



**EDUCATIONAL OBJECTIVE:** Readers will consider laryngopharyngeal reflux in the workup of patients with chronic throat symptoms

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# Laryngopharyngeal reflux: More questions than answers

## ABSTRACT

Laryngopharyngeal reflux (LPR), an extraesophageal variant of gastroesophageal reflux disease, is associated with hoarseness, chronic cough, throat-clearing, sore throat, and dysphagia. But because these symptoms are nonspecific, laryngoscopy is often done and the diagnosis of LPR is considered if edema, erythema, ventricular obliteration, pseudosulcus, or postcricoid hyperplasia is noted. Most patients with suspected LPR are given a 2-month trial of a proton pump inhibitor. Yet there is still little or no solid evidence on which to base the diagnosis or the treatment of LPR. We review the current understanding of the pathophysiology and discuss current diagnostic tests and treatment regimens in patients with suspected LPR.

## KEY POINTS

Laryngoscopy has high interrater variability, and results of pH monitoring do not reliably predict who will respond to treatment.

A proton pump inhibitor twice daily for 2 months is currently recommended for patients with laryngeal signs and symptoms. If the condition responds to therapy, tapering to once-daily therapy and then to minimal acid-suppression to control symptoms is prudent.

Patients whose symptoms do not respond to a proton pump inhibitor are unlikely to benefit from surgery. Other diagnoses should be entertained, while the drug is tapered to prevent rebound acid reflux.

**T**HE SCENARIO IS COMMON: a patient complains of chronic hoarseness, cough, throat-clearing, sore throat, dysphagia, or a lump in the throat and undergoes laryngoscopy. If this test rules out cancer, the patient is given a diagnosis of laryngopharyngeal reflux (LPR), ie, a form of gastroesophageal reflux disease (GERD) in which the stomach contents get all the way up into the pharynx and down into the larynx. A proton pump inhibitor (PPI) is often prescribed, usually twice daily for 2 months.<sup>1-6</sup>

Unfortunately, the diagnosis and treatment of LPR remain controversial in the absence of solid evidence from randomized, placebo-controlled trials. The signs and symptoms (TABLE 1) are not specific, and even though the diagnosis of LPR is considered if edema, erythema, ventricular obliteration, pseudosulcus, or postcricoid hyperplasia is documented on laryngoscopy,<sup>4</sup> interpretation of the laryngoscopic features is subjective.

In this article, we review the current understanding of the pathophysiology of LPR and evaluate current diagnostic tests and treatment regimens for patients with suspected LPR.

## THE PATHOPHYSIOLOGY OF LPR IS POORLY UNDERSTOOD

### Transient relaxation of the lower esophageal sphincter

In a study in 10 healthy volunteers, Dent et al<sup>7</sup> found that the pressure in the lower esophageal sphincter varies considerably over a 12-hour period. Episodes of reflux were not related to low basal (resting) pressure. Rather, 70% to 100% of reflux episodes occurred during random episodes of transient, complete, and

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TABLE 1

### Symptoms often attributed to laryngopharyngeal reflux

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

inappropriate relaxation of the sphincter that lasted about 5 to 30 seconds. The mechanism of this relaxation is not known but is thought to be related to activation of the vagus nerve, possibly as a consequence of gastric distention.<sup>8</sup>

#### Gastric, not duodenal products seem to cause the damage

In a study in dogs, Adhami et al<sup>9</sup> evaluated the possible role of gastric juices (acid and pepsin) vs duodenal juices (bile acids and trypsin) in laryngeal tissue damage. After taking baseline biopsy samples of the larynx, the investigators applied a variety of gastric and duodenal enzymes at varying pH levels (pH 1–7) to the larynxes. After 9 to 12 applications, they took another biopsy and assessed the changes visually and histologically.

At low (ie, acidic) pH levels, pepsin and conjugated bile acids were the most injurious, causing erythema and histologic evidence of inflammation. The authors concluded that gastric and not duodenal substances cause laryngeal injury and that acid-suppressive therapy “should eliminate the injurious potential” of acid reflux.<sup>9</sup>

#### The larynx is more sensitive than the esophagus

Monitoring of esophageal pH has shown that healthy people can tolerate as many as 50 episodes a day of acid reflux (pH < 4) in the

esophagus. However, Koufman<sup>10</sup> found that as few as three episodes of laryngeal reflux per week can cause severe laryngeal inflammation and injury.

#### Does pepsin deplete buffers, worsening acid damage?

Johnston et al<sup>11</sup> took biopsies from a control group of healthy volunteers and from patients diagnosed with LPR. They detected pepsin in the samples from eight of the nine patients with LPR but in none of the controls. Furthermore, the tissue from patients with LPR had low levels of carbonic anhydrase III. The authors hypothesized that pepsin depletes the laryngopharynx of carbonic anhydrase III, and that therefore these tissues cannot produce enough bicarbonate to buffer the gastric acid. Less bicarbonate would mean greater acidity, so the pepsin would remain active and would be more likely to cause cellular damage.<sup>11</sup>

However, this contention is controversial. What is universally agreed upon is that reflux of gastric or gastroduodenal contents is most likely causing injury, most likely through direct exposure, although indirect effects through vagal mechanisms cannot be ruled out.

#### CURRENT DIAGNOSTIC TESTS FOR LPR HAVE SHORTCOMINGS

The diagnosis of LPR has become more common over the last few years,<sup>4</sup> and by some estimates up to 10% of patients presenting to ear-nose-throat physicians have complaints related to GERD.<sup>12</sup> However, current diagnostic tests for reflux and LPR have many shortcomings and can lead to misdiagnosis of this disease (TABLE 2).

A careful history is important. Many patients report they have sore throat, hoarseness, cough, dysphasia, or chronic throat-clearing.<sup>13</sup> Factors that may predispose a patient to esophageal reflux should be discussed, eg:

- Tobacco use
- Diet (eg, soda, spicy foods, fatty foods)
- Alcohol use
- Certain drugs (calcium channel blockers, nitrates, steroids).

Up to 50% of patients presenting with extraesophageal symptoms may not have classic reflux symptoms such as heartburn and regur-

**Key features of LPR: chronic hoarseness, cough, throat-clearing, sore throat, dysphagia, globus pharyngeus**

TABLE 2

**Advantages and disadvantages of tests for reflux**

TEST	ADVANTAGES	DISADVANTAGES
<b>Endoscopy</b>	Easy visualization of mucosal damage and erosions	Poor sensitivity, specificity, positive predictive value Requires sedation High cost
<b>Laryngoscopy</b>	No sedation required Direct visualization of the larynx and laryngeal pathology	No specific laryngeal signs for reflux High interrater variability May contribute to overdiagnosis of reflux
<b>pH monitoring</b>	Easy to perform Relatively noninvasive Prolonged monitoring Ambulatory	Catheter-based, may have up to 30% rate of false negatives Wireless system (Bravo) is costly No pH predictors of treatment response in laryngopharyngeal reflux (LPR)
<b>Bilirubin monitoring</b>	Easy to perform Relatively noninvasive Prolonged monitoring Ambulatory Good correlation with gastric bile acid concentrations	Current design underestimates reflux by about 30% in acidic medium (pH < 3.5) Requires modified diet Does not detect acid Not studied in LPR
<b>Impedance monitoring</b>	Easy to perform Relatively noninvasive Prolonged monitoring Ambulatory Measures acidic and nonacidic gas and liquid reflux (combined with pH)	Catheter-based False-negative rate unknown but most likely similar to catheter-based pH monitoring Unknown clinical relevance when abnormal on proton pump inhibitor therapy Unknown importance in LPR

**Classic reflux symptoms are absent in up to 50% of patients with LPR symptoms**

gitation.<sup>14</sup> However, the existence of “silent reflux” is currently controversial.

### **Laryngoscopy is nonspecific and subjective**

Because the key symptoms of LPR are nonspecific, many patients who present to an otolaryngologist undergo laryngoscopy, mainly to rule out malignancy. Once cancer is ruled out, many patients are given a diagnosis of LPR.

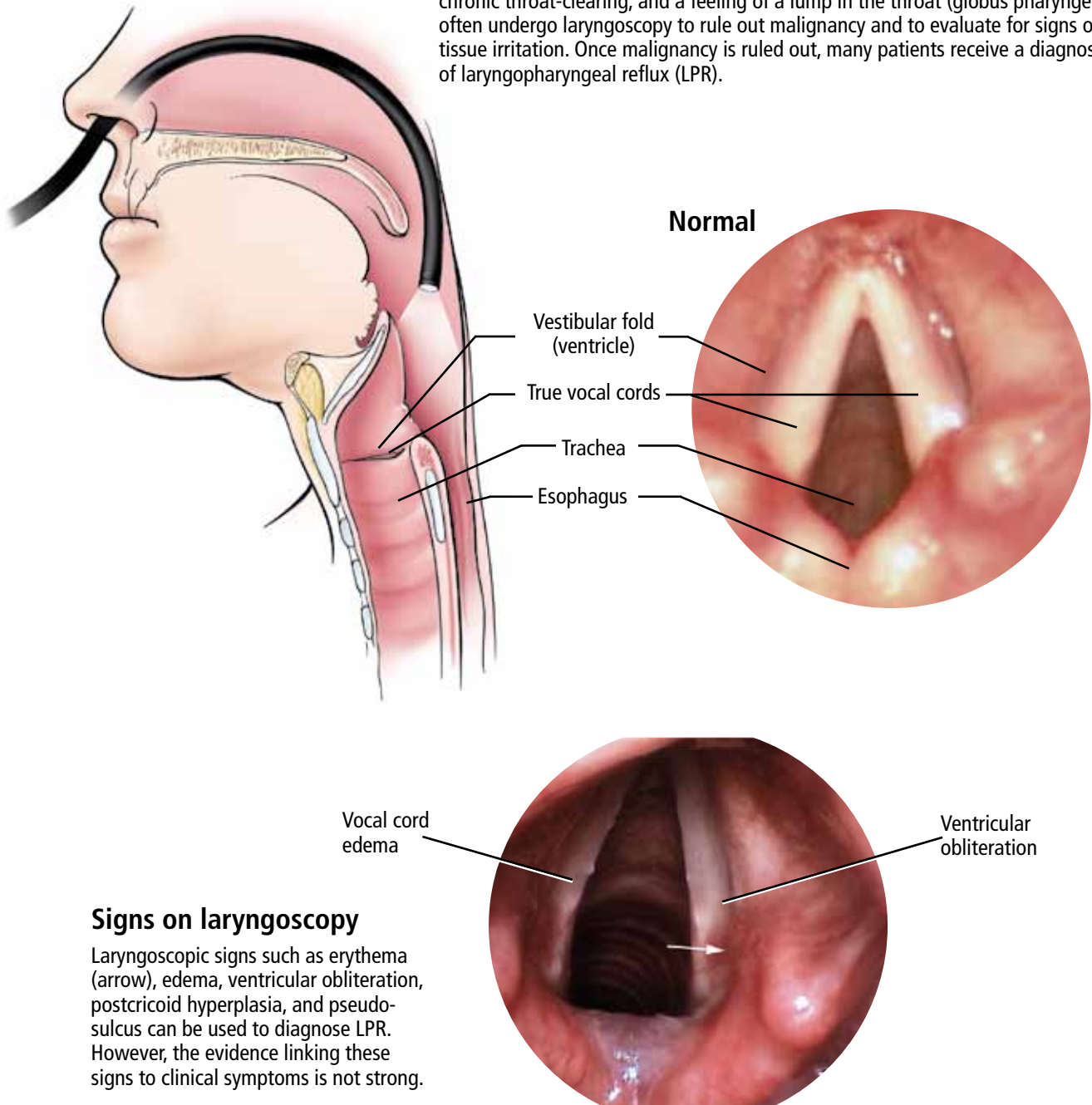
Laryngoscopic findings often imputed to LPR (FIGURE 1) include erythema, edema, ven-

tricular obliteration, postcricoid hyperplasia, and pseudosulcus.<sup>4</sup> Of these, edema was the finding most often used to diagnose LPR in one analysis.<sup>15</sup> However, Milstein et al<sup>16</sup> discovered at least one sign of laryngeal tissue irritation in 80% to 90% of patients tested who did not have a history of an ear-nose-throat complaint or a diagnosis of GERD.

Furthermore, Branski et al<sup>17</sup> performed transoral rigid laryngoscopy with videorecording in 100 consecutive patients presenting

## Laryngopharyngeal reflux: A challenging diagnosis

Patients with complaints such as sore throat, hoarseness, cough, dysphasia, chronic throat-clearing, and a feeling of a lump in the throat (globus pharyngeus) often undergo laryngoscopy to rule out malignancy and to evaluate for signs of tissue irritation. Once malignancy is ruled out, many patients receive a diagnosis of laryngopharyngeal reflux (LPR).



### Signs on laryngoscopy

Laryngoscopic signs such as erythema (arrow), edema, ventricular obliteration, postcricoid hyperplasia, and pseudo-sulcus can be used to diagnose LPR. However, the evidence linking these signs to clinical symptoms is not strong.

with a chief complaint of dysphonia. Five board-certified otolaryngologists individually viewed each recording, scored the degree of erythema and edema, and assessed the likelihood that LPR played a role in dysphonia and the severity of the LPR findings. The physicians' ratings showed considerable interobserver variability. In other words, this study showed that laryngeal findings are often nonspecific and that the laryngoscopic diagnosis of LPR tends to be subjective.<sup>17</sup>

**The Reflux Finding Score.** Concerned by the lack of consistency in the diagnosis of LPR, Belafsky et al<sup>18</sup> created a scoring system for documenting the physical findings and severity of disease on a standardized scale. Their Reflux Finding Score is based on eight laryngoscopic findings: subglottic edema, ventricular edema, erythema, vocal cord edema, diffuse laryngeal edema, hypertrophy of the posterior commissure, granuloma or granulation tissue, and thick endolaryngeal mucus. The total score can range from 0 (best) to 26 (worst).

In 40 patients with LPR confirmed by pH monitoring, the mean score was 11.5, compared with 5.2 in 40 age-matched controls. The authors calculated they could be 95% certain that a person with a score higher than 7 has LPR.<sup>18</sup>

However, this diagnostic method has not been validated in a large-scale randomized trial and so has yet to be incorporated into routine otolaryngology practice.

### **Ambulatory pH monitoring is not so golden for diagnosing LPR**

Although pH monitoring was once the gold standard for diagnosing reflux, it has since been shown to be unreliable in patients who have laryngeal symptoms.<sup>4</sup>

How high or low in the esophagus the probe is placed is clearly critical for useful results.<sup>4</sup> But the test is subject to variability: different physicians place the probe in different locations, and the probe may shift. Another problem is that reflux may occur during untested periods.<sup>19</sup>

A pH of less than 4 in the esophagus had originally been shown to have high sensitivity and specificity,<sup>20</sup> but Reichel and Issing<sup>21</sup> suggested using a pH of less than 5 as the cutoff, which would identify more patients as hav-

ing LPR. Further trials are needed to more precisely determine the pH threshold for the diagnosis of LPR.

### **Enthusiasm is waning for pharyngeal pH monitoring**

In LPR, it was initially thought that pH monitoring in the pharynx was more accurate than in the distal or proximal esophagus.

Shaker et al<sup>22</sup> monitored the pH in the pharynx, proximal esophagus, and distal esophagus in four groups: 14 patients who had both laryngeal signs and symptoms, 12 patients who had laryngeal symptoms only, 16 patients who had GERD but no laryngeal symptoms, and 12 healthy volunteers. They found that pharyngeal reflux was more frequent and in greater quantity in patients with laryngeal signs and symptoms than in the other groups. This study suggested that pharyngeal pH monitoring may be useful in diagnosing LPR in patients who have laryngeal signs and symptoms.

However, hypopharyngeal pH monitoring has several problems. One issue is that, even in this trial, 2 of 12 healthy volunteers had episodes of pharyngeal reflux.<sup>22</sup> In other studies, the rate of false-positive results ranged from 7% to 17%.<sup>23,24</sup> Additionally, in 12 previous studies, only 54% of 1,217 patients with suspected LPR had esophageal acid exposure, regardless of where the pH probe was placed.<sup>25</sup>

More importantly, another study found that patients with pharyngeal reflux documented by pH monitoring were no more likely to respond to acid-suppressive therapy than patients with no documented reflux.<sup>26</sup> These findings dampen the enthusiasm for pharyngeal pH monitoring in LPR.

### **Impedance monitoring on therapy may be useful in refractory cases**

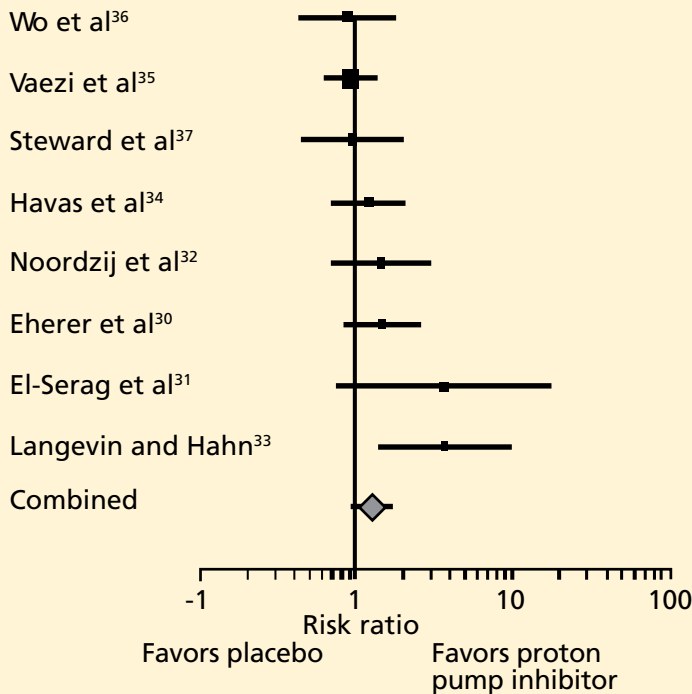
Esophageal impedance monitoring, a newer test, uses a catheter that measures electrical resistance (impedance) between different points along the esophagus. Thus, it can detect the reflux of acid and nonacid liquid or gaseous material.

Pritchett et al<sup>27</sup> performed esophageal impedance and pH monitoring in 39 patients who were on twice-daily PPI therapy and then evaluated the same patients with wireless pH monitoring while they were off therapy. The

**For those with laryngeal symptoms, pH testing does not reliably predict who will respond to therapy**



### Nonsignificant reduction in laryngeal symptoms with proton pump inhibitors



**FIGURE 2.** Forest plot depicting the risk ratio and 95% confidence intervals of individual studies assessing the efficacy of proton pump inhibitors in reflux laryngitis, and the pooled risk ratio by the random effects method.

FROM QADEER MA, PHILLIPS CO, LOPEZ AR, ET AL. PROTON PUMP INHIBITOR THERAPY FOR SUSPECTED GERD-RELATED CHRONIC LARYNGITIS: A META ANALYSIS OF RANDOMIZED CONTROLLED TRIALS. *AM J GASTROENTEROL* 2006; 101:2646–2654. USED WITH PERMISSION FROM NATURE PUBLISHING GROUP.

most prevalent complaint in the study group was cough (56%), followed by heartburn (18%) and sore throat (10%).

Of the 39 patients, 25 (64%) had normal results on impedance/pH monitoring while on therapy, ruling out reflux. On pH monitoring off therapy, 28 (72%) of the 39 patients had abnormal results; this group included 13 (93%) of the 14 patients who had abnormal results on impedance/pH monitoring while on therapy. The authors recommended on-therapy testing with impedance monitoring in patients with refractory reflux, since it provides more useful clinical information.<sup>27</sup> If the results of impedance/pH monitoring are negative in these patients, a diagnosis other than reflux should be considered.

### EMPIRIC PPI TREATMENT HAS SHOWN DISAPPOINTING RESULTS

Because laryngoscopy and pH monitoring are not very sensitive or specific for LPR, experts recommend empiric therapy with a PPI twice daily. However, the results have been disappointing when PPIs were compared with placebo in clinical trials.

In a randomized controlled trial,<sup>28</sup> we found that patients who had complaints of chronic throat-clearing, cough, globus, sore throat, and hoarseness had a similar response to twice-daily esomeprazole (Nexium) compared with placebo: their primary symptom had resolved by 16 weeks in 14.7% of the esomeprazole group vs 16.0% of the placebo group ( $P = .799$ ). Similarly, the final findings on laryngoscopy such as edema, erythema, and surface irregularity were not significantly different between groups.

In addition, a meta-analysis<sup>29</sup> of randomized controlled trials of PPIs for suspected GERD-related chronic laryngitis also had disappointing results (FIGURE 2). In this study, Qadeer et al analyzed eight trials<sup>30–37</sup> with a total of 344 patients (195 on a PPI, 149 on placebo). In five of the trials,<sup>30–34</sup> PPI therapy was superior to placebo in terms of the proportion of patients who had more than a 50% reduction in self-reported laryngeal symptoms, although the difference was statistically significant in only one of them.<sup>33</sup> In the other three studies, more patients responded to placebo than to a PPI.<sup>35–37</sup> When data from all eight trials were pooled, there was no significant difference between a PPI and placebo (risk ratio 1.28, confidence interval 0.94–1.74). The absolute rate of response to PPIs was 50%, vs 41% for placebo.<sup>29</sup>

### Adding a histamine-2 receptor antagonist is not recommended

Adding a histamine-2 receptor antagonist to PPI therapy has also been considered as a treatment for LPR.

Fackler et al<sup>38</sup> studied 16 GERD patients and 18 healthy volunteers to determine if adding ranitidine (Pepcid) to the PPI omeprazole (Prilosec) could improve GERD symptoms. Patients underwent baseline manometry and then gastroesophageal pH monitoring before

starting the drugs. They first received omeprazole 20 mg twice daily alone for 2 weeks, and then added ranitidine 300 mg at bedtime. A pH test was done again after the first day of treatment with ranitidine, at the end of 1 week of combination therapy, and after 4 weeks of combination therapy. The combination reduced nocturnal acid breakthrough on day 1; however, due to tolerance to ranitidine, no significant difference in acid suppression was seen after 1 week of therapy. Therefore, this combination is not recommended.

### Surgery is not recommended either

Some experts have argued for surgical fundoplication in patients whose symptoms persist despite drug therapy.

Swoger et al<sup>39</sup> treated 72 patients who had symptoms consistent with LPR with a PPI for 4 months; 25 patients in this group had less than a 50% improvement despite maximal drug therapy. Ten of these patients underwent surgical fundoplication, and 15 remained on drug therapy alone. At 1 year of follow-up, only one surgical patient (10%) reported improvement in laryngeal symptoms.

In view of this report and prior studies of surgical fundoplication,<sup>40</sup> surgery is not recommended for patients whose symptoms do not respond to aggressive PPI therapy.

### IF A PPI FAILS, LOOK FOR OTHER CAUSES OF SYMPTOMS

Although gastroesophageal reflux and laryngeal signs and symptoms have been associated with one another, this relation may have been overstated, leading to the overdiagnosis of LPR.

The diagnosis of LPR is difficult, as laryngoscopy has high interrater variability and as the results of pH monitoring do not dependably predict who will respond to treatment.

Because PPI therapy is easy and appears to be safe, patients with extraesophageal symptoms thought to be related to reflux should undergo a trial of twice-daily PPI therapy for at least 2 months. If the patient responds to therapy, then tapering to once-daily therapy initially and then to minimal acid suppression to control symptoms would be prudent.

In patients who show no improvement, other causes of symptoms should be explored. Diseases that can mimic LPR include postnasal drip, allergies, sinus inflammation, and various pulmonary diseases. These patients should also be advised to adopt lifestyle modifications—eg, to stop smoking, lose weight, and decrease activities that cause stress on the voice. Surgery is not likely to provide any benefit in this situation. The patient should be tapered off the PPI to make sure no rebound acid reflux occurs. ■

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