Optimal treatment of laryngopharyngeal reflux disease

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Irene Martinucci, Nicola de Bortoli, Edoardo Savarino, Andrea Nacci, Salvatore Osvaldo Romeo, Massimo Bellini, Vincenzo Savarino, Bruno Fattori and Santino Marchi

Abstract: Laryngopharyngeal reflux is defined as the reflux of gastric content into larynx and pharynx. A large number of data suggest the growing prevalence of laryngopharyngeal symptoms in patients with gastroesophageal reflux disease. However, laryngopharyngeal reflux is a multifactorial syndrome and gastroesophageal reflux disease is not the only cause involved in its pathogenesis. Current critical issues in diagnosing laryngopharyngeal reflux are many nonspecific laryngeal symptoms and signs, and poor sensitivity and specificity of all currently available diagnostic tests. Although it is a pragmatic clinical strategy to start with empiric trials of proton pump inhibitors, many patients with suspected laryngopharyngeal reflux have persistent symptoms despite maximal acid suppression therapy. Overall, there are scant conflicting results to assess the effect of reflux treatments (including dietary and lifestyle modification, medical treatment, antireflux surgery) on laryngopharyngeal reflux. The present review is aimed at critically discussing the current treatment options in patients with laryngopharyngeal reflux, and provides a perspective on the development of new therapies.

Keywords: gastroesophageal reflux disease, laryngopharyngeal reflux, proton pump inhibitor, treatment

Introduction

Laryngopharyngeal reflux (LPR) is defined as the reflux of gastric content into the larynx and pharynx [Vakil *et al.* 2006]. According to the Montreal Consensus Conference, the manifestations of gastroesophageal reflux disease (GERD) have been classified into either esophageal or extraesophageal syndromes and, among the latter ones, the existence of an association between LPR and GERD has been established [Vakil *et al.* 2006]. LPR may be manifested as laryngeal symptoms such as cough, sore throat, hoarseness, dysphonia and globus, as well as signs of laryngeal irritation at laryngoscopy [Vaezi *et al.* 2003]. Laryngopharyngeal symptoms are increasingly recognized by general physicians, lung specialists and ear, nose and throat (ENT) surgeons [Richter, 2000]. In particular, there is a large number of data on the growing prevalence of laryngopharyngeal symptoms in up to 60% of GERD patients [Jaspersen *et al.* 2003; Koufman *et al.* 1996; Richter, 2004]. In addition, some studies support the notion that GERD, as well as smoking and alcohol use, are risk factors for laryngeal cancer [Freije *et al.* 1996; Vaezi *et al.* 2006a]. According to the Montreal Consensus Conference, some critical issues have been highlighted, as follows:

(1) the rarity of extraesophageal syndromes occurring in isolation without a concomitant manifestation of typical GERD symptoms (i.e. heartburn and regurgitation);
(2) extraesophageal syndromes are usually multifactorial with GERD as one of the several potential aggravating cofactors;
(3) data supporting a beneficial effect of reflux treatment on the extraesophageal syndromes are weak [Vakil *et al.* 2006].

Subsequently, the American Gastroenterological Association guidelines for GERD recommended against the use of acid-suppression therapy for acute treatment of patients with potential extraesophageal GERD syndromes (laryngitis, asthma)

Correspondence to:
Nicola de Bortoli, MD
Gastroenterology Unit, University of Pisa, and Cisanello Hospital, Via Paradisa 2 – 56124 Pisa (PI), Italy
nick.debortoli@gmail.com

Irene Martinucci, MD
Massimo Bellini, MD, PhD
Santino Marchi, MD
Gastroenterology Unit, University of Pisa, Pisa, Italy

Edoardo Savarino, MD, PhD
Division of Gastroenterology, University of Padua, Padua, Italy

Andrea Nacci, MD
Salvatore Osvaldo Romeo, MD
Bruno Fattori, MD
Ear, Nose and Throat Audiology Phoniatrics Unit, University of Pisa, Pisa, Italy

Vincenzo Savarino, Prof, MD
Division of Gastroenterology, Department of Internal Medicine (DIMI), University of Genoa, Genoa, Italy

in the absence of typical GERD symptoms [Kahrilas *et al.* 2008].

The specific reflux-related mechanisms leading to laryngopharyngeal symptoms and signs are currently unknown. Acidity of gastric juice alone may cause tissue damage at the upper airway level [Wiener *et al.* 2009], but several studies have demonstrated that this is not the only etiologic factor involved in the pathogenesis of laryngopharyngeal reflux disease (LPRD). Indeed, recently, Pearson and colleagues [Pearson *et al.* 2011] highlighted that, although acid can be controlled by proton pump inhibitor (PPI) therapy, all of the other damaging factors (i.e. pepsin, bile salts, bacteria and pancreatic proteolytic enzymes) remain potentially damaging on PPI therapy and may have their damaging ability enhanced. Particularly, pepsin can damage all extragastric tissues at pH up to 6 [Ludemann *et al.* 1998]. Of note, detectable levels of pepsin have been shown by Johnston and colleagues to remain in laryngeal epithelia after a reflux event [Johnston *et al.* 2007a]. The same authors described that pepsin is taken up by laryngeal epithelial cells by receptor-mediated endocytosis [Johnston *et al.* 2007b], thus it may represent a novel mechanism, besides its proteolytic activity alone, by which pepsin could cause GERD-related cell damage independently of the pH of the refluxate [Pearson *et al.* 2011].

To date, the diagnosis of LPR is a very difficult task and several controversies remain regarding how to confirm LPRD. Laryngoscopic findings, especially edema and erythema, are often used to diagnose LPR by ENT surgeons [Vaezi *et al.* 2003]. However, it should be pointed out that, in a well-performed prospective study, laryngoscopy revealed one or more signs of laryngeal irritation in over 80% of healthy controls [Milstein *et al.* 2005]. Moreover, it has been demonstrated that accurate clinical assessment of LPR is likely to be difficult because laryngeal physical findings cannot be reliably determined from clinician to clinician, and such variability makes the precise laryngoscopic diagnosis of LPR highly subjective [Branski *et al.* 2002]. The sensitivity and specificity of ambulatory pH monitoring as a means for diagnosing GERD in patients with extraesophageal reflux symptoms have been challenged [Vakil *et al.* 2006]. Furthermore, the sensitivity of 24-h dual-probe (simultaneous esophageal and pharyngeal) monitoring has ranged from 50% to 80% [Koufman, 1991]. Recently, the availability of multichannel intraluminal impedance and pH monitoring (MII-pH) seems to show better performances in diagnosing extraesophageal manifestations of GERD thanks to its ability to evaluate acid and nonacid refluxes other than their proximal extension [Carroll *et al.* 2012; Savarino *et al.* 2009; Sifrim *et al.* 2005; Tutuian *et al.* 2006]. However, the poor sensitivity and specificity of all currently available diagnostic tests for LPR has been highlighted by several review articles [Altman *et al.* 2011; Katz *et al.* 2013; Vaezi *et al.* 2003]. In a population of patients with laryngoscopic findings of LPR, our group showed that MII-pH confirmed GERD diagnosis in less than 40% of patients [de Bortoli *et al.* 2012], thus highlighting the critical issue of nonspecific symptoms and laryngoscopic findings of LPR [Zerbib and Stoll, 2010]. New promising diagnostic techniques have been developed for extraesophageal reflux syndromes, in particular, an immunologic pepsin assay (Peptest^{TM}), which has been shown to be a rapid, sensitive, and specific tool [Bardhan *et al.* 2012; Samuels and Johnston, 2010], and a new pH pharyngeal catheter (manufactured by Restech, San Diego, CA, USA) that recent study documented as highly sensitive and minimally invasive device for the detection of liquid or vapors of acid reflux in the posterior oropharynx [Sun *et al.* 2009]. However, limited data on their diagnostic accuracy and potential clinical application are available.

In this review, we will discuss the current treatment options in patients with LPRD and their pro/cons, and we will provide a perspective on the development of new therapies.

Lifestyle modifications

Diet and lifestyle modifications are effective interventions for GERD, despite the fact that few robust data have been published (Table 1) [De Groot *et al.* 2009; Kaltenbach *et al.* 2006]. According to treatment used in a UK district general hospital, dietary and behavior modification has also been supposed to be very effective in the management of LPR [Pearson *et al.* 2011].

Obesity

The incidence of obesity in Western countries has increased dramatically [Nicholls, 2013], and this has occurred in concordance with an increase in the number of patients suffering from GERD [El-Serag and Sonnenberg, 1998]. Multiple

Table 1. The positive effects of lifestyle modifications compared with those of uncertain efficacy in the treatment of laryngopharyngeal reflux disease (LPRD).

Lifestyle modifications in LPRD treatment	
Suggested	**Uncertain**
Treating obesity/overweight • Reduce daily caloric intake • Aerobic physical activity	• Reducing weight in normal BMI
Changing alimentary habits • Increase fiber intake • Increase fruit and vegetable intake • Reduce spicy and sweet food intake • Reduce carbohydrate beverage intake	• Reducing acid beverage intake (orange or apple juice) • Reducing tomato, tomato sauce, mint, and garlic intake
Reducing alcohol and coffee intake	Reducing cigarette smoking
Elevating the head of the bed	
Avoiding strenuous exercises	

BMI, body mass index.

epidemiological studies clearly demonstrate an association between obesity and GERD and physiologic investigations support a biologically plausible relationship between obesity and GERD.

In particular, different studies have shown an association between higher body mass index (BMI) and GERD [Fass *et al.* 2005; Nasseri-Moghaddam *et al.* 2008; Ruigomez *et al.* 2004; Savarino *et al.* 2011] and both obesity (BMI >30 kg/m^2) and being overweight (BMI 25–30 kg/m^2) are associated with GERD [Dore *et al.* 2008; Nocon *et al.* 2007].

The effect of BMI on GERD occurrence seems to be independent of total caloric intake, dietary intake of fiber, fruits and vegetables, or other macro or micronutrients [El-Serag, 2008]. Obesity is supposed to modify esophagogastric joint (EGJ) morphology and function. Indeed, obesity generates a mechanical disruption of EGJ by promoting an axial separation between the lower esophageal sphincter (LES) and the extrinsic crural diaphragm [Pandolfino *et al.* 2006]. LES incompetence has also been observed in obese patients [Fisher *et al.* 1999; Suter *et al.* 2004] and among morbidly obese patients a higher esophageal acid exposure was significantly associated with a lower LES pressure [Sabate *et al.* 2008].

Observational studies of overweight and obese patients found that weight loss resulted in improvement in GERD symptoms [Anderson and Jhaveri, 2010; Fraser-Moodie *et al.* 1999]. Moreover, reflux symptoms have been shown to be exacerbated or improved over time concomitant with weight gain or loss, respectively [Jacobson *et al.* 2006]. The HUNT study showed that, among individuals with GERD-related symptoms, a reduction higher than 3.5 units in BMI is related to a reduction or cessation in weekly antireflux medication use [Ness-Jensen *et al.* 2013]. On the other hand, whether weight reduction may improve the subjective or objective manifestations of reflux is still controversial [Kjellin *et al.* 1996]. Moreover, few data are available to determine whether weight loss is able to improve GERD-related symptoms such as LPR.

Eating habits

Although few data are available on this matter, in clinical practice different foods are indicated to influence the occurrence of refluxes and, generally, patients are advised against taking food late in the evening [Pearson *et al.* 2011].

High-fat foods and chocolate are empirically indicated as foods able to reduce LES pressure or to prolong gastric emptying; however, there have been no cessation trials evaluating the impact on GERD outcomes [Murphy and Castell, 1988; Wright and Castell, 1975]. Heartburn may be exacerbated by spicy foods attributable to direct irritation of already inflamed lower esophageal mucosa. In particular, Nebel and colleagues [Nebel *et al.* 1976] described that 88% of patients

reported spicy foods as the cause of their heartburn. Orange juice has been implicated in GERD symptoms even if orange juice infusion did not change LES pressure [Cranley *et al.* 1986].

In a cross-sectional study in patients followed at Veterans Administration healthcare facilities, high dietary fat intake was associated with an increased risk of GERD and erosive esophagitis [El-Serag *et al.* 2005]. However, several other studies reported conflicting data showing that a high-fat diet had no effect on transient LES relaxation or esophageal acid exposure [Mangano *et al.* 2002; Pehl *et al.* 2001; Penagini, 2000; Penagini *et al.* 1998]. Although it is unclear whether caloric density contributes to esophageal symptoms and acid exposure, a recent randomized study including a small group of patients found that esophageal acid exposure was higher with ingestion of a high-calorie diet (1000 kcal *versus* 500 kcal), and reflux symptoms were affected by the fat content but not density [Fox *et al.* 2007].

Carbonated beverages have been associated with promoting GERD symptoms by decreasing LES pressure and were found to predict GERD symptoms in a multivariate analysis [Fass *et al.* 2005].

Coffee has been reported to precipitate reflux episodes [Brazer *et al.* 1995]. A Norwegian case–control study reported a negative association between GERD and coffee (odds ratio [OR] 0.5; 95% confidence interval [CI] 0.4–0.6) among subjects who drank 4–7 cups per day compared with those who did not drink coffee [Nilsson *et al.* 2004]. In the same study, consumption of dietary fibers was found to be a protective factor [Nilsson *et al.* 2004]. In a large cross-sectional population-based study, consuming bread and fibers at least two meals per day caused a 50% reduction in reflux symptoms [Terry *et al.* 2001]. Likewise, in another cross-sectional study, high fiber intake correlated with a reduced risk of GERD symptoms [El-Serag *et al.* 2005]. The mechanism through which fiber is associated with a decreased risk is unknown, however increased gastric empting could be a reasonable hypothesis.

Voluptuary habits: tobacco and alcohol consumption

Few data are available for voluptuary habits such as cigarettes smoking and alcohol consumption. Smokers have an increased incidence of reflux symptoms compared with nonsmokers [Talley *et al.* 1994; Watanabe *et al.* 2003]. Nilsson and colleagues [Nilsson *et al.* 2004] revealed, in a multivariate analysis, that among individuals who had smoked daily for more than 20 years, the risk of reflux was significantly increased by 70%, compared with those who had smoked daily for less than a year (OR 1.7; 95% CI 1.5–1.9). A relation has been considered between smoking cigarettes and a prolonged acid exposure, a decrease in LES pressure, and diminished salivation, which decreases the rate of esophageal acid clearance [Kahrilas and Gupta, 1989]. However, pH-metry failed to report an increased esophageal acid exposure time in smokers compared with nonsmokers despite the former experiencing increased reflux episodes [Pehl *et al.* 1997]. Overall, there are inconclusive data regarding the effect of cessation of cigarette smoking on GERD outcome.

Alcoholic beverages are considered able to precipitate heartburn perception [Pehl *et al.* 1993]. Even if few data are available, there are no differences in increasing risk between large amounts of high-alcohol beverages such as whiskey and vodka [Kaufman and Kaye, 1978; Vitale *et al.* 1987], and even moderate amounts of beer or red and white wine [Pehl *et al.* 1993]. However, when compared with red wine, white wine caused more esophageal acid exposure and a greater decrease in LES pressure [Pehl *et al.* 1998]. Similar effects were demonstrated after ingestion of white wine and beer in patients with endoscopic evidence of reflux esophagitis and abnormal pH study [Pehl *et al.* 2006].

Sleep position

There are different indications that body position during the sleeping period is related to reflux of gastric content in the esophagus. The sleep period alters basic physiologic mechanisms that physiologically protect against GERD. The mechanisms that are depressed during sleep include the warning signal of heartburn, the frequency of swallowing, and the suppression of salivary secretion [Freidin *et al.* 1989]. Several investigations have shown that esophageal acid clearance is significantly prolonged during sleep compared with the waking state; this is true even when sleeping subjects are compared with awake subjects in the supine position [Orr *et al.* 1981].

Head-of-the-bed elevation can be achieved by putting either 6–8 inch blocks under the bed legs

at the head of the bed or a foam wedge under the mattress. Randomized trials have shown that this practice can decrease esophageal acid exposure and lead to shorter reflux periods and a rapid esophageal clearance [Hamilton *et al.* 1988]. Elevating the head of the bed is important for people with nocturnal or laryngeal symptoms. Right lateral recumbent position has also been shown to cause prolonged reflux time and increased LES relaxations, thus patients with GERD or LPRD should avoid recumbence in this position [Khoury *et al.* 1999].

Physical exercise

Physical exercise has been found to be a protective factor against reflux. In particular, in a large population-based study, a correlation has been documented between the number of exercise sessions lasting at least 30 min and a decreased risk of GERD symptoms (OR 0.5; 95% CI 0.4–0.7) [Nilsson *et al.* 2004]. Frequently, scheduled programs of body weight reduction, which are considered helpful to reduce reflux symptoms, are often associated with aerobic physical activity [Djarv *et al.* 2012; Ness-Jensen *et al.* 2013; Yamamichi *et al.* 2012]. Indeed, a mechanism of an exercise-strengthened antireflux barrier, probably constituted by striated muscle, was hypothesized [Nocon *et al.* 2006]. What is more, Nocon and colleagues have also reported that subjects with GERD symptoms are physically less active than those without symptoms [Nocon *et al.* 2006]. However, esophageal acid exposure increases significantly in healthy volunteers and GERD patients during intense exercise periods compared with the nonexercise periods [Pandolfino *et al.* 2004]. Pandolfino and colleagues have suggested that the anatomical compromise of the esophagogastric junction, as a consequence of frequent abdominal straining associated with strenuous exercise, may predispose to exercise-induced reflux [Pandolfino *et al.* 2004]. Different studies have suggested that an agonistic physical activity could play a pathogenetic role in inducing GERD symptoms (i.e. running, cycling, resistance exercise) [Collings *et al.* 2003; Pandolfino *et al.* 2004; Parmelee-Peters and Moeller, 2004]. It has been suggested that GERD may be increased in athletes because of a decreased gastrointestinal blood flow, alterations of hormone secretion, changes in the motor function of the esophagus and the ventricle, and constrained body position during exercise [Jozkow *et al.* 2006].

Medical therapy

Considering the poor sensitivity and specificity of all currently available diagnostic tests, an empiric trial of therapy represents the first step to confirm LPRD and to treat it accordingly. However, there is no accepted protocol for the most effective treatment of patients with LPRD. Since their introduction in the 1980s, PPIs have demonstrated the most potent suppression of gastric acid secretion, clearly showing a distinct advantage (either for healing and symptom relief) over H2 receptor antagonists [Chiba *et al.* 1997]. Thus, H2 receptor antagonists have restricted their role mainly for patients who suffer from nocturnal acid breakthrough despite twice-daily PPI therapy [Xue *et al.* 2001], or for long-term management of reflux symptoms on an 'as-needed' basis [Scarpignato *et al.* 2006]. Prokinetic agents, although scarcely evaluated, are usually considered unhelpful in LPRD [Pearson *et al.* 2011]. A summary of different pharmacological options to treat LPRD are reported in Table 2.

Proton pump inhibitors

PPI therapy is considered to be the mainstay of care in patients with GERD; however, its efficacy for the treatment of LPRD remains doubtful. In clinical practice, consistently with the assumption that the upper aerodigestive tract is more sensitive to acid refluxes than the esophagus, it is believed that patients with reflux-related laryngitis require higher doses and a longer trial of PPIs to achieve an improvement of laryngeal symptoms than those with typical GERD symptoms [Ford, 2005; Koufman *et al.* 2002; Park *et al.* 2005]. On the other hand, placebo-controlled trials have failed to demonstrate any therapeutic benefit of PPIs [Eherer *et al.* 2003; El-Serag *et al.* 2001; Noordzij *et al.* 2001; Steward *et al.* 2004; Wo *et al.* 2006]. In 2006, a prospective multicenter randomized study, with 145 patients having symptoms and endoscopic signs of LPR, did not show any benefit in patients treated with esomeprazole 40 mg twice daily for 4 months *versus* placebo [Vaezi *et al.* 2006b]. In addition, a Cochrane systematic review of 302 studies did not find any high-quality trials meeting the inclusion criteria to assess the effectiveness of antireflux therapy for hoarseness [Hopkins *et al.* 2006]. A systematic review and a meta-analysis of randomized controlled trials failed to demonstrate superiority of PPIs over placebo for the treatment of suspected LPR [Karkos and Wilson, 2006; Qadeer *et al.* 2006].

Table 2. Summary of different medical therapies in laryngopharyngeal reflux disease (LPRD) with proven or uncertain efficacy.

	Medical therapy in LPRD treatment	
	Proven	Uncertain
PPI	Double dosage for 12 weeks in patients with laryngeal and typical GERD symptoms	Patients without typical GERD symptoms
H2RA	Useful in add-on therapy in patients with nocturnal acid breakthrough	Alternative to PPI therapy
Prokinetic		Usually considered unhelpful
Alginate	Useful in add-on therapy as mechanical barrier	
Neuromodulator		
Reflux-reducing agent	Baclofen is effective in reducing the total number of refluxes	Arbaclofen placarbil, lesogaberan (few available data)
Visceral pain modulator	TCA, SSRI are effective in patients with hypersensitive esophagus	

GERD, gastroesophageal reflux disease; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Conversely, more recent studies have demonstrated effectiveness in treating reflux symptoms and improving laryngeal inflammation. Reichel and colleagues [Reichel *et al.* 2008] reported a randomized, double-blind, placebo-controlled trial with esomeprazole 20 mg twice daily for 3 months in patients with symptoms and endoscopic signs of LPR, which found significant improvement in both symptoms and laryngeal examination. Likewise, Lam and colleagues [Lam *et al.* 2010] performed a prospective, randomized, double-blind, placebo-controlled study with rabeprazole 20 mg twice daily for 3 months in patients with symptoms and endoscopic signs of LPR, resulting in a significant improvement of symptoms, but not laryngeal findings. However, on the basis of a closer examination of these two studies, Vaezi [Vaezi, 2010] argued that the real significant improvement was for heartburn symptoms and not for chronic throat symptoms.

Some uncontrolled and observational data recommend the use of twice-daily PPIs for LPRD [Kamel *et al.* 1994; Klopocka *et al.* 2004; Shaw and Searl, 1997; Williams *et al.* 2004]. Furthermore, some studies have shown that the proportion of patients with improvement in laryngeal symptoms after PPI therapy is higher in GERD patients than in those without GERD [Lien *et al.* 2013; Masaany *et al.* 2011; Qua *et al.* 2007]. On the other hand, some studies assessed that the presence of abnormal acid reflux on pH monitoring did not predict response to therapy [Vaezi *et al.* 2006b; Williams *et al.* 2004].

Overall, considering that most of the therapeutic evidence is based on uncontrolled open-label studies only and the lack of high-quality evidence supporting treatment efficacy, assessing the optimal treatment for LPRD is still challenging. Furthermore, the dosage and duration of PPI therapy in LPRD represent further current matters of debate. To date, whenever typical GERD symptoms are present in addition to the extraesophageal symptoms and/or there is objective evidence of GERD by endoscopy or reflux monitoring [Katz *et al.* 2013], it is a pragmatic clinical strategy to start with an empirical 2-month therapy with twice-daily PPIs [Kahrilas *et al.* 2008]. If there is symptom improvement, then tapering to once-daily PPI followed by reducing the dose or the interval of acid suppression is highly recommended [Vaezi, 2010]. On the other hand, failing such an empirical PPI trial, etiologies other than GERD should be explored through concomitant evaluation by ENT, pulmonary, and allergy specialists [Kahrilas *et al.* 2008; Katz *et al.* 2013; Vaezi, 2010; Zerbib *et al.* 2013].

Refractory patients with objective evidence (reflux monitoring) of ongoing reflux as the cause of symptoms should be considered for additional antireflux therapies that may include transient LES relaxation (TLESR) inhibitors or surgery

[Katz *et al.* 2013], which are further discussed in the present review.

Alginate

Traditional antacids are frequently used as add-on therapy in order to neutralize gastric acidity and to help control heartburn in GERD patients [Giannini *et al.* 2006; Savarino *et al.* 2012; Zentilin *et al.* 2005]. They are polysaccharides found in algae and convert into a gel form when they combine with cations. In particular, they form a physical barrier for gastroduodenal contents, and have the advantage of being a nonsystemic medication.

In a prospective, randomized controlled study, liquid alginate preparations (taken four times daily) have been shown to be effective in treatment of LPR symptoms and signs [McGlashan *et al.* 2009]. Of note, considering that pharyngeal and laryngeal cancer might represent LPR complications, a statistically significant reduction in squamous cell carcinoma volume was observed in hamsters that received alginate prior to known carcinogen [7,12-dimethylbenzanthracene (DMBA)] and human pepsin application, compared with hamsters painted with DMBA and human pepsin alone. Thus, alginate suspension provided protection from pepsin-enhanced tumor growth [Pearson *et al.* 2011].

Alginates should be given after each meal and last thing at night, and nothing should be taken by mouth after the nocturnal dose [Pearson *et al.* 2011].

Neuromodulators

PPI-refractory patients with persistent reflux (nonacid or weakly acid), assessed with ambulatory 24-h MII-pH monitoring, could benefit from reflux-reducing agents or visceral pain modulators [Zerbib *et al.* 2013]. Reflux-reducing agents, including $GABA_B$ agonists and metatropic glutamate receptor antagonists, are supposed to reduce the frequency of TLESR, representing the main pathophysiological mechanism underlying GERD. In particular, $GABA_B$ receptor agonists (i.e. baclofen) have been shown to decrease acid reflux occurrence, esophageal acid exposure, and improved reflux-related symptoms [Ciccaglione and Marzio, 2003; Cossentino *et al.* 2012]. However, their use in clinical practice is limited by a poor tolerability profile. Several researchers have tried to develop more-efficient and better-tolerated compounds (i.e. lesogaberan, ADX10059, arbaclofen) without attempting such results [Vakil *et al.* 2011; Zerbib *et al.* 2011].

Visceral pain modulators [i.e. tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs)] decrease the perception of reflux episodes increasing the esophageal perception threshold [Broekaert *et al.* 2006; Clouse *et al.* 1987; Peghini *et al.* 1998], thus may induce beneficial effects in patients with hypersensitive esophagus, as diagnosed through reflux monitoring in the case of normal acid exposure time and positive correlation between symptoms and refluxes [Viazis *et al.* 2011]. These observations, although preliminary in nature, encourage the performance of studies aimed at assessing the efficacy of visceral pain modulators in patients with LPRD refractory to an optimal treatment with PPIs.

Surgical therapy

Laparoscopic antireflux surgery (LARS) is a well-established and highly efficacious treatment for GERD and has been shown to provide durable relief from the typical reflux symptoms [Papasavas *et al.* 2003]. In particular, the surgical therapy is helpful in allowing the majority of patients suffering from GERD to discontinue acid suppression therapy, to achieve resolution of associated esophagitis, and to arrest or perhaps even reverse the metaplasia/dysplasia induced by frequent exposure of the esophageal mucosa to gastric contents [Oelschlager *et al.* 2003; Parise *et al.* 2011; Rossi *et al.* 2006].

Few controversial data are available about surgical outcome of LPRD. A clinical prospective study in patients with LPRD selected for surgical treatment, in which the symptoms and signs had responded to antireflux medication, the laparoscopic fundoplication was found to be an effective and safe treatment of LPRD [Sala *et al.* 2008]. Moreover, in patients with objective evidence of GERD, LARS was effective in relieving LPR symptoms [Catania *et al.* 2007; Lindstrom *et al.* 2002]. On the other hand, LARS has shown disappointing results in controlling LPR-related symptoms in patients unresponsive to aggressive PPI therapy [Swoger *et al.* 2006]. Likewise, prior studies demonstrated a poor surgical outcome for the resolution of laryngeal symptoms especially in PPI nonresponders [Chen and Thomas, 2000; So *et al.* 1998].

It is necessary for the surgeon to perform a detailed workup including esophagogastroduodenoscopy, esophageal manometry, gastric emptying test, MII-pH or pH-metry, and upper gastrointestinal radiography for all patients scheduled for LARS, primarily to exclude malignancy and motility problems such as achalasia and gastroparesis and then to detect a cause–effect relation between pathological acid exposure time and laryngeal symptoms/findings [Zerbib *et al.* 2013].

The patients who are selected for LARS must be informed that laparoscopic fundoplication may correct the underlying mechanical defect but they should be warned that the response of their laryngeal symptoms to surgery would still be uncertain [Chen and Thomas, 2000]. The LARS approach could be more strongly suggested if patients showed a complete relief of laryngeal symptoms during PPI therapy or if 24-h pathophysiological studies demonstrated that nonacid reflux events are predominant. Moreover, the surgeon must carefully select patients before suggesting LARS and a Regional Referral Center specialized in esophageal surgery is recommended to reduce postoperative complications. In this matter, patients should be warned of possible postoperative dysphagia, bloating, flatulence, diarrhea, and recurrence of the symptoms [Richter, 2013].

To date, the clinical guidelines of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) recommend antireflux surgery for patients who: (1) have failed or are unable to tolerate medications; (2) have significant extraesophageal manifestation such as aspiration, asthma, or cough; (3) have the complication of GERD-like peptic stricture.

Speech therapy and rehabilitation techniques

Actually, newer treatment options are considered as alternative possibilities in the treatment of GERD, and in particular LPRD, deserving careful investigations.

The LES, surrounded by diaphragmatic muscle, prevents gastroesophageal reflux and, indirectly, LPR. It is believed that synergy of the function of the LES and its surrounding crura of the diaphragm, when superimposed, are of importance for competent closure [Mittal and Balaban, 1997]. When these structures became incompetent, gastric contents may be traced back along the esophagus and cause LPR. The importance of the diaphragm muscle is also demonstrated by experimental studies: even after surgical removal of LES, a pressure zone is detectable due to contractions of the crura of the diaphragm [Klein *et al.* 1993]. Like any other striated muscle of the body, the diaphragm muscle should be amenable to improved performance by physical exercise. For these reasons, alternative therapies for the treatment of reflux disease have recently been studied, and in particular speech therapy/relaxation techniques such as training of the diaphragm muscle with maneuvers and breathing exercises have been considered.

In the literature, there are few scientific publications regarding the rehabilitation treatment of reflux and in some centers such therapy is proposed in an empirical way without medical evidence-based support. In addition, the proposed rehabilitation treatments have been studied in relation to the symptoms and not in relation to the demonstration of a real reduction of acid reflux events.

One of the most characteristic symptoms of the LPRD is globus pharyngeus [Chevalier *et al.* 2003; Park *et al.* 2006; Tokashiki *et al.* 2002]. Given the benign nature of the condition and the recent notion that GERD is a major cause of globus, empirical therapy with high-dose PPIs has been tried [Lee and Kim, 2012]. In patients nonresponsive to this therapy, when GERD was demonstrated by tests such as endoscopy, MII-pH monitoring, and manometry, alternative therapies may be considered, including speech and language techniques. In some studies, a number of exercises to relieve pharyngolaryngeal tension, voice exercises, and vocal tract voice hygiene to relieve discomfort and tension have provided significant results in reducing persistent globus symptoms [Khalil *et al.* 2003]. However, further research is needed to determine whether speech and language rehabilitation techniques have a specific effect or whether patients with globus pharyngeus simply benefit from general attention and reassurance [Millichap *et al.* 2005].

More recently laryngeal rehabilitation therapies have been applied in cases of chronic cough associated with GERD, with significant symptom improvement [Pacheco *et al.* 2013]. Carvalho de Miranda Chaves and colleagues [Carvalho de Miranda Chaves *et al.* 2012]

showed, by performing esophageal manometry, that inspiratory muscle training incremented LES pressure in patients with GERD after an 8-week program. Eherer and colleagues [Eherer *et al.* 2012], in a randomized controlled study, showed that actively training the diaphragm muscle by breathing exercise, can improve reflux disease. Quality-of-life scales, pH-metry, and on-demand PPI usage were assessed to monitor patients in the short- and long-term follow up [Eherer *et al.* 2012].

All of these studies confirm that the rehabilitation therapy that acts on the crural diaphragm is a potential alternative method to treat GERD and LPRD, reducing long periods of drug treatment or surgical procedures. These findings need to be confirmed in further studies with a larger sample, longer follow up and controlled with quality of life scores and instrumental examinations such as MII-pH.

Discussion

The effects of the symptoms of both GERD and LPRD are believed to be secondary to the irritative effects of gastric refluxate on the sensitive esophageal and pharyngeal mucosa [Bough *et al.* 1995]. The optimal treatment of LPRD is neither standardized nor validated [Hogan and Shaker, 2001]. This is due to the multifactorial nature of the disease, whose symptoms are nonspecific, and to the difficulty of making an accurate diagnosis of LPRD for the poor sensitivity and specificity of all currently available diagnostic tests. New techniques (i.e. Peptest, Restech) may be of great interest to improve the diagnostic accuracy of LPRD, paving the way towards the development of new targeted therapies. Indeed, pepsin inhibitors and pepsin receptor antagonists are the new possible frontiers of research [Pearson *et al.* 2011].

As we discussed in this review, the management of LPRD can be divided into lifestyle modifications, medical and/or surgical treatment. Behavior changes and lifestyle modifications are considered the first-line treatment with the lowest possibility of side effects. Weight loss, smoking cessation, alcohol avoidance, meal habit modifications, and head elevation during sleep need to be strongly suggested to patients. As to the medical therapy, currently, the treatment is focused on increasing the pH of the refluxate, thus it is recommended to start with PPIs twice daily for a period of 8–12 weeks. Refractory patients with objective evidence (reflux monitoring) of ongoing reflux as the cause of symptoms should be considered for alternative therapies, such as visceral pain modulators or laparoscopic antireflux surgery. The surgical approach needs to be tailored for each patient and very carefully considered. Up and coming results are available with speech therapy but these results need to be evaluated in future trials. Surgery should be indicated in select patients, in which high-volume refluxate and incompetence of LES are demonstrated with esophageal pathophysiological evaluations.

To date, we can conclude that, although many studies are still needed to assess the optimal therapeutic management in LPRD, a multidisciplinary approach including providers in ENT, pulmonology, and gastroenterology evaluations is recommended to improve diagnosis and therapy in patients with LPRD.

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