Rethinking gastroesophageal reflux disorder

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Abstract

Gastroesophageal reflux disease (GERD) is a common clinical condition for which our understanding has evolved over the past decades. It is now considered a cluster of phenotypes with numerous anatomical and physiological abnormalities contributing to its pathophysiology. As such, it is important to first understand the underlying mechanism of the disease process for each patient

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before embarking on therapeutic interventions. The aim of our paper is to highlight the mechanisms contributing to GERD and review investigations and interpretation of these results. Finally, the paper reviews the available treatment modalities for this condition, ranging from medical intervention, endoscopic options through to surgery and its various techniques.

Keywords: gastroesophageal reflux disease; fundoplication; hiatus hernia; lower esophageal sphincter

Introduction

Gastroesophageal reflux disease (GERD) is a common condition affecting 13% of the population worldwide.¹ It is defined by the American College of Gastroenterology (ACG) as symptoms or complications resulting from the reflux of gastric contents into the esophagus, oral cavity, or lungs.² ³ The clinical sequelae of GERD can be varied. Recurrent exposure of the esophagus to refluxate may lead to reflux esophagitis. Chronic exposure can also result in structural changes to the lower esophagus, including ulceration, peptic strictures, and intestinal-type metaplasia known as Barrett's esophagus (BE), which may represent a protective mechanism against acid injury.⁴⁻⁶ The underlying pathophysiology of GERD is complex with anatomical, functional, and neuromuscular factors all contributing to the disease process. Our understanding of this disease process is evolving and GERD is now increasingly referred to as a cluster of phenotypes as opposed to one distinct disease process.⁷ Given the inherent complexity of GERD, a proper diagnostic workup is important to optimize patient-specific treatment. A better understanding of GERD is important to avoid the inappropriate long-term use of proton pump inhibitors (PPIs) and inappropriate surgical interventions. The goal of therapy should be to address the underlying physiological and anatomical process responsible for the GERD, which differs from patient to patient. The aim of our article is to review the anatomical and pathophysiological mechanisms underpinning GERD and discuss how these relate to current diagnostic and treatment modalities.

Anatomy and pathophysiology of GERD

The underlying pathophysiology of GERD is complex and multifactorial. Given the inherent heterogeneity of the disease process,^{7–10} a consensus definition for GERD has been difficult to attain. GERD is fundamentally a failure of the antireflux mechanisms that protect the esophagus from noxious gastric contents.¹¹ These mechanisms include anatomical and physiological factors, both intrinsic and extrinsic to the esophagus. It may also be further confounded by other functional defects such as delayed gastric emptying, poor mucus and bicarbonate secretion, and esophageal chemical hypersensitivity.¹² Furthermore, the more recently recognized brain–esophagus axis also influences the perception of heartburn through cognition, memory, and emotion is also thought to play a role in GERD.¹³ These factors are summarized in Table 1. Importantly, this list is not exhaustive with many factors overlapping and working in concert.

Intrinsic factors to the esophagus include the lower esophageal sphincter (LES) with its associated high-pressure zone, the presence of normal lining cells, and tight intercellular junctions that create a protective epithelial layer, and the secretion of mucus and bicarbonate from the submucosal glands. The LES is one of the main contributors to the antireflux mechanism that normally maintains a resting tone of 15–35 mmHg and measures 2–4 cm in length at the distal esophagus just above the gastric folds.¹⁷ It is made up of a composite of muscles rather than a simple continuous circular smooth muscle. It consists of an oblique arrangement of gastric muscle fibers on the left that become continuous with the lesser curve and an arrangement of clasp-like c-shaped esophageal smooth muscle cells on the right. Each set of musculature has distinct electrophysiological properties and are under separate nitrergic control.¹⁸ The upper segment of the LES lies at the level of the esophageal hiatus and the lower segment within the abdomen and is loosely fixed to the hiatus by the phrenoesophageal ligament (PEL).¹⁴

Extrinsic factors include the diaphragmatic sphincter, the presence of an intra-abdominal portion of the esophagus, the “angle of His,” and the PEL.¹⁹ The diaphragmatic sphincter is formed by right crural fibers that wrap around the distal esophagus as it passes into the abdominal cavity, acting like a “pinchcock” clamp. The PEL is a layer of fascia that connects the gastroesophageal junction (GEJ) to the diaphragm and is important in maintaining the “angle of His” and an intra-abdominal length of the esophagus. The “angle of His” is the acute angle formed between the distal esophagus and gastric cardia. Such an angulation contributes to antireflux mechanisms by creating a flap valve

effect. An intra-abdominal portion of the esophagus is also mechanically advantageous, as it exposes the distal esophagus to the positive pressure of the abdomen, as opposed to the negative pressure of the thorax. This leads to compression of the distal esophagus. Disruption to any of these mechanisms has the potential to lead to gastroesophageal reflux.

There are a number of lifestyle factors that influence the pathophysiology of GERD. Caffeine, alcohol, nicotine, and many medications (e.g., benzodiazepines, calcium channel blockers, nitrates, B2 agonists, and xanthines) all contribute to GERD through relaxation of the LES.²⁰⁻²⁴ Dietary factors also contribute to GERD, including the size of meal and fat, protein and carbohydrate content leading to gastric distension, delayed emptying, and increased gastric content acidity, as well as the timing of meals.²⁵

Obesity has a significant role in the pathophysiology of GERD. Research from the Nurses' Health Study found a dose-dependent relationship between BMI and GERD.^{26, 27} Furthermore, weight loss has been shown to decrease or completely resolve GERD symptoms.²⁸ The mechanism underpinning the correlation between obesity and GERD are complex. Increased intra-abdominal pressure led to increased transdiaphragmatic pressure gradient (TPG) and slowed the esophageal transit time, leading to the development of reflux.^{29, 30} This correlates specifically with central obesity rather than increasing BMI alone.³¹ There is an increased prevalence of hiatus hernia (HH) in the obese population, occurring in nearly 40% of morbidly obese patients.^{32, 33} The anatomical structure and barrier function of the LES is thereby impaired, as described earlier.³⁴ Obesity also leads to an increase in transient lower esophageal relaxation (tLESR) episodes, leading to GERD.³⁵ This may be partly explained by diet whereby excessive fat consumption promotes secretin and cholecystokinin secretion, which, in turn, stimulates LES relaxation.^{36, 37} Obstructive sleep apnea (OSA) is commonly associated with obesity and is hypothesized to contribute to the pathophysiology of GERD. One study reported that 75% of patients with OSA experience nocturnal reflux as compared with 14% of the U.S. population.³⁸ This is thought to occur through increased intra-abdominal pressure and decreased intrathoracic pressure during inspiratory efforts in apnoeic episodes. This increases the TPG and disrupts the LES, which leads to reflux.³⁹ Adipokines have also been implicated in GERD. Increased leptin levels have an association with clinical GERD severity,⁴⁰ whereas ghrelin levels have an inverse relationship with GERD.⁴¹ The mechanism underpinning the association between obesity

and GERD is complex and multifactorial, working in concert, increasing the TPG, and impairing acid clearance from the esophageal lumen.

The key noxious contents of duodeno-esophageal reflux include acid, pepsin, and bile. By disturbing the local pH-ion balance, acid has a direct injurious effect on the epithelium. It also acts indirectly by activating pepsin, a proteolytic enzyme, from pepsinogen, leading to an impaired mucosal barrier. By contrast, bile can pass directly into cells and disrupt cellular function by virtue of its lipophilic properties.³ All of these processes eventually lead to tissue injury and the ensuing inflammatory response. The failure of esophageal barrier function and esophageal permeability is critical in the pathogenesis of mucosal damage from noxious refluxate.¹⁶

Reflux events are thought to occur through four mechanisms: tLESR, low LES pressure, swallow-associated LES relaxation, and low LES pressure associated with increased intra-abdominal pressure or straining.¹⁶ The degree to which the intrinsic and extrinsic protective factors contribute to reflux differs depending upon the mechanism and physiological conditions.

tLESR underlies 90% of GERD in patients without structural defects at the GEJ.¹⁶ It is defined as LESR occurring independently to swallowing, not accompanied by peristalsis, accompanied by diaphragmatic inhibition, and persisting for longer than the swallow-induced LES relaxation (>10 s).^{14, 42} The dominant stimulus is distension of the proximal stomach and is thought to be a vagally mediated mechanism to vent gas.¹⁶ There is also evidence to suggest that axial stretch of the esophagus also causes LES relaxation.⁴³ Animal studies have highlighted the role of nitric oxide in the control of LES continence, mainly through the neurogenic response of neuronal nitric oxide synthase (nNOS).^{15, 44} Activation of gamma-aminobutyric acid (GABA) receptors inhibit tLESRs.⁴⁵ As such, tLESRs are an important therapeutic target in the management of GERD.

The contribution of the gastroesophageal flap valve or the “Hill flap” valve to antireflux mechanisms is important but often underrecognized.⁴⁶ It is formed by the intraluminal extension of the angle of

His that abuts the lesser curve of the stomach and creates a flap valve allowing the one-way passage of food, as outlined in Table 2.⁴⁷ Impairment of this flap has been associated with GERD, poor response to PPI therapy, HH, and lower LES pressure.^{47–50} Despite its importance, it is often underreported or without a properly retroflexed endoscopic examination of the insufflated stomach.⁵⁰

The presence of HH is an important contributor to the etiology of GERD. One study has found that despite not all patients with HH having symptoms of GERD, up to 94% of patients with reflux esophagitis have HH.⁵² Furthermore, the HH size has also been shown to correspond with GERD symptoms with large herniae associated with abnormal pH monitoring, however, a small HH are poor predictors of GERD symptoms.⁵³ When the proximal stomach and abdominal esophagus herniate into the thoracic cavity, there is a separation of the LES with the crural diaphragm that shortens the high-pressure segment and impairs sphincteric function.¹⁴ Additionally, migration of the GEJ into the thoracic cavity leads to an increased pressure gradient during inspiration and subsequent LES relaxation due to negative intrathoracic pressure.¹⁴

Another mechanism that contributes to GERD, particularly in the presence of HH, is the postprandial acid pocket. The acid pocket is a normal physiological response following the ingestion of food. Following the secretion of acid from gastric parietal cells, excess acid rises and sits above the food bolus forming a “pocket.” This acid pocket sits in the proximal stomach adjacent to the GEJ and can lead to reflux during periods of low LES pressure.^{14, 16, 54} Evidence suggests that the location of the acid pocket relative to the diaphragm influences the development of GERD. In the presence of HH, the acid pocket represents a major risk factor for GERD. As it sits above the diaphragm, it is subjected to negative pressure during inspiration. In combination with tLESRs, reflux ensues.⁵⁵

Diagnostic testing

Given the heterogeneous nature of the disease, there is no single method to diagnose GERD; multiple investigations are required to properly assess the diagnosis and underlying mechanism on an individualized basis.

The first step in making a diagnosis of GERD is to elicit a clinical history and perform a physical examination of the patient. Importantly, a significant number of patients with PPI-refractory GERD will have a significant improvement in their symptoms if given explicit instructions to take their prescribed PPI 30–45 min before breakfast.⁵⁶ The best efficacy of PPIs has been shown to be in the morning when generally the optimal number of proton pumps can be blocked after a period of fasting. Furthermore, for patients that are suffering from predominately nocturnal symptoms, a twice-daily regimen of PPIs has been shown to be more effective than the morning dose alone.⁵⁷ In addition to being a treatment modality, the use of PPI has also been advocated as the first step and most cost-effective means of diagnosing GERD.^{58, 59}

Traditionally, upper gastrointestinal (GI) endoscopy has been considered as an important adjunct in both the diagnosis of GERD and its associated complications. Despite being an invasive procedure, it enables visual inspection of the lower esophagus, histopathological assessment of the tissues, and dynamic assessment of the Hill flap valve mentioned above (Table 2).² This is demonstrated with a retroflexed gastroscope with gastric insufflation and is graded from I to IV according to the prominence of the ridge and its apposition with the gastroscope.⁴⁶ This is a dynamic endoscopic maneuver to assess the valve, particularly functionally with gastric distension, and also assesses the presence of HH. This has a greater sensitivity than standard radiological investigations that may be unable to provide this dynamic assessment without the use of effervescent tablets and exerting external abdominal pressure (and perhaps the Valsalva maneuver) during the exam. Grades I to II are considered physiological whereas grade III and IV are abnormal and associated with GERD with grade IV implying the existence of HH.⁴⁶ The Hill flap valve is demonstrated to be highly reproducible on endoscopy and assist in the diagnosis of GERD.⁶⁰ The assessment of the length and width of the HH is important, as hernias greater than 2 cm are not amenable to endoscopic management. Moreover, insufflation may reveal previously unrecognized paraesophageal or mixed hernias that may be responsible for dysphagia or postprandial dyspepsia.

The importance of adequate assessment of the Hill grade is a key step in the endoscopic examination of a patient with suspected GERD. The Hill flap valve is predictive of failure of PPI therapy. One study examining PPI response found in patients with symptomatic GERD and Hill flap

valve found of those who responded to 4 weeks of PPI therapy, 77.1% were grade I to II and 22.9% were grade III to IV. These numbers were similar after 8 weeks of PPI therapy.⁴⁹ Given the presence of abnormalities in the Hill flap valve is predictive of failure of PPI therapy, assessment should be routine in patients undergoing endoscopy for GERD symptoms. If Hill grading suggests pathology, prompt consideration of therapy to correct anatomy should be considered to improve defensive mechanisms of the GEJ. To persist with long-term PPIs in these patients is likely futile and puts the patient at risk of long-term side effects associated with PPIs.^{47, 49}

Routine biopsies are not recommended in the diagnosis of GERD.² Erosive esophagitis is only present in about one-third of untreated patients and is an uncommon finding in those already trialed on PPI therapy. In patients with symptomatic GERD, 70% will have the normal esophageal mucosa. Of those already on a PPI, 90% will have a normal endoscopic examination.⁹ Random esophageal biopsies are not useful in diagnosing GERD, although they are useful at tracking resolution of disease complications, such as Barrett's and esophagitis or ruling out eosinophilic esophagitis in patients with heartburn or dysphagia, as an alternative diagnosis to peptic disease and strictures. Endoscopy is an important investigation in identifying complications or anatomical pathology predisposing to GERD, however, is not able to make a conclusive diagnosis of GERD itself.⁹

There are several other key aspects of the upper endoscopy that need to be considered when examining the dyspeptic patient. These mostly involve the exclusion of other pathologies that can mimic GERD. These include reporting the presence of bile in the stomach, assessment for *Helicobacter pylori* infection and associated gastritis, retained food, which is common in gastroparesis in a properly fasted patient, the presence or absence of antral peristaltic waves, and the appearance of the pyloric sphincter (wide gaping with bile refluxate, for instance, may suggest the additional need of sucralfate or bile acid binders, but negate the role of botox in a patient later found to have gastroparesis).⁶¹ Bile acid reflux appears to be associated with the development of Barrett's metaplasia and carcinogenesis as well as triggering GERD symptoms through inflammatory stimulation and oxidative stress.⁶² *Helicobacter Pylori* is significant as the presence is associated with a greater acid-reducing effect of PPI therapy.⁶³ Furthermore, there is a protective association between *H. pylori* and reflux though this is thought to be correlative rather than causative.^{64, 65}

The gold standard for objective diagnosis of GERD is ambulatory pH monitoring performed while off acid-suppressing medications,⁶⁶ while studies performed on medications are suited to address their treatment efficacy. pH monitoring is used in the assessment of the refluxate entering the lower esophagus. Both the timing of the pH changes and the duration of acid exposure are important assessments. The pH tracings should be reviewed to confirm that the probe had not migrated into the stomach during the study and that meals and supine periods are properly labeled. Esophageal acidification is quantified using the DeMeester score and acid exposure time (AET).⁶⁷ Making a distinction between the reflux occurring when the patient is in the supine and erect positions may provide important insight. Accurate recording of the meal times and periods of supination is important as standard meal times are excluded from the analysis. In the supine position, the intra-abdominal pressures are higher and, as such, also the risk of reflux. However, predominant reflux during the erect position suggests that the natural defensive mechanisms at the GEJ are not effective. Thus, patients are advised to remain in the upright position during waking hours of the recording. As a further adjunct to this investigation, impedance testing can be used to identify the presence of reflux of any type. Impedance monitoring improves the assessment of the reflux to symptom association, helping to distinguish between functional heartburn and NERD or the acid-sensitive esophagus.⁶⁸ Three indices are used to quantify the relationship between reflux and symptoms, namely the symptom association probability (SAP), symptom index (SI), and the symptom sensitivity index (SSI).⁶⁹

A potential limitation of this test is the alteration of the natural physiology of the esophagus by having an electrode within the lumen of the esophagus or traversing the GEJ with a dual-channel probe and, as such, may alter the underlying physiology of the patient. Also, some refluxate may not be acidic yet still predisposing patients to symptoms as discussed above. As such, an impedance-pH study is generally favored to assess the role of volume reflux and correlation with symptoms. A dual-channel probe is also helpful in ascertaining that the patient has been compliant in withholding PPIs and H-blockers for a week before the study or even revealing achlorhydria in patients with atrophic gastritis, for example.

Importantly, those patients with a negative DeMeester score but positive SAP on the impedance study, are experiencing nonacidic GERD. This cohort of patients have been shown to benefit most

from sucralfate or bile acid binders or surgical intervention as their symptoms are independent of acid and as such will have little benefit to PPI therapy.⁵⁶

Given the importance of the LES in the pathology of GERD, it is necessary to consider the role of manometry in the assessment of this condition. Given that there has been a discordance between the traditional interpretation and the current literature about LES, the role of manometry as an investigation has also evolved. The Chicago Classification of esophageal motility uses algorithms to analyze high-resolution manometry (HRM) and was first published in 2009. The International High-Resolution Manometry Working Group has since made updates in 2012 and 2014.^{70, 71}

Earlier manometric classifications focused only on achalasia, EGJ outlet obstruction, motility disorders, and abnormalities. In the revised classification in 2014, however, the emphasis was placed on EGJ resting pressure morphology and contractility. In addition, the concept of the distal contractile integral (DCI) for defining hypo- and hypercontractility has also been highlighted. As a result of this improved understanding, patients previously thought to have motility disorders have been reclassified as having small HHs and transient esophageal shortening.^{70, 72}

The HRM Working Group has also recently acknowledged the importance of the LES and its role in GERD. In their recent guidelines, they have classified EGJ morphology into three subtypes, which are based on an assessment of the manometric values of the crural diaphragm and the LES. This also assesses the anatomical relationship of the two pressures. In particular, the working group highlights the important physiological role this has in GERD and stresses the importance of its reporting on manometry results. The significance of this illustrates the evolving understanding of the pathophysiology of GERD and the role that manometry has in making a diagnosis and understanding of the particular underlying pathophysiology.⁷⁰

Manometry not only has a role in the workup of patients requiring fundoplication but has a role in both the diagnosis of GERD itself. The strongest predictor of GERD is the inspiratory augmentation pressures at the EGJ when compared with other diagnostic measures such as pH monitoring.⁷⁰

Furthermore, the DCI has been shown to be elevated in patients with manometric proven GERD. This is also essential in ruling out primary motility disorders of the esophagus, including achalasia which frequently presents with heartburn (13 to 68% of cases) and would largely contraindicate traditional Nissen, for example.⁷³ It may also reveal underlying systemic sclerosis that can present without overt cutaneous manifestations but may explain pulmonary findings previously attributed to GERD alone.⁷⁴

Historically, a barium esophagogram has been used to assess patients with esophageal reflux. They have poor sensitivity and specificity, however, compared with more modern assessments.^{75, 76}

Although they can provide important anatomical information and structural abnormalities (e.g., strictures, hiatal hernia size, and diverticulum) and can be useful preoperatively, they have been largely phased out and are not recommended in the ACG guidelines in the diagnosis of GERD.²

Nuclear medicine studies are an important adjunct to the assessment of GERD, as they allow for the diagnosis of other pathologies that may mimic GERD, such as delayed gastric emptying. More recently, this has also been evaluated using a SmartPill™ (Medtronic, Fridley, MN, USA),⁷⁷ or the 13-C Gastric Emptying Breath Test (Cairn Diagnostics, Franklin, TN, USA).⁷⁸ Such distinctions are important to make, as they are associated with different pathophysiological processes and require different management.

Assessment tools and therapeutic options

The existing literature of antireflux therapy comparing the success of different antireflux treatments is largely qualitative and fails to assess the underlying process that is targeted by each treatment.

Assessment of success typically relies on the resolution of heartburn symptoms, absence of complications (belching, gas bloat, and dysphagia), and no ongoing PPI requirement. In addition to symptomatic assessment, qualitative questionnaires such as the REFLUX questionnaire that incorporate health-related quality of life with reflux symptoms and the Visick score are also used to assess the success of intervention.⁷⁹ These are primarily used as research tools with limited clinical application.

The therapeutic options for the treatment of GERD are broad and include antireflux surgery, medical therapy, lifestyle modification, and both novel surgical and endoscopic adjuncts. Traditionally, the treatment of GERD relied upon a stepwise approach from lifestyle modification to medical therapy to surgery.⁸⁰ However, given the variation in the underlying pathophysiology and mechanism of action of existing therapies, treatment should be targeted and guided by thorough investigations and postintervention evaluation.⁸¹ These are summarized in Table 3.

Lifestyle modification

Lifestyle modification aims to minimize risk factors for symptomatic GERD, such as dietary modification, bed head elevation, minimizing alcohol intake, avoiding certain drugs, smoking cessation, minimizing caffeine, and weight loss.^{82, 83} While these measures are recommended for all patients with GERD, particularly at initial presentation, there is a minimal or variable effect on patient symptoms and should be an adjunct to surgical and/or medical therapy.^{79, 83-85}

Medical therapy

Acid suppression with PPIs is the mainstay of the medical management of GERD and acts through the irreversible blockade of H^+K^+ -ATPase proton pumps within the parietal cells of the stomach.⁸⁵ Up to 30% of patients fail to respond to PPI therapy either partially or completely.⁸⁶ PPIs are effective in reducing acid reflux and the volume of gastric secretions to an extent however nonacidic reflux remains an issue.⁸⁷ PPIs also do not address the underlying anatomic and neuromuscular causes for GERD.⁷⁹ Furthermore, PPIs have an effect on bile acids and other enzymatic secretions from the duodenum that are associated with nonacidic reflux and BE.¹⁶ As acid is required in the cleavage of proenzymes to enzymes, an absence of acid may affect gastric content and flow.⁸⁸ Clear instructions for timing and medication compliance is critical to the success of PPI therapy; it must be taken 30–45 min prior to the first meal of the day with the addition of a second dose if required.⁸⁹ In one major randomized trial examining PPI refractory GERD, 11% of patients with PPI refractory heartburn had resolution of symptoms after a 2-week trial of omeprazole twice-daily under strict instruction.⁵⁶

Although there have also been concerns regarding side effects of long-term PPI use based on population studies, including malabsorption, osteoporosis, dementia, and both GI and pulmonary infections, the evidence for these side effects is weak and lacks rigorous long-term data.^{90, 91} Another consideration with the use of PPIs is the interaction with other medications. In some studies, it has been suggested that PPIs block the conversion of the prodrug clopidogrel to its active form by preferentially utilizing the cytochrome P450 enzymes within the liver.^{92, 93} A more recent meta-analysis, however, has shown that the use of PPIs and dual antiplatelet therapy improves outcomes of GI bleeding, without compromising cardiovascular outcomes and that further randomized trials are required in this area.⁹⁴

There are numerous alternatives to PPIs that have been trialed with various degrees of success. Histamine 2 receptor antagonists (H₂RA), such as ranitidine, nizatidine, famotidine, and cimetidine, although historically the first-line therapy, are less effective than PPIs in symptom control and esophageal healing and are often used as the step-down therapy or as an adjunct to PPIs. They work through reversible blockade of histamine 2 receptors of the parietal cells in the stomach thereby decreasing acid secretion.⁹⁵ Some trials have demonstrated an initial response to combination therapy of twice-daily PPI and H₂RA reduces the incidence of nocturnal acid breakthrough; however, the clinical effect lasted approximately 1 week and had no long-term benefit due to tolerance to the H₂RA.⁹⁶

Alginates, derivatives of alginic acid derivatives, are a further pharmacological option in the treatment of GERD. They have been demonstrated to colocalize with the acid pocket, either displacing or neutralizing it and, as such, increasing the pH of the postprandial refluxate.⁹⁷ A further mechanism has also been proposed by forming a barrier to reflux through molecular cross-linking and formation of a cap over the gastric contents, as such has been shown to reduce the number of reflux episodes.⁹⁸ A recent systematic review and meta-analysis by Leiman and colleagues found that alginates are more effective than placebos or antacids, however appear to be less effective than PPIs and H₂RA, although not statistically significant.⁹⁹ A call for further research in assessing these medications in combination is warranted.

Baclofen, a GABA agonist is effective in reducing reflux events and GERD symptoms through the reduction of tLESRs as well as increasing the postprandial LES tone. The role of the stretch receptors in the fundus is also a mechanism being explored with the use of GABA agonists to aid in increased LES tone. However, its use is limited by central side effects including dizziness and somnolence.^{100, 101} Furthermore, the long-term efficacy has not been demonstrated.¹⁰² There are several emerging therapeutic agents that show promise in the treatment of GERD. Colesevelam (IWX-3718), a novel bile acid sequestrant has been shown to reduce heartburn and regurgitation symptoms when taken with PPI in a recent randomized controlled trial.¹⁰³ It is currently entering phase III trials. There is also emerging evidence on the use of acid-sensing ion channel inhibitors to improve heartburn symptoms by reducing esophageal hyperalgesia.¹⁰⁴ Antacid medications are commonly used in the management of intermittent heartburn symptoms however they do not provide long-term symptomatic relief nor do they heal esophagitis, prevent complications, or address the underlying cause of GERD.⁸⁵

Surgical management

There is an important distinction between surgery for GERD and HH, although the two surgeries are often performed in conjunction. In the case of HH, surgery aims to restore the normal anatomical configuration by returning the stomach from the thorax into its native position and closing the hiatal defect. Given the contribution of HH in GERD, the repair will help treat and prevent reflux. By contrast, the fundoplication is primarily an antireflux procedure. However, given the correlation between HH and PPI refractory GERD, HH repair and fundoplication are frequently performed together. Furthermore, a fundoplication reduces the risk of HH recurrence by buttressing the crural repair with the fundic wrap.¹⁰⁵

For patients with GERD in the absence of HH, laparoscopic fundoplication is the gold standard operation and mainstay of antireflux surgery.⁵ Fundoplication has been demonstrated to be efficacious and durable in treating GERD with persistent symptomatic relief demonstrated in 90% of patients at 10 years.^{5, 106} Patients with the best overall outcomes from antireflux surgery are those who have typical GERD symptoms and are responding to PPI therapy in addition to a prolonged AET

(pH < 4, >12% of the time) .⁸¹ The LOTUS trial, which published its final outcomes in 2011, supports this demonstrating that patients with a complete response to PPIs have a high overall remission rate with either long-term PPI use or antireflux surgery.¹⁰⁶ Furthermore, it should be noted that patients with atypical symptoms and those not responding to PPIs need very careful assessment (ie: with pH/impedance monitoring both whilst taking and not taking PPIs) before considering surgical intervention. As such, despite surgery being an effective treatment modality for GERD, a careful assessment of the patient's symptoms and workup is required to isolate the patients who are best suited to this treatment modality.

The international consensus regarding preoperative examinations and clinical characteristics assessment to select adult patients for antireflux surgery (ICARUS) published their guidelines in August 2019. As well as emphasizing the above, they have highlighted that endoscopy, oesophageal manometry (to rule out major motor disorders), and esophageal pH monitoring (+/- impedance testing) are mandatory assessment tools prior to antireflux surgery. Furthermore, patients with a large HH should be assessed with barium swallow preoperatively to assess the length of the esophagus .¹⁰⁷

Currently performed procedures include the Nissen fundoplication consisting of a 360° wrap and partial fundoplications. These include both the Toupet fundoplication, consisting of a posterior 270° posterior wrap and the Dor, which consists of an anterior 180° wrap. Worldwide, the Nissen fundoplication is the most commonly performed procedure and has been shown to have superior durability. However, it has been demonstrated to have a higher side effect rate compared with partial fundoplications, notably dysphagia (8–12) and gas bloating symptoms (19%).^{108, 109}

The augmentation of the stretch receptors in the fundus and inhibition of vagal tone may increase the resting pressure at the LES. Fundoplication utilizes this by stretching the fundus to form part of the wrap, as such utilizing both anatomical and physiological mechanisms to improve patient outcomes. Unfortunately, magnetic sphincter augmentation (MSA) devices are not able to use this

mechanism to reestablish increased basal tones at the LES, rather utilizes extrinsic compression from the device itself.

Antireflux surgery is pursued in three settings: where long-term definitive management of GERD is desirable over indefinite use of PPI, where there is persistent reflux disease despite maximal medical therapy and where there is structural alteration at the GEJ. Further to this last setting, in the case of a large HH, surgery allows for repositioning of the LES to the level of the diaphragm.⁸⁵ Fundoplication works through a number of mechanisms. Anatomical antireflux mechanisms are restored through the repair of any HH and the realignment of the LES with the crural sling, the restoration of the intra-abdominal esophageal segment, the recreation of the esophageal Hill flap valve and the angle of HIS as well as further mechanical compression of the distal esophageal and increased basal LES pressure.^{43, 110} Fundoplication also has a physiological mechanism with evidence suggesting it reduces transient LES relaxation by reducing axial stretch fibers at the LES and altering fundic tone, thereby minimizing LES relaxation.⁴³

Despite the developments of new techniques, and in keeping with our developing understanding of GERD pathogenesis, fundoplication remains an appropriate tool in the management of GERD in the correct circumstances. In the presence of HH, in many cases, this anatomic defect needs to be repaired alongside a fundoplication as an antireflux procedure. As mentioned above, once hernias are greater than 2 cm, they are not amenable to the endoscopic technique. The success of the fundoplication and assessment of the basal pressures at the LES can be difficult to appreciate at the time of operation. Commonly, the wrap is made around a bougie to ensure adequate laxity to prevent dysphagia and a tactile judgment is made to ensure it is adequately tight. Given the multitude of factors contributing to the GEJ antireflux mechanism, in particular, the active basal tone of the LES, the intraoperative subjective assessment of wrap tightness cannot predict the success of the fundoplication. It is not possible to assess objectively the likely outcome of a fundoplication intraoperatively. Surgeons rely to an extent upon tactile feedback in determining the appropriate tightness of a wrap; however, this is limited with the use of laparoscopic surgery. Furthermore, the closure of the crura around the esophagus relies on the esophageal diameter as a guide. In instances of a dilated esophagus, closure of the crura may still leave a large and clinically significant defect despite having a tight appearance. There is evidence that postoperative on-table endoscopy can reduce the rate of dysphagia through addressing excessive esophageal narrowing but it is not shown to improve the success from an antireflux point of view.¹¹¹ New endoscopic devices such as

EndoFLIP® (Crospon Ltd., Dangan, Galway, Ireland) may be used to determine these pressures intraoperatively and trials are ongoing to determine its clinical application.¹¹²

In addition to its association with reflux disease, obesity is also a strong risk factor for the failure of laparoscopic antireflux surgery with one meta-analysis finding a 53% increased risk over nonobese patients.¹¹³ This has driven the use of Roux-en-Y gastric bypass (RYGB) for patients with a BMI > 35 and GERD with favorable outcomes over fundoplication demonstrated in the literature.^{114–116} RYGB has a different antireflux mechanism to fundoplication. The creation of a small proximal gastric pouch separates the majority of the acid-producing stomach from the distal esophagus and the creation of a Roux-en-Y reconstruction of the small bowel prevents the reflux of bile into the distal esophagus.¹¹⁵ The treatment of obesity also leads to an overall decrease in intra-abdominal pressure, a known risk factor for GERD.

Novel surgical alternatives

LINX® Reflux Management System (Torax Medical, Shoreview, MN, USA) magnetic sphincter augmentation (MSA) is a novel therapy in the treatment of GERD whereby a chain of interconnected magnetic beads is laparoscopically inserted around the distal esophagus to create a dynamic circumferential pressure around the LES, thereby allowing the passage of food boluses but providing enough pressure to prevent the reflux of gastric contents.^{115, 117} Furthermore, it allows patients to retain the ability to belch and vomit with less gas bloating. It was designed to address a therapy gap for patients with disease inadequately controlled by medical therapy who did not want to undergo a fundoplication with its associated side effects and is easily reversible if needed.¹¹⁸ The LINX® MSA system provides 15–25 mmHg pressure at the LES that exceeds gastric pressures (5–10 mmHg) but is easily overcome by peristaltic pressure (35–80 mmHg).^{117, 119} MSA leads to a similar improvement in HR-QOL scores when compared with fundoplication surgery and has been demonstrated to be safe and reversible and is associated with fewer side effects.¹²⁰ The LINX® system can lead to esophageal erosion or formation of a fibrotic capsule around the ring, leading to dysphagia.¹²¹ Importantly, the MSA does not restore anatomy at the GEJ. It is, therefore, unlikely to be useful in the presence of an anatomical disruption, such as HH, or significant esophageal dysmotility.¹²² Low basal LES tone,

identified on manometry studies in the presence of normal hiatal anatomy, may be aided by the insertion of MSA.

Electrical neuromodulation is another emerging antireflux therapy. The EndoStim® (EndoStim BV, Nijmegen, the Netherlands) treats GERD through augmentation of the LES using two electrodes placed at the LES controlled by a pulse generator implanted in the abdominal wall.¹²³ It is associated with a reduction in distal esophageal acid exposure time with a minimal side effect profile.¹²⁴

Endoscopic therapy

While many endoscopic techniques have been developed and trialed, there are currently two that are presently available. These include radiofrequency (RF) treatment at the GEJ namely Stretta (Mederi Therapeutics, Greenwich, CT, USA),^{125–127} and Transoral Incisionless Fundoplication (TIF).¹²⁸ RF involves delivering energy to the region of the LES to evoke muscular hypertrophy. This prevents GERD by increasing lower esophageal wall thickness and LES pressure and minimizing tLESRs. It is as effective as PPIs in reducing GERD symptoms short term,¹²⁵ however has been shown in a number of studies with objective outcomes such as AET do not reduce acid exposure. It has been hypothesized that this is due to the ablation of the sensory nerves in the distal esophagus during the procedure.¹²⁹ Despite this, a 10-year follow-up study showed durability of results and a favorable cost-effectiveness compared with PPI therapy.^{130, 131}

TIF works by creating an anatomic barrier at the GEJ by restoring the angle of His through the endoscopic placement of either sutures or staples.¹²⁸ Compared with RF treatment, it is a technically difficult procedure, performed in the operating theatre and carries a risk of perforation and is associated with poor durability. Studies have shown the procedure to be associated with 80% PPI dependence at 4 years and a 64% treatment failure rate.¹³² While the literature demonstrates these to be effective in subjective measures, they have not demonstrated improvement in objective measures, such as esophageal acid exposure.¹³³

The Medigus Ultrasonic Surgical Endostapler (MUSE) device (MediGus Ltd, Omer, Israel) is an endoscopic procedure designed to perform a partial fundoplication. This uses ultrasound guidance to staple the gastric mucosa to the intraabdominal esophagus and recreate the angle of His. This procedure is limited to patients with HHs less than two cm and Hill Grade I/II only.¹³⁴

The role of RE, TIF, and MUSE are controversial, with numerous conflicting opinions on the utility of endoscopic therapies to manage GERD. While there is evidence that they provide some degree of relief from GERD, they remain second-line to surgical intervention.¹³⁵ More research is required at this time to better demonstrate the long-term outcomes of these interventions.

Conclusion

A thorough assessment of patients with PPI refractory GERD is important in assessing the most effective therapy for patients and also to exclude alternative pathology (eg: esophageal dysmotility or delayed gastric emptying). A recent trial has shown antireflux surgery has greater improvement in quality of life when compared with medication alone, however, a secondary finding was that a large number of patients being considered for these interventions either do not have GERD or have conditions not amenable to treatment by either medical therapy or surgery.^{56, 131} As such, although a thorough clinical history and trial of pharmacological measures in the first instance are important, a comprehensive workup with more invasive testing is vital in appreciating the true underlying pathophysiological cause of each patient's disease process. With numerous investigations available, an understanding of the factors contributing to the patient's GERD enables clinicians to utilize appropriate therapeutic strategies. GERD is a complex cluster of phenotypes. A more nuanced approach is important in the investigation and treatment of GERD through a deeper understanding of the pathophysiology of the disease, the strengths and limitations of investigations, and the specific targets or mechanisms of each available therapy. The proper assessment might include a broader interpretation of pH/manometry data, meticulous dynamic endoscopic evaluation before nonmedical therapies, and proper patient selection for antireflux procedures. The step-wise approach from lifestyle modification to medical therapy to surgery can overlook the complexity of

the disease and lead to suboptimal management. Proper workup and in-depth consideration of the underlying process on a case-by-case basis is necessary to properly tailor the best therapy.

Competing interests:

H.M. H.B. and S.B. declare no competing interests. M.R. is the recipient of the Senior Lecturer Fellowship from the Royal Australasian College of Surgeons.

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Table 1. Summary of factors responsible for the pathophysiology of GERD¹³⁻¹⁶

Intrinsic□	Extrinsic□	Physiological□	Secretory□
<ul style="list-style-type: none"> ● → The lower esophageal sphincter¶ ● → Esophageal permeability□ 	<ul style="list-style-type: none"> ● → The crural diaphragm¶ ● → The intra-abdominal esophagus¶ ● → The Hill flap valve¶ ● → The angle of His¶ ● → Phreno-esophageal ligament¶ ● → The acid pocket¶ 	<ul style="list-style-type: none"> ● → tLESR¶ ● → Swallow-associated LES relaxation¶ ● → Basal LES pressure¶ ● → Abdominal pressure¶ ● → Gastric emptying¶ ● → Esophageal emptying¶ ● → Esophageal hypersensitivity¶ ● → The brain-esophagus axis□ 	<ul style="list-style-type: none"> ● → Gastric HCl and pH¶ ● → Mucous¶ ● → Bicarbonate¶ ● → Saliva¶ ● → Bile/bile acids¶ ● → Digestive enzymes□

Table 2. Gastroesophageal flap valve (Hill) classification^{46, 51}

Hill flap grade	Description	
I	A prominent fold of tissue originating at the angle of "His" in close apposition with the lesser curve and abuts the endoscope	Normal
II	The fold of tissue present with an intermittent rapid period of opening around the endoscope with respiration	
III	The fold is not prominent and the endoscope is not gripped tightly by the ridge	Abnormal
IV	An absent fold, the esophageal lumen gapes widely open, and the esophageal mucosa visible from below	

Table 3. Therapeutic options in the treatment of GERD, mechanism, and evidence

Therapy	Mechanism	Efficacy
Lifestyle		
Lifestyle modification	Risk factor avoidance, dietary modification, and head-of-bed-elevation ⁸⁴	Poor evidence that lifestyle changes have a significant impact on GERD symptoms ⁸⁴
Weight loss	Reduces intra-abdominal pressure in abdominal or generally obese patients ⁸²	Improves GERD symptoms but not esophagitis ⁸²
Medical Management		
PPI	Gastric acid secretion suppression by irreversible blockade of H ⁺ K ⁺ ATPase proton pumps ⁸⁰	Symptomatic relief in 57% to 80% of patients with NERD EE healing in 85% of patients ⁸⁰
H ₂ RA	Gastric acid secretion suppression by competitive histamine receptor blockade ⁸⁵	EE healing 41% of patients, symptomatic resolution 48 to 56% of patients ⁸⁵
GABA agonists (e.g., baclofen)	Reduction of tLESRs ¹⁰²	Reduces number reflux episodes with central side effects ¹⁰²
Antacids	Acid neutralization	Short term symptomatic relief, no long-term symptomatic relief of EE healing ⁸⁵
Prokinetic agents	Increase LES tone and accelerate gastric emptying ⁸⁵	A modest reduction in symptoms when given PPI ¹³⁶
Colesevelam (IWX-3718)	Colesevelam. Sequestration of bile in the stomach to reduce bile exposure to the esophagus	Improved heartburn and regurgitation symptoms when combined with PPI. ¹⁰³
Surgical management		
Fundoplication	Restoration of GEJ anatomy, reduction of HH, mechanical esophageal compression, and reduction in LES relaxation triggering ⁴³	90% of patients are symptom-free at 10 years, ¹³⁷ 60% off PPI at 17 years. ¹³⁸ Better outcomes for those with HH preop. ¹³⁹ Superior durability with Nissen over partial but higher dysphagia rate. ¹⁰⁸ Superior to optimized medical therapy in a select population of treatment-refractory patients ⁵⁶

RYGB	Precipitates weight loss, separation of the acid-producing stomach from the esophagus and bile diverting anastomosis ¹¹⁴	Significant reduction in GERD symptoms at 12 months. Suitable for patients BMI > 35 ¹¹⁴
MSA (LINX®)	Magnetic ring providing 15–25 mmHg to LES	Similar HRQOL improvement compared with fundoplication, easily reversible, and fewer side effects ¹²⁰
Endoscopic management		
Radiofrequency treatment (Stretta®)	Radiofrequency treatment to LES region causing muscular hypertrophy and decreased TLESR ¹²⁵	EE incidence reduced by 24%, 49% remain on PPI post-Rx, LES tone increases by 1.73 (mean) ¹²⁶ May reduce symptoms and QOL scores up to 8 years postintervention. No sustained improvement in objective outcomes. No evidence of improved outcomes as compared with surgical intervention. ¹³⁵ Sham-controlled randomized trial demonstrated in the treatment of PPI refractory heartburn ¹⁴⁰
Electrical neuromodulation (EndoStim®)	Pacemaker delivers electrical energy to LES to increase resting pressure	Reduction in the distal esophagus acid exposure time with acceptable side effect profile. ¹²⁴
TIF	Mechanical repair of GEJ valve and reduction of small HH using endoscopic stapler ¹²⁸	Normalization of esophageal pH 45–69% of patients, EE healing 77–100% of patients, and poor durability ¹²⁸
RYGB, Roux-en-Y gastric bypass; MSA, magnetic sphincter augmentation; TIF, transoral incisionless fundoplication; PPI, proton pump inhibitor; H ₂ RA, Histamine-2 receptor antagonist; EE, erosive esophagitis; RFA, radiofrequency ablation; HH, hiatus hernia; HR-QOL, health-related quality of life

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