probes via laryngoscopic visualization. This difference results in heterogeneous findings and uncertainty regarding their clinical utility. For example, a study with LES-referenced proximal catheter placement did not reveal an association between reflux and extraesophageal symptoms.[61] Therefore, pH studies are confusing, rather than informative, in LPR patients, and further studies are needed to better define the role of pH studies in this disorder.

Recent studies have suggested that nonacid reflux may play a role in causing symptoms in patients who remain symptomatic despite aggressive acid suppression therapy.[62-65] Studies assessing patients with heartburn and regurgitation, as well as patients with extraesophageal symptoms, have sug-

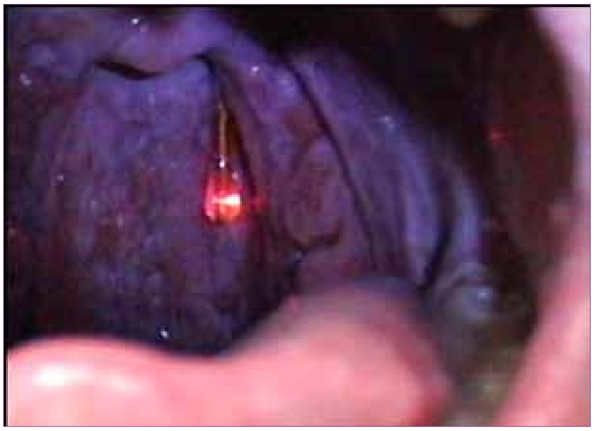

Figure 4. A Dx-pH probe (Respiratory Technology Corp.) and light-emitting diode in a patient's oropharynx.

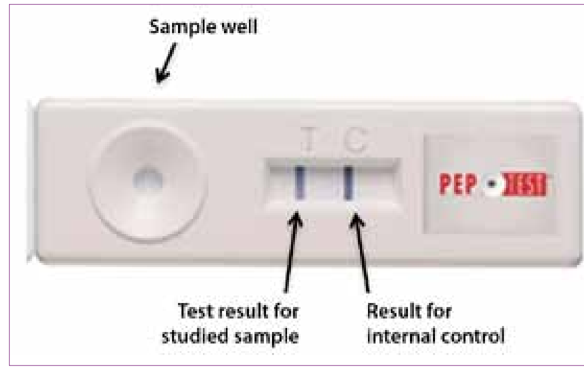

Figure 5. A lateral flow device showing a positive pepsin test result relative to the control band from a gastric juice sample.

gested that 10–40% of patients on twice-daily PPI therapy may have persistent nonacid reflux.[64,66] However, causation is difficult to establish between these nonacid reflux events and persistent symptoms.[67] A recent study found that abnormal impedance findings in patients on PPI therapy predict acid reflux in patients off therapy.[68] The study also concluded that combined impedance/pH monitoring of patients with refractory reflux might provide the single best strategy for evaluating reflux symptoms in these patients. However, the clinical significance of abnormal impedance findings in this group of patients awaits further study. The most recent uncontrolled study in surgically treated patients suspected of having LPR found that impedance monitoring did not predict LPR symptom response to fundoplication, regardless of whether the patients were on or off therapy; important predictors of symptom response were the presence of hiatal hernia, significant acid reflux at baseline, and the presence of regurgitation concomitant with LPR symptoms.[69]

The Dx–pH measurement system (Respiratory Technology Corp.), which is a sensitive and minimally invasive device for detecting acid reflux in the posterior oropharynx, is increasingly being used in patients with LPR.[70] This device uses a nasopharyngeal catheter (the Restech pH catheter) to measure pH in either liquid or aerosolized droplets (Figure 4). This device has a faster detection rate and time to equilibrium pH than traditional pH catheters. A recent, prospective, observational study in healthy volunteers developed normative data for this device at pH cutoffs of 4, 5, and 6 for the distal esophagus and oropharynx.[71] Although initial studies of this device in LPR patients are encouraging, controlled studies are needed to assess its future role.[70]

Over the last few years, the detection of salivary pepsin has been advocated as an objective method for diagnosing reflux.[72] Pepsin is a proteolytic enzyme secreted as pepsinogen from the chief cells in the gastric fundus and activated in acidic environments.[73] Using an enzymatic method, Potluri and colleagues compared salivary pepsin activity with proximal and distal esophageal pH results in 16 reflux patients and noted a correlation between these pH values and salivary pepsin assay findings.[72] The authors thus concluded that the salivary pepsin assay might be a noninvasive method of assessing proximal reflux. Although Ozmen and associates found a 100% sensitivity and a 92.3% specificity for the pepsin assay in the nasal lavage fluid of chronic rhinosinusitis patients, Printza and coworkers did not find any peptic activity in the saliva samples of 93 LPR patients.[74,75] Using the Western blot technique to measure pepsin in sputum and salivary samples from patients with EER, Kim and colleagues reported a sensitivity and specificity of 89% and 68%, respectively, based on pH monitoring results.[76]

Recently, a novel, rapid, pepsin test (Peptest, Biomed) has also been used as a convenient, office-based, noninvasive, quick, inexpensive technique for the diagnosis of LPR. This lateral flow device (LFD) utilizes 2 monoclonal antibodies to human pepsin, and its results can be read in 5–15 minutes (Figure 5).[77] In a recent, prospective, blinded study of the rapid LFD in 59 patients with objective GERD (based on esophagitis or abnormal pH testing) and 51 control subjects, we found positive and negative predictive values of 87% and 78%, respectively.[78] The sensitivity and specificity of the assay were both 87% via in vitro bench testing. Thus, this study suggests that the use of rapid LFD for detection of salivary pepsin has acceptable test characteristics in GERD patients. However, the clinical role of this assay in LPR patients is unknown and remains the subject of ongoing studies. Table 3 summarizes the advantages and disadvantages of commonly used diagnostic methods for detection of LPR.

PPI therapy is the standard of care when GERD is suspected to be the etiology of chronic throat symptoms. However, a recent, large-scale, multicenter study of 145 patients suspected of having LPR did not show a benefit in those treated with esomeprazole 40 mg twice daily

Table 3. Advantages and Disadvantages of Various Methods for Detection of Laryngopharyngeal Reflux

Method	Advantages	Disadvantages
Endoscopy	• Easy visualization of mucosal damage and erosions	• Poor sensitivity, specificity, and positive predictive value • Sedation required • High cost
Laryngoscopy	• No sedation required • Direct visualization of the larynx and laryngeal pathology	• No specific laryngeal signs for reflux • Overdiagnosis of gastroesophageal reflux disease
pH monitoring	• Easy to perform • Relatively noninvasive • Prolonged monitoring • Ambulatory	• Catheter-based method • False-negative rate of up to 30% • No pH predictors of treatment response in patients with laryngopharyngeal reflux
Impedance monitoring	• Easy to perform • Relatively noninvasive • Prolonged monitoring • Ambulatory • Measurement of acidic and nonacidic gas and liquid reflux (combined with pH)	• Catheter-based method • Unknown false-negative rate (but likely similar to that of catheter-based pH monitoring) • Unknown clinical relevance when abnormal results are found in patients taking proton pump inhibitors • Unknown importance in patients with laryngopharyngeal reflux
Dx–pH measurement system	• Faster detection rate and time to equilibrium pH than traditional pH catheters	• Unknown clinical usefulness in patients with laryngopharyngeal reflux
Lateral flow device for pepsin detection	• Fast and easy detection of salivary pepsin • Acceptable sensitivity and specificity	• Has only been examined in limited outcome studies so far

for 4 months compared to placebo.[59] The disappointing negative findings from this study and other controlled trials in LPR patients stem from the dilution effect of patients enrolled in these trials (Figure 6).[79] Given the lack of a gold standard for diagnosing GERD in patients with LPR, many patients may not have had the disease for which they were being randomized. Otolaryngologists usually suspect GERD-related laryngitis based on symptoms (such as throat clearing, cough, and globus pharyngeus) and signs (such as laryngeal edema and erythema); however, these signs and symptoms are nonspecific for reflux. Patients who are unresponsive to PPI therapy may have either nonreflux-related causes or a functional component to their symptoms. The placebo response rate in LPR studies is approximately 40%, which is similar to that seen in studies of functional gastrointestinal disorders such as irritable bowel syndrome.[80] Although clinical response to an empiric trial of PPIs does not prove a causal link, persistent response or symptom recurrence with the discontinuation of PPIs may be suggestive of GERD-related symptoms.

Some investigators argue that continued acid and/or pepsin-related injury to the larynx is the cause of symptoms, despite a lack of response to PPI therapy. Altman and coworkers evaluated the laryngeal tissue of 15 patients and found expression of the a and/or b subunits of H^+/K^+–ATPase, suggesting that proton pumps in laryngeal seromucinous glands and duct cells may play a role in the pathogenesis of LPR signs and symptoms.[81] It has been suggested that laryngeal proton pumps may activate in response to reflux or other causes of inflammation or infection in order to preserve intracellular pH and, thus, viability. An alternative explanation for the lack of response to PPI therapy in LPR patients is that reflux may be intermittent and/or may occur in low volumes. Proponents argue that the larynx is highly sensitive to acid, so even low levels of acid may result in laryngeal signs and symptoms without abnormal findings on endoscopy, pH tests, or impedance monitoring.[82] Other doctors have suggested that pepsin can cause cellular damage even in nonacid environments.[53,83] For example, Golgi complex and mitochondrial damage have been demonstrated in laryngeal tissue exposed only to pepsin. Moreover, studies have shown pepsin-related alterations in laryngeal gene expression in nonacid conditions, as well as specific receptor-mediated membrane transfer of pepsin.[48,84] The above arguments may be appealing and academically thought-provoking; however, they do not explain why patients continue to be symptomatic despite aggressive therapy such as surgical fundoplication.[85,86] This procedure should correct any reflux of nonacid materials, including

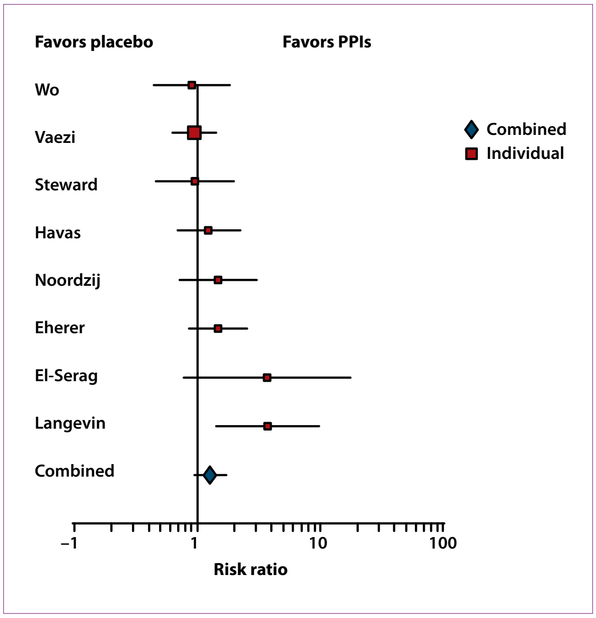

Figure 6. A Forest plot depicting the risk ratios of studies assessing the efficacy of proton pump inhibitors (PPIs) in patients with reflux laryngitis. The combined risk ratio is calculated via the random effects method.

Data from Qadeer MA, et al.[79]

pepsin and/or low-volume acid, to the larynx. The role of surgical intervention in patients who are refractory to PPI therapy is evolving. The most recent study conducted in this area suggests that baseline regurgitation, hiatal hernia, and moderate-to-severe acid reflux (defined as >10% when pH <4) predict symptomatic response to surgery.[28]

Therefore, patients who are suspected of having LPR but who do not have any warning symptoms or signs should initially be treated with empiric PPI therapy for 1–2 months. If symptoms improve, the therapy may need to be prolonged for up to 6 months to allow healing of laryngeal tissue, after which time the dosage should be tapered to the smallest amount that still results in continued response. In unresponsive patients, impedance and/or pH monitoring may be the best alternative to rule out reflux as the cause of continued symptoms and to move forward by considering other causes.

Summary

GERD commonly presents with EER symptoms. Patients may or may not also have the typical GERD symptoms of heartburn and/or regurgitation. In this group of patients, empiric acid suppression therapy is indicated if there are no warning symptoms. A lack of response to acid suppression therapy necessitates diagnostic testing with pH and/or impedance monitoring. However, due to limited outcome studies, the role of the latter test alone is currently uncertain. New diagnostic modalities and treatment options discussed in this paper may be helpful in patients who continue to be symptomatic despite acid suppression therapy.

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