Refractory Gastroesophageal Reflux Disease – Evaluation and Management

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Kerry B. Dunbar, MD, PhD

Division of Gastroenterology and Hepatology

University of Texas Southwestern Medical Center

VA North Texas Heath Care Center

Kerry B. Dunbar, MD, PhD has disclosed that she does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Dunbar will be discussing off-label uses in her presentation.

Dr. Kerry Dunbar is an Associate Professor of Medicine in the Division of Gastroenterology and Hepatology at UTSW and a staff physician in the Gastroenterology Section at the Dallas VA Medical Center. She received her medical degree from UT Southwestern, then completed her internal medicine residency, gastroenterology fellowship, and clinical research training at Johns Hopkins in Baltimore, Maryland. After several years as a faculty member at Johns Hopkins, she returned to Dallas in 2011 to join the faculty at UT Southwestern and the Dallas VA. Her research and clinical interests include novel endoscopic imaging techniques and esophageal disorders such as GERD, Barrett's esophagus, and esophageal motility disorders.

Purpose & Overview

This presentation reviews the clinical features, evaluation and management of refractory gastroesophageal reflux disease (GERD). GERD is very common in the United States, affecting 20% of the population. A significant portion of these patients have an incomplete response to standard GERD treatment, with persistent symptoms of heartburn and regurgitation. This presentation reviews the pathophysiology, evaluation, and management of refractory GERD.

Educational Objectives

1. To understand the pathophysiology of GERD and the factors contributing to refractory GERD.
2. To describe the options for evaluation of refractory GERD
3. To understand the options for management of refractory GERD

Introduction to Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is defined as heartburn or regurgitation of acidic contents that are troublesome[1]. GERD is very common, affecting approximately 20% of US adults on a weekly basis[2]. Patients with GERD classically complain of heartburn and regurgitation, which can have significant impact on quality of life, responsible for more than 8 million outpatient visits to physicians a year at a cost of approximately $12-$14 billion per year[3-5].

The mainstay of therapy for treatment of GERD is the proton pump inhibitor (PPI), which was first introduced in the US in 1989. Proton pump inhibitors block acid secretion from parietal cells in the stomach and are more effective for healing erosive esophagitis and controlling the symptoms of GERD than histamine-2 receptor antagonists (H2RAs) and antacids[6,7]. 'GERD' is the term used to describe the constellation of symptoms reported by patients. The endoscopic appearance of GERD is variable. Of patients with GERD, 40% are found to have erosive esophagitis on endoscopy, while the remaining 60% of patients do not have signs of erosive disease, and are labeled as having non-erosive reflux disease (NERD)[8,9].

Pathophysiology of Gastroesophageal Reflux Disease

There are several factors which contribute to the development of GERD, including both anatomic factors and modifiable risk factors. Modifiable factors that are associated with GERD include obesity, dietary factors, and lifestyle factors, such as tobacco use[10]. Anatomic factors that increase the propensity of developing GERD include a weak lower esophageal sphincter, the presence of a hiatal hernia, esophageal motility disorders, and gastroparesis. The lower esophageal sphincter (LES) is the primary barrier against reflux of gastric contents. Located at the junction of the esophagus and stomach, the LES relaxes with swallowing. The pressure barrier of the LES helps prevent reflux with deep inspiration, when the intrathoracic pressure decreases. Gastroesophageal reflux is thought to occur with episodes of transient lower esophageal sphincter relaxation (TLESR), in which the LES relaxes without the presence of a swallow[11,12]. These TLESRs are mediated by the vagal nerve and occur more frequently with gastric distention, such as after a meal.

The histopathological changes of GERD can be identified by acquiring mucosal biopsies during endoscopy. Classic histopathological features of GERD include dilation of intercellular spaces, increased thickness of the basal cell layer, and elongation of the esophageal papillae[13]. The cause of the histopathology changes seen in GERD is unclear. For many years, the prevailing theory has been that reflux esophagitis results from a chemical injury, with an acid burn to the surface of the esophageal mucosa. When the esophageal squamous epithelium is exposed to acid and pepsin refluxed from the stomach, the tight junctions between cells are damaged, causing the intercellular spaces to dilate[14]. This allows acid to enter the epithelium, followed by granulocyte infiltration, leading to destruction of the esophageal mucosa. As the injury progresses and the surface cells die, this triggers a proliferative response leading to basal cell and papillary hyperplasia to replace the damaged squamous cells.

However, this model may not be correct. In a study performed at the Dallas VAMC, a model of severe reflux esophagitis was developed by performing an esophago-duodenostomy in rats. Despite constant exposure of the esophageal mucosa to refluxed acid and bile after surgery, the histology

evaluation in the first weeks after surgery did not show any damage to the surface of the esophageal mucosa. Instead, histological evaluation showed lymphocytic infiltration beginning in the submucosa and progressing to the mucosa, followed by basal zone hyperplasia and elongation of the papillae[15]. In this study, esophageal squamous cell cultures exposed to acid and bile released the inflammatory cytokine interleukin-8. These findings suggested an alternate pathway to development of GERD and esophagitis, with reflux esophagitis occurring as a chemokine-mediated inflammatory injury. In this model, gastroesophageal reflux causes the esophageal epithelial cells to produce and secrete chemokines. The chemokines induce the migration of lymphocytes initially to the submucosa with subsequent progression to the mucosal surface. This is followed by the infiltration of granulocytes, basal cell and papillary hyperplasia, which precede the development of surface erosions. If this model is applicable to humans, than future therapies maybe directed at preventing chemokine-mediated inflammation.

These findings were examined in a recent study by our Esophageal Diseases Center, as the early histological changes of reflux esophagitis have not been characterized in humans (clinicaltrials.gov NCT01733810)[16]. Study subjects were treated with twice daily PPI for at least a month, then underwent pH testing to assess the adequacy of acid suppression. This was followed by endoscopy with biopsy of the esophageal squamous mucosa. PPIs were then discontinued for the rest of the study. Endoscopy with biopsy was repeated 1 and 2 weeks after discontinuation of PPIs. The histological changes of GERD were assessed at baseline, and 1 and 2 weeks after PPI discontinuation. The results of the study showed that all patients had significant increases in acid reflux as measured by pH monitoring and developed reflux esophagitis after PPI discontinuation. Histological changes noted one week after PPI cessation included lymphocytic infiltration of the mucosa with few to no neutrophils or eosinophils present. Papillary and basal cell hyperplasia also developed in the absence of histological erosions. These findings suggest that acute reflux esophagitis is not the result of a caustic chemical injury, and may be due to a cytokine-mediated pathogenesis.

Defining Refractory GERD

Despite improved control of symptoms with PPI treatment and success with healing erosive esophagitis, between 10% and 40% of patients have persistent GERD symptoms despite PPI use[17-20]. Various definitions of 'refractory GERD' have been proposed, from persistent symptoms of heartburn and/or regurgitation on once daily PPI to persistent symptoms on twice daily PPI[21,22]. Persistent GERD symptoms are distressing to patients, leading to visits with physicians and impacting quality of life. Compared to patients with good control of GERD symptoms on PPI treatment, patients with an incomplete response to treatment report more emotional distress and sleep disturbances, with poorer social and physical function[23].

Persistent heartburn symptoms are not uncommon with once daily dosing of PPIs, but are less common with twice daily dosing. In some cases, these persistent symptoms are due to ongoing abnormal acid reflux into the esophagus. For patients with typical GERD symptoms, one-third of patients on once daily PPI have abnormal esophageal acid exposure on pH testing, while only 7%-11% of patients on twice daily PPI therapy have abnormal esophageal reflux[24-26].

For the purposes of this lecture, refractory GERD is defined as:

Ongoing heartburn and/or regurgitation despite changes in diet, lifestyle, and the use of proton pump inhibitors

What is the cause of refractory GERD? It may be due to anatomical factors, such as a weak LES or the presence of a hiatal hernia, which disrupt the normal barrier to gastroesophageal reflux. If this is the case, then surgery or a medication to reduce reflux events may be effective. Alternatively, the symptoms of refractory GERD may be due to hypersensitivity to physiologic amounts of acid reflux. In this scenario, medications that affect the nervous system may be of benefit for reducing sensitivity to reflux events. A third possibility is that the symptoms of refractory GERD may be due to non-GERD causes of chest discomfort.

The causes and proper treatment of refractory GERD have been a focus of GI research for many years. Currently, this question is being addressed in a large multicenter randomized controlled trial funded by the Department of Veterans Affairs Cooperative Studies Program. The study 'A Randomized Trial of Medical and Surgical Treatments for Patients with GERD Symptoms that are Refractory to Proton Pump Inhibitors' is being performed at the Dallas VA (clincaltrials.gov NCT01265550). Patients with persistent heartburn despite BID PPI therapy complete symptom questionnaires, undergo endoscopy with biopsy, high resolution esophageal manometry, and multichannel impedance/pH testing while on BID PPI. Patients with normal endoscopy, biopsy, and manometry, but who have abnormal impedance/pH testing are then randomized to either laparoscopic Nissen fundoplication or further medical therapy with baclofen/baclofen placebo (to reduce reflux events) or desipramine/desipramine placebo (to reduce esophageal hypersensitivity). This study is ongoing with results expected in approximately 1.5 years.

Evaluation and Causes of Refractory GERD Symptoms

<u>Assess Medication Compliance and Timing</u>

Assessing patient compliance is the first step when evaluating patients with refractory GERD symptoms. Improper use of proton pump inhibitors has been found to be a significant contributor to persistent GERD symptoms. Missing doses of medications and improper timing of medication dosing can lead to breakthrough heartburn. In patients with chronic GERD symptoms, proper dosing of most PPIs is to take the dose approximately 30-60 minutes before the first meal of the day, or before breakfast and dinner for twice daily dosing[27]. One study examined symptom control and compliance rates of patients on a daily PPI. Patients reporting good control of symptoms were compliant with 84% of doses, while patients with persistent GERD symptoms on daily PPI were compliant only 55% of the time[28]. In this same study, of patients with persistent GERD prescribed a twice daily PPI, only 46% were taking the medication correctly. In another study examining PPI timing in patients with refractory GERD, poor timing of medication consumption was very common. In this study, 30% of patients took their PPIs

after meals, 28% took PPIs at bedtime only, and 4% only took medication when they had symptoms[29]. Addressing medication compliance and the timing of PPI ingestion is the initial step when evaluating patients with uncontrolled GERD symptoms.

Endoscopy

Endoscopy is recommended for some patients with GERD, including those with refractory symptoms. In 2010, 2.9 million upper endoscopies were performed in the U.S., and reflux was the indication for endoscopy in 24% of cases[4]. Overuse of endoscopy for uncomplicated GERD has become a concern, and thus, several sets of guidelines for evaluation and management of GERD have been published in the last few years. These include guidance from the American Gastroenterological Association (AGA), American College of Gastroenterology (ACG), American Society of Gastrointestinal Endoscopy (ASGE), and American College of Physicians (ACP)[27,30-33]. While there is some variation between the guideline recommendations, all provide specific guidance about use of endoscopy in GERD.

The guidelines 'Upper endoscopy for GERD: best practice advice from the clinical guidelines committee of the American College of Physicians' make several reasonable recommendations[30].

Best practice advice 1: Upper endoscopy is indicated in men and women with heartburn and alarm symptoms (dysphagia, bleeding, anemia, weight loss, and recurrent vomiting).

Best practice advice 2: Upper endoscopy is indicated in men and women with:

Typical GERD symptoms that persist despite a therapeutic trial of 4–8 wk of twice-daily PPI therapy.

Severe erosive esophagitis after a 2-mo course of PPI therapy to assess healing and rule out Barrett esophagus. Recurrent endoscopy after this follow-up examination is not indicated in the absence of Barrett esophagus.

History of esophageal stricture who have recurrent symptoms of dysphagia.

Best practice advice 3: Upper endoscopy may be indicated:

In men older than 50 y with chronic GERD symptoms (symptoms for more than 5 y) and additional risk factors (nocturnal reflux symptoms, hiatal hernia, elevated BMI, tobacco use, and intra-abdominal distribution of fat) to detect esophageal adenocarcinoma and Barrett esophagus.

For surveillance evaluation in men and women with a history of Barrett esophagus. In men and women with Barrett esophagus and no dysplasia, surveillance examinations should occur at intervals no more frequently than 3–5 y. More frequent intervals are indicated in patients with Barrett esophagus and dysplasia.

Adapted from Shaheen, *et al*. Upper Endoscopy for GERD: Best Practice Advice from the Clinical Guidelines Committee of the American College of Physicians[30]

Alarm symptoms, including dysphagia, vomiting, weight loss, bleeding, and anemia are a clear trigger to recommend endoscopic evaluation, as these symptoms can be suggestive of cancer (esophageal or gastric) and peptic ulcer disease. Endoscopy is also suggested to treat esophageal strictures in patients with dysphagia and to assess healing of erosive esophagitis after PPI treatment. Endoscopy is also indicated in patients with typical GERD symptoms that persist despite 4-8 weeks of twice-daily PPI treatment. In this situation, endoscopy is used to assess for complications of GERD, such as erosive esophagitis and esophageal stricture, and to acquire mucosal biopsies to evaluate for

eosinophilic esophagitis. The presence of erosive esophagitis can suggest persistent acid reflux despite PPI therapy. Barrett's esophagus (BE) can also be identified during endoscopy and confirmatory biopsies obtained. BE is found in approximately 8% - 13% of patients with chronic GERD, and while it would not explain refractory GERD symptoms, patients with biopsy-confirmed Barrett's esophagus should be considered for a dysplasia surveillance program[34,35].

Eosinophilic esophagitis (EoE), characterized by eosinophilic infiltration of the esophagus leading to esophageal dysfunction, should be considered when evaluating patients with uncontrolled GERD. The classic EoE patient is a young man with atopy who presents with a food impaction. While the predominant symptoms of this disorder include dysphagia and food impaction, heartburn is also commonly reported, occurring in approximately half of patients with EoE[36,37]. Diagnosis of EoE is made during endoscopy when biopsies of the esophageal mucosa show > 15 eosinophils per high power field[38]. The relationship between eosinophilic esophagitis and GERD is complex, as some patients with eosinophilic infiltration of the esophageal mucosa will have improvement of symptoms with PPI treatment, labeled PPI-responsive esophageal eosinophilia[39]. At this time, the first step in treatment for patients with suspected eosinophilic esophagitis is a trial of PPI therapy[40].

<u>High Resolution Esophageal Manometry</u>

Motility disorders of the esophagus can lead to symptoms of heartburn and chest pain. Some motility disorders lead to reduced clearance of esophageal reflux, while others may cause chest discomfort independent of acid reflux. Achalasia, one of the major motility disorders of the esophagus, leads to abnormal motor function of the body of the esophagus and failure of the lower esophageal sphincter to relax. In studies of patients with achalasia, heartburn has been reported in 37%-49% of patients[41,42]. Heartburn and regurgitation are also common in the motility disorder esophageal aperistalsis, which historically has been known as 'scleroderma esophagus.[43] Most patients with aperistalsis do not have scleroderma or other autoimmune diseases, but do report GERD symptoms. Other motility disorders that can cause chest pain, although not classically heartburn, include nutcracker/jackhammer esophagus and distal esophageal spasm.

Patients with ineffective esophageal motility (IEM), also called weak peristalsis, have poor contractility in the body of the esophagus, which can lead to incomplete clearance of refluxed material and GERD symptoms. It is unclear if IEM is the cause of GERD symptoms or if IEM is the result of damage from GERD. In the first scenario, the esophagus with IEM is weak and cannot clear reflux, leading to symptoms of heartburn and regurgitation. Conversely, if IEM is the result of GERD, esophageal weakness may be due to esophageal damage from acid reflux. Researchers have attempted to study this question with conflicting results, as some studies identify changes in motility due to GERD, while others do not[44,45]. We recently completed a study assessing esophageal motility in patients with acute reflux esophagitis[46]. Patients with a past history of reflux esophagitis underwent endoscopy, multichannel impedance/pH testing, and high resolution esophageal manometry at baseline (on BID PPI) and 2 weeks after discontinuation of PPI treatment. After two weeks without PPIs, 8 of 10 patients developed erosive esophagitis and had significant reflux on pH testing. There were significant decreases in peristaltic pressure and LES relaxation pressure as measured by high resolution esophageal

manometry. These findings suggest that reflux esophagitis is a cause of hypocontractile esophageal motility disorders, such as ineffective esophageal motility.

Reflux testing: pH testing and multichannel impedance/pH testing

Persistent symptoms of heartburn can also be addressed by quantifying the amount of reflux present through pH testing and multichannel impedance/pH testing. Traditional catheter based pH testing can be used to detect acid reflux, but has largely been replaced by multichannel impedance/pH testing. Multichannel impedance/pH testing is also catheter-based, but has the ability to distinguish between acid reflux (pH< 4), and weakly acidic reflux (pH 4-7) and nonacid reflux (pH>7) over a 24 hour period. An endoscopically-placed wireless pH capsule is also available, providing 48 hours of pH monitoring. Wireless pH testing can detect acid reflux, but not weakly acidic or nonacid reflux. Regardless of the type of pH testing performed, patients keep a diary of symptoms that occur during the testing period, such as heartburn and regurgitation. The association between the symptoms reported on the patient's test diary and reflux events detected can be determined using the data obtained from the pH recorder. Symptoms strongly associated with reflux events are more likely to be related to GERD.

The decision to perform reflux testing on or off of PPI therapy depends on the patient presentation. If it is unclear if the patient has GERD at all, then testing should be performed after discontinuation of PPIs for approximately a week. Examples of patients where the diagnosis of GERD may be in doubt include patients without classic symptoms of heartburn or regurgitation, patients with no improvement on PPIs, and patients with purely extra-esophageal symptoms of GERD such as chronic cough, which has numerous non-GI causes. In this situation, pH testing off PPI therapy can be used to determine whether GERD is present or absent. If no acid reflux is present, then other non-reflux causes of the patient's symptoms should be considered. Reflux testing on PPI treatment can be used to assess patients with partial symptom improvement on PPIs, but who have breakthrough symptoms. Some of these patients may have other evidence of GERD, such as erosive esophagitis, Barrett's esophagus, or prior abnormal pH test results. Testing on PPI may help identify whether residual symptoms on PPI therapy are related to reflux events.

Reflux testing can identify patients who have persistent acid reflux on PPI, as well as identify other explanations for refractory GERD symptoms. Esophageal hypersensitivity is identified by reflux testing and is seen in patients with physiologic (i.e. normal) esophageal acid exposure and a strong correlation between symptoms and reflux events[25]. Patients with physiologic esophageal acid exposure and no correlation between symptoms and reflux events have functional heartburn[24]. Medications other than PPIs may be helpful in patients with esophageal hypersensitivity and functional heartburn.

Radiology: Barium Esophagram

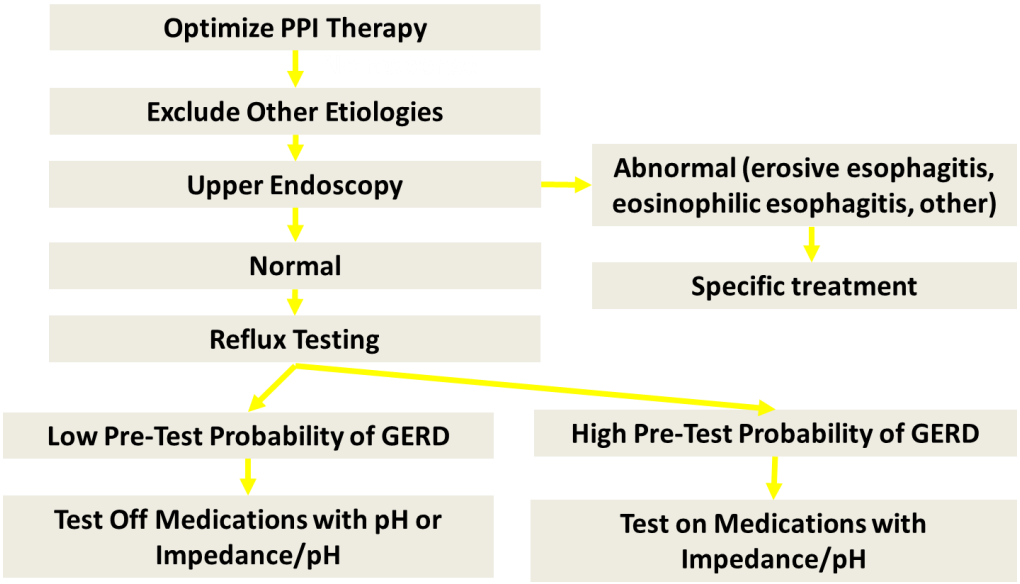
Barium esophagram is not recommended for evaluation of GERD[27]. It has a low sensitivity and specificity for GERD, and does not provide enough information for determining the cause of refractory GERD. It does have some utility in evaluation of dysphagia.

Other Gastrointestinal and Non-Gastrointestinal Disorders Causing Heartburn or Chest Discomfort

Other GI disorders can contribute to GERD symptoms. Gastroparesis, or delayed gastric emptying, can be identified in some patients with difficult-to-manage GERD symptoms. Symptoms of gastroparesis include nausea and vomiting, but patients may also report heartburn and regurgitation. Gastroparesis can be diagnosed with a nuclear medicine solid phase gastric emptying study. Non-ulcer dyspepsia is another upper gastrointestinal disorder that can be confused with GERD. Patients with dyspepsia will report epigastric discomfort (often burning), fullness, and early satiety. Endoscopy is often normal, and some patients will have a partial response to PPI.

Non-GI causes of chest discomfort should also be considered. Coronary artery disease is very common in the U.S. population and can present with chest discomfort. Appropriate cardiac evaluation should take precedence over extensive GI evaluation in patients with unexplained chest discomfort[27]. Musculoskeletal causes of chest pain, such as costochondritis, can also be considered. The following algorithm summarizes the evaluation of refractory GERD.

Algorithm for Evaluation of Refractory GERD



Algorithm adapted from Katz, et *al*. American College of Gastroenterology Guidelines for Diagnosis and Management of Gastroesophageal Reflux Disease[27].

Management of Refractory GERD

Once the evaluation of refractory GERD is complete, there are several options for addressing symptoms.

Medications

Compliance with PPI dosing and proper timing of PPI ingestion is important for control of symptoms. Most PPIs work best when dosed 30 minutes before breakfast, or 30 minutes before breakfast and dinner for BID dosing. Pre-dinner dosing allows the PPI to inhibit the parietal cell proton pumps in the gastric mucosa prior to ingestion of the evening meal, and will control nocturnal acid more successfully than bedtime dosing[27]. Switching to a different PPI is frequently done in clinic practice in an attempt to improve symptom control. The few research studies that have examined this question suggest that it may be helpful[47,48]. For patients on BID PPI therapy with persistent nocturnal symptoms, adding a bedtime dose of an H2-receptor antagonist can be considered[49]. Baclofen, typically used to treat spasticity, has been used to control GERD symptoms. Baclofen has been shown to reduce transient lower esophageal sphincter relaxation (TLESR) events, and can potentially reduce reflux symptoms. Baclofen has been examined in several small research studies as a potential anti-reflux agent[50].

Dietary Modification

Several foods have been associated with increased acid reflux, and several studies have tried to address the effect of diet on reflux symptoms, lower esophageal sphincter pressure, and reflux events. Research studies using esophageal manometry have identified foods that appear to lower the LES pressure, including high-fat foods, alcohol, caffeine, chocolate, and carbonated beverages[51]. However, while dietary changes make intuitive sense, research studies of diet modification have shown mixed results. A study of alcohol cessation did not show an improvement in symptoms or pH test results[52]. The studies of cessation/decreasing carbonated beverages to improve GERD have shown conflicting results[52,53]. Studies of dietary changes in GERD are difficult to perform and the studies are generally small.

Lifestyle Modification and Weight Loss

GERD is more common in overweight and obese patients[54]. Several factors may contribute to this, including the type of food consumed, increased intra-abdominal pressure due to intra-abdominal fat, and the quantity of food consumed (larger meals cause gastric distention, leading to additional TLESRs and reflux events)[55-57]. In physiologic studies of meals, high-fat diets produce more reflux symptoms than low-fat diets[58]. The amount of acid reflux measured during pH testing is higher with a high-calorie diet compared to low-calorie diet. One study of a low-carbohydrate diet showed fewer symptoms and fewer reflux events during pH testing compared to a standard diet[59]. Several other lifestyle changes have been proposed to improve GERD symptom. Tobacco cessation, elevating the head of the bed, and avoiding late meals have been shown to improve GERD symptoms[10].

Surgical Management of GERD

Surgical treatment of GERD is an option for some patients. The most common surgery for GERD treatment is the Nissen fundoplication, which is often performed via laparoscopy. Most patients are able to discontinue PPI treatment after surgery, but with longer-term follow-up, 10%-65% of patients resume some acid suppressive therapy[60,61]. Roux-en-Y gastric bypass is another option for control of GERD in obese patients, with symptom improvement attributed to weight loss and alterations in gastric anatomy. Most patients have improved GERD symptoms and take fewer anti-reflux medications after gastric bypass surgery[62]. Another option for surgical treatment of GERD is an implantable ring of magnetic beads that is placed near the lower esophageal sphincter[63]. At rest, the ring increases pressure at the LES, reducing reflux. With swallowing, the magnetic beads move apart, allowing passage of the food bolus down the esophagus. Five-year follow up data was recently published, showing that heartburn and regurgitation were significantly improved compared to pre-surgery, and use of acid suppressive medications had decreased from 100% to 15%[64].

Many patients obtain adequate control of GERD with medications, dietary modification, and lifestyle changes. Some patients with persistent symptoms, complications from GERD, or patients who do not want to take medications may consider surgery. Patients with at least a partial response to PPI treatment are more likely to have a good outcome from anti-reflux surgery[65]. Preoperative testing to confirm the diagnosis of GERD is often requested prior to surgical intervention, and may include endoscopy, esophageal manometry, pH testing and radiological studies. Ruling out other disorders that can cause heartburn, such as eosinophilic esophagitis and achalasia, is important to complete prior to surgical treatment of GERD.

Endoscopic Treatment of GERD

Endoscopic treatments for GERD have been the focus of research over the last 15 years. Multiple techniques have been attempted, with the goal of increasing the anti-reflux barrier at the LES. The clinical efficacy of these techniques has been variable and some techniques had unacceptable complication rates. Two endoscopic GERD treatments are currently available. One technique is transoral incisionless fundoplication (TIF). During endoscopy using a special device, an endoscopic fundoplication is created at the GE junction. Initial studies suggest that TIF reduces GERD symptoms and PPI use[66]. A second endoscopic treatment for GERD is radiofrequency treatment of the LES. Radiofrequency energy is delivered, causing thickening at the LES and reducing GERD symptoms and PPI use in some studies[67]. One caveat to the use of endoscopic therapies for GERD is that many of the published studies were performed in patients with mild to moderate symptoms and small hiatal hernias. Long-term follow up data is still in development and it is unclear what role these treatments will have in the future.

Summary

Refractory GERD is not uncommon and can be a challenge for physicians and patients. Evaluation of patients with refractory GERD can include assessing PPI use, reviewing diet and lifestyle changes, and considering non-GI causes of chest discomfort. Endoscopy in GERD patients is indicated in

patients with alarm symptoms, for screening and surveillance of Barrett's esophagus, and to evaluate for GERD complications and eosinophilic esophagitis in patients with a poor response to PPI treatment. Research continues to better understand the pathophysiology of GERD and identify new treatment options.

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