

# Treatment Options for Gastroesophageal Reflux Disease

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**G**astroesophageal reflux disease (GERD) is very common. Approximately 20% of adult Americans have heartburn at least once a week. The goals of therapy for GERD are to eliminate symptoms, to heal injured esophageal mucosa, and to prevent reflux complications.<sup>1</sup> Treatment options for GERD have been highlighted by potent acid suppression with proton pump inhibitors (PPIs) and minimally invasive antireflux surgery. Recently, endoscopic therapies for GERD have been introduced. Treatment selection should be individualized and dependent upon underlying pathophysiology, anatomy, and clinical presentation coupled with the expected success or limitations of each therapeutic option. This article reviews the pathophysiology of GERD and the spectrum of clinical presentation, and discusses how these factors affect treatment considerations. Medical, surgical, and emerging endoscopic treatment options are discussed.

## **UNDERLYING PATHOPHYSIOLOGY**

### **Lower Esophageal Sphincter**

The lower esophageal sphincter (LES) is the most important physical barrier for prevention of acid reflux.<sup>1</sup> The LES consists of specialized smooth muscle fibers at the gastroesophageal junction (GEJ) with a normal basal resting pressure of 15 to 45 mm Hg by esophageal manometry. Low LES pressure is associated with GERD and erosive esophagitis.<sup>2</sup> However, many patients with GERD have normal LES resting pressures. Studies have revealed that acid reflux occurs primarily during episodes of transient LES relaxation.<sup>2,3</sup> Acid suppression is used most often for the treatment for GERD, but because acid suppression does not affect the LES function, heartburn readily recurs when therapy is withdrawn.

### **Hiatal Hernia**

The crural fibers of the diaphragm also contribute to the antireflux barrier.<sup>4</sup> With the presence of a hiatal

hernia, the diaphragmatic component of LES competence is diminished and GERD may result. Patients with paraesophageal herniation, whereby a portion of stomach resides in the mediastinum and the gastric fundus is cephalad to the GEJ, are at increased risk for intrathoracic incarceration. Surgical repair should be considered for these cases. Currently available endoscopic therapies for patients with a large hiatal hernia or complicated anatomy may not be feasible.<sup>5,6</sup>

### **Esophageal Acid Clearance**

Once reflux occurs, esophageal peristalsis clears the esophagus and thus limits the contact time between acid and the esophageal mucosa. Impaired esophageal motility is not uncommon in patients with GERD, occurring in approximately 20% of patients evaluated by preoperative esophageal manometry.<sup>7</sup> In patients with severe esophageal motility disorder, which is often seen in patients with scleroderma, surgery may be contraindicated. Swallowed saliva is also important to neutralize the refluxed acid to protect the esophageal mucosa from damage.<sup>8</sup> However, excess swallowing can cause aerophagia, resulting in frequent belching. Patients with significant aerophagia may be at risk for postoperative gas bloating following antireflux surgery.

### **Gastric Emptying**

Delayed gastric emptying (gastroparesis) promotes reflux of gastric contents. Gastroparesis can be diagnosed by solid-phase nuclear gastric scintigraphy; this test is recommended in patients with GERD who have significant nausea, vomiting, bloating, or diabetes.

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Medical therapy with prokinetic agents may be more appropriate than surgery in patients with gastroparesis because gas bloating may increase following antireflux surgery.

## CLINICAL PRESENTATION

### Typical Versus Atypical Symptoms

Gastroesophageal reflux can present with a broad spectrum of typical and atypical symptoms. The most recognized typical symptoms are heartburn and regurgitation. Daytime symptoms predominate for those with nonerosive GERD, whereas those with nocturnal symptoms are at increased risk for erosive esophagitis. Most patients with typical heartburn respond favorably to strong acid suppression, and the response is usually rapid. Symptoms are predictable and readily recur when medications are discontinued.

Noncardiac chest pain, asthma, chronic cough, hoarseness, globus sensation, and throat discomfort are atypical manifestations of GERD and may occur in conjunction with other pathophysiologic mechanisms, such as altered esophageal pain sensation, impaired airway protective reflexes, and lower cough threshold.<sup>9-11</sup> Treatment response to acid suppression is more variable in persons with atypical symptoms compared to those with typical GERD. More aggressive acid suppression and longer duration of treatment are often required for patients with reflux-associated laryngitis and asthma.<sup>12,13</sup> Overall clinical improvement with medical and surgical therapy is generally less favorable in patients with atypical GERD.<sup>14</sup> Aggressive acid suppression should be attempted first before considering surgical therapy. Currently, no published data are available on the efficacy of endoscopic treatment for atypical GERD.

### Complications of GERD

If left untreated, acid reflux can result in esophageal erosion or ulceration with progression to fibrosis and stricture formation. Patients with longstanding or severe GERD may present with dysphagia, odynophagia, iron deficiency anemia, or weight loss, indicating significant complications.<sup>1</sup> The development of specialized metaplastic intestinal epithelium (Barrett's esophagus) occurs in 8% to 20% of patients with chronic GERD. Although rare, the risk of esophageal adenocarcinoma associated with Barrett's esophagus is 30 to 40 times greater than in the general population. Chronic therapy is required in individuals with moderate to severe symptoms and GERD with complications in order to control symptoms and to prevent erosive esophagitis and peptic stricture.<sup>1</sup>

### Nonerosive Reflux Disease

Approximately 70% of patients with heartburn have nonerosive reflux disease (NERD), defined by the absence of reflux-induced mucosal complications.<sup>15</sup> Symptom severity in patients with NERD is similar to that of patients with GERD associated with complications, yet the esophageal acid exposure time is usually significantly less.<sup>16</sup> Patients with NERD may have an exaggerated pain response to even small amounts of refluxed acid; therefore, control of symptoms may be quite difficult. Acid reflux should be measured by pH monitoring and response to aggressive acid suppression documented in patients with NERD before pursuing surgical or endoscopic therapy.

### MEDICAL THERAPY

Cimetidine, ranitidine, famotidine, and nizatidine are the histamine-2 receptor antagonists (H<sub>2</sub>RAs) that are available in both over-the-counter and in generic prescription formulations. They are well tolerated with very few side effects and are efficacious in most patients with mild or infrequent GERD. Among those with erosive esophagitis, however, H<sub>2</sub>RA therapy heals fewer than 50% of patients.<sup>1</sup>

Prokinetic agents improve gastric emptying and modestly increase the force of esophageal contractions. Metoclopramide improves symptoms of GERD but does not heal erosive esophagitis and is ineffective as maintenance therapy. Furthermore, central nervous system side effects, such as tremors, nervousness, and extrapyramidal symptoms, are common. Cisapride is no longer approved by the US Food and Drug Administration (FDA) owing to serious cardiac conduction disturbances.

Omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole are the PPIs approved for use in the United States. All PPIs profoundly suppress gastric acid by irreversibly binding to the proton pumps on gastric parietal cells. They are similar to each other in their ability to control symptoms and heal esophagitis with a variable intersubject dose-response relationship.<sup>17</sup> Esomeprazole is the isolated, S-optical isomer of omeprazole and is more effective for severe esophagitis compared with omeprazole.<sup>18</sup> The healing rate of erosive esophagitis with PPI use is 85% to 95%, which includes patients who failed prior medical therapies.<sup>19,20</sup> Currently, PPIs are the most efficacious medical therapy available for individuals with moderate to severe symptoms or with complicated GERD. Additionally, chronic PPI use is generally safe, with minimal reported side effects.

## **SURGICAL THERAPY**

Fundoplication is an antireflux surgery whereby the gastric fundus is wrapped around the LES to augment its barrier function. If a hiatal hernia or diaphragmatic crural defect is present, it is addressed during the procedure, as well. Indications for surgery include refractory symptoms, bronchopulmonary aspiration, presence of a large hiatal hernia, and preference over medical therapy. Successful outcomes are dependent on patient selection, preoperative evaluation, and surgical expertise. Fundoplication can now be achieved via laparoscopy, allowing patients to recover more quickly and minimizing hospital stays. Aggressive acid suppression should be attempted before considering surgery. A good predictor of surgical success is a positive response to medical therapy prior to surgery.<sup>21</sup>

### **Preoperative Evaluation**

Preoperatively, upper endoscopy is recommended to identify Barrett's esophagus, distal esophageal scarring, or the presence of a large hiatal hernia (sliding or paraesophageal). The finding of a shortened esophagus may indicate the need for an esophageal lengthening procedure, which requires laparoscopic expertise to complete successfully. Esophageal manometry should be performed to assess whether esophageal peristalsis is impaired, in which case a partial 270° (Toupet) fundoplication may be required rather than a complete 360° (Nissen) fundoplication, to avoid postoperative dysphagia.<sup>7</sup> Esophageal aperistalsis is a contraindication for fundoplication.

Ambulatory pH monitoring is recommended for patients with NERD, atypical GERD, or in those whose symptoms are not improved with PPIs. A gastric emptying study should be performed for patients with significant nausea, vomiting, or postprandial bloating.

### **Surgical Outcomes**

Surgical outcomes depend on the preoperative symptom complex. In selected patients with heartburn, excellent relief in up to 93% after laparoscopic fundoplication has been reported.<sup>14,22</sup> However, in a follow-up study of a prospective long-term trial, Spechler et al<sup>23</sup> reported that 62% of patients who had undergone surgical treatment for GERD were still using antireflux medications regularly. Patients with atypical symptoms are less likely to have complete resolution of symptoms and overall respond less favorably to surgery compared to those with typical GERD.<sup>14</sup>

Intraoperative complications of surgery, including bleeding, splenic injury, and perforations, are rare. Transient dysphagia is common in the early postopera-

tive period because edema is present. However, 6% to 13% of patients require endoscopic dilation for post-fundoplication dysphagia.<sup>14,24</sup> Increased flatus is common after fundoplication. Approximately 20% of patients can have difficulty belching postoperatively, with troublesome gas-bloat symptoms occurring in 5% to 15%.<sup>14,25</sup>

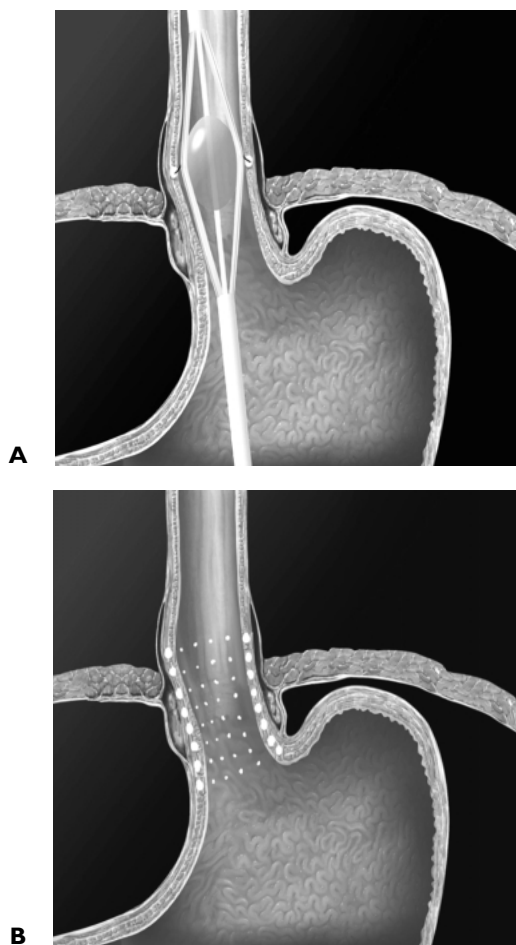
## **ENDOSCOPIC THERAPIES**

Endoscopic therapies for GERD are gaining attention as alternative treatments. However, the precise role for these new therapies is unclear. Published clinical trials are nonrandomized, uncontrolled studies with small numbers of patients. Long-term efficacy and safety data are limited. Randomized, controlled trials are needed before these procedures are clinically accepted as effective treatment options. In addition, cost comparison studies between endoscopic and other therapies are needed. Ideal endoscopy therapy should be relatively simple, very safe, efficacious long-term, and cost-effective. Currently, 3 endoscopic therapies for GERD have been approved by the FDA: delivery of radiofrequency energy (the Stretta System, Curon Medical Inc., Sunnyvale, CA), endoluminal gastroplasty (the EndoCinch System, Bard Interventional Products Division, Billerica, MA), and endoscopic implantation of ethylene vinyl alcohol (Enteryx, Boston Scientific, Boston, MA).

### **Radiofrequency Energy Delivery**

Radiofrequency (RF) energy refers to a range of frequencies within the electromagnetic spectrum. Application of RF causes vibration of water molecules in tissues, which generates heat and results in collagen contraction followed by deposition of fibroblast and repair collagen. RF energy has been used to disrupt cardiac arrhythmias and for vagal and facial nerve ablation. In the esophagus, RF treatment reduces the number of transient LES relaxations in patients with GERD, most likely by interruption of vagal pathways.<sup>26</sup>

For treatment of GERD, RF energy is delivered using the flexible Stretta catheter with 4 retractable RF needles mounted on an inflatable balloon. The catheter is introduced to the desired location near the LES. The balloon is inflated, the needles are deployed, and RF energy is delivered for about 90 seconds at each treatment site (**Figure 1**). Elevated temperatures generated by RF energy at the tip and base of each needle, which presumably represent the submucosal layer and epithelial surface, respectively, are continuously monitored by thermocouples. Chilled water is perfused toward the base of the RF needle to cool the epithelial



**Figure 1.** Endoscopic radiofrequency (RF) energy delivery (Stretta procedure). **(A)** RF energy is delivered at the desired location by inflating the balloon and deploying the RF needles. **(B)** The RF procedure is repeated at multiple locations by rotating and repositioning the catheter at different levels proximal and distal to the gastroesophageal junction. (Reprinted courtesy of Curon Medical Inc., Sunnyvale, CA.)

surface, and each needle will automatically shut off if the temperature exceeds a predetermined safe level. When RF delivery is completed, the needles are retracted and the balloon is deflated. The procedure is repeated at multiple levels proximal and distal to the GEJ (Figure 1). The optimal number of treatment sites needed for effective therapy is unclear.

Currently, all published trials with RF therapy are open-label and uncontrolled.<sup>5,27,28</sup> The first trial published was a multicenter study that included 47 patients with mild to moderate typical GERD.<sup>5</sup> Patients with hiatal hernia larger than 2 cm, moderate to severe erosive esophagitis, or Barrett's esophagus were excluded.

At 6 months after RF therapy, heartburn significantly improved from a median score of 4 to a median score of 1.<sup>5</sup> In a subsequent trial of 118 patients by Triadafilopoulos et al,<sup>27</sup> heartburn was significantly improved at 12-month follow-up, and medication requirement was reduced. At 6-month follow-up, esophageal acid exposure (duration of exposure of median distal esophagus to pH of less than 4.0) was reduced from 10.2% to 6.4% as measured by 24-hr ambulatory pH monitoring. (Because the cut-off point for normal acid exposure was considered in this study to be 4.0%, many patients still had abnormal acid reflux.) A randomized, controlled crossover study comparing RF with sham-procedure is completed, and results should be available soon. Long-term outcome data are needed before RF therapy can be widely advocated.

In the study by Triadafilopoulos et al,<sup>27</sup> complications of RF were reported in 9% of subjects and included chest pain, fever, mucosal injury, and transient dysphagia. Other reported serious complications of RF were gastroparesis and hematemesis.<sup>28</sup> Rare cases of perforation have been reported postmarketing. Complications may be reduced by using lower inflation pressures, decreasing the number of RF lesions, and improving the technique of cooling the epithelial surface.

A major concern regarding RF therapy is the risk of impairing the patient's ability to sense acid in the esophagus. Acid reflux may still be present despite the patient reporting no more symptoms. Complications of GERD, such as erosive esophagitis and peptic stricture, may develop despite RF therapy. Vagal neuropathy causing gastroparesis is also a potential complication that may worsen overall outcome.<sup>28</sup> Long-term safety data with RF therapy are needed.

#### Endoluminal Gastroplication

Endoscopic suturing for treating GERD was first reported in Europe.<sup>29</sup> This technique has been shown to augment the LES pressures in animals and in humans.<sup>29,30</sup> A specially engineered endoluminal gastroplication (ELGP) system, EndoCinch, has been FDA-approved. The EndoCinch suturing capsule is mounted on the tip of a standard upper endoscope. A suture-tag is loaded over a needle within the capsule. The assembly (endoscope/capsule, suture, and suction catheter) is introduced through an overtube. Suction is applied to draw in tissues just below the GEJ into the suturing capsule, and the needle is fired (**Figure 2**). The suture-tag is pushed out of the needle through the fold, but the suture-tag is recaptured at the tip of the capsule. The entire assembly is removed with the

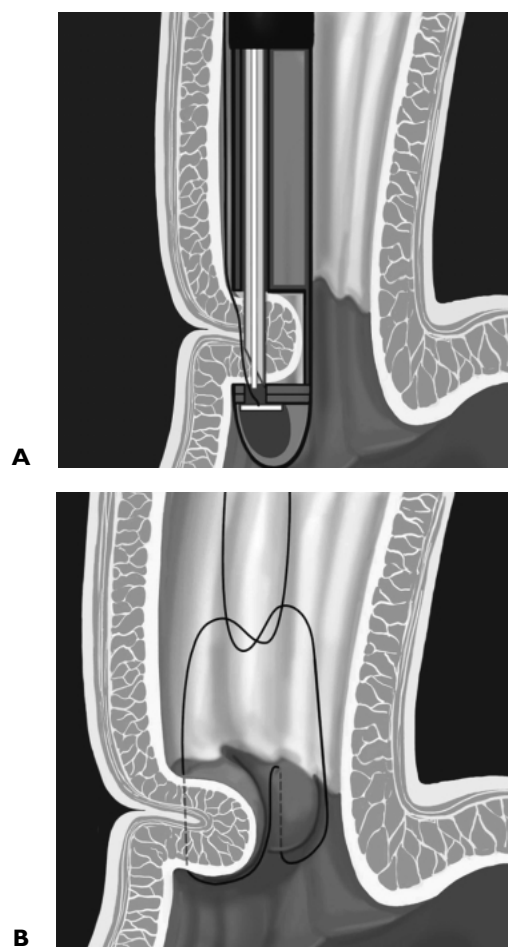
suture stitched through the tissue fold. The suture-tag is reloaded over the needle, and the procedure is repeated on an adjacent tissue fold. A knot is made outside the body and is pushed toward the 2 folds to form a plication (Figure 2). A knot-tying catheter is introduced to push and tighten the plication and to cut excess sutures. Endoscopic findings before and after ELGP are provided in **Figure 3**. The optimal number and orientation of plications in each case is uncertain; currently, 2 or more plications are recommended.

Currently, all published clinical trials with ELGP are open-label and uncontrolled.<sup>29,31</sup> The first US trial was a multicenter study with 64 patients with mild to moderate GERD.<sup>29</sup> Similar to the RF trial, patients with a hiatal hernia larger than 2 cm or moderate to severe erosive esophagitis were excluded. At 6-months follow-up, mean heartburn scores significantly improved from 62.7 to 17.0, but overall quality of life did not improve.<sup>31</sup> In most cases, total esophageal acid exposure decreased significantly, as measured by ambulatory pH testing. However, many patients still had clinically significant acid reflux, and recumbent acid exposure did not improve. LES pressures were not significantly changed. At 2-years follow-up in 33 patients who underwent ELGP, only 25% were completely off antireflux medications.<sup>32</sup> Procedure-related complications included transient pharyngitis, chest pain, vomiting, and suture site bleeding. Thus far, 1 case of perforation during ELGP has been reported; this patient was managed nonoperatively with antibiotics.<sup>31</sup>

The clinical benefit of ELGP has been modest. Because many patients in the aforementioned studies still required antireflux medications, cost-effectiveness may be limited. Early operator experience may have influenced these outcomes. No controlled studies comparing ELGP with a sham procedure have been performed. Additionally, ELGP is likely not feasible for patients with a large hiatal hernia. ELGP is technically difficult, and the number of procedures required to attain expertise is unknown. Studies are needed to determine the optimal technique and patient selection.

### Endoscopic Injection

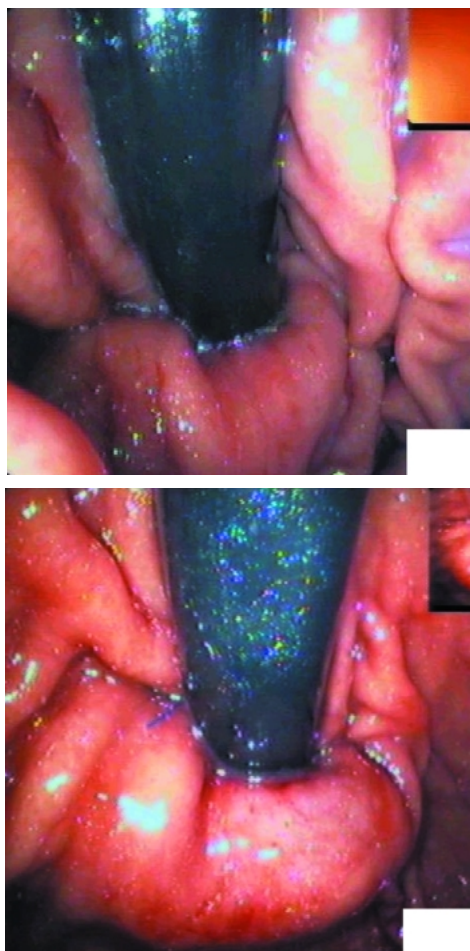
Endoscopic injection therapy is potentially easier to perform than other endoscopic therapies for GERD. Ideal materials for implantation should be biological inert, non-migrating, durable, and induce a negligible systemic inflammatory response.<sup>33</sup> An earlier study of collagen injection at the LES revealed only short-lived benefits.<sup>34</sup> The Enteryx copolymer consists of a solu-



**Figure 2.** Endoluminal gastroplication (EndoCinch procedure). (A) Suction is applied to draw a mucosal fold below the gastroesophageal junction into the EndoCinch capsule, and the needle is deployed. (B) A knot is made outside the body and pushed toward the 2 sutured adjacent folds. (Reprinted courtesy of Bard Interventional Products Division, Billerica, MA.)

tion of ethylene vinyl alcohol (EVOH) dissolved in dimethyl sulfoxide (DMSO). EVOH has also been used as a vascular embolization agent for cerebral aneurysms and arteriovenous malformations.

When Enteryx is injected into the gastric cardia, the solvent DMSO rapidly diffuses away, causing precipitation of EVOH into an inert spongy mass. The endoscopic injections should be aimed at the deep muscular layer because the implant will slough off if injected in the superficial mucosa.<sup>35</sup> In a porcine model, injection of Enteryx caused a marked acute inflammatory response followed by chronic granulomatous changes and the formation of extensive



**Figure 3.** Endoscopic retrograde views of the gastric cardia before (*top*) and after (*bottom*) the EndoCinch procedure.

fibrous tissues surrounding the implants.<sup>36</sup> The physiologic effects of Enteryx implantation are unclear. In the latter study, the length and pressure of the LES were unaffected.<sup>36</sup> The fibrous tissue formation may decrease the distensibility of the GEJ and increase its competency as an antireflux barrier.

Currently, all published clinical trials with endoscopic Enteryx injection are open-label and uncontrolled.<sup>37,38</sup> In a multicenter study, 85 patients with heartburn responsive to PPI therapy underwent Enteryx therapy and were followed for 6 months.<sup>37</sup> The Enteryx solution was injected in a circumferential manner at 1 to 2 mm below the GEJ along the muscle or deep submucosal layer to form a ring visible by fluoroscopy. At 6-months' follow-up, 74% of patients were able to stop PPI therapy. Heartburn and quality-of-life measurements were significantly improved compared to pretreatment scores off PPI therapy.

Esophageal acid exposure times improved, but in many patients, acid exposure did not normalize. There were no significant changes in LES pressures. Another open-label trial consisted of 15 patients with mild to moderate GERD.<sup>38</sup> At 6 months' follow-up, 75% of patients had improvement in heartburn scores, and LES pressures were increased.

Most patients reported retrosternal pain after Enteryx therapy.<sup>37</sup> Pain was mostly mild to moderate and resolved within 2 weeks. Transient dysphagia occurred in 20% of patients, but all cases resolved within 12 weeks.<sup>37</sup>

These preliminary studies of Enteryx therapy are encouraging; however, long-term safety and sustained benefits need to be demonstrated. In the study by Johnson et al,<sup>37</sup> 22% of patients required a second injection for recurrent heartburn, which significantly increases the cost of the Enteryx procedure. Randomized, controlled trials of Enteryx therapy are currently in progress. Furthermore, analysis of cost effectiveness is needed to compare Enteryx and medical antireflux therapy.

#### SUMMARY

The treatment options for GERD are expanding rapidly. Medical therapy with H<sub>2</sub>RAs and PPIs is well tolerated with proven efficacy in eliminating symptoms, treating reflux complications, and preventing recurrence. Medical antireflux therapy should be first-line treatment in all patients with GERD. Aggressive medical therapy should be tried first before considering surgical or endoscopic therapies. In patients who fail medical management or who have bronchopulmonary aspiration or a large hiatal hernia, minimally invasive antireflux surgery may be indicated. Successful surgical outcome depends on patient selection, preoperative evaluation, and surgical expertise.

Endoscopic therapy is emerging, but only patients with mild to moderate typical GERD have been selected thus far for clinical trials. The endoscopic therapy efficacy data are derived from small, short-term, uncontrolled studies. Randomized, controlled trials comparing endoscopic therapy with sham procedures as well as with medical therapy are needed. Potential complications of endoscopic therapy are a concern. Long-term efficacy, safety, and cost-effectiveness of endoscopic therapy need to be established to clarify its role in the treatment of GERD. **HP**

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