

# Medical, Surgical, and Endoscopic Management of Gastroesophageal Reflux Disease

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## Introduction

Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal diseases facing society today. In the US alone, more than 19 million people have the disease. Approximately 20% of US adults have one episode of GERD in a week, with about 7% reporting significant daily heartburn symptoms requiring some type of treatment.<sup>1</sup> Medical treatments for GERD, both prescription and over the counter, cost approximately \$19 billion per year in the US. Fortunately the majority of GERD symptoms are minor and self-limiting; however, complications, including esophagitis, Barrett syndrome, and adenocarcinoma, are on the rise in Western countries, suggesting that GERD does not have a benign course in all patients. The term *nonerosive reflux disease* (NERD) has been used to describe the majority of patients that have a benign, uncomplicated disease course. This group has GERD symptoms without evidence of esophagitis on endoscopy.

The clinical management of GERD has evolved rapidly since the early 1990s with the introduction of potent medications as well as less invasive surgical techniques to help treat patients with medically refractory disease. Novel medications to help prevent transient lower esoph-

ageal sphincter relaxations (tLESRs) are being developed and may be added to the armamentarium.<sup>2</sup> Additionally, endoscopic therapies have gained some support, though long-term data suggest that these techniques are not durable.

This article reviews the pathophysiology, presentation, workup, treatment, and emerging therapies for GERD with an emphasis on surgical management and outcomes to help primary care physicians have a better understanding of the role of surgery in this complex disease.

## Terminology

The classification of GERD has been confusing because of numerous definitions based on symptomatic, physiologic, and/or diagnostic criteria. In simplistic terms, GERD refers to the pathologic reflux of gastric contents into the esophagus through the gastroesophageal junction. This refluxate can be acidic, neutral, or basic (bile). It can be gas, liquid, semisolid, or a combination. The operative term in this definition is *pathologic*, in that belching and vomiting would not be considered pathologic because they are typically isolated events. Previously GERD was defined as a reflux event resulting in a decrease in pH of <4, several centimeters above the gastroesophageal junction. With introduction of impedance

testing (see below), this definition will likely be abandoned as our knowledge of nonacid reflux comes into focus.

## Pathophysiology

The normal anatomy of the gastroesophageal junction allows for relaxation of the lower esophageal sphincter (LES) as a bolus of food approaches the distal esophagus. Once the bolus is passed into the stomach, the LES contracts and remains a zone of high pressure until another bolus is swallowed. In patients with GERD, the tLESR is not coordinated with a swallow and can occur spontaneously, allowing for gastric contents to reflux into the distal esophagus. Additionally, the tLESR lasts several seconds in healthy patients, but in those with GERD, it can last more than ten seconds, resulting in significant gastric reflux. Studies have also shown that patients with pathologic GERD have more frequent tLESRs than healthy people do.<sup>3</sup> Why this occurs in some people and not others is currently under investigation.

In healthy people, the LES has a baseline pressure preventing the reflux of gastric contents into the esophagus. In patients with GERD, the baseline LES pressure is lower, which increases the likelihood of reflux events. This is worse in patients who tend to eat a large meal,

which increases the intragastric pressure more than that of the LES, resulting in GERD. Esophageal body dysmotility does not directly result in GERD; however, if a patient has poor esophageal emptying, this can result in delayed clearance of esophageal contents when a reflux event occurs.<sup>4</sup> The longer a refluxate is allowed to come in contact with the esophageal mucosa, the more damage it can produce. Similarly, delayed gastric emptying is known to increase the transit time of gastric contents into the duodenum. Stasis of gastric contents in the stomach of patients with gastroparesis who also have tLESR, LES hypotension, or both may result in more frequent and prolonged GERD events. Finally, a hiatal hernia is strongly associated with GERD most likely caused by a breakdown in the LES mechanism, resulting in decreased LES pressure.

Risk factors for GERD are numerous, and each likely plays some role in increasing the frequency and length of tLESR (Table 1). Obesity, for instance, is known to be a risk factor for increased reflux, and tLESR is likely due to larger meals, which result in gastric distention, increased acid production, increased intra-abdominal pressure from larger girth, or increased relaxation due to higher levels of certain hormones (eg, estrogen) that stimulate tLESR.<sup>5</sup> Foods and beverages known to either relax the LES or irritate the distal esophagus include citrus drinks, spicy food, caffeinated beverages (tea, cola, coffee), chocolate, and peppermint. Patients who eat large fatty meals will also have worse symptoms most likely because of increased acid production with associated decreased LES pressure. Medications known to exacerbate GERD by decreasing the LES pressure

include calcium-channel blockers, theophylline, meperidine, some oral contraceptives, and nitrates.

**Presentation**

The presentation of GERD is fairly characteristic, with the majority of patients treating their condition before they come to clinical attention. The most common presentation is a burning pain arising from the epigastrium and radiating retrosternally to the throat and neck. Meals (especially those containing some of the already-described foods), recumbency, and bending over worsen the symptoms, whereas antacids, milk, and sitting or standing up relieve the symptoms. Patients report acidic fluid coming up to the mouth and at times the sensation that solid material is coming back up. Frank vomiting is rare in uncomplicated GERD and should raise suspicion for another underlying disease. It is not uncommon for patients to present with chest pain; however, all patients deserve an appropriate cardiac workup before their chest pain is attributed to GERD.<sup>6</sup> Globus is another symptom usually associated with GERD. Dysphagia, weight loss, and hematemesis are part of the “alarm symptoms” and require a more aggressive workup to rule out peptic or malignant stricture, ulcerative esophagitis, and other causes of acute upper gastrointestinal bleeding that may or may not be related to GERD.

Extraesophageal manifestations of GERD have been widely studied and debated. Chronic reflux-associated cough, laryngitis, asthma, and dental erosions have all been found to be associated with GERD. Other proposed extraesophageal manifestations of GERD include pharyngitis, sinusitis, idiopathic pulmonary fibrosis, and recurrent otitis media.<sup>7</sup>

**Evaluation**

The mainstay in diagnosing GERD involves six-week trial of empiric therapy with a proton pump inhibitor (PPI). Patients should be reassessed after the trial to determine improvement. If symptoms have decreased, then no further workup is required and patients may continue taking the PPI either continuously or intermittently as needed. If, however, the patient’s disease responds inadequately, then further testing is necessary. The next step is to perform esophagogastroduodenoscopy (EGD). This strategy has been found to adequately diagnose GERD with a sensitivity of 75% and a specificity of 80%.<sup>8</sup> It allows EGD to be reserved for those patients with persistent and refractory symptoms who are more likely to have a dis-

<b>Table 1. Potential causes of gastroesophageal reflux disease</b>
<b>Physiologic</b>
LES hypotension
Transient LES relaxation
Esophageal dysmotility
Delayed gastric emptying
Hyperchlorhydria
<i>Helicobacter pylori</i>
Duodenogastroesophageal reflux
<b>Anatomic</b>
Obesity
Hiatal hernia
<b>Social habits</b>
Alcohol
Smoking
Stress
High-fat diet
Chocolate
Caffeine and coffee
<b>Medications</b>
Theophylline
Nitrates
Calcium-channel blockers
Meperidine
Nonsteroidal anti-inflammatory drugs
Oral contraceptives

LES = lower esophageal sphincter.

ease other than GERD. Some notable exceptions to this strategy include patients with alarm symptoms who are likely to have a more serious lesion, patients older than age 55 years who may have a higher risk of a serious lesion, and patients taking esophagotoxic medications such as nonsteroidal anti-inflammatory drugs and bisphosphonates who may have a complication related to their medication.<sup>9</sup> If patients' disease responds minimally or not at all to PPIs and they undergo EGD and no abnormality is found to explain their symptoms, then the workup should be directed at the differential for dyspepsia (Table 2).

As already mentioned, EGD is the standard clinical test for GERD and an important test in patients with alarm symptoms.<sup>9</sup> It is highly sensitive and specific for esophagitis and complications of GERD such as ulcerative disease. EGD allows the ability to determine the exact extent of mucosal injury and is capable of performing biopsy if necessary. EGD allows identification of Barrett esophagus because of the characteristic salmon color of the mucosa on endoscopy, and biopsy allows pathologic staging.

Ambulatory pH monitoring is the most sensitive test for acid reflux, but it does not detect nonacidic reflux events. The standard test requires placement of a nasal pH probe that monitors esophageal pH for 24 hours while the patient resumes his or her usual diet and activities. The patient then documents activities and esophageal symptoms either in a diary or with an external monitoring system. At the completion of the study, the patient's symptoms are correlated with the pH monitoring results and several criteria are used to determine the extent of the patient's reflux disease.<sup>10,11</sup> This test should

**Table 2. Differential diagnosis for dyspepsia**

Cholelithiasis
Choledocholithiasis
Acute viral hepatitis
Alcoholic hepatitis
Acute pancreatitis
Gastroduodenal ulcers
Gastritis
Pyelonephritis
Nephrolithiasis
Shingles
Mesenteric ischemia

be used only to confirm acid reflux if surgery is anticipated or to optimize medical treatment in patients with continued symptoms while taking PPIs. If surgery is anticipated, then the study should be performed while the patient has discontinued PPI therapy to allow documentation of the exact severity of acid reflux. If patients continue taking their PPI, then the study may produce false negative results. If surgery is not anticipated but the clinician would like to determine whether the patient's medical treatment is optimum, then the study should be performed while the patient is still taking a PPI to determine whether the patient is having asymptomatic acidic reflux. Newer technology allows for a small pH probe to be placed 6 cm above the gastroesophageal junction, which then sends signals to an external monitoring system.<sup>12</sup> This allows both for more comfort for the patient and for longer monitoring times (48 hours).

A barium esophagram can be ordered to evaluate a patient with suspected GERD; it may demonstrate a GERD episode, detect esophageal mucosal injury, and identify a sliding or paraesophageal hernia. It may also exclude complications of GERD, such as esophagitis, stricture, ulcers, and adenocarcinoma. EGD has largely replaced the barium esophagram as a diagnostic test in

GERD because of its higher sensitivity and ability to obtain tissue for diagnosis. The best use of a barium esophagram is in patients presenting with dysphagia, because the test has a better sensitivity than other tests for diagnosing Schatzki rings, webs, diverticula, and strictures.

Although acid reflux is what most clinicians think causes GERD, recent evidence has shown that nonacidic reflux may be just as detrimental to the esophageal mucosa. Bile in duodenogastroesophageal reflux has been associated with Barrett esophagus.<sup>13</sup> Monitoring of bile levels by using a miniature fiberoptic probe (such as the Bilitest device from Medtronic, Minneapolis, MN, US) can be performed on an outpatient basis. This test is not widely available, however, and should be interpreted by someone experienced in its use.

Impedance monitoring is another emerging technology that is currently being evaluated to determine nonacidic reflux events.<sup>14,15</sup> A special probe is placed nasally and used to detect changes in the electrical conductance of the intraluminal contents of the esophagus. This allows the physician to determine what substance (liquid, solid, gas) is passing through the esophagus as well as which direction it is going (antegrade or retrograde). For instance, swallowed liquid will cause an antegrade decrease in impedance, whereas liquid reflux produces a retrograde decrease in impedance regardless of pH. Several small studies have shown, through impedance monitoring, that in GERD that does not respond to PPIs, the underlying process is nonacidic GERD.<sup>14</sup> Again, this technology is not widely available and requires experienced clinicians to meaningfully interpret the results before making recommendations for treatment.

Esophageal manometry is an important test to perform especially in those patients with abnormal esophageal complaints or those patients desiring surgical intervention for GERD.<sup>16</sup> In patients with atypical GERD symptoms that are refractory to PPIs, manometry may help diagnose achalasia, esophageal spasm, or other esophageal motility disorders. In patients desiring surgery, manometry should be performed to document normal peristalsis before fundoplication.

## Treatment Overview

The goals for treatment of GERD are to resolve symptoms, heal esophagitis and ulcers, and prevent complications such as stricture, Barrett esophagus, and bleeding. Strictures are known to occur in 0.1% of patients and occur most often in males, whites, and older patients. Barrett esophagus occurs as a complication of GERD and is characterized by the replacement of the distal squamous esophageal mucosa with intestinal metaplasia.<sup>17</sup> Barrett esophagus is uncommonly found in patients younger than age 50 but is found in up to 2% of patients older than age 50 who are referred for endoscopy. The etiology of Barrett esophagus is unknown, but the most popular theory suggests that it is the mucosa's attempt to adapt to the long-term reflux of gastric contents. Although esophagitis without the changes of Barrett disease is not associated with esophageal adenocarcinoma, patients with changes from Barrett disease have a 1% per year risk of developing adenocarcinoma.

Medical and surgical therapies have varying success rates. Reports of study results favoring each modality have been widely published and touted by their proponents. It

is more likely that medical, surgical, and potentially endoscopic therapies all play a role in the management of GERD; the following discussion will help primary care physicians and gastroenterologists decide which modality is best for a particular patient.

## Lifestyle and Dietary Modifications

Minor GERD symptoms can be initially treated with simple lifestyle and dietary modifications. Elevating the head of the bed (at least six inches) can help prevent nighttime symptoms. Additionally, avoiding late-night snacks and eating small dinners can help treat minor nighttime symptoms. Avoiding clothes that fit tightly around the mid-abdomen may help occasional symptoms as well. Avoidance of foods that increase reflux events or are caustic to the esophageal mucosa, as mentioned earlier, can help reduce symptoms. Weight loss can produce dramatic results in some patients; however, patients overweight for a long time have a high rate of weight regain and subsequent recurrence of GERD symptoms. Smoking and alcohol use should be reduced or ideally completely stopped. Although stress has not been shown to increase the frequency of GERD events, patients' perception of GERD is increased during high stress events. Patients should be encouraged to avoid stressful situations at either work or home. Because GERD seems to be a progressive disease, it is likely that many patients will require medical therapy at some point.

## Medical Therapy Antacids and Proton Pump Inhibitors

Traditionally, many patients

have self-medicated with over-the-counter antacids before they seek medical attention. Antacids are generally quick and effective for intermittent symptoms. H<sub>2</sub>-blockers were the first medical treatment for GERD that showed substantial improvement over antacids for the chronic GERD. H<sub>2</sub>-blockers have also made their way into self-medication, with the general public being able to buy them over the counter. The limitations of H<sub>2</sub>-blockers include twice-daily dosing and limited response in moderate esophagitis (75%). PPIs have become the preferred medical therapy for erosive esophagitis because they produce a higher rate of response (80%–95%).<sup>18</sup>

PPIs, which act by blocking the hydrogen potassium adenosine triphosphatase, are typically given only once a day. Side effects are minimal and include diarrhea and headaches. PPIs have been shown to be both safe and effective, even when taken for long periods. Chronic PPI therapy has been associated with small reductions in vitamin B<sub>12</sub> levels because of decreases in protein-bound vitamin B<sub>12</sub> absorption. There has been an association of chronic PPI use with an increase in community-acquired pneumonias and *Clostridium difficile* infection.<sup>19</sup> PPIs are not meant for patients with intermittent GERD, as the medications can take several hours to take effect.

Once patients have had symptom remission for more than two or three months, a trial of tapering their dosage can be attempted. Patients taking PPIs twice daily should taper to once daily, whereas patients taking PPIs once daily can switch to twice-daily H<sub>2</sub>-blockers. Patients taking H<sub>2</sub>-blockers can have their dose tapered in a similar

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manner. If a patient is found to have erosive esophagitis, then that patient should be monitored with endoscopy during the tapering phase to determine if remission is occurring at the mucosal level as well as the symptomatic level. The majority of patients taking PPIs for esophagitis will require long-term—if not lifetime—therapy with the lowest dose of either PPIs or H<sub>2</sub>-blockers. Acute cessation of PPI therapy should be avoided, as there is a rebound hypersecretion of acid when the medication is abruptly stopped.

**Limitations of Medical Therapy**

Although PPIs have been found to be both safe and effective for GERD, current studies suggest that in approximately 30% of patients, the disease responds incompletely or, in some cases, not at all to therapy.<sup>20</sup> Mechanisms of failure include poor compliance, visceral hypersensitivity, duodenogastroesophageal reflux, nonacid reflux disease, delayed gastric emptying, PPI resistance, and poor bioavailability. Additionally, in patients with psychologic disorders and concomitant bowel disorders, PPI therapy may fail. These patients will likely benefit more from treatment of their underlying psychologic and bowel disorders. In patients with erosive esophagitis, there is a small group of patients whose esophagitis heals but who continue to have significant symptoms (27%).<sup>21</sup> Additionally, 80% of patients with erosive esophagitis have a relapse of their symptoms within 6 to 12 months after cessation of medical therapy. In a large review of published study results, the overall relapse rate of erosive esophagitis in patients treated with PPIs was 22% and in those treated with H<sub>2</sub>-blockers was 58%.<sup>20</sup>

**Surgical Therapy Techniques**

GERD has been treated surgically since the early 1950s, with the most common procedure being the Nissen fundoplication. Other procedures include the Hill, Belsey, and Toupet repairs. A complete review of all of these techniques and their outcomes is beyond the scope of this review. Unless otherwise stated, the data presented here are from studies of the Nissen fundoplication.

In the era of open antireflux operations, symptom response rates of 80% to 90% were commonly reported. Many patients, however, did not undergo surgical intervention because of the high morbidity of the procedure. With the introduction of laparoscopic techniques, there was an exponential growth in the number of antireflux operations despite no clear evidence of its superiority. Recent long-term studies have confirmed that laparoscopic fundoplication is not only as effective as open surgery but also results in fewer incisional hernias, shorter hospital stays, less pain, quicker return to work, and fewer defective wraps

at follow-up endoscopy.<sup>22</sup> Laparoscopic fundoplication has fallen out of favor as a primary treatment for GERD since the introduction of more potent medical therapy.

Although medical therapy is the first-line therapy for GERD, there are still select indications for surgical treatment (Table 3). Because GERD is a chronic condition that is due to a mechanical failure of the antireflux mechanism and because current medical treatment is directed only at the suppression of acid, there is concern about the effectiveness of long-term medical therapy. As mentioned earlier, current data show that not all GERD is due to acid reflux. Alkaline reflux likely contributes to esophagitis and possibly Barrett esophagus. Because GERD is a chronic condition, most patients will require intermittent if not lifetime therapy. The expense, the psychologic burden of a lifetime of medical therapy, and the uncertainty of the long-term effects of a lifetime of medical therapy should be addressed with all patients considering long-term medication use.

Patients who are averse to surgery and get excellent results with

<b>Table 3. Indications for surgical referral for GERD</b>
<b>Failure of medical therapy</b>
Complications of GERD
Stricture
Barrett esophagus
Bleeding
Recurrent esophagitis despite medical therapy
<b>Patient not wanting lifelong medication</b>
<b>Atypical symptoms</b>
Asthma related to GERD
Hoarseness
Chronic cough
Noncardiac chest pain
Recurrent aspiration pneumonia
<b>Medical problems attributable to a large hiatal hernia</b>
Bleeding
Dysphagia

GERD = gastroesophageal reflux disease.

medications can be monitored safely. If patients have any uncertainty about taking medications and would like to explore surgical options, they should be referred to an experienced esophageal surgeon. This is especially true for young patients who face taking medications for 30 to 50 years, especially if they get excellent results with medications. These are the ideal candidates for antireflux surgery, with success rates approaching 90% in experienced hands.<sup>23</sup> The opposite is true for patients who have limited life expectancy; these patients are best suited for medical treatment.

Other patients who should be evaluated for surgical therapy include those in whom medical management has failed, those with complications of GERD (eg, esophagitis not responding to medical therapy, Barrett esophagus, stricture), and those with medical complications attributable to a large hiatal hernia, such as bleeding and dysphagia. Those patients with atypical symptoms of GERD such as asthma, hoarseness, cough, noncardiac chest pain, and recurrent aspiration pneumonia may also benefit from surgery. It is very important that a complete workup, including a 24-hour pH study, be performed in these patients to confirm acid reflux.

Patients who are evaluated by their primary care providers and desire surgical intervention should be referred to an experienced esophageal surgeon. The appropriate workup in these cases begins with EGD to evaluate for esophageal complications and rule out gastric or duodenal causes for the symptoms. If EGD produces normal findings, then a 24-hour pH study while the patient is not taking medications should be performed to document acid reflux. If EGD shows esophagi-

tis, a pH study is not mandatory. Before surgery, a motility study is paramount to evaluate the contractility of the patient's esophagus. If this shows weak peristalsis, then a partial wrap may be the best option for the patient. Some surgeons will also obtain upper gastrointestinal swallow studies. This is helpful only if the patient has an associated hiatal hernia to determine the size of the hernia and length of the esophagus. If findings for all of the above studies are normal but the patient still has significant symptoms, then consideration should be made to referring these patients to an institution with impedance testing or testing with a Bilitech probe to evaluate for nonacid reflux disease.

### Surgical Outcomes

Results of laparoscopic Nissen fundoplication have been excellent in experienced hands. Conversion rates to open surgery are <5% and typically occur early in a surgeon's experience. Patients undergoing this procedure typically spend one night in the hospital, although some studies have reported excellent results with same-day procedures. Common complaints immediately after fundoplication include early satiety (84%), bloating and flatulence (61%), and dysphagia (32%). At examination three months after surgery, however, no patients complain of early satiety, 3% have bloating, and <1% have dysphagia. Patients with continued dysphagia after three months should undergo a contrast study to determine whether the wrap has slipped, which is the usual cause for this problem (80%).<sup>24</sup>

Long-term studies have shown that when patients are properly selected for surgery and undergo fundoplication by experienced surgeons, the results are excellent. Patients can expect a remission rate

>90%, with no need for medical therapy.<sup>23</sup> Patients who do require some medication will usually require doses that are lower and less frequent than their preoperative dose. Long-term quality-of-life studies have shown that up to 95% of patients rate their surgery outcomes as either good or excellent and would undergo the surgery again.<sup>25</sup> The results for those who undergo open surgery are equivalent. The laparoscopic technique does result in lower perioperative morbidity, making it the current gold standard.

### Endoscopic Therapy

Several endoscopic therapies have recently been developed as an alternative to surgical treatment of medically refractory GERD. The most widely studied include the Stretta device (Curon Medical, Inc, Fremont, CA), the EndoCinch suturing system (CR Bard, Inc, Murray Hill, NJ), the Enteryx system, and the Plicator (NDO Surgical, Inc, Mansfield, MA). Each of these procedures works by improving the mechanical barrier of the LES. The results from these endoscopic therapies have been generally disappointing and have limited widespread application.<sup>26</sup> Although it is thought that these are relatively benign procedures, this is not the case. Indeed, the Enteryx system was voluntarily withdrawn from the market because of several deaths directly related to the procedure. The other techniques are typically done on an outpatient basis, but chest pain, dysphagia, and vomiting are some of the most common, albeit rare, complaints. Endoscopic therapies have not gained widespread

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application, and many experts from both surgical and gastroenterology fields believe that they are still experimental.

### Conclusion

GERD is a progressive, lifelong disease that can severely limit up to 20% of patients who have it, despite optimal medical therapy. Primary care clinicians should not assume that patients are satisfied with their medical therapy for GERD and should refer appropriate candidates to discuss surgical therapy. Laparoscopic Nissen fundoplication has proven safe and effective in long-term studies when performed by experienced esophageal surgeons. Endoscopic therapies hold out the promise of decreased morbidity and increased efficacy that has yet to be realized and thus should be limited to specialized centers under supervised protocols. ❖

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