Detecting the *other* reflux disease

Laryngopharyngeal reflux is a disorder, unlike GERD, that few patients (and too few physicians) are familiar with. Misdiagnosis is common—unless you know what to look for.

Laryngopharyngeal reflux (LPR), the retrograde movement of gastric content into the upper aerodigestive tract, is a common—and commonly underdiagnosed—condition. Characterized by inflammation of the laryngopharynx, LPR can coexist with gastroesophageal reflux disease (GERD), but it is a distinct disorder. In GERD, the lower esophageal sphincter malfunctions, whereas LPR involves a dysfunctional upper esophageal sphincter.

Because both conditions involve acid reflux, LPR is sometimes mistaken for GERD. Often, too, patients and physicians alike attribute LPR's signs and symptoms, which are largely nonspecific, to other causes. The hoarseness and laryngitis that are characteristic of LPR may be blamed on vocal cord abuse or smoking, for instance; the chronic cough and throat clearing associated with LPR thought to be caused by allergies; and the sore throat and postnasal drip that often accompany LPR attributed to infection. Another reason LPR is underdiagnosed: Primary care physicians, who are often the first clinicians from whom symptomatic patients seek treatment, are often unfamiliar with this lesser-known reflux disease.

The failure to recognize and provide timely treatment for LPR may increase patients’ risk for a number of conditions, including laryngeal ulcers, granulomas, subglottic stenosis, chronic sinusitis, laryngospasm, nasal congestion, and asthma. Evidence suggests that LPR increases the risk for esophageal and laryngeal carcinomas, and for laryngeal injury from intubation, as well. To minimize these risks, it is important for primary care physicians to promptly identify this disorder, treat it appropriately, and recognize red flags that warrant referral to a specialist.

How LPR develops, what to look for

There is no gold standard for the diagnosis of LPR. Nonethe-
Patients with LPR are particularly prone to developing hoarseness, globus pharyngeus—a sensation of a foreign body in the larynx—and sore throat.

less, a review of the pathophysiology and clinical presentation of this reflux disorder and the ways in which it differs from GERD will help you identify cases of LPR. The prevalence of LPR in the general population is uncertain. But reports suggest that as many as 10% of otolaryngology referrals are for patients with a classic presentation of LPR, and that 50% to 60% of cases of chronic laryngitis are related to LPR.1,3,6

The laryngopharynx becomes irritated and inflamed
When the physiological barriers protecting the laryngopharynx from the retrograde flow of gastric content break down, gastric contents can directly irritate the ciliated columnar epithelial cells of the upper respiratory tract, leading to ciliary dysfunction. A lack of mucous clearance leads to mucous stasis and, subsequently, to excessive throat clearing and the sensation of postnasal drip.7 In addition, the laryngopharyngeal epithelium becomes inflamed, and this affects the sensitivity of laryngeal sensory endings and leads to laryngospasm and coughing.8 The inflammatory reaction in turn leads to vocal fold edema, contact ulcers, and granulomas. These changes make patients with LPR particularly prone to developing hoarseness, globus pharyngeus—a sensation of a foreign body in the larynx—and sore throat.5,7 The gastric content can also act indirectly by initiating laryngeal reflexes through irritation of the esophagus, leading to vagally mediated changes such as chronic cough and bronchoconstriction.

Enzyme production declines. Under normal circumstances, carbonic anhydrase isoenzyme III (CAIII) is produced in the posterior aspect of the larynx, catalyzing the production of bicarbonate and neutralizing stomach acid.9-11 In LPR, however, the production of CAIII decreases significantly, thereby exposing the larynx to stomach acid without the enzyme’s protective effect.9,10 At the same time, a marked increase in pepsin levels intensifies laryngeal injury.10,12,13

The larynx is highly vulnerable. The laryngopharynx is much more susceptible to pathology from gastric reflux than the esophagus, for a number of reasons. Damage can occur with much less exposure to acid,7 not only because of the decrease in CAIII, but also because of the absence of peristalsis in the larynx.

What’s more, the esophagus has the ability to clear gastric reflux and minimize damage to the epithelial layer.5,10,14,15 In most patients who develop signs and symptoms of LPR, there has been enough gastric reflux to
Heartburn, esophagitis, and nighttime reflux, characteristics of GERD, are not common in patients with LPR.

Common signs and symptoms that signal LPR
LPR is primarily a clinical diagnosis based on signs and symptoms—which are also used to rule out GERD. Notably, less than 50% of patients with LPR suffer from heartburn and regurgitation. Those who do have heartburn and regurgitation typically suffer with reflux during the day, when they’re in an upright position, whereas reflux associated with GERD develops primarily at night. The results of a recent survey of members of the American Bronchoesophageological Association highlight the most common signs and symptoms of LPR, listed below from the most to the least frequent:

- throat clearing
- persistent cough
- globus sensation
- hoarseness
- choking episodes.

Additional signs and symptoms include excessive and chronic throat clearing, sore throat, postnasal drip, and dysphagia.

Use a validated symptom index. To further assess the probability and severity of LPR, use the Reflux Symptom Index (TABLE 1). A recent cohort study validated the index, with an average score of 21.2 for those with LPR, vs an average of 11.6 for controls ($P<.001$). A score $>13$ is suggestive of LPR (odds ratio=9.19), the researchers found.

If the diagnosis remains uncertain and the patient continues to be troubled by signs and symptoms suggestive of LPR, refer him or her to an otolaryngologist for further investigation. A referral is needed, too, to rule out malignancy in any patient with 3 or more of the following red flags: older than 50 years, otalgia, weight loss, progressive hoarseness, neck mass, a significant history of alcohol use, and a history of smoking.

Diagnostic tools the specialists will use
- Fiber optic laryngoscopy is the most common test used by otolaryngologists to confirm LPR and rule out other pathology. The test reveals inflammatory findings (FIGURE), such as erythema, edema, granulomas, and contact ulcers, in several anatomical locations of the larynx—especially the posterior aspect and the true vocal folds. It is important to note, however, that as many as 70% of the general population will have some laryngeal...
inflammation, so these findings alone are not definitive evidence of LPR.7

Ambulatory 24-hour dual sensor pH probe monitoring is sometimes used as an adjunctive test to confirm LPR. In 2005, 2 meta-analyses found that the pH probe is reliable and sensitive and specific enough to identify significantly more acid reflux in patients with LPR than in controls.19,20 However, not everyone agrees: Some clinicians question its use as a diagnostic tool for LPR, citing problems with observer reliability, among other things. Because it increases costs to the patient and is impractical, pH monitoring is not widely used by specialists, but primarily as a research tool.21,22

Barium swallow and esophagogastroduodenoscopy (EGD) are relatively common diagnostic tools used to identify anatomical abnormalities in the gastrointestinal tract, such as a Schatzki’s ring or hiatal hernia, that can lead to symptoms of GERD and/or LPR. Some studies suggest that all patients with symptoms of LPR should undergo EGD to screen for esophageal adenocarcinoma.23,24 Because LPR symptoms are relatively common, however, many clinicians believe that EGD should be considered only when heartburn is a primary complaint in a patient with signs and symptoms of LPR—or when a patient believed to have LPR fails to respond to medical management.24

Treating LPR: Lifestyle changes, drug therapy
For all patients with LPR, dietary and lifestyle modifications have been shown to be both clinically effective and cost effective.25 In addition to dietary restrictions (TABLE 2), advise patients to avoid eating too rapidly or drinking large quantities of fluid. Late night meals—indeed, eating within 3 hours of bedtime—should also be avoided, as should heavy lunches and dinners. Tell patients to eat small, frequent meals instead.7,25,26

Recommend other behavioral changes, as well. Tell patients to avoid tight clothing, lying down immediately after a meal, and applying pressure to the abdomen, whether through exercise, heavy lifting, singing, or bending over. Smoking and overuse (or misuse) of the voice—screaming at a concert or singing for hours, for instance—are contraindicated, as well.7,25,26

* A score >13 is considered suggestive of laryngopharyngeal reflux.


**TABLE 1**
The Reflux Symptom Index for laryngopharyngeal reflux

<table>
<thead>
<tr>
<th>Within the last month, how did the following problems affect you?</th>
<th>0 = NO PROBLEM</th>
<th>5 = SEVERE PROBLEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hoarseness or a problem with your voice</td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>2. Clearing your throat</td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>3. Excess throat mucus or postnasal drip</td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>4. Difficulty swallowing food, liquids, or pills</td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>5. Coughing after you ate or after lying down</td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>6. Breathing difficulties or choking episodes</td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>7. Troublesome or annoying cough</td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>8. Sensations of something sticking in your throat or a lump in your throat</td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>9. Heartburn, chest pain, indigestion, or stomach acid coming up</td>
<td>0 1 2 3 4 5</td>
<td></td>
</tr>
</tbody>
</table>

**TOTAL SCORE**=

**CONTINUED**
Tell patients that weight loss, as needed, is likely to bring some symptom relief. Using wooden blocks to elevate the head of the bed about 4 to 6 inches may also be helpful, particularly for patients who suffer from both LPR and GERD.7,25,26

Drug therapy: Straightforward, but not without controversy

- Acid suppression with proton pump inhibitors (PPIs) is the primary treatment for LPR, as it is for GERD. But because the larynx is extremely susceptible to injury from acid reflux, LPR typically requires more aggressive and prolonged treatment, compared with GERD.1,5

  Clinical trials have shown that PPIs do not inhibit acid production to an intragastric pH of >4 for more than 16.8 hours.1,27 Thus, most patients need twice-daily dosing (although once-a-day dosing or conservative management may be sufficient for those with mild and intermittent symptoms).27,28 Regardless of dosing, PPIs should be taken on an empty stomach, 30 minutes before a meal to increase bioavailability. For maximum benefit, patients should continue the twice-daily regimen for 4 to 6 months, although the optimal duration is unknown.29

  One study found 4 months of therapy to be effective;28 others suggest that while symptom relief should begin after 6 to 8 weeks of treatment, 6 months of PPI therapy is needed for laryngeal lesions and edema to resolve.1,8 Despite the time frame, patients should be weaned gradually to prevent the delayed rebound effect associated with abrupt cessation of PPIs.

  - The PPI controversy. Not only the length of treatment is controversial, however, but the efficacy of PPIs for LPR. Many studies, including several prospective cohort studies and 9 RCTs, have reported significant improvement in laryngeal symptoms, but evidence that PPIs are significantly better than placebo is weak.25,29,30 In fact, a systematic review and 2 meta-analyses concluded that not only is there a lack of sufficient evidence to draw reliable conclusions about the efficacy of PPIs vs placebo for the treatment of LPR, but there seems to be a significant response to placebo among patients with this condition, as well.25,29,30

  - The role of adjunctive therapy. Histamine type 2 (H2) blockers have been shown to be helpful in the treatment of GERD. But data showing their efficacy for LPR, either as a single agent or in combination with a PPI, are limited. Indeed, 3 clinical trials have found that H2 blockers do not provide any added benefit to PPI therapy for LPR. All 3 were cohort studies that compared the treatment outcomes of PPI alone vs PPI and H2 blockers, and found no statistically significant difference (P>.05).28,31,32 Despite these findings, recent studies suggest that 300 mg ranitidine twice a day provides added benefit (P<.01).33,34

Given these mixed findings, H2 blockers may be considered as adjuvant therapy to the PPI regimen to further reduce acid production in patients with more severe symptoms. Antacids and prokinetic agents are sometimes used for this purpose, as well.

When medical management fails

Surgery has a limited, but useful, role in the treatment of LPR.

- Nissen fundoplication—a procedure in which the fundus of the stomach is passed posteriorly behind the esophagus to encircle

### TABLE 2

**Dietary management of LPR: What to tell patients**7,14,24

<table>
<thead>
<tr>
<th>Avoid*</th>
<th>Enjoy†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>Meat</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Poultry</td>
</tr>
<tr>
<td>Spicy foods</td>
<td>Seafood</td>
</tr>
<tr>
<td>Tomatoes</td>
<td>Milk</td>
</tr>
<tr>
<td>Chocolate</td>
<td>Fresh vegetables</td>
</tr>
<tr>
<td>Fats</td>
<td></td>
</tr>
<tr>
<td>Citrus fruits</td>
<td></td>
</tr>
<tr>
<td>Carbonated beverages</td>
<td></td>
</tr>
<tr>
<td>Jams/jellies</td>
<td></td>
</tr>
<tr>
<td>Barbecue sauces</td>
<td></td>
</tr>
<tr>
<td>Salad dressings</td>
<td></td>
</tr>
<tr>
<td>Hot mustard</td>
<td></td>
</tr>
<tr>
<td>Curry</td>
<td></td>
</tr>
<tr>
<td>Hot peppers</td>
<td></td>
</tr>
</tbody>
</table>

*Other acidic foods.
†Other foods and beverages that are neither spicy nor acidic.
‡Except tomatoes.
it and provide mechanical obstruction to the retrograde movement of acid—may be considered for patients with a confirmed diagnosis, severe symptoms, and little response to treatment. However, there is little evidence that this procedure will result in long-term improvement in LPR symptoms. Laryngeal surgery can be used to treat vocal fold sequelae of LPR, such as granulomas—with a higher likelihood of success.35

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References
35. H2 blockers may be considered as adjuvant therapy to the PPI regimen to further reduce acid production in patients with more severe symptoms.