Airway reflux

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An ever-increasing number of adult and pediatric disorders have been shown to be influenced or caused by airway reflux. This has become a controversial and complicated aspect of medicine that requires a multidisciplinary approach. Evidence indicates that it is not only the acidic components of gastric refluxate that injure extraesophageal tissues but also the nonacidic components, such as pepsin and bile. There is a realization that proton pump inhibitors will not be effective when nonacidic components of refluxate are causing the problem. New in vitro and in vivo models for the study of airway reflux and new therapeutic and surgical approaches are discussed in this review article.

Keywords: reflux; airway; laryngopharyngeal reflux (LPR); extraesophageal reflux (EER); pepsin; surgical approaches; therapeutic approaches

Introduction

Reflux of gastric contents into the esophagus, termed gastroesophageal reflux, is a normal physiological phenomenon that occurs in most people, particularly after meals. Brief and infrequent exposure of the esophagus to gastric contents does not result in injury and disease, implying that there are intrinsic defense mechanisms that act to maintain mucosal integrity. In fact, based on pH-monitoring studies, up to 50 reflux episodes a day (below pH 4) are considered normal. It is thought that esophageal symptoms and complications arise when reflux is prolonged and/or there is a breakdown in the defense mechanisms, making an individual more susceptible to harm from gastric refluxate. This is termed gastroesophageal reflux disease (GERD). GERD is accepted as possibly the most common chronic disease of adults in the United States and affects more than 30% of individuals in Western society.1

When gastric reflux travels more proximally into the laryngopharynx, it is termed laryngopharyngeal reflux (LPR). Other terms such as gastropharyngeal reflux and esophagopharyngeal reflux have been used synonymously. These are all considered as parts of extraesophageal reflux (EER), reflux involving structures other than, or in addition to, the esophagus, and airway reflux involving proximal gastric reflux into the airways. LPR contributes to several otolaryngologic symptoms and inflammatory disorders, and perhaps also to neoplastic diseases of the laryngopharynx, and appears to be as common in children and infants as adults. It is estimated that 10% of patients visiting otolaryngology clinics have reflux-attributed disease, and up to 55% of patients with hoarseness have reflux into their laryngopharynx.2 LPR is actually one of the most common factors associated with inflammation in the upper airways. Connection of EER to specific disease states has been demonstrated in an ever-expanding list of conditions of the aerodigestive
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tract, including otitis media, sinusitis, cough, sleep disordered breathing, laryngitis, laryngospasm, airway stenosis, and lower airway problems, such as asthma, chronic obstructive pulmonary disease, interstitial pulmonary fibrosis, and chronic lung transplant rejection. Evidence for these has been based largely on clinical findings that correlate to pH probe studies confirming EER or detection of elements of refluxate in the subsite in question. Animal and basic science studies have been used to propose or confirm a mechanism, but in most cases direct cause and effect in the human condition has yet to be confirmed.

Diagnosis of LPR has traditionally relied on symptomatology, laryngoscopic identification of inflammatory changes, and pH monitoring. However, the sensitivity and specificity of such have been questioned. Combined multichannel intraluminal impedance (MII) and pH monitoring (MII–pH) provided an advance in LPR/EER diagnostics through its ability to detect reflux events independent of the pH of the refluxate. By demonstrating the inefficacy of acid-targeting therapeutics for LPR, association of symptoms with nonacid reflux, and symptom alleviation upon surgical interventions that abrogate reflux of all gastric contents, the data garnered through MII–pH technology brought about a shift in perception of LPR/EER as a primarily acid-mediated disease to one significantly mediated by nonacidic components of reflux for which typical GERD treatment would not suffice.

Pepsin: biomarker, mediator, and therapeutic target for reflux and aspiration

Biomarker

Pepsin A is only produced in the stomach and thus is a specific biomarker for gastric reflux. Furthermore, pepsin is present in all refluxate, in contrast to the other gastric components, such as acid or bile, which may or may not be present. Unlike MII–pH, pepsin analysis can provide direct detection of refluxate at sites of airway damage potentially attributed to EER. Johnston et al. reported pepsin in laryngeal epithelia from 26/27 confirmed LPR patients, but not in any of the 19 control subjects without LPR ($P < 0.001$). In another study in which they assessed the prevalence of aspiration in children with reflux-associated pulmonary disease, pepsin was detected in the bronchoalveolar lavage (BAL) of more than 70% (47/65) of patients with pulmonary disease who underwent bronchoscopy and tracheostomy, compared to 0/11 controls who had elective surgery with no history of pulmonary disease.$^{10}$ Furthermore, the detection of pepsin in BAL samples was found to be superior (more sensitive and specific) to the current method of measuring lipid-laden macrophages for the detection of aspiration.

In 2012, Saritas Yuksel et al. reported the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of a salivary pepsin test in patients with GERD compared to controls. Both sensitivity and specificity of a rapid lateral flow test (PeptestTM) were reported to be at 87%. For patients with objective GERD (abnormal pH and/or esophagitis), salivary pepsin showed a PPV of 85% and an NPV of 68%. It was concluded that a positive salivary pepsin test may obviate the need for more invasive and expensive diagnostic testing. More recently, Hayat et al. tested 111 patients with heartburn and 100 asymptomatic controls who underwent MII–pH and simultaneous salivary pepsin determination. They reported that a positive pepsin sample with a concentration $>210$ ng/mL suggests that symptoms are 98.2% specific for reflux. These results strongly suggest that pepsin could represent a sensitive and specific biomarker for the occurrence of reflux. Strugala et al. also recently used Peptest in patients with chronic cough. They found the mean pepsin concentration in patients with chronic cough to be comparable to that in GERD patients at the time of symptomatic episodes, suggesting that the level of refluxed pepsin in chronic cough patients may be physiologically relevant.

Mediator

Agents that reduce acid levels are unlikely to demonstrate efficacy among those with nonacid reflux. This has been demonstrated in several studies that used MII–pH to detect reflux events.$^{4,5,14}$ Studies have also demonstrated that pepsin plays a role in mucosal damage and inflammation during nonacidic reflux.$^{15-18}$ At a neutral pH, pepsin is enzymatically inactive but stable (below pH 8.0) and is taken up by laryngeal and hypopharyngeal cells via receptor-mediated endocytosis. Once taken up, pepsin is retained in intracellular vesicles of low pH, where it is presumed to be reactivated.$^{15}$ Additional studies analyzing cellular morphology, mitochondria function, and the expression of stress-response genes in laryngeal specimens and cultured
hypopharyngeal cells treated with pepsin confirmed that the endocytosed pepsin causes mitochondrial damage and changes the expression of several genes implicated in stress and toxicity. Thus, pepsin may contribute to the signs and symptoms associated with weakly and nonacidic LPR. Johnston et al. further investigated the potential of pepsin to contribute to mucosal damage and demonstrated that endocytosed nonacidic pepsin induces a proinflammatory cytokine gene expression profile in hypopharyngeal cells in vitro similar to that which contributes to disease severity in GERD patients.

**Therapeutic target**

While proton pump inhibitor (PPI) therapy is a mainstay in the treatment of GERD, its efficacy for the treatment of LPR disease (LPRD) remains doubtful. Placebo-controlled trials have failed to demonstrate any therapeutic benefit of PPIs. Given pepsin’s role in nonacidic LPR, it has been proposed as a novel therapeutic target, especially for patients experiencing refractory symptoms on PPIs. Approximately $26 billion per year is currently being spent on PPIs for the treatment of LPR, despite their poor efficacy for this patient population. The promise of irreversible inhibitors of peptic activity and/or receptor antagonists as potential new therapeutics for LPRD has been discussed. It has been proposed that EER is much more dependent on pepsin-mediated damage in the laryngeal and airway mucosa than acid-mediated damage. In this regard, Johnston’s research group is currently leading an international drug discovery program to develop a drug that specifically targets pepsin. There are two mechanisms by which one can target pepsin: (1) irreversibly inactivate the enzyme to prevent it from becoming reactivated inside intracellular compartments of lower pH, and (2) via a receptor antagonist to prevent pepsin uptake via receptor-mediated endocytosis. It should be noted that pepstatin A, a commercially available, potent inhibitor of pepsin, has poor water-soluble characteristics and poor pharmacokinetic properties. Thus, preclinical evaluations of new pepsin inhibitor compounds to document bioavailability and efficacy are underway.

**What is the role of reflux biomarkers in predicting clinical outcomes in children?**

Multiple biomarkers of EER have been proposed for use in pediatrics. Despite their widespread use in clinical practice, there are limited data on the role of EER biomarkers as predictors of clinical outcome. The most commonly studied biomarkers are MII–pH, pepsin, and bile, but outcome studies are only available for MII–pH testing and pepsin in children. MII–pH has significant appeal in pediatrics because many if not most reflux episodes in children are nonacidic. Despite the ability to test for nonacid reflux, limited studies have shown that this added information changes the outcome. In a study of MII–pH by Duncan et al., there was no relationship between pathologic reflux and hospitalization risk (number of hospitalizations or number of admission days), even in high-risk patients with aspiration. Similarly, Rosen et al. found that the standard MII–pH results did not predict which patients had a favorable outcome after fundoplication, although the amount of full-column reflux may be an important predictor. Hart et al. also found that impedance did not predict clinical outcome of airway-reconstruction surgery, and these results held up when they also showed that, when patients with abnormal MII–pH testing underwent fundoplication, their outcomes were not improved.

Recently, pepsin in bronchial and tracheal fluid has been measured as a marker for aspiration of gastric contents into the lung. Farhath found that preterm infants with higher concentrations of pepsin in tracheal secretions were at greater risk for more severe bronchopulmonary dysplasia than patients with lower concentrations. In older patients, the results are less encouraging. Duncan et al. found that pepsin in BAL fluid did not predict hospitalization risk, and Rosen et al. found that BAL pepsin did not predict which patients had extraesophageal symptoms, such as croup, asthma, or cough.

While studies are frequently performed comparing new biomarkers to reference standards, there are very few studies that then evaluate these biomarkers as predictors of clinical outcome. These studies are critical to determine the true value of these new tests.

**Laryngeal seromucinous gland response to acidotic environments**

Patients with EER have been noted to have abnormal secretions and patterns of edema in the larynx. The concept of this atypical reflux is controversial, since some patients may have normal levels
of acid, as determined on pH-metry, and partial response to PPI pharmacotherapy. A body of research has emerged that reveals the presence of the H+/K+ -ATPase proton pump in the seromucinous glands of the human larynx and elsewhere, beyond the parietal cell of the stomach. Consistent immunohistochemistry staining of both the α and β subunits was noted in multiple human cadaveric studies, as well as western blot confirmation on fresh human tissue. Although fairly low levels of expression were recognized, the findings call into question the possible pathophysiology associated with the larynx mucosa of these patients. The human proton pump is physiologically similar to the vacuolar-type H+ -ATPase (V-ATPase) enzyme, which has been demonstrated in the salivary glands of rats and cockroaches, with a concentration in the main excretory and striated ducts. While this finding suggests a role in modifying H+ and HCO3− concentrations in saliva, adaptive changes have been observed during acid–base disturbances to induce an activated state of this transporter enzyme in the presence of metabolic acidosis. This suggests a complex physiology in response to mucosal acid exposure and potentially to metabolic acidosis. Similar to the animal model, acidic secretions may be an attempt to maintain the intracellular pH of the submucosa, with the by-product of increasing mucosal edema and laryngeal sensitivity.

What is the consequence of biliary reflux in the larynx?

Nonacid reflux may have a number of definitions relative to the esophagus and supraesophagus: (1) regurgitation of normal gastric secretions whose acidic pH has been blunted by the use of acid-suppressive pharmacotherapy such as PPIs or (2) bilious regurgitation from the duodenum through the stomach to the esophagus. Although less frequent, the latter is particularly serious. Sun et al. performed esophagojejunostomy with and without gastrectomy on Wister rats, and performed a second experiment feeding bile acids and gastric acid. Bile acid exposure in the esophagus was shown to induce Barrett’s esophagitis, demonstrating that it is more damaging than acid exposure alone. Nehra et al. performed 15-h continuous esophageal aspiration with simultaneous pH monitoring in four groups of 10 patients each with normal esophageal mucosa, minimal esophagitis, erosive esophagitis, and Barrett’s esophagitis. They found that bile in the refluxate was required in all Barrett’s patients, and conjugated bile acids were more prominent than unconjugated bile acids.

Bile acids are produced in the liver, where they are conjugated before secretion as bile salts, lowering the pKα and improving its water solubility in acidic environments. The danger of treating all patients with esophageal reflux with acid-suppressive therapy is that the less acidic stomach pH precipitates out conjugated bile, making it available to induce more aggressive esophageal injury. There may also be a “danger zone” pH range where the unionized form of bile acids may diffuse through the mucosa more efficiently. Although controversial, there is mounting evidence that bile plays an increasingly important role in the complex physiology inducing reflux esophagitis.

Can we model airway inflammation in vitro to gain insight regarding mechanisms of extraesophageal reflux disease?

EER disease is a common ailment affecting the airway. It is hypothesized that airway disease results from full-column reflux and microaspiration of gastric contents. Aspired material capable of triggering inflammation at the airway mucosa likely underlies symptoms, such as coughing and wheezing, associated with this disease; however, diagnosis and treatment of EER are challenging and costly. PPIs are frequently prescribed to patients with reflux to reduce stomach acidity and minimize damage to esophageal and extraesophageal tissue, despite a paucity of data to support the efficacy of this treatment. While microaspiration of acid may contribute to inflammation, acid may not represent the only driver of reflux-associated airway disease. The gastric milieu contains other potential inflammatory triggers, including microbes and digestive enzymes, such as pepsin, that might independently or collectively be responsible for airway inflammation. It has been demonstrated that gastric microbes can enter the lung through microaspiration, and the magnitude and population of microbes are affected by PPI usage. Enteric microbes invading the airway represent a potential source of inflammation. Certain bacteria can stimulate neutrophil migration across lung epithelial barriers in a mechanism that involves the generation of multiple chemotactic eicosanoid mediators. Pepsin has also been detected in the
Figure 1. Instrumentation for human and rodent direct laryngoscopy. (A) Typical human laryngoscopes. (B) Biopsy forceps. (C) The scale-down in magnitude of what was used to retract the tongue (above) and wound the larynx for carcinogen instillation (below). (D) The design of the OR table, its incline for orientation to the operating microscope, and a bridle wire that was used to uniformly orient the animals to the microscope in a repetitive fashion.

lung, and elevated levels of pepsin correlate with neutrophil counts in BAL fluid, which predicts more severe pulmonary symptoms. Future exploration employing airway inflammatory model systems will elucidate key mechanisms and drivers within gastric contents that trigger airway inflammation, leading to chronic cough.

Rodent models to investigate laryngeal carcinogenesis

Aerodigestive cancers affect over 300,000 individuals yearly in the United States. They occur from the oral cavity through the pharynx, larynx, tracheobronchial tree (and lung fields), and the esophagus to the gastroesophageal junction. They are typically researched by separate disciplines, as either head and neck, lung, or esophageal cancers. However, they share the common risk factor of tobacco exposure as a typical precedent. Frank Ondrey’s group sought to harmonize separate scientific expertise between a lung cancer laboratory (Lee Wattenberg) and a head and neck cancer molecular oncology program to develop small animal models of squamous cancers that affect the larynx and hypopharynx, the entry portal to the tracheobronchial tree. Interestingly, the rodent and human laryngeal anatomy is very similar. Syrian hamsters and 6- to 8-week-old A/J mice have a larynx with only 1–3% the cross-sectional area of a human. Their strategy was to employ techniques from the human operating room to rodents, with the aid of an operating microscope for otology. First, they scaled down the human instruments for direct laryngoscopy so that they could retract an anesthetized rodent’s tongue to expose the larynx. This allowed for glottic/subglottic wounding and the application of the carcinogen N-nitroso-N-methylurea (MNU) (Fig. 1). Second, careful axial orientation and embedding of the hypopharynx, larynx, and trachea for sectioning was performed for accurate cross sections at an axis perpendicular to the length of the structures. Finally, degrees of dysplasia or invasive cancer were read by human head and neck pathologists.

In the hamster model, 88% of animals developed invasive carcinomas, and, in the A/J mouse model, 60% of animals developed cancers. Two weekly woundings were performed with five MNU applications with each species under general anesthesia. Ondrey’s group developed both hamster and mouse models of laryngeal carcinogenesis with direct laryngoscopy techniques. Both can be used to
study carcinogenesis, inflammation, and proximal airway cancer chemoprevention.28–40

### Clinical relevance of regional agent delivery techniques for inflammation and carcinogenesis

The oral cavity, larynx, trachea, lungs, and proximal esophagus are organs at the front line of receiving carcinogens and other insults that are either ingested, smoked, or subject to refluxate (esophago/larynx). They can also be targeted for regional delivery of therapeutic agents, including mouthwashes, lozenges, chewing gum, conventional aerosols, mucoadhesive patches, and nanoparticle aerosols. Typical clinical examples of this technique for drug delivery would be chlorhexidine mouthwash for periodontal conditions, clotrimazole lozenges for oral cavity thrush, or a variety of aerosol steroid and β2 agonist inhalers (e.g., albuterol) for the treatment of asthma.

Direct epithelial delivery is potentially attractive because high concentrations of drug can be deposited directly onto the organ site of interest. There is reduced concern for systemic toxicity if the agent is not significantly soluble transepithelially. For example, the cardiac drug nitroglycerin is typically utilized sublingually and has rapid access to the venous circulation for vasodilation, whereas the drug clotrimazole in a lozenge (troche) form is not bioavailable sublingually and is deposited at high levels to local oral fungal infections. Careful attention needs to be paid to the chemical structures of the agents and their packaging, both of which can affect epithelial solubility and systemic versus local solubility. Ondrey and colleagues have a specific interest in the development of topical upper aerodigestive cancer prevention drugs through native compounds or chemical modifications that improve local residence time in the milieu.

Many agents can be complexed to microspheres or conjugated nanoparticles in order to increase the targeting accuracy. By altering the particle size, drug delivery to the larynx versus the distal trachea can occur to any or all sites through multiple sizes of aerosol particles. One complexity of this approach is that novel agents, as well as the devices, would need to undergo separate regulatory approval from different divisions of drug regulatory organizations (e.g., the U.S. Food and Drug Administration (FDA)). Additionally, there is emerging concern that nanoparticles alone might cause cellular toxicity after targeted delivery. Regional delivery approaches have been used in aerodigestive malignancies in animal models and human studies by Ondrey’s group and others (Table 1).41–43

### What is the role of reflux in chronic cough?

Cough lasting longer than 8 weeks, outlasting acute infection, and not related to smoking, medications, or pulmonary disease, is considered chronic and often attributed to allergy, asthma, and reflux.44 However, this idiopathic group of patients present with characteristic history, cough triggers, and cough features, with the common underlying problem being neurogenic.45 The root cause is an alteration of the cough threshold mediated via a vagal nerve loop. Because the vagus receives multiple sensory inputs, central convergence occurs, amplifying the cough response. Once the sensory pathway has been perturbed, the cough threshold becomes hypersensitive and is triggered by non-noxious

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**Table 1. Example studies of drug approaches for direct epithelial delivery for cancer prevention**

<table>
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<th>Disease</th>
<th>Delivery technique</th>
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<th>Species</th>
<th>Investigators</th>
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<td>A/J mouse</td>
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5-FU, 5-fluorouracil; DMFO, difluoromethylornithine.
stimuli. These may include talking, laughing, odors, temperature, humidity, air flow, and refluxate. It is likely that transient receptor potential vanilloid receptors present in the esophagus and airway are activated and enhance the cough reflex. Both acid and nonacid reflux, including volume and gaseous reflux, may contribute to vagal sensitization. Management requires a multifaceted approach, including behavioral suppression and substitution, trigger control, and in some cases direct neuromodulator therapy. Blocking agents, such as alginates or sucralfate, are often more useful than acid suppression. Neuromodulation using amitriptyline or gabapentin has demonstrated success in modifying cough response, as has cough speech therapy. Often all treatments are required together to “reset” the cough threshold and provide symptom control. Thus, reflux of gastric content into the esophagus is one of a number of triggers responsible for chronic cough and should be managed as part of a coordinated treatment plan.

**Reflux and chronic rhinosinusitis**

Chronic rhinosinusitis (CRS) is an inflammatory condition involving the mucosa and possibly the bone of the nasal cavity and paranasal sinuses. Mucosal inflammation results in dysfunction of the mucociliary clearance mechanism, stasis of secretions, and possible obstruction of the outflow tracts of the sinuses. CRS is likely a multifactorial disease process in most individuals, with many possible etiologies, including bacteria, fungi, viruses, biofilms, allergy, genetic conditions, and anatomic factors. LPR has also been implicated as a factor contributing to the pathogenesis of CRS. Multiple studies have shown a higher incidence of reflux events in patients with CRS, especially CRS refractory to medical and/or surgical treatment compared to controls without CRS. DelGaudio used pH probe studies to evaluate patients who had persistent inflammatory sinus disease after endoscopic sinus surgery (ESS) and compared them to control groups of patients who had undergone ESS and had no persistent inflammation and normal controls. Patients with refractory CRS had significantly more reflux at the distal esophagus and the upper esophageal sphincter and in the nasopharynx (pH < 4 and pH < 5) compared to the other groups. Loehrl et al. found that 19 of 20 refractory CRS patients had LPR on pH study and 5/5 patients tested had positive nasal pepsin assays, compared to 0/5 controls. Ozmen et al. performed pH studies and nasal pepsin assays in 33 CRS patients and 20 controls, finding significantly greater pharyngeal reflux events and positive pepsin assays in CRS than controls (88% and 82% vs. 50% and 50%).

**Reflux and postnasal drip**

Postnasal drip (PND) is a common symptom that is frequently attributed to sinonasal pathology. In the absence of other nasal symptoms, the likelihood of a sinonasal etiology is lower. Limited but good evidence exists for LPR as a causative factor in PND. Wise et al. found that patients with PND complaints based on symptom questionnaires have a significantly higher incidence of reflux of gastric contents into the nasopharynx and laryngopharynx, especially weakly acidic reflux at the nasopharynx (pH < 5). Another study showed that patients receiving rabeprazole 20 mg BID for 3 months had significantly less PND, cough, and hoarseness than those treated with placebo. Of these subjects, 55.6% had positive pH study with EER events < pH 5. Vaezi et al. performed a parallel-group, double-blind, multispecialty trial of 75 patients without allergy or sinusitis treated with BID lansoprazole versus placebo. PND symptoms improved significantly in the study group compared to placebo (3.12- and 3.5-fold more likely to improve at 8 and 16 weeks). At 16 weeks, 50% of patients treated with lansoprazole improved, compared to 5% with placebo. Neither baseline presence of typical reflux symptoms nor physiologic measures (pH study or impedance testing) predicted response to therapy.

**Is magnetic sphincter augmentation an effective therapy for laryngopharyngeal reflux?**

The association between GERD and laryngeal disorders has been recognized since the 1960s. Despite the long history of antireflux surgery (Rudolf Nissen described the fundoplication that bears his name in 1955), overall there are scant and conflicting results to assess the effects of antireflux surgery on LPR. Fundoplication for LPR has demonstrated the highest degree of efficacy in patients who respond at least partially to PPI therapy and in patients with objective evidence of GERD and typical esophageal symptoms, such as heartburn and regurgitation. Laparoscopic fundoplication is associated with side
effects, such as bloating and difficulty belching. A new treatment recently approved by the FDA is magnetic sphincter augmentation (MSA), also known by the trade name of LINX. The MSA device has been demonstrated to result in excellent control of reflux symptoms in patients with typical esophageal symptoms and a low rate of side effects, such as bloating and difficulty belching. As clinical experience accrues, many patients with GERD and LPR symptoms have undergone implantation of an MSA device with results that parallel those seen in fundoplication for LPR. The LINX device has not yet been studied in patients with morbid obesity, a large hiatal hernia, or Barrett's esophagus. Further investigation is needed, but the LINX MSA device is likely an effective treatment for LPR related to GERD in patients who would otherwise qualify for antireflux surgery.

Conclusions

EER is associated with a number of adult and pediatric inflammatory disorders of the airway, including chronic cough, CRS, PND, and perhaps even neoplastic disease. The effects of nonacid components, such as pepsin and bile, as well as local acid production by proton pumps, need to be investigated further, and studies assessing biomarkers for EER (pepsin and bile) as predictors of clinical outcome are needed to determine the true value of these diagnostic tests. New in vitro and in vivo models are now available to our research community to elucidate the key mechanisms of disease and to test new therapeutic compounds. A mouse in vivo model is currently being used to perform preclinical evaluations of a new therapeutic for reflux that specifically targets pepsin for those patients with persistent EER symptoms despite PPI therapy and associated with nonacid reflux events. Surgery utilizing the MSA device also holds promise for these patients, but larger studies are needed to confirm its efficacy for EER.

Conflicts of interest

The authors declare no conflicts of interest.

References


