Gastroesophageal reflux disease (GERD) is common, accounting for more than 5.6 million physician visits each year.1 From 10% to 20% of adults in Western countries and nearly 5% of those in Asia experience GERD symptoms at least weekly.2 The prevalence of GERD symptoms is increasing by about 4% per year, in parallel with increases in obesity rates and reduction in prevalence of Helicobacter pylori over the past several decades.3 However, patients may not have symptoms of GERD even if they have objective evidence of it such as erosive esophagitis or Barrett esophagus.4

In 2015, the total direct economic impact of GERD and its complications was estimated to be over $18 billion, with use of proton pump inhibitors (PPIs) accounting for $12.4 billion, while the indirect costs driven by decreased work productivity were as much as $75 billion.1,5

Troublesome symptoms, complications

An international consensus group has defined GERD as a condition that develops when reflux of stomach contents causes troublesome symptoms with or without complications.6 Typical symptoms that lead to the diagnosis of GERD are regurgitation and heartburn. As much as 16% of the US population complains of regurgitation, and 6% report clinically troublesome heartburn.7 However, while these symptoms are specific for the disease, they are insensitive markers of reflux.

GERD symptoms can worsen with lying recumbent, especially after meals.

Of note, dysphagia can be a symptom of uncomplicated GERD, but its presence warrants more intensive examination and potential in-
GERD

Managing gastroesophageal reflux disease

Alarm symptoms:
Dysphagia, odynophagia, bleeding, anemia, weight loss, early satiety, vomiting

Yes

Start PPI therapy
(8 weeks)

No

Response?

Yes

EGD

Normal

Any extraesophageal symptoms?

No

Consider referral
to ear, nose, and throat, pulmonary, allergy services

Abnormal

Taper to lowest possible dose

Consider functional heartburn or reflux hypersensitivity

Normal

Treat in response to findings

pH monitoring

Optimize medical therapy

Consider surgical and endoscopic therapies

Figure 1. Approach to gastroesophageal reflux disease (PPI = proton pump inhibitor, EGD = esophagogastroduodenoscopy).

PATHOPHYSIOLOGY

Since GERD was first described in 1879 by Heinrich Quincke, our understanding of its pathophysiology has slowly expanded and evolved. Factors now known to contribute to GERD include:

- Transient lower esophageal sphincter (LES) relaxation
- Sliding hiatal hernia
- Low LES pressure
- Acid pocket development due to poor mixing of acid with chyme in the proximal stomach
- Increased gastroesophageal junction distensibility
- Obesity
- Delayed gastric emptying.

Most symptoms are caused by acid reflux, but if symptoms persist on PPI therapy, they are likely due to either weakly acidic or weakly alkaline secretions.

The distance up the esophagus that the reflux travels also plays a role in the symptoms of GERD. Acid reflux episodes that extend...
higher into the esophagus are associated with worse symptoms, regardless of the acidity of the bolus.12,13 Trimble et al13 found that patients with GERD have enhanced esophageal sensation and likely have heightened perceptions of normal nonacidic reflux events due to lower sensory thresholds. Another hypothesis is that sustained esophageal longitudinal muscle contractions may lead to transient ischemia of the esophageal wall, resulting in GERD symptoms in some patients.14

**DIAGNOSIS AND MANAGEMENT**

GERD is mainly a clinical diagnosis based on typical symptoms. Its diagnosis and management are summarized in Figure 1.

If no alarm symptoms, first try a PPI

Current guidelines indicate that patients with typical symptoms should first be given a trial of PPI treatment.15 However, patients with alarm symptoms including dysphagia, anemia, weight loss, bleeding, and recurrent vomiting should proceed directly to upper endoscopy.

There are limitations to this approach: a meta-analysis showed that a short course of PPI therapy has a 78% sensitivity and 54% specificity in accurately diagnosing GERD.16

In general, if typical symptoms resolve with an initial trial of a PPI, GERD should be diagnosed and the patient should continue taking a PPI daily.

**Figure 2.** Endoscopic views of esophagitis grades. (A) Grade A—1 or more mucosal breaks (arrow) no longer than 5 mm that do not extend between the tops of two mucosal folds. (B) Grade B—1 or more mucosal breaks (arrow) longer than 5 mm that do not extend between the tops of two mucosal folds. (C) Grade C—1 or more mucosal breaks (arrows) that are continuous between the tops of 2 or more mucosal folds, but involve less than 75% of the circumference. (D) Grade D—1 or more mucosal breaks (arrows) that involve at least 75% of the esophageal circumference.
Heartburn? Or heart attack?
In patients with chest pain, a cardiac condition should be ruled out before considering GERD. In one study, patients with noncardiac chest pain and endoscopic evidence of GERD had a significant response to PPI therapy, while those without endoscopic evidence had little or no response to therapy.17

Upper endoscopy
Endoscopy should be performed in any patient with the alarm symptoms described above, and also in patients whose symptoms do not respond to a PPI. Abnormal endoscopic findings in GERD may include erosive esophagitis, strictures, and Barrett esophagus. However, many patients with GERD have normal findings on endoscopy. In 1999, the Los Angeles classification system was published and is now the standard method for classifying esophagitis (Figure 2).18,19 In addition, during endoscopy, biopsy samples from the esophagus should be obtained to rule out eosinophilic esophagitis.

Esophageal pH monitoring
Esophageal pH monitoring is indicated in patients with persistent symptoms and normal findings on endoscopy before surgical or endoscopic interventions are considered. Esophageal pH monitoring can be done using a 24-hour transnasal pH or pH-impedance catheter or a 48-hour Bravo wireless capsule.

In clinical practice, pH testing is performed with the patient off PPI therapy when there is low clinical suspicion for GERD, whereas pH-impedance testing is performed while the patient is still on PPI therapy when there is higher likelihood of GERD, to evaluate refractory symptoms (Figure 3).20
Barium esophagography is not indicated in the workup of reflux disease as it has poor sensitivity and specificity for GERD.

**TREATMENT: LIFESTYLE, DRUG THERAPY, SURGERY**

**Lifestyle modifications**

Lifestyle modifications are the first option for most patients.

**Weight loss** can help reduce and eliminate GERD symptoms. A prospective cohort study found that 81% of obese patients who completed a structured weight loss program had a reduction in symptoms, and 65% had complete resolution of symptoms. Another large retrospective study, with more than 15,000 patients, showed an association between improvement in GERD symptoms and reduction in body mass index (BMI) in obese patients who lost at least 2 kg/m² in BMI (odds ratio 2.34).

**Diet, smoking cessation, alcohol moderation.** Numerous studies have aimed to find foods that exacerbate reflux symptoms. Historically, patients have been advised to avoid smoking, chocolate, carbonated beverages, spicy food, fatty food, alcohol, and large meals. Thus far, no study has found improvement in GERD symptoms with cessation of either smoking or alcohol. In terms of food consumption, no food has been conclusively linked with increased GERD symptoms. No consistent associations have been established between GERD symptoms and fatty food, spicy food, coffee, carbonated beverages, chocolate, citrus, or mint.

**Sleep position.** Other studies have promoted elevating the head of the bed, sleeping in the left decubitus position, and, in those with nocturnal GERD symptoms, avoiding meals in the 2 to 3 hours before bedtime. A sleep positional therapy device has been shown to reduce acid exposure times and improve nocturnal reflux symptoms. This device places the user in the left decubitus position at an incline and has been an effective tool for those with nocturnal symptoms.

**Drug therapy**

If lifestyle interventions fail, drug treatment options are PPIs, histamine 2 receptor antagonists (H2RAs), and antacids.

PPIs are considered the therapy of choice for symptomatic relief and healing of erosive esophagitis. Compared with H2RAs, PPIs have been shown to provide improved healing rates and fewer relapses in patients with erosive esophagitis. To date, no study has shown a major difference in symptom control between the multiple PPIs. However, esomeprazole was shown, in a meta-analysis comparing it with other PPIs, to increase the probability of healing erosive esophagitis at 4 and 8 weeks.

PPIs inhibit gastric acid secretion by inactivating the hydrogen potassium ATPase molecules of the parietal cell. Optimal acid suppression occurs when the proton pumps are activated as the parietal cell is maximally stimulated after a meal.

All PPIs should be taken 30 to 60 minutes before a meal for optimal pH control except dexlansoprazole, which employs dual delayed-release technology leading to sustained plasma drug concentrations; it can therefore be taken at any time of day. For patients with daytime symptoms, a PPI should be taken once daily in the morning, and for nighttime symptoms, the dose should be taken in the evening.

After the initial 8-week course of therapy, most patients with GERD should attempt to take the lowest dose required to manage their symptoms. For some, this could mean only taking the medication when symptoms arise. However, patients with severe erosive esophagitis (grade C or D), Barrett esophagus, and peptic strictures need long-term PPI treatment.

**Adverse effects of PPIs.** All patients need to be counseled about possible long-term adverse effects of PPIs. However, a recent randomized controlled trial found no association of PPIs with any adverse event when used for 3 years, with the possible exception of an increased risk of enteric infections.

Vaeri et al reviewed the complications of PPI therapy and listed the relative risk and absolute excess risk in randomized controlled trials. From their data, we have calculated the number needed to harm, ie, the number of patients who would need to be treated for 1 year to observe 1 adverse effect:

- Chronic kidney disease, 333–1,000
- Dementia, 67–1,429
An 8-week course of PPI is needed to allow for healing; patients should not be considered nonresponders until after this, unless alarm symptoms are present.
A trial comparing laparoscopic fundoplication with esomeprazole therapy found similar remission rates after 3 years and a higher rate with esomeprazole after 5 years. While esomeprazole was associated with more symptoms of reflux compared with fundoplication, patients who underwent this surgery reported higher rates of dysphagia, flatulence, and bloating.

Antireflux surgery should be recommended with caution, as it can have severe side effects such as dysphagia, gas bloat syndrome, and flatulence and the intended effect may only be temporary, as up to 60% of patients will require antireflux medications regularly in the decade afterward. Esophageal manometry should be obtained before surgery to screen for esophageal aperistalsis, as this is an absolute contraindication to the procedure. Furthermore, manometry will exclude other motility disorders that can present similarly to GERD as discussed. Of note, antireflux surgery is not recommended in PPI nonresponders.

The Linx procedure (magnetic sphincter augmentation; Torax Medical Inc., Shoreview, MN) is a minimally invasive alternative. It involves laparoscopic insertion of a band of magnetic beads around the LES, which allows passage of food and then closes to prevent acid reflux. The procedure is associated with improvement in symptom scores and reduced need for PPI therapy but not with consistent reduction in esophageal acid exposure.

Roux-en-Y gastric bypass is a surgical option for morbidly obese patients. A prospective study with 53 patients showed an improvement in GERD symptoms, reflux esophagitis, and esophageal acid exposure for more than 3 years following bypass.

ENDOSCOPIC THERAPIES

Alternatively, several endoscopic treatments for GERD have been developed over the last 2 decades. These include:

- Transoral incisionless fundoplication (TIF) using the Esophyx device (EndoGastric Solutions, Redmond, WA)
- Radiofrequency energy delivery to the LES (the Stretta procedure; Respiratory Technology Corporation, Houston, TX)
- Endoscopic anterior fundoplication using the Medigus ultrasonic surgical endostapler (Medigus, Omer, Israel).

Of these, the first 2 have the most evidence. TIF involves creation of a partial gastric wrap around the lower esophagus with an Esophyx device mounted on the endoscope. TIF is associated with symptom control and PPI reduction or cessation for at least 6 years and is a viable option for a select group of GERD patients with small hiatal hernias and preserved esophageal function.

A large randomized trial comparing TIF with PPIs showed symptomatic control in 67% vs 45% patients. TIF was associated with a reduction in esophageal acid exposure time from 9.3% to 6.4% and DeMeester score reduction from 33.6 to 23.9.

In 2018, a meta-analysis was performed to compare TIF with Nissen fundoplication, a sham procedure, and PPIs. TIF was associated with a larger increase in quality of life measures, while Nissen fundoplication had a greater ability to improve physiologic parameters associated with GERD including LES pressure and the percentage of time the pH was less than 4.

The Stretta device was developed in 2000 and works by delivering thermal energy to the LES, which is postulated to increase sphincter thickness through scar tissue deposition, thereby reducing reflux. However in a meta-analysis of randomized controlled trials, Stretta treatment did not reduce percentage of time when pH is less than 4 or increase LES pressure or ability to stop PPIs.

REFERENCES

Weight loss and waist reduction is associated with improved symptoms in patients with gastroesophageal reflux disease (GERD). Weight loss can lead to resolution of GERD symptoms, and this improvement is likely due to changes in body composition and the reduction of esophageal acid exposure. The role of weight loss in the management of GERD should be considered in clinical practice, as it may provide therapeutic benefits in addition to traditional treatments.

The Los Angeles classification of gastroesophageal reflux disease (GERD) is a well-established system for grading the severity of acid reflux episodes. Newer classifications, such as the tubular esophageal classification, offer additional insights into the pathophysiology of GERD and may be useful in clinical practice.

The impact of lifestyle factors, such as dietary habits and sleep habits, on GERD symptoms is also important. Early dinner and the use of a novel sleep positioning device both provide potential benefits in managing GERD symptoms. Further research is needed to fully understand the impact of these factors on GERD.

In conclusion, weight loss and lifestyle modifications can improve GERD symptoms, and these strategies should be considered in the management of GERD. Future research should focus on elucidating the mechanisms underlying these therapeutic benefits, as well as identifying new targets for treatment in GERD.