Laryngopharyngeal Reflux and Voice Disorders: An Overview on Disease Mechanisms, Treatments, and Research Advances

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Abstract: Laryngopharyngeal reflux (LPR) is common. Nevertheless, controversy persists regarding its pathophysiology, diagnosis, and treatment. Research studies have been unconvincing, and contradictory in some cases. Standards of diagnosis remain controversial, and there is a paucity of incontrovertible data confirming efficacy of treatment. Because of the high prevalence of LPR and its potential serious consequences (including laryngeal carcinoma), it is important for physicians to be familiar with contemporary perspectives on this disorder, current standards of patient care, and the need for additional multidisciplinary research.

Introduction

Laryngopharyngeal reflux (LPR) is an extraesophageal variant of gastroesophageal reflux disease (GERD) that affects the larynx and pharynx. In recent years, many otolaryngologists have acknowledged the existence and potential importance of LPR in patients with otolaryngologic complaints (Sataloff et al., 2006a), although the association between acid reflux and laryngeal abnormalities has been recognized for more than four decades (von Leden and Moore, 1960; Pesce and Caligaris, 1966; Cherry and Margulies, 1968; Dalhunty and Cherry, 1968; Hallewell and Cole, 1970; Cherry et al., 1970; Johnson, 1981; Ward et al., 1980; Bain et al., 1983; Delahunty, 1972; Sataloff, 1993; Sataloff, 2008; Gupta and Sataloff, 2009). As otolaryngologists have been more diligent about looking for signs of LPR such as posterior laryngeal edema and erythema, obliteration of the laryngeal ventricles, and interarytenoid hypertrophy, treatment for LPR based upon these findings has become increasingly common. Because of a paucity of convincing evidence regarding techniques for establishing definitive diagnosis and causation in individual patients, and because of a plethora of imperfect studies that have produced conflicting conclusions, LPR diagnosis and management remain controversial. This article includes observations written previously by the authors (Sataloff et al., 2006a; Sataloff, 2008; Gupta and Sataloff, 2009).

Voice Symptoms, Signs, and Physical Examination

The most recent evidence indicates that LPR represents a complex spectrum of abnormalities, and it is important for physicians to understand the latest concepts in the relevant basic science and clinical care of patients with LPR. Symptoms and signs related to reflux have been identified in 4% to 10% of all patients seen by otolaryngologists (Koufman, 1991; Toohill et al., 1990; Koufman et al., 2000; Ross et al., 1998; Koufman et al., 1988), and it is probable that these estimates are low. Among patients with laryngeal and voice disorders, LPR appears to be associated strongly with, or be a significant etiologic cofactor in, about half of these patients. Many of the current concepts regarding reflux laryngitis and related controversies have been reviewed in the otolaryngologic and gastroenterologic literature (Koufman and Wright, 2006; Ormseth and Wong, 1999; Richter and Hicks, 1997). Among patients who present with voice disorders, the estimated prevalence of LPR is much higher. In 1989, Wiener et al. (1989) reported that 78% of 32 patients with voice complaints had LPR documented by pH probe. Koufman et al. (2000) found LPR in 78% of patients with hoarseness, and in roughly 50% of all patients who presented with voice complaints. Many other publications have addressed the
LPR has been associated with numerous laryngeal conditions, including muscle tension dysphonia, Reinke’s edema, globus pharyngeus, laryngeal hyperirritability, laryngospasm, delayed wound healing, posterior laryngitis, diffuse laryngitis, laryngeal pyogenic granuloma, glutotic and subglottic stenosis, cricoarytenoid joint ankylosis, carcinoma, and other conditions (Sataloff et al., 2006a; Chen et al., 1998).

Common symptoms and signs of reflux laryngitis include morning hoarseness, prolonged voice warm-up time (greater than 20 to 30 minutes), halitosis, excessive phlegm, frequent throat clearing, xerostomia (dry mouth), coated tongue, sensation of a lump in the throat (globus sensation), throat tickle, dysphagia, regurgitation of gastric contents, chronic sore throat, possibly geographic tongue, nocturnal cough, chronic or recurrent cough, difficulty breathing (especially at night), aspiration, occasionally pneumonia, closing off the airway (laryngospasm), poorly controlled asthma, recurrent airway problems, occasionally dyspnea (epigastric discomfort) or pyrosis (heartburn). LPR has also been associated with sudden infant death syndrome (Halstead, 1999; Wetmore, 1993; Landler et al., 1990; Spitzer et al., 1984; Jeffery et al., 1983; Camfield et al., 1982; Kahn et al., 1990; Ramet, 1994; Sacre et al., 1989; Kurz et al., 1985), probably mediated through the laryngeal chemoreflex (Davies et al., 1988; Pickens et al., 1988; Downing and Lee, 1975; Heman-Ackah and Goding, 2000; Goding and Pernell, 1996; Lanier et al., 1983; Heman-Ackah, 2005).

Traditionally, the diagnosis of LPR was missed because symptoms associated classically with reflux (GERD) such as dyspepsia and pyrosis are frequently absent because patients with LPR either do not develop esophagitis, or do not respond to acid reflux with typical symptoms such as heartburn, both in our experience and that of others (Ossakow et al., 1987; Wiener et al., 1989; Koufman, 1991). Ossakow et al. (1987) studied reflux symptoms in 36 gastrointestinal (GI) patients and 63 otolaryngologic (ORL) patients (Ossakow et al., 1987). In their population, none of the GI patients had hoarseness, but all the ORL patients complained of hoarseness. Only 6% of the ORL patients had heartburn; however, heartburn was reported in 89% of the GI patients. This low prevalence of heartburn is consistent with our experience. In a particularly important study, Wiener et al. (1989) evaluated 32 patients with hoarseness. Esophageal manometry findings were normal in all 32 patients. Of interest, many pharyngolaryngology study findings were abnormal in 76%, esophageal biopsy findings were normal in 72%. These results highlight the important fact that gastric acid can reflux through the esophagus to the larynx without causing esophageal injury in transit. Koufman’s data on patients undergoing barium esophagram revealed that only 18% of patients with LPR had esophagitis identified on barium study (Koufman, 1991), although the barium swallow study is a very insensitive test for esophagitis. Presumably, the incidence of esophagitis is relatively low because distal esophageal mucosa has specialization and defense mechanisms that help it tolerate acid exposure. Esophageal protective mechanisms include peristalsis, which clears acid from the esophagus; a mucosal structure that may be specialized to tolerate intermittent acid contact; the acid-neutralizing capacity of saliva that passes through the esophagus (Helm et al., 1982); and bicarbonate production in the esophagus, which has been recognized since the 1980s (Tobey et al., 1989; Hamilton and Orlando, 1989). Of interest, however, if some patients stop reflux treatment after a few months, classic dyspepsia and pyrosis seem to be present commonly when symptoms recur, although this clinically observed phenomenon has not been studied formally. It should be noted that the larynx and pharynx do not have protective mechanisms to guard against mucosal injury such as those found in the esophagus. Thus, exposure to acid and pepsin that may be of no consequence in the distal esophagus may cause substantial symptoms and signs in the larynx and/or pharynx of some patients. Preliminary data reported by Axford et al. (2001) suggest that laryngeal mucosa has different cellular defenses from those of esophageal mucosa. These investigators also suggested that there may be specific differences in MUC gene expression and carbonic anhydrase that suggest a pattern of abnormality in patients with LPR.

In addition to prolonged vocal warm-up time, professional singers and actors may also complain of voice practice intolerance, manifested by frequent throat clearing and excessive phlegm, especially during the first 10 to 20 minutes of vocal exercises or singing. Hyperfunctional technique during practice and especially singing is also associated with reflux laryngitis, which is probably due to the vocalist’s unconscious tendency to guard against aspiration. Voice professionals can be helped somewhat in overcoming this secondary muscular tension dysphonia through voice therapy with speech-language pathologists, singing voice specialists, and acting voice specialists, but it is difficult to overcome completely until excellent reflux control has been achieved.

In addition to the paucity of typical gastroesophageal reflux disease symptoms in patients with LPR, the tendency to under-diagnose LPR has been increased by three additional factors. First, the importance of a thorough physical examination is under-appreciated. Posterior laryngitis and interarytenoid pachydermia are frequently ignored. It is even more common to fail to recognize the causal relationship between reflux and edema with little or no erythema, especially if the edema is diffuse, rather than most prominent on the arytenoids. Second, therapeutic medication trials may fail because patients are under-medicated (with a proton pump inhibitor given only once daily, for example) or assessed before signs of LPR have had time to resolve (which may require a few months or more). Third, results of routine tests for GERD can be falsely negative. This problem involves not only barium esophagrams, the Bernstein acid-hyperperfusion test, and radionuclide scanning but also esophagoscopy and 24-hour pH monitoring studies (depending on the norms used). Consequently, physicians must maintain a high index of suspicion in the presence of symptoms consistent with LPR, evaluate such patients aggressively, and interpret test results knowledgeably and with awareness of their sensitivities, specificities, limitations, and controversies.
Physical examination of patients with throat and voice complaints must be comprehensive. A thorough head and neck examination is always included, with particular attention paid to the ears and hearing, nasal patency, signs of allergy, the oral cavity, temporomandibular joints, the larynx, and the neck. In some patients with LPR severe enough to involve the oral cavity, there is also loss of dental enamel. Hence, transparency of the lower portion of the central incisors may be seen occasionally in reflux patients, although it may be more common in patients with bulimia and those who habitually eat lemons. At least a limited general physical examination is conducted to look for signs of systemic dysfunction that may present as throat or voice complaints. More comprehensive specialized physical examinations by medical consultants should be sought when indicated.

When the patient complains of vocal difficulties, laryngeal examination is mandatory. It should be performed initially using a mirror or flexible fiberoptic laryngoscope, but comprehensive laryngeal examination requires strobovideolaryngoscopy for slow-motion evaluation of the vibratory margin of the vocal folds. Formal assessment of the speaking voice and signing voice also should be performed, when appropriate. Objective voice analysis quantifies voice quality, pulmonary function, valvular efficiency of the vocal folds, and harmonic spectral characteristics. The neuromuscular function can be measured by laryngeal electromyography (EMG). These aspects of the physical examination and tests of voice function are discussed elsewhere (Sataloff, 2005).

Most commonly, laryngoscopy in patients with LPR reveals erythema and edema. Classically, reflux laryngitis involves erythema of the arytenoid cartilages and frequently interarytenoid pachydermia (a knobby or cobblestone appearance), as well as other signs (Al-Sabbagh and Wo, 1999; McMurray et al., 2001). However, many additional features may be observed, including edema of the false and true vocal folds, partial effacement or obliteration of the laryngeal ventricle, Pseudosulcatus (a longitudinal groove extending below the vibratory margin throughout the length of the vocal fold, including the cartilaginous portion), Reinke’s edema, granulomas or ulcers (most commonly in the region of the vocal process), nodules and other masses, an interarytenoid bar, laryngeal stenosis, and other abnormalities. Koufman and colleagues reported that edema was even more common than erythema: edema was diagnosed in 89% of 46 patients, compared with 87% who had erythema, 19% with granuloma or granulation tissue, and 2% with ulceration (Koufman et al., 1988).

Belafsky et al. (2001a) developed a reflux finding score (RFS) that rates signs and appears to correlate with the presence of laryngopharyngeal reflux. They advocate use of this instrument in combination with the reflux symptom index (RSI) (Belafsky et al., 2002). The RFS depends on observations of subglottic edema, ventricular obliteration, erythema/hyperemia, vocal fold granuloma/granulation tissue, and thick endolaryngeal mucus. Although additional research from other centers is needed to confirm the validity and reliability of the RFS, the authors found excellent inter- and intraobserver reproducibility (although all observers were practicing at the same medical center); they found the RFS to be an accurate instrument for documenting treatment efficacy in patients with LPR.

In patients with severe LPR, the finding of a hyperactive gag reflex is also common; of interest, they may also have decreased laryngeal sensation. One of us (RTS) has performed functional endoscopic evaluation of sensory threshold (FEEST) testing on patients with LPR and found that responses were diminished prior to treatment and were improved following treatment. These findings are consistent with preliminary observations by Aviv (Jonathan Aviv, M.D., personal communication, 2000).

It should be noted that controversy exists regarding the significance of laryngeal findings. Credible studies of the sensitivity and specificity of laryngoscopy for diagnosis of LPR are needed, although a few initial reports exist in the literature. Carr et al. (2000) studied 155 children retrospectively. In a chart review of direct laryngoscopy and bronchoscopy findings, they reported a positive predictive value of 100% for the combination of posterior chronic edema with any vocal fold or ventricular abnormality. McMurray et al. (2001) evaluated 39 children prospectively with laryngoscopy, bronchoscopy, esophagoscopy, and pH monitoring prior to airway reconstruction. Full-thickness laryngeal mucosal biopsy specimens were obtained from the posterior cricoid area and the interarytenoid area, and esophageal biopsy specimens were also obtained. These investigators were unable to demonstrate a correlation among pH probe data, laryngoscopic findings, and histologic findings. Hicks et al. (2002) studied 105 healthy, asymptomatic volunteers. On laryngoscopy, more than 80% had at least one “abnormal” finding, including (in order of frequency from most frequent to least) interarytenoid bar, medial arytenoid erythema, posterior pharyngeal cobblestoning, medial arytenoid granularity, and true vocal fold erythema. This study did not include 24-hour pH monitoring or any other tests to rule out the presence of “silent” reflux as a cause of the laryngoscopic abnormalities.

Despite many articles exploring signs and symptoms of reflux including those cited above and other recent literature (Close, 2002; Tauber et al., 2002; Vaezi, 2002; Book et al., 2002; Branski et al., 2002; Noordzi and Khidir, 2002; Marambaia et al., 2002; Siupsinskiene and Adamonis, 2003; Vaezi, 2003; Lassing, 2003; Maronian et al., 2003; Burati et al., 2003; Wang et al., 2004; Ahmad and Batch, 2004; Grillo et al., 2004; Hill et al., 2004), evidence confirming the diagnostic significance of various complaints and findings is scarce and contradictory. This problem is due to various problems including the lack of a standard definition of “normal” in populations being studied. Continued interdisciplinary discourse and multicenter studies should be encouraged to answer important questions regarding the sensitivity and specificity of the many findings associated commonly with laryngopharyngeal reflux, as well as the impact of laryngopharyngeal reflux on quality of life and general health (Lenderking et al., 2003).

**Pathophysiology**

Laryngeal abnormalities may be caused by direct injury or by a secondary mechanism. Direct injury is due to contact of acid and pepsin with laryngeal mucosa, resulting in mucosal damage (Chen et al., 1998; Wetmore, 1993; Landler et al., 1990; Spitzer et al., 1984; Jeffery et al., 1983; Camfield et al., 1982; Kahn et al., 1990; Ramet, 1994; Ludemann et al., 1998). Alternatively, irritation of the distal esophagus by acid may cause a reflex mediated by the vagus nerve, resulting in chronic cough and throat clearing, which may produce traumatic injury to the laryngeal mucosa (Toohill et al., 1990; Koufman et al., 2000; Ramet, 1994; Sacre and Vandenplas, 1989; Kjellen and Brudin, 1994).
bile reflux also may cause laryngeal irritation (Galli et al., 2003). It has long been asserted that nonacid reflux also can trigger cough and throat clearing and cause mucosal irritation that is troublesome to some voice patients, and recent experience with impedance monitoring has confirmed the association between nonacid reflux and such symptoms. In addition, recent findings raise many new questions about the pathophysiology of laryngopharyngeal reflux. Eckley and colleagues reported that decreased salivary epidermal growth factor may be associated with laryngopharyngeal reflux (Eckley et al., 2004; Eckley and Costa, 2003) and warrants further study, for example; and Altman’s discovery of laryngeal serous cells and ducts of submucosal glands is particularly intriguing (Altman et al., 2003). A multidisciplinary effort initiated by Dr. Jamie Koufman to elucidate the cellular biology of laryngopharyngeal reflux to clarify the nature of acidic and peptic injury processes at a more fundamental level is particularly promising.

Diagnostic Tests

Diagnostics tests will not be reviewed in this article. The subject is covered in other sources (Sataloff et al., 2006b).

Treatment

Details of treatment for reflux-induced voice disorders also will not be reviewed in detail in this brief article. Many are covered elsewhere in other sources (Sataloff et al., 2006c). Mainstays of therapy are lifestyle modification, proton pump inhibitors, H2 receptor antagonists, over-the-counter antacids, and prokinetic agents. Treatment of Helicobacter pylori also may be appropriate. A gradually increasing number of patients have been undergoing laparoscopic Nissen fundoplication, which, when successful, treats reflux, rather than just treating acidity. For patients who have symptomatic non-acid reflux (common among voice professionals), as well as those who do not achieve adequate acid suppression even on high doses of proton pump inhibitors, surgical intervention may be a good option (Sataloff et al., 2006d). However, this article will review current common practice, and many of the questions that need to be answered in order to improve the standard of care for patients with LPR.

Traditionally, otolaryngologists have managed patients with LPR by therapeutic trial. If definite improvement in symptoms and signs is noted after treatment with a proton pump inhibitor (PPI), some physicians consider the diagnosis confirmed. For patients who show no response to reflux therapy, some otolaryngologists assume reflux has been ruled out and discontinue the PPI, substituting treatment for allergy or some other conditions. In the absence of studies, this approach is particularly problematic since many patients continue to produce at least some acid despite proton pump inhibitors twice daily, and it has been recognized for many years that some patients with reflux do not respond to proton pump inhibitors and continue to produce normal amounts of acid despite treatment (Bough et al., 1995). Other otolaryngologists assume that if the patient has failed a therapeutic trial, the LPR is severe and requires even higher doses of PPI therapy, and the addition of other reflux or promotility medications which often are prescribed empirically (without tests objective for reflux).

At present, this field is in need of definitive, prospective, and evidence-based studies. However, while we are awaiting such data, we might benefit from another consensus conference regarding appropriate clinical management with the technology available to us currently. The last such consensus conference statement was published in 1996 (Koufman et al., 1996). There are many critical questions that need to be addressed to guide clinical care. Among others, they include the following questions that have been addressed in greater detail elsewhere (Sataloff, 2008):

What constitutes normal acid exposure in the larynx?

The definition of “normal” pH monitor results remains controversial, and there are differences in opinion between laryngologists and gastroenterologists regarding this important topic. Most of the support for laryngologic opinion is anecdotal, but such clinical judgments should be studied, not dismissed. Many laryngologists (this author among them) believe that in some patients, any laryngeal acid exposure can cause signs and symptoms, even occasional laryngeal acid contact that may only occur once every day or two (perhaps less). This seems intuitively plausible. If one were to place a single drop of gastric juice in an individual’s eye every day or two, that eye would probably remain erythematous and more prone to injury than the normal eye, if both eyes were traumatized by a foreign body such as sand, for example. There is no evidence that laryngeal mucosa is any more equipped to tolerate acid contact than the eye. While this hypothesis is probably true for some patients, it is important for physicians to recognize biologic variability, about which there is surprisingly little discussion in the LPR literature. Just as some patients smoke three packs of cigarettes a day for 60 years without developing cancer and others develop cancer after smoking just one pack a day for ten years, it is likely that laryngeal response to acid contact varies among individuals. This issue requires study; and it also requires consideration when interpreting results of LPR diagnostic studies, therapeutic response, and clinical trials, especially when sample size is small.

Despite the paucity of solid evidence, laryngologists have reached many of their opinions about LPR through considered clinical experience and meticulous patient observation. Unless/until beliefs grounded in the art of medicine are contradicted by evidence-based data, it is reasonable to consider clinical “wisdom” when considering protocols for diagnosis and treatment, but clinical judgments should be tested and augmented by data whenever possible. For example, the author (RTS) has a growing number of patients who have had persistent symptoms and signs of reflux while using proton pump inhibitors, and whose 24-hour pH impedance monitors have shown continued acid production reaching the proximal sensor. Some of these patients improve with increased proton pump inhibitor therapy, others have continued to have symptoms and signs on proton pump inhibitors four times a day and have responded to fundoplication. Interestingly, we also have had some successful fundoplication results in patients who remained symptomatic (positive symptom index) from non-acid reflux alone. Many gastroenterologists remain uncomfortable with our interpretation of these findings and especially with the trend toward surgery. In general, if a gastroenterologist reads a 24-hour pH impedance study performed on medications that reveals four or five episodes of acid reflux at the proximal sensor, he/she will interpret the study as showing “normal acid exposure.” The problem is that the normative data for pH studies were established in patients who were not on proton pump inhibitors and who had…
How should we diagnose LPR, and what constitutes an appropriate evaluation protocol?

Gastroenterologists established criteria for esophageal screening based primarily on age and duration of heartburn. The criteria were selected to identify people at risk for Barrett’s esophagus and esophageal cancer. However, many LPR patients are young (well under 40) and have no heartburn; but they may have a 30-year history of reflux beginning at birth (or perhaps before birth). These patients may form a distinct population that falls outside the current guidelines for screening. Should they all undergo transnasal esophagoscopy (TNE), esophagogastroduodenoscopy (EGD) or some other physical examinations? This author (RTS) suspects that the standard of care will trend in that direction.

How should we manage patients who have persistent signs and symptoms (including those who have improvement but not resolution) following treatment with PPIs?

Twenty-four-hour pH impedance studies with symptom indices have proven invaluable and offer striking advantages over empirical management alone. Some patients require more than two PPIs a day to accomplish complete, or adequate, proximal acid suppression and improvement in symptoms and signs. Others have complete acid control but persistent symptoms caused by non-acid reflux as confirmed by symptom index. Still others appear to have symptoms and signs that are not causally related to reflux, and other causes must be sought. However, despite complete acid control, if they had documented reflux off medications, should they undergo esophagoscopy even if the documented reflux is not responsible for their laryngeal complaints?

Latest Research Findings

A review of selected recent research highlights the problems discussed above. It also reveals attempts by some investigators to address the pertinent questions.

Perhaps of greatest global significance, there is persistent controversy regarding the accuracy of diagnosis of LPR, the efficacy of treatment, and the quality of research that has been performed. The lack of reliable data is apparent in a recent study from the Cochrane Database of Systemic Reviews. The investigators examined existing data to determine the efficacy of anti-reflux therapy for patients with hoarseness. Of the 302 studies identified, none met their inclusion criteria (Hopkins et al., 2008). Their conclusion that there is a “need for high quality randomized controlled trials to evaluate the efficacy of anti-reflux therapy” echoes the frustration of many current practitioners.

Some promising research has been undertaken. For example, studies are attempting to delineate pathophysiology. To show LPR as an extra-esophageal manifestation of GERD, Groome et al. (2007) hypothesized that GERD patients would have some LPR symptoms if the pathophysiology were truly common. Through a questionnaire administered to 1,383 GERD patients, they determined that the prevalence of LPR increases with the severity of GERD. Although based on non-standardized questionnaires, the finding suggests a relationship. A similar study sought to exclude other etiologies of laryngitis and found LPR in 24% of patients with reflux esophagitis. The presence of LPR was predicted mostly by age, hoarseness, and hiatal hernia (Lai et al., 2008). A third study, strengthened by confirmed diagnoses of GERD and LPR with EGD and 24-hour pH monitoring, respectively, similarly showed that when both GERD and non-GERD patients were treated with proton pump inhibitors, laryngitis symptoms and signs improved in the GERD group only (Qua et al., 2007). These studies seem to point towards a common pathophysiology, suggesting that laryngeal symptoms are indeed caused by acid exposure.

Other investigators disagree. Nino et al. (2007) created an animal model for reflux and examined the reflux finding score (RFS), lipid-laden macrophage index (LLMI), and bronchoalveolar lavage (BAL) fluid differential before and two weeks after the induction of GERD. While reflux was induced in these animals, there was no significant difference in LLMI (a marker for aspiration), neutrophils in BAL fluid (markers of inflammation), or RFS. While the authors used these findings to question the link between reflux and laryngitis and aspiration, their short study period, single observer for RFS grading, lack of histopathology of the larynx, and small number of subjects (five) do not fully support the conclusions of the study. Nevertheless, the questions raised deserve further investigation using a more rigorous study design.

It has been established that pepsin in the larynx results in depletion of carbonic anhydrase isoenzyme III (CAI III) and squamous epithelial stress protein (Sep70), two laryngeal protective proteins (Johnston et al., 2006; Johnston et al., 2004). Pepsin is taken up by laryngeal cells and can be reactivated by a drop in pH, as seen in LPR. Pepsin is found in the esophageal mucosa of patients with Barrett’s esophagus and laryngeal mucosa of those with LPR (Johnston et al., 2007a). Interestingly, pepsin irreversibly affects CAI III at pH below 4 only in laryngeal, not esophageal, epithelium (Johnston et al., 2003). These laryngeal receptors for pepsin may be another future target for intervention. They also might explain the presence of symptoms and signs of LPR with weakly acidic reflux, as pepsin may be active to some degree at any pH between 3 and 6.5 (Johnston et al., 2007b), although a longer exposure time may be necessary at pH 5 to produce damage (Yitlalo et al., 2006). Possible pepsin activity at pH much above 5 remains controversial. Mucin gene expression is also found to be down-regulated in the presence of pepsin (Samuels et al., 2008).

One of the major controversies both in clinical practice and research is diagnosis of LPR. Studies are hampered by the lack of stringent inclusion and diagnostic criteria, and subsequent meta-analyses compound these errors.
In a quest for empiricism, pH impedance testing seems to offer the most objective data to allow accurate diagnosis and help establish causation through the symptom index. It is the current “gold standard,” but the accuracy of this measure also has come into question. This examination is subject to variability, including probe placement or movement, intermittent reflux not occurring during the test period, and data interpretation. Pharyngeal probes (versus esophageal probes) have been developed to assess the degree of acid that reaches the pharynx. However, impedance (and acid) probes may be inaccurate when allowed to dry, as may occur in the pharynx, resulting in “pseudoreflux” (Wiener et al., 1989). The yield on hypopharyngeal probes has been demonstrated to be less than 50% when all artifacts are excluded (Harrell et al., 2007). Despite this, studies often rely on pH impedance testing with pharyngeal sensors to diagnose LPR (Joniau et al., 2007). However, 24-hour pH monitoring is not always used due to patient resistance, expense, difficulty in interpretation, and equipment availability, making data even more difficult to interpret. pH monitoring also requires manometry to determine the location of the lower esophageal sphincter. If placement is not accurate, data are not valid. Even a 1-cm discrepancy in placement causes spurious readings (Postma et al., 2002). Finally, norms have not been established for pH in the hypopharynx, although the number of drops below pH 4 and the percentage of time below pH 4 are commonly used parameters.

Proton pump inhibitors are the mainstay of treatment for LPR, despite studies showing effects comparable to placebo. Caution must be exercised in interpretation of available literature. An insightful analysis by Johnson (1981) revealed that in a meta-analysis, all but two studies fell within a funnel plot. The only two that did not showed PPI effect, which indicates publication bias (Reichel et al., 2007a). Meta-analyses commonly magnify inherent flaws in the included studies, and more rigorous studies need to be performed.

It has been argued that without the presence of GERD symptoms, improvement in laryngeal symptoms with PPI is unlikely. Behavioral changes and investigation for alternative causes, such as allergy, pulmonary causes, and sinus problems, should be instituted (Reichel et al., 2008). However, significant data have shown at least partial improvement of laryngitis symptoms and laryngoscopic appearance with PPI treatment and behavioral changes. Lifestyle modifications include avoidance of heavy meals, smoking, alcohol, and late meals. Sleeping with the head of bed elevated and reducing body weight similarly show benefit (Kaltenbach et al., 2006).

Of note, it is common for laryngeal reflux findings and symptoms to take longer to resolve than esophageal symptoms. Also, symptoms often improve before clinical findings, which may take six months or longer to reverse (Belafsky et al., 2001b). Reichel et al. (2007a) noted control of LPR symptoms on daily PPI after an average of 4 weeks when combined with lifestyle modifications. Resistant cases could be treated with twice daily medication at higher doses. Improvement can be seen not only in symptoms and signs but also in objective assessments, such as acoustic parameters. Jin et al. (2008) reported that jitter, shimmer, and harmonic-to-noise ratio improved significantly after 1-2 months of treatment.

Refractory cases may be particularly challenging. Inadequate medication dosage, resistance to medication, reactivity to non-acid reflux in adequately controlled patients, and misdiagnosis are all potential factors. Medication dosages can be increased, as can the frequency of administration in some cases, although such modifications in treatment are “off label.” Pro-motility agents and histamine receptor antagonists can be added. pH monitoring on medication can be useful in this population in determining the etiology of persistent signs and symptoms in patients receiving treatment for LPR.

Belafsky et al. (2008) describes the presence of esophagoglaryngeal reflux (EPR) as a distinct from of LPR that should also be considered as a possible cause for treatment failures. This disorder is characterized by regurgitation of proximal esophageal contents into the laryngopharynx secondary to inadequate volume clearance and dysmotility, rather than acid and peptic injury. Further studies are needed to elucidate this process, as treatment with antireflux medications, prokinetics, dilatation, and diet modification ameliorates symptoms in 50% of affected individuals.

Studies have also examined the potential carcinogenic role of LPR. Conflicting data exist, complicated recently by published studies that show no carcinogenic effects, but that were limited by short periods of acid injury (Ling et al., 2007; Del Negro et al., 2008). Although some studies have shown LPR as a risk factor in animal models, others have not, and the true relationship between LPR and laryngeal malignancy remains uncertain. However, there are enough data indicating a possible link to suggest that at present, known reflux patients should be screened for laryngeal cancer and be made aware of this risk (Qadeer et al., 2006).

Given the risk of esophageal adenocarcinoma in reflux patients, the value of EGD screening has been assessed. It has been argued that LPR symptoms are better indicators of esophageal adenocarcinoma than gastroesophageal symptoms (Reavis et al., 2004). Studies have shown esophagitis in 12-18% of LPR patients, and Barrett’s metaplasia in 3-7% (Reichel et al., 2007b). Additionally, in patients on long-term PPI, H. pylori is known to accelerate the loss of specialized gastric glands, causing atrophic gastritis and gastric cancer (Kuipers et al., 1997). Serologic testing may screen for this infection.

Clinicians should be aware also of the prevalence of LPR in children. pH monitoring is valuable in infants with laryngitis, including pharyngeal monitoring which may diagnose undertreated LPR or LPR missed on esophageal monitoring (Ulalp et al., 2007). LPR is a known common cause of hoarseness in children and should be in the differential diagnosis (Block et al., 2007). It may be misdiagnosed as recurrent croup, when reflux triggers intermittent airway obstruction (Hoa et al., 2008). The diagnosis of LPR is still often missed in children with hoarseness or frequent respiratory disorders.

Conclusion

LPR represents a complex spectrum of pathophysiology, diagnostic challenge, and therapeutic controversy. Patient management can be optimized only through excellently designed studies with rigorous inclusion criteria, involving close collaboration among laryngologists, gastroenterologists, research scientists, and reflux surgeons. Considering the rapidly growing body of knowledge regarding reflux disease, the potentially serious consequences of under-treated reflux, the importance of other
entities that may be missed when they are misdiagnosed as reflux, and considering the interdisciplinary collegiality that exists currently nationally and internationally, there is every reason to believe that it is possible to establish interinstitutional, unbiased collaboration that should provide answers to these important clinical questions in the near future and that should lead to consensus regarding rational diagnosis of and treatment for laryngopharyngeal reflux.

Disclosure
The authors report no conflicts of interest.

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