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Issue: *The 11th OESO World Conference: Reflux Disease***Laryngopharyngeal reflux and GERD**Nikki Johnston,¹ Peter W. Dettmar,² Vicki Strugala,² Jacqui E. Allen,³ and Walter W. Chan⁴¹Department of Otolaryngology, Medical College of Wisconsin, Milwaukee, Wisconsin. ²Technostics Ltd, Castle Hill Hospital, Kingston-Upon-Hull, United Kingdom. ³Department of Otolaryngology, North Shore Hospital, Auckland, New Zealand.⁴Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital, Harvard Medical School, Cambridge, MassachusettsAddress for correspondence: annals@nyas.org

In patients with laryngopharyngeal reflux (LPR), gastric contents exhibit retrograde flow into the upper aero-digestive tract, causing extraesophageal symptoms including chronic cough, hoarseness, indigestion, difficulty swallowing, globus pharyngis, and asthma. The following on laryngopharyngeal reflux includes commentaries on the use of patient-completed questionnaires and anti-human pepsin antibodies and other non-invasive tests in diagnosis; the role of pepsin and acid in the etiologies of laryngeal cancers; and the application of proton pump inhibitor (PPI) therapy for the treatment of LPR.

Keywords: laryngopharyngeal reflux; laryngeal cancer; pepsin; diagnostic tests; proton pump inhibitor

Concise summaries

- The anti-human pepsin antibodies used in studies investigating the presence of pepsin in clinical samples are sensitive. While laryngoscopy and pH monitoring do not have strong predictive value, measurement of pepsin in patients with laryngopharyngeal reflux (LPR) holds promise as a diagnostic test and, in addition, the detection of pepsin seems to predict clinical improvement of LPR after antireflux surgery.
- It is apparent that the pathophysiology of LPR is different to that of classical gastroesophageal reflux disease (GERD). A range of patient-completed questionnaires is a very useful tool to assist patient-history documentation. They also help in recording symptoms over time and the effects of therapy. A number of invasive diagnostic tests can be performed (some of which are only marginally invasive) to identify LPR, and there are non-invasive tools and diagnostic tests available to assist in the assessment: empiric trial of proton pump inhibitor (PPI) therapy, noninvasive collection of refluxate for bile acid, and pepsin detection.
- Exposure of human hypopharyngeal and laryngeal cell cultures to pepsin, both in the presence of acid and in nonacid conditions, induces expression of proinflammatory cytokines, and several authors have identified bile acids as pro-carcinogenic, with marked increase in laryngeal cancer prevalence in patients who have undergone gastrectomy. Molecular changes may be induced by components of refluxate and may be involved in the pathway to cell dysregulation. Given that the majority of daily reflux events are likely weakly acidic or nonacidic, the effect of exposure in these conditions is most important and likely to have long-reaching effects that may alter cell function and regulation. Current studies support the role of reflux in carcinogenesis but do not prove that reflux alone is sufficient for tumor growth or a direct causative agent.
- Many clinical studies have shown a high prevalence of LPR in patients with laryngeal cancer, but these studies are confounded by the fact that the majority of patients with laryngeal cancer have a significant smoking and alcohol history, and many lack appropriate controls. The larynx lacks many of the defense mechanisms to protect against damage by

refluxate present in the esophagus, such as peristalsis, saliva, and bicarbonate production. Thus, it seems logical that chronic laryngeal inflammation from LPR could lead to a neoplastic lesion as in GERD. Pepsin and bile acids have a significant role in carcinogenesis, in a dose-dependent manner with greater toxicity at lower pH. Gene ontology and pathway analyses strongly suggest that pepsin exposure will increase cell proliferation and thus may contribute to oncogenic transformation by causing aberrant cell growth. Growth curve and Click-iT EdU proliferation assay data also demonstrate a significant increase in cell proliferation by pepsin in normal laryngeal primary epithelial cells and FaDu hypopharyngeal epithelial cells.

- There is currently no diagnostic gold standard for LPR. The diagnosis remains challenging, and often controversial. Early uncontrolled studies have shown significant improvement in symptoms with PPIs and suggested that an empiric trial may be useful for both therapy and diagnosis. More recently published controlled studies continued to demonstrate variable results. However, without other reliable diagnostic gold standards, an empiric trial of PPIs is an easy and safe choice, although the length of therapy remains unclear. On the basis of outcomes of LPR studies to date and prior experience with treatment of GERD and erosive esophagitis, a trial of 2–3 months should be used, with dose tapering if symptomatic response is achieved.

1. Is pepsin a sensitive and specific marker for laryngopharyngeal reflux?

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Pepsin is thought to be solely produced by gastric chief cells in zymogen form as pepsinogen, and subsequently cleaved by the HCl in the stomach, generating active pepsin protein. To confirm that the laryngeal tissue specimens, which we and others detect pepsin in, do not synthesize their own pepsinogen and pepsin, real-time (RT)-PCR and Western blot analysis has been performed on specimens from the same patient to measure pepsinogen mRNA and pepsin protein, respectively.¹ Pepsinogen is not detected in laryngeal tissue specimens which are positive for pepsin protein, confirming that the laryngopharynx does not produce pepsin. Thus, the pepsin detected in patients with LPR was presumably deposited from a reflux event. Pepsin is only produced in the stomach, and thus when detected in the laryngopharynx, it is a specific marker for reflux.

The anti-human pepsin antibodies used in studies investigating the presence of pepsin in clinical samples are sensitive. For example, our anti-human pepsin detects less than 0.05 ng of pepsin.² Furthermore, one can discriminate between pepsin at

35 kDa and pepsinogen at 43 kDa using Western blot analysis. This is important due to potential contamination of blood in clinical samples. Using this antibody, we have reported the presence of pepsin in 26 of 27 laryngeal biopsy specimens taken from patients with clinically diagnosed LPR, not detected in any of the 19 control subjects.²

Earlier this year, Yuksel *et al.* reported the sensitivity, specificity, and positive and negative predictive values (PPV and NPV, respectively) of a salivary pepsin test in patients with GERD compared to healthy controls.³ Fifty-two gastric juice and 54 water samples were used to assess test sensitivity and specificity, reported at 87%. Saliva was collected from 58 patients with GERD and 51 control subjects. Patients with GERD underwent esophagoduodenoscopy (EGD) and 48-h pH monitoring. Six of 51 (12%) control subjects and 13 of 58 (22%) patients with GERD tested positive for pepsin, with a significant stepwise increase in the prevalence of pepsin: GERD symptoms only (24%), abnormal pH monitoring (43%), and esophagitis (55%). Salivary pepsin, therefore, showed a PPV of 81% and NPV of 78% for those with GERD, as determined by abnormal pH and/or esophagitis. The authors concluded that a positive salivary pepsin test may obviate the need for more expensive diagnostic testing by EGD or pH monitoring. Regarding the low prevalence of

pepsin in GERD patients (22%), the authors noted that for pepsin to be present in saliva, refluxate must travel to the oropharynx, which is not common in GERD.

Jiang *et al.* investigated the use of immunohistochemical (IHC) detection for pepsin in laryngeal mucosa in diagnosing LPR.⁴ Biopsy specimens were obtained from the interarytenoid mucosa of 15 LPR patients (7 with acid LPR and 8 with nonacid LPR) and 21 control subjects and stained for pepsin. The diagnosis of LPR was based on 24-h combined multichannel intraluminal esophageal impedance–pH monitoring. Six of seven acid LPR (85.7%) and six of eight nonacid LPR (75%) specimens stained positively for pepsin, while only three of 21 control samples tested positive for pepsin. The authors therefore concluded that the presence of pepsin in laryngeal mucosa detected by IHC is 80% sensitive and 85.7% specific for the detection of LPR. This is, however, an invasive test for LPR compared to saliva samples.

Li *et al.* investigated whether the presence of pepsin in sputum could be used to detect LPR.⁵ They recruited 56 patients with symptoms of laryngopharyngitis and 15 healthy controls. The 56 patients were divided into two groups: an LPR group and a chronic laryngitis group, by the Reflux Symptom Index (RSI) and Reflux Finding Score (RFS). Sputum samples were analyzed for the presence of pepsin using an ELISA. Pepsin was detected in 30 of 32 LPR patients, 18 of 24 patients with chronic laryngitis, and 3 of 15 normal controls. The authors concluded that detection of pepsin in sputum by immunoassay might provide a sensitive and noninvasive method for LPR.

Our group prospectively used pepsin in a group of 10 patients with clinical LPR undergoing antireflux surgery with the intent of determining (1) the incidence of pepsin detection in patients with LPR; (2) the concordance between pepsin biopsy and sputum detection; (3) the ability of antireflux surgery to eradicate pepsin from the upper airway; and (4) the ability of pepsin detection to predict clinical response to antireflux surgery.⁶ Seven women and three men were included in the study. One patient withdrew before any postoperative testing, so data was available on nine patients. The most common primary LPR symptom was hoarseness; two patients recorded cough and one recorded globus as their primary symptom. Postoperatively, six patients have good symptom improvement, two had mild im-

provement, and one had no improvement. Pepsin was detected in eight of nine patients preoperatively. Five patients had both biopsies and sputum for analysis preoperatively, and in four of these there was a correlation between pepsin detection in biopsy and sputum. The patient without preoperative pepsin remained negative and was the only patient that did not have normalization of reflux measured by pH monitoring. We evaluated the correlation between all preoperative diagnostic studies (pH monitoring, laryngoscopy, and pepsin) for potential predictive trends. Unlike the DeMeester score and RFS, which were not predictive, all patients with positive preoperative pepsin and postoperative elimination had symptom improvement. Thus, while laryngoscopy and pH monitoring do not have strong predictive value, measurement of pepsin in patients with LPR holds promise as a diagnostic test for the following reasons: (1) in patients with clearly documented GERD and signs of LPR, pepsin is frequently detected in the airway (by biopsy or sputum), providing further evidence for aspiration of gastric contents as the primary mechanism of disease; (2) there is good concordance between pepsin detection in biopsy and sputum specimens, which is encouraging for the practical application of the test; (3) antireflux surgery is successful in eradicating pepsin from the upper airway; and (4) unlike the RFS and DeMeester scores, pepsin detection seems to predict clinical improvement of LPR after antireflux surgery.

In conclusion, the studies performed to date demonstrate that pepsin is a sensitive and specific marker for reflux, but larger studies need to be performed.

2. What are the current diagnostic tests for LPR?

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Introduction

The pathophysiology of LPR is often poorly understood. The otolaryngological manifestations attributed to LPR include dysphonia, vocal fatigue and voice breaks, dysphagia, and globus pharyngeus, as well as altered salivation and excessive throat mucus. It is apparent that the pathophysiology of LPR is different to that of classical GERD.

The process of clinical diagnosis of LPR begins by taking a detailed patient history taking particular interest in classical and otolaryngological symptoms including those attributed to silent reflux. A detailed medical history should be taken including pharmacological agents being used, as some may elicit LPR symptoms as side effects (e.g., angiotensin-converting-enzyme (ACE) inhibitors).

Patient-completed questionnaires

A range of patient-completed questionnaires is a very useful tool to assist patient-history documentation. They also help in recording symptoms over time and the effects of therapy.

- **RSI.** This was developed and validated by Belafsky *et al.*⁷ and is a widely used instrument. The RSI is made up of nine questions each with a score of 0–5 (total 0–45). The higher the score, the greater the symptoms experienced by the patient. A score of less than 13 is indicated as normal in the published validation study, but in the clinical setting a score of 10 is often indicated as normal.
- **Quality-of-Life Index (QLI) for LPR.** The disease-specific QLI for LPR was developed and validated by Carrau *et al.*⁸ and comprises 43 questions in five domains including a domain related to the overall effects of acid reflux. The score ranges from 9 to 256 with a higher score indicative of greater effects of LPR on quality of life.
- **Glottal closure/function index (GCI).** The glottal function index, also known as the glottal closure index, was developed and validated by Bach *et al.*⁹ and is a brief self-administered instrument with four questions giving a score ranging from 0 to 20. It evaluates symptom-focused vocal impairment and a score of greater than 4 is considered to be abnormal.
- **Voice handicap index (VHI).** The VHI quantifies the psychosocial effect of voice disorders in a 30-item questionnaire developed by Jacobson *et al.*¹⁰ Each item scores between 0 and 4 with a maximum total score of 120. A change in reduction in score of 18 is indicative of a clinically significant shift in psychosocial voice function.

Invasive tests

A range of invasive diagnostic tests can be performed (some of which are only marginally invasive) to identify LPR.

- **Fiber-optic transnasal laryngoscopy.** First-line diagnostic strategy of the otolaryngologist to visualize the larynx and quantify the extent of damage can be done using the RFS.¹¹
- **24-h ambulatory dual probe pHmetry.** Measures acid reflux (pH < 4) and requires probes in the esophagus and pharynx in order to evaluate laryngeal acid reflux events.
- **24-h pHmetry/multichannel intraluminal impedance (MII).** Similar to pHmetry, but the multiple impedance channels can detect reflux in general and not just acid reflux events but also weak acid and nonacid reflux events.
- **Pharyngeal pHmetry.** Using the Restech Dx-pH probe, this minimally invasive technique measures acidic reflux events into the pharynx/airway.
- **Transnasal esophagoscopy (TNE).** This is a diagnostic tool (designed for pharyngo-esophagoscopy) for the laryngologist to examine the upper gastrointestinal (GI) tract with a small-diameter scope such that sedation is not required and it is well tolerated.
- **Biopsy.** Biopsies of the larynx can be used as a research tool to detect biomarkers of reflux by immunohistochemistry or Western blot. Biomarkers can include mucins, carbonic anhydrase, E-cadherin, Il-6, and heat shock proteins.¹²

Noninvasive tests

There are noninvasive tools and diagnostics available to assist in the assessment of LPR.

- **Empiric trial of PPI therapy.** This may be successful in assisting the diagnosis of GERD but has little utility in LPR, despite the widespread use.
- **Noninvasive collection of refluxate.** Sampling the refluxate can be achieved by collecting expectorated saliva, sputum, or exhaled breath condensate (EBC). Refluxate can also be harvested invasively during endoscopy procedures (e.g., aspiration of esophageal or laryngeal

fluid). These refluxate-containing samples can then be used to detect biomarkers of reflux events.

Bile acid detection

Bile acids are a marker of duodeno-gastroesophageal reflux and can be detected accurately with mass spectrometry. Simple assay kits can be used (3 α -hydroxysteroid enzymatic total bile acid kits) but it must be stressed that these are designed to detect large changes indicative of liver disease and may not be sensitive enough for diagnosis of LPR.¹³

Pepsin detection

Pepsin, secreted into gastric juice, is an excellent marker of reflux.¹⁴ There are a range of techniques available to detect pepsin in refluxate, including enzymatic assays, immunohistochemistry, Western blot, and ELISA, all of which are time-consuming and require technical knowledge. Rapid lateral flow tests (Peptest™) to detect pepsin are the most recent addition to the diagnostic portfolio.

Peptest is an *in vitro* diagnostic medical device in the form of a lateral flow test that uses two unique monoclonal antibodies to human pepsin. Peptest enables the rapid detection of pepsin in a clinical sample of refluxate (e.g., expectorated saliva). It has been validated in LPR patients compared to normal controls¹⁵ and it is a sensitive and specific test.¹⁶ It is commercially available worldwide.

3. Do *in vitro* studies support a role for LPR in laryngeal cancer?

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The primary risk factors for laryngeal cancer are smoking, gender, and alcohol. Additional putative risk factors have been proposed, including human papillomavirus and reflux exposure. Thirty manuscripts have been published in the last decade examining the association between reflux and laryngeal carcinogenesis. The majority (70%) supports the hypothesis. Population studies have demonstrated contradictory results regarding the effect of reflux in laryngeal cancer, largely owing to the presence of confounding risk factors. Animal and *in vitro* studies have been performed in an attempt to isolate reflux effects and determine the true risk associated with reflux and cancer development.

There is biological plausibility for reflux resulting in carcinogenesis, as demonstrated by the evolution of esophageal adenocarcinoma (EAC) in patients with GERD. The larynx lacks the protective mechanisms of the esophagus such as mucus, peristalsis, and carbonic anhydrase enzyme, making it more prone to the inflammatory effects of refluxate. Chronic inflammation may result in metaplasia and cellular changes that predispose to carcinogenesis. The agent (or agents) that may be responsible for tumorigenesis is not clear. Acid, pepsin, bile acids, and any combination of these may be implicated.

Animal studies in rodents have demonstrated a significant enhancement of tumor growth when acidified pepsin is added to known carcinogens.^{17,18} However, some studies did not demonstrate any effect of simulated reflux in rat larynges.¹⁹ Exposure of human hypopharyngeal and laryngeal cell cultures to pepsin, both in the presence of acid and in nonacid conditions induces expression of proinflammatory cytokines.²⁰ There is also increased proliferation of laryngeal epithelial cells in culture when exposed to pepsin.¹ Pepsin is also known to be endocytosed, giving rise to the opportunity for pepsin to alter transcriptional processes intracellularly.^{1,20} Several authors have identified bile acids as procarcinogenic and note the marked increase in laryngeal cancer prevalence in patients who have undergone gastrectomy.^{21–23} Tutar *et al.* identified bile acids in hypopharyngeal and tumor tissue at a significantly higher rate in patients with laryngeal cancer than in subjects with benign lesions of the larynx.²²

Molecular changes that may be induced by components of refluxate and be involved in the pathway to cell dysregulation are being studied more closely. Sung *et al.* noted increased expression of cyclooxygenase-2 enzyme (COX2) in pharyngeal cells cultured with bile acids. COX2 affects cell-cycle function, reducing apoptosis, and thus may influence cell proliferation.²³ Reichel *et al.* demonstrated reduced E-cadherin expression in cultures from patients with LPR and from smokers. E-cadherin is a critical cell–cell adhesion molecule, and loss of function may predispose to early metastasis and cell migration.²⁴ Johnston *et al.* have examined hypopharyngeal and laryngeal cell cultures exposed to pepsin both with and without acid microenvironments using the human cancer PathwayFinder and RNA analysis.¹ They have identified more than 20 genes that show altered expression, including cell

cyclins and cell adhesion molecules. Furthermore, they have also demonstrated changes in downstream protein products such as Ras protein and cell receptors. Given that the majority of daily reflux events are likely weakly acidic or nonacidic, the effect of exposure in these conditions is most important and likely to have long-reaching effects that may alter cell function and regulation.

These findings support the role of reflux in carcinogenesis but do not prove that reflux alone is sufficient for tumor growth or is a direct causative agent. Further research is required to demonstrate progression from altered cells through dysplasia to frank carcinoma.

4. What is the prevalence and role of laryngopharyngeal reflux in laryngeal cancer?

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The 2012 cancer statistics from the American Cancer Society estimate that there will be over 25,000 new cases of laryngeal and pharyngeal squamous cell carcinoma diagnosed this year, resulting in over 6000 deaths.²⁵ Despite a decrease in the number of people who smoke in the United States, the incidence of laryngeal and pharyngeal cancer is rising. Unfortunately, the prognosis remains poor and the mortality rate high, with a 5-year survival rate of 40%.²⁵ Tobacco and alcohol are well-known established risk factors. LPR has also been proposed as a significant risk factor,²⁶ however its exact role in cancer of the laryngopharynx remains controversial. It is difficult to prove that reflux is a causal agent in the development of laryngeal cancer. Many clinical studies have shown a high prevalence of LPR in patients with laryngeal cancer,^{27,28} but these studies are confounded by the fact that the majority of patients with laryngeal cancer have significant smoking and alcohol histories, and many lack appropriate controls. There is also a lack of uniformity in establishing the diagnosis of GER and LPR in the literature. Further investigation is required, especially since LPR has become a common chronic disease of adults in the United States. Prolonged GER is known to cause chronic esophageal inflammation and Barrett's esophagus (BE), which in turn increases the risk of EAC. Unlike the esophagus, where up to 50 reflux episodes (below pH 4) per

day is considered normal, the larynx is much more susceptible to damage from reflux, with three or fewer reflux episodes per week causing injury and symptoms. The larynx lacks many of the defense mechanisms to protect against damage by refluxate present in the esophagus, such as peristalsis, saliva, and bicarbonate production. Thus, it seems logical that chronic laryngeal inflammation from LPR could lead to a neoplastic lesion as in GERD. Research in cell biology of reflux is needed to determine if LPR can promote and/or cause laryngeal cancer, since population and other clinical studies have too many confounding variables.

Gabriel and Jones were among the first to present evidence suggesting that chronic laryngitis from LPR is associated with and may promote cancer of the laryngopharynx.²⁹ In 2003, Wight *et al.* reported a high frequency of reflux in laryngeal cancer patients who do not drink or smoke, resulting in an increased interest in the relationship between reflux and laryngeal cancer.³⁰ Last year, Tae *et al.* reported the frequency and severity of LPR by 24-h double-probe pH monitoring in patients with laryngeal cancer and in a control group: LPR patients with chronic cough and globus.²⁸ The prevalence and severity of LPR was significantly higher in laryngeal cancer patients than in the control group. To further explore the association between LPR and laryngeal cancer, several investigators have examined the direct effect of the individual components of gastric refluxate—mainly acid, pepsin, and bile acids—on laryngeal cell and molecular biology and pathology.¹⁹ These studies demonstrated a significant role for pepsin and bile acids in carcinogenesis, in a dose-dependent manner with greater toxicity at lower pH. Interestingly, several clinical studies suggest that the components of nonacidic reflux promote the development of laryngeal cancer.³¹ Our group has recently reported that exposure of hypopharyngeal FaDu and normal human primary epithelial cells to pepsin (0.1 mg/mL; pH 7) causes a significant change in the expression of multiple genes implicated in carcinogenesis.¹ Gene ontology and pathway analyses of these data strongly suggest that pepsin exposure will increase cell proliferation and thus may contribute to oncogenic transformation by causing aberrant cell growth. This was investigated further using propidium iodide staining and flow cytometry. Pepsin was indeed found to significantly increase the percentage of cells in

S phase in a time- and dose-dependent manner in both FaDu hypopharyngeal and normal human primary laryngeal epithelial cells. Growth curve and Click-iT EdU proliferation assay data also demonstrate a significant increase in cell proliferation by pepsin in normal laryngeal primary epithelial cells and FaDu hypopharyngeal epithelial cells. Pepsin (0.1 mg/mL; pH 7) also changes the expression of multiple miRNAs specifically known to play a role in head and neck squamous cell carcinoma (HNSCC). These data demonstrate that pepsin, present in laryngopharyngeal cancer specimens but not in normal laryngeal control tissue, may initiate epithelial cell dysregulation promoting laryngopharyngeal cancer. Furthermore, using an *in vivo* hamster buccal pouch model of squamous cell carcinoma, we found a significant increase in tumor volume in hamster cheek pouches exposed to pepsin (0.1 mg/mL; pH 2) plus DMBA compared to DMBA alone (control), suggesting that pepsin in acid reflux does promote tumorigenesis. We are currently measuring the effect of pepsin at pH 7, with and without 7,12-Dimethylbenz(a)anthracene (DMBA), to determine whether pepsin (in LPR, which is predominantly nonacidic, and in the laryngopharynx, which has a mean pH of 6.8) is a promoter and initiator of carcinogenesis *in vivo*. Cell transformation, clonogenic, migration/invasion, and anoikis assays are also being performed to investigate its carcinogenicity in the laryngopharynx.

In conclusion, LPR pathology and number of episodes are more prevalent in patients with laryngeal cancer, but larger clinical studies are needed. *In vitro* and *in vivo* studies also suggest a role for LPR in carcinogenesis of the laryngopharynx, but further cell and molecular biology studies are needed to elucidate the exact role and mechanism.

5. How long should the PPI trial be in patients with ENT symptoms suspected to be due to GERD?

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Ear, nose, and throat (ENT) symptoms, including hoarseness, sore throat, cough, postnasal drip, and globus sensation, have long been associated with GERD from LPR. Earlier studies have estimated that about 10% of all patients presenting to ENT specialists have GERD-related complaints.³² However, the

determination of whether or not ENT symptoms reported by patients are GERD related can be difficult, as up to 50% of patients with extraesophageal symptoms of GERD may not experience typical esophageal symptoms such as heartburn.³³ Moreover, there is currently no diagnostic gold standard for LPR. LPR symptoms and laryngoscopic findings are nonspecific and subjective, with high interobserver variability.^{34,35} Ambulatory esophageal and pharyngeal monitoring for LPR may also be unreliable and not predictive of outcome.³⁶ Therefore, the diagnosis of LPR remains challenging and often controversial.

Early uncontrolled studies have shown significant improvement in LPR symptoms with PPIs and suggest that an empiric trial may be useful for both therapy and diagnosis. Belafsky *et al.* studied 40 patients with LPR symptoms who were treated with PPIs for 6 months. They noted significant decrease in LPR symptoms at the 2-month follow-up, but not at 4 or 6 months. Improvement in laryngoscopic findings was milder and trailed symptom response, with continual progression throughout the whole 6-month period. Therefore, the authors concluded that treatment with PPIs for LPR should continue for a minimum of 6 months.³⁷

Later controlled studies, however, showed little to no benefit of PPIs over placebo for LPR. Vaezi *et al.* randomized 146 patients to receive esomeprazole versus placebo for 16 weeks in a multicenter study. No benefit over placebo in LPR symptoms or laryngoscopic findings was noted, as there was significant placebo response.³⁸ In 2006, a meta-analysis of placebo-controlled trials for treatment of chronic laryngitis showed no benefits for PPIs (Fig. 1). In addition, no clear correlation between duration of PPI trial and symptom response was noted.³⁹ More recently published controlled studies continued to demonstrate variable results. Reichel *et al.* studied 62 patients placed on esomeprazole versus placebo for 3 months. There was significant reduction in RSI, with the majority coming from heartburn-related symptoms. In addition, 41% of patients in the placebo group were also free of symptoms at the end of the trial.⁴⁰ Lam *et al.* randomized 51 patients to rabeprazole twice daily versus placebo for 12 weeks, followed by 6 weeks off treatment. Rabeprazole led to decrease in RSI at weeks 6 and 12, although, once again, the improvement resulted mainly from reflux-related symptoms.⁴¹

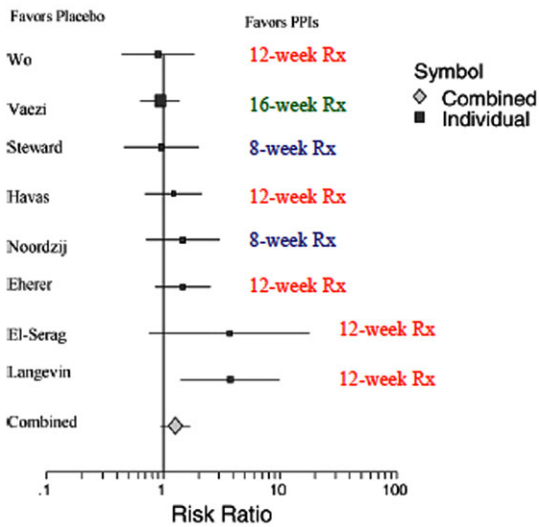


Figure 1. Meta-analysis of placebo-controlled trials in treatment of chronic laryngitis showed no benefits for PPI. There was no clear correlation between duration of PPI trial and symptom response.³⁹

Overall, there is currently no clear evidence that an empiric PPI trial results in significant reduction in LPR symptoms or laryngoscopic findings over placebo. Therefore, its use as a diagnostic or therapeutic tool in the management of patients with ENT symptoms remains controversial. However, without other reliable diagnostic gold standards, an empiric trial of PPIs is an easy and safe choice, although the length of therapy remains unclear. On the basis of outcomes of LPR studies to date and earlier experience with treatment of GERD and erosive esophagitis, a trial of 2–3 months should be used, with dose tapering if symptomatic response is achieved. Given the unreliability of laryngoscopic findings, therapy should be based on symptoms. Longer therapy aimed solely toward changing laryngoscopic signs would not be necessary.

Conflicts of interest

The authors declare no conflicts of interest.

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