

Update on Endoscopic Approaches for the Management of Gastroesophageal Reflux Disease

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Abstract: Gastroesophageal reflux disease (GERD) is one of the most commonly encountered gastrointestinal diseases in outpatient clinics. Proton pump inhibitors (PPIs) are the cornerstone of the treatment of GERD. However, approximately one-third of patients have suboptimal response to PPIs. The management options in such cases include antireflux surgery or endoscopic antireflux treatments. Antireflux surgery is not popular due to its invasive nature and potential for adverse events. Therefore, minimally invasive endoscopic antireflux therapies are gaining popularity for the management of PPI-dependent and PPI-refractory GERD. These endoscopic therapies include radiofrequency application, endoscopic fundoplication modalities, and mucosal resection techniques. In appropriately selected patients, the response to these endoscopic modalities is encouraging. Unlike surgical fundoplication, endoscopic antireflux therapies are less likely to be associated with complications such as dysphagia and gas-bloat syndrome. On the other hand, antireflux surgery remains the ideal treatment in patients with a large hiatal hernia (laparoscopic Nissen fundoplication), morbid obesity (gastric bypass), and severe reflux esophagitis. Endoscopic treatment modalities bear the potential to narrow the treatment gap between PPIs and antireflux surgery. Long-term follow-up studies and randomized comparison with antireflux surgery are required to provide a clear understanding of the current role of endoscopic modalities in patients with PPI-refractory and PPI-dependent GERD.

Proton pump inhibitors (PPIs) have been the cornerstone of the management of gastroesophageal reflux disease (GERD) for several decades. However, in up to 30% of patients, acid suppressive therapy does not produce complete relief of symptoms, particularly regurgitation.¹ Nonresponsiveness to PPIs is multifactorial. Although PPIs are effective at neutralizing gastric acid and improving distal esophageal acid exposure, they are incapable of augmenting lower esophageal sphincter (LES) pressure and

Keywords

Endoscopy, gastroesophageal reflux disease, fundoplication, catheter ablation, surgery

Table 1. Endoscopic Antireflux Therapies and Devices

Radiofrequency ablation (Stretta)
Endoscopic fundoplication <ul style="list-style-type: none"> • Transoral incisionless fundoplication (EsophyX) • Endoscopic full-thickness plication (GERDx) • Medigus Ultrasonic Surgical Endostapler
Endoscopic mucosal resection

rectifying the underlying anatomic abnormality such as a hiatal hernia. Therefore, the underlying anatomic defect remains unaddressed, leading to inadequate control of symptoms. In addition, several recent studies have raised concerns among both patients and physicians regarding the potential consequences of long-term PPI therapy.^{2,3} The mainstay of management of patients with PPI-refractory GERD has been laparoscopic fundoplication, but there are concerns with this procedure because of its invasive nature and potential for adverse events such as gas-bloat syndrome (10%-32%), dysphagia (10%-50%), diarrhea (18%-33%), and recurrent reflux (10%-32%).^{4,6}

Consequently, there is a large treatment gap for patients who have inadequate symptom control on PPIs and patients who are unwilling to undergo antireflux surgery. Over the past several decades, a number of endoscopic devices and techniques have been tried and tested in this group of patients (ie, those with PPI-refractory GERD). This article describes the current spectrum of endoscopic antireflux therapies.

Endoscopic Antireflux Devices and Techniques

The endoscopic antireflux devices currently available include a radiofrequency ablation (RFA) device (Stretta, Mederi-RF) and several endoscopic fundoplication devices (Table 1). In addition, a few endoscopic antireflux techniques have been described that utilize the principles of endoscopic mucosal resection to achieve constriction of the gastric cardia. Several other modalities, including the injection of bulking agents (Enteryx, the Gatekeeper Reflux Repair System, Plexiglas, Durasphere) and endoscopic suturing (EndoCinch and the NDO plicator), have been withdrawn from the market due to poor efficacy or safety concerns.⁷

Radiofrequency Ablation

RFA is an endoscopic technique in which thermal energy is delivered to the muscle of the LES and gastric cardia via a 4-channel radiofrequency generator and catheter system equipped with 4 needle electrodes.⁸ The position of the RFA catheter is adjusted systematically using rotation and

linear movements to cover an area spanning 2 cm above and below the gastric cardia. The mechanism of action of Stretta therapy is incompletely understood. Unlike the use of RFA for other conditions, such as hepatocellular carcinoma and cholangiocarcinoma in which high temperatures are required for tissue destruction, Stretta therapy utilizes lower temperatures (65°C-85°C at the muscularis propria and 35°C at the mucosa). The putative mechanisms of action include increased gastric yield pressure, increased thickness of the LES muscle, decreased gastroesophageal junction compliance, and transient LES relaxations.^{8,9} Stretta therapy can be performed as an outpatient procedure under sedation in an endoscopy suite. Major adverse events are rare, and mucosal erosions are the most commonly reported minor adverse events.

Multiple cohort and randomized, controlled studies have examined the safety and efficacy of Stretta therapy for the management of GERD.⁹⁻¹² In addition, 2 systematic reviews and meta-analyses concluded that Stretta therapy produced subjective and objective improvements.^{13,14} In the more recent systematic review and meta-analysis, which included 28 studies (4 randomized trials, 23 cohort studies, and 1 registry), significant improvement was noticed in health-related quality of life (HRQL), heartburn score, esophageal acid exposure, and erosive esophagitis. Requirement of PPI therapy was eliminated in nearly half of the patients on follow-up.¹³ However, a systematic review and meta-analysis that included only randomized trials concluded otherwise. In this review of 165 patients, Stretta therapy was not found to significantly improve physiologic parameters, including esophageal acid exposure, LES pressure, ability to stop PPIs, or HRQL.¹⁵ Although the majority of the published literature vouches for the safety and efficacy of Stretta therapy, high-quality randomized trials are warranted to address the controversy generated by the latter meta-analysis.

Endoscopic Fundoplication Devices

Currently, the endoscopic fundoplication devices available commercially are the transoral incisionless fundoplication (TIF) device (EsophyX, EndoGastric Solutions), the GERDx device (GERDx System, G-SURG GmbH), and the Medigus Ultrasonic Surgical Endostapler (MUSE; Medigus) (Figure 1 and Table 2).

Transoral Incisionless Fundoplication The TIF device is the oldest of the endoscopic fundoplication devices currently available (Figure 1A). Originally introduced as endoluminal fundoplication (ELF) in 2005, the TIF procedure has received several modifications, in 2007 (as TIF1) and 2009 (as TIF2). As opposed to the previous versions, a greater number of fasteners (12-23) are deployed, a 270° fundoplication wrap is created, and

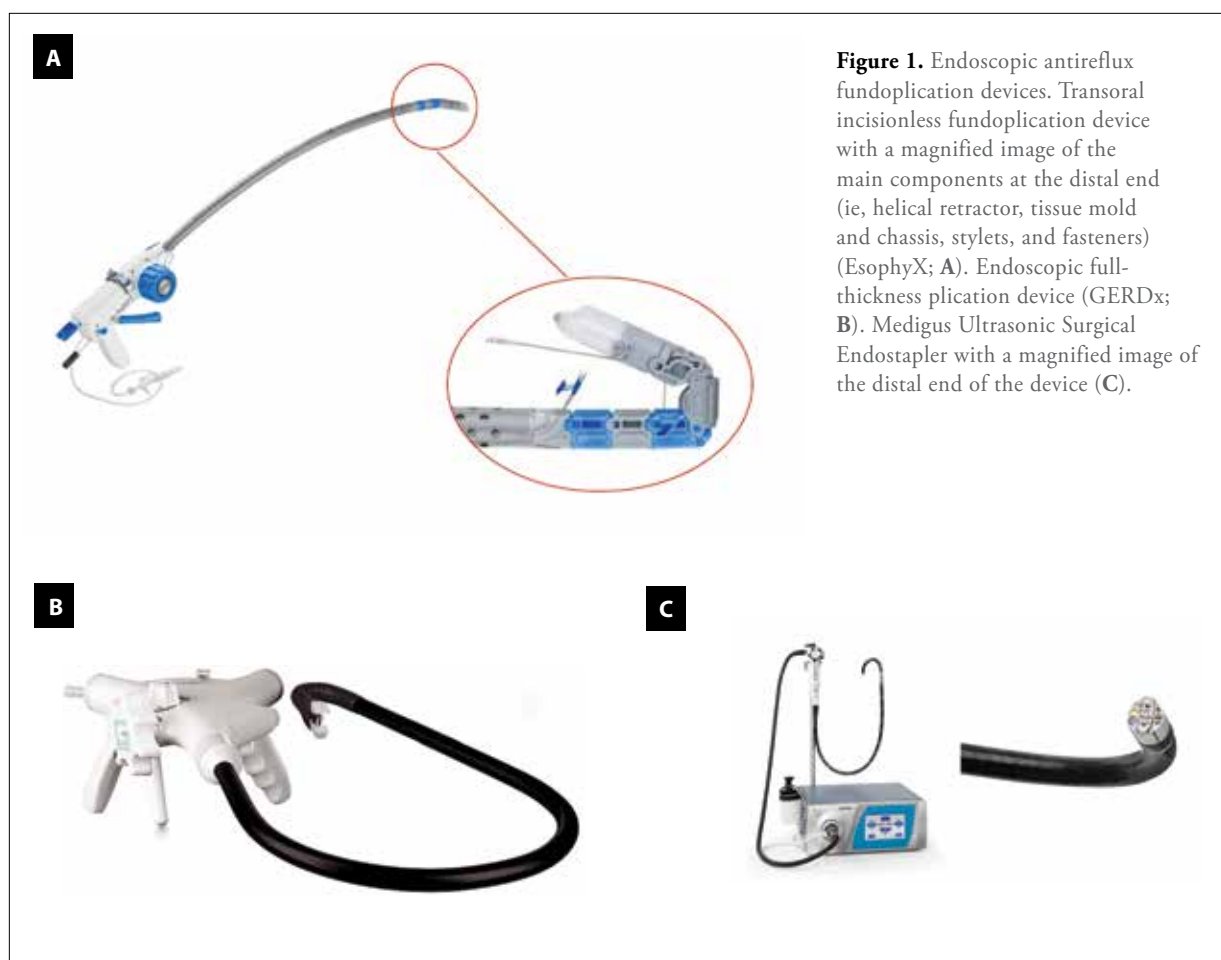


Table 2. Comparison of Endoscopic Fundoplication Devices

	TIF ¹⁶	GERDx ³⁶	MUSE ^{37,38,44}
Improvement in Quality of Life^a	+++	+++	+++
Cessation of PPI Use	89% at 15.5 months (95% CI, 82%-95%)	73.3% at 3 months	84% at 6 months 70%-77% at 4-5 years
DeMeester Score Improvement (Mean)	10.42 (95% CI, 8.47-12.36)	15.65 (one study)	20.30 (one study)
Esophageal Acid Exposure Time (Mean Difference)	53.18% (95% CI, 49.49%-56.87%)	NA	70.40% (95% CI, 21.84%-118.96%)
Improvement in Esophagitis	75%-100%	65%: Before device 20%: After device	NA
Follow-Up	Up to 6 years	3 months	Up to 4 years
Quality of Data/ Limitations of Studies^a	Randomized trials ++ Long-term studies +	No randomized trial Long-term studies lacking	No randomized trial Long-term studies lacking
Serious Adverse Events	2% ¹⁶	10% ³⁶	13.9% ³⁷

MUSE, Medigus Ultrasonic Surgical Endostapler; NA, not available; PPI, proton pump inhibitor; TIF, transoral incisionless fundoplication.

^a+ indicates weak quality or improvement, ++ indicates intermediate quality or improvement, and +++ indicates good quality or improvement.

esophagogastric plication is performed above the Z line in the current version (ie, TIF2). Objective improvement in pH study parameters, including esophageal acid exposure time, number of reflux episodes, and DeMeester scores postprocedure, was better with TIF2 as compared to the older versions (ie, TIF1 and ELF).¹⁶

There is ample evidence regarding the safety and efficacy of TIF in patients with PPI-dependent and PPI-refractory GERD (Table 2). Several randomized trials have compared TIF to PPIs or sham interventions in patients with GERD.¹⁷⁻²⁰ Hakansson and colleagues randomized 44 patients to TIF or sham intervention groups.¹⁸ At 6 months, 59% of the patients in the TIF group were in clinical remission without PPI therapy. There was a significant improvement in the quality of life, and normalization of esophageal acid exposure was achieved in 69% of patients in the TIF group.¹⁸ Witteman and colleagues randomized 60 patients with PPI-responsive GERD to TIF and PPI arms.²⁰ The patients in the PPI group were allowed to cross over into the TIF arm after 6 months of follow-up. TIF outperformed PPIs with respect to improvement in GERD-HRQL and increase in LES pressure at 6 months. Complete cessation of PPI use was recorded in 66% and 39% of patients at 6 and 12 months of follow-up, respectively. However, distal esophageal acid exposure did not improve significantly, and normalization of pH was accomplished in only 44% and 29% of cases at 6 and 12 months of follow-up, respectively.²⁰ Trad and colleagues compared TIF and PPIs in patients with troublesome regurgitation and extraesophageal symptoms of GERD (the TEMPO [TIF 2.0 EsophyX Vs Medical PPI Open-Label] trial).¹⁹ Troublesome regurgitation was relieved in 97% of patients after TIF as compared to 50% in the PPI group. Overall, complete elimination of all troublesome GERD symptoms (except heartburn) was achieved in a significantly higher proportion of patients after the TIF procedure (62% vs 5%; $P < .001$).¹⁹ Recently, encouraging results have surfaced with regard to the long-term outcomes of TIF.²¹⁻²³ In a study from Greece ($n=45$), clinical remission was found in approximately 73% of patients at a median follow-up of 59 months.²¹ In another long-term follow-up study ($n=23$), improvement in GERD-HRQL was maintained at a median follow-up of 97 months after TIF. However, PPIs were resumed by the majority of patients (73%) in this study.²² The long-term results of the TEMPO trial also confirmed the durability of the TIF procedure. In this study, the resolution of troublesome regurgitation and atypical symptoms of GERD was documented in 86% and 80% of patients, respectively, at 5 years.²³

Recurrence of symptoms after the TIF procedure has been reported in several studies.^{24,25} Disruption of fasteners and the presence of hiatal hernia have been found in patients with relapse of symptoms.²⁴ Revision of failed

TIF by subsequent Nissen fundoplication has been found to be feasible, safe, and effective in a few small series.²⁴⁻²⁶ In a recent study, recurrent symptoms of GERD were noticed in 15% of patients between 13 and 50 months after the TIF procedure. Laparoscopic Nissen fundoplication was successfully performed in all of the patients, with no major intraoperative or postoperative adverse events.²⁴

There has been no randomized trial comparing TIF with laparoscopic Nissen fundoplication. A recent systematic review and network meta-analysis compared the outcomes of TIF, laparoscopic fundoplication, and PPIs. Laparoscopic fundoplication had the highest probability of reducing esophageal acid exposure and increasing LES pressure. However, TIF had the least probability of reducing esophageal acid exposure and the highest probability of persistent esophagitis.²⁷

Major adverse events are rare with the TIF procedure. In a systematic review and meta-analysis, the incidence of serious adverse events, including perforations, bleeding, pneumothorax, and severe epigastric pain, was 2.4%.²⁸

Overall, the available evidence suggests that the TIF procedure is capable of eliminating reflux symptoms and improving the quality of life in the vast majority of patients with PPI-dependent or PPI-refractory GERD. However, the improvement in esophageal acid exposure is not impressive, and a significant proportion of patients may resume PPIs in the long run.

Endoscopic Full-Thickness Plication Endoscopic full-thickness plication was initially performed using the Plicator device (Ethicon Endo-Surgery). Several studies confirmed the safety and efficacy of this device for the management of refractory GERD.²⁹⁻³³ In preliminary trials, a single plicator implant was used.²⁹⁻³¹ Subsequent studies revealed better outcomes with multiple serially placed plicator implants as compared to a single implant.^{32,34} However, the Plicator device was withdrawn from the market due to unclear reasons. Recently, the plicator technology was acquired and re-introduced by a different manufacturer. The new device, called GERDx, uses the same plicator technology and is meant for single use (Figure 1B). The device uses hydraulic elements for control and requires a slim gastroscope that works as a light source, and it has been evaluated in a few small studies.^{35,36}

Weitzendorfer and colleagues prospectively assessed the outcomes of 40 patients with refractory GERD who were treated with the GERDx device.³⁶ There was significant improvement in reflux symptoms, quality of life, and DeMeester scores in 30 patients who completed 3 months of follow-up. Six patients required antireflux surgery within 3 months of the plication procedure due to persistent symptoms. The presence of a small hiatal hernia (all 6 patients) and disruption of sutures (3 patients) presumably led to failure in these cases. There were 4

serious adverse events: gastroesophageal junction hematoma resulting in severe postoperative pain and dysphagia, pneumonia with pleural effusion, Mallory-Weiss tear, and intractable postprocedure pain requiring surgical removal of the suture.³⁶ The authors attributed these adverse events partly to the manufacturer's change of the suture material (from 2.0 monofilament to 0.0 braided nonabsorbable suture) and suture length (from 6 to 7.6 mm).

Endoscopic full-thickness plication using the original Plicator device appeared effective. Initial data with the new device (GERDx) appear promising in the short term. Randomized trials and long-term follow-up studies are required to establish the role of this treatment in the management of GERD.

Medigus Ultrasonic Surgical Endostapler MUSE is distinct from the other available endoscopic fundoplication devices, as it contains a light source, an ultrasonic transducer, and a miniature video camera (Figure 1C). The camera along with the light source allow for direct visualization of the staple site selection, and the ultrasonic range finder helps in assessing the tissue thickness before firing the staples.

The safety and efficacy of MUSE have been evaluated in a few nonrandomized cohort studies. Zacherl and colleagues evaluated the outcomes of endoscopic fundoplication using MUSE in 66 patients.³⁷ Nearly three-fourths of patients achieved greater than 50% improvement in GERD-HRQL, and two-thirds of patients could discontinue PPIs at 6 months of follow-up. However, there were 8 severe adverse events during the initial part of the study, including pneumomediastinum, pneumothorax, empyema, and upper gastrointestinal hemorrhage. This led the authors to amend their protocol, and additional safety measures were incorporated while performing endostapling with this device. Subsequent to these amendments, the rate of adverse events reduced considerably, and no additional cases of leakage or pneumomediastinum were reported. Kim and colleagues reported long-term results with MUSE in 37 patients.³⁸ There was significant improvement in GERD-HRQL, and 69.4% of patients remained off daily PPIs at 4 years of follow-up.³⁸

Unlike with TIF, the data are limited with regard to the safety and efficacy of MUSE. There has been no randomized trial, and only 1 small cohort study evaluated the long-term outcomes of MUSE in GERD.³⁸

Mucosal Resection Technique for Endoscopic Constriction of Gastric Cardia Opening

Antireflux mucosectomy (ARMS) was initially described by Inoue and colleagues.³⁹ The principle of ARMS is that mucosal defect leads to healing by scar formation, which, in turn, induces narrowing of the gastric cardia opening. In this procedure, crescentic resection of half

to two-thirds of the circumference of the gastric cardia mucosa is performed using endoscopic submucosal dissection or multifragment endoscopic mucosal resection. In the seminal study by Inoue and colleagues, there was significant improvement in the appearance of flap valve, and PPIs could be discontinued in all patients.³⁹ Subsequently, Hedberg and colleagues published the outcomes of multiband endoscopic mucosal resection in 19 patients with refractory GERD.⁴⁰ The authors performed a 270° mucosal resection of the gastric cardia. The symptoms of GERD improved in 13 patients (68%). Of note, early dysphagia requiring balloon dilatation was noticed in 3 patients.⁴⁰

Other Techniques

Besides ARMS, a few other techniques have been described that utilize endoscopic band ligation or mucosal resection to reduce the gastric cardia opening.⁴¹⁻⁴³

Seleem and colleagues described the outcomes of endoscopic band ligation in a randomized trial that included 150 patients with refractory GERD.⁴¹ In this technique, several bands were applied at the gastroesophageal junction over 1 to 2 sessions. There was significant improvement in GERD-HRQL and erosive esophagitis in the banding group as compared to the baseline. Mild dysphagia and epigastric pain were the only reported adverse events.⁴¹

Hu and colleagues described a new endoscopic technique of gastric cardia constriction for GERD.⁴² In this technique, referred to as peroral endoscopic cardiac constriction, an endoscopic band ligation device was used to place 2 bands at the greater and lesser curvature. Subsequently, the 2 ends of the ligation devices were fixed with endoclips. There was significant improvement in GERD-HRQL and esophageal acid exposure in 13 patients who underwent peroral endoscopic cardiac constriction.⁴²

Benias and colleagues described a technique that involves limited mucosal resection followed by plication with the OverStitch device (Apollo Endosurgery).⁴³ In this pilot study, all 10 patients had a significant improvement in GERD-HRQL scores, and daily PPI dependence was eliminated in 8 patients.⁴³

The available evidence regarding the efficacy of ARMS as well as other mucosal resection or banding techniques is bleak. There have been no controlled trials. Moreover, the techniques are not yet standardized, and, therefore, the results may not be reproducible.

Indications and Patient Evaluation for Endoscopic Antireflux Treatments

Endoscopic modalities have been found to be effective in a select group of patients (ie, those with mild esophagitis, small hiatal hernia [<2 cm], endoscopic Hill Grade II-III,

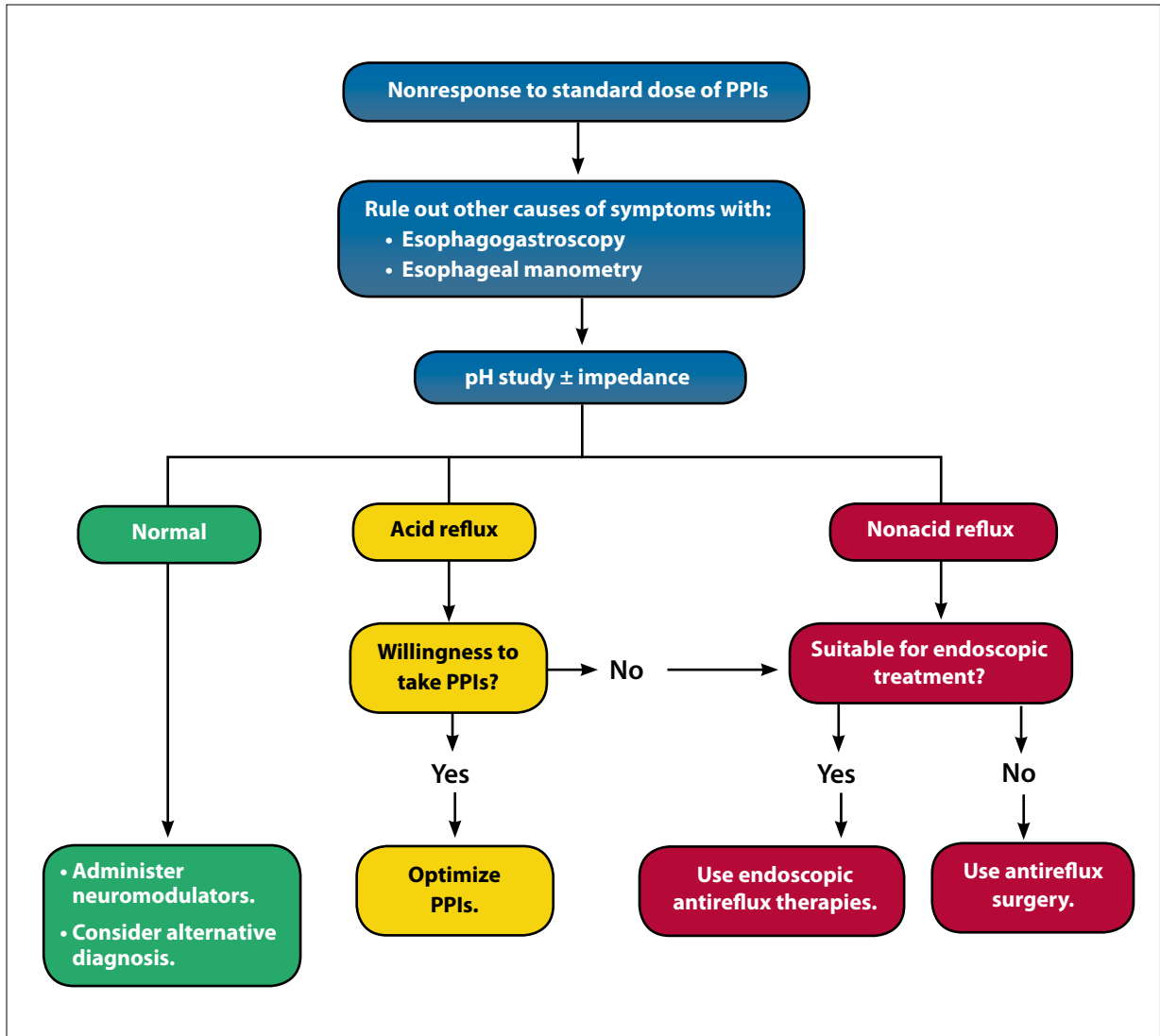


Figure 2. Algorithm showing the role of endoscopic antireflux therapies in the management of refractory gastroesophageal reflux disease.

PPI, proton pump inhibitor.

absence of Barrett esophagus, and nonmorbid obesity). Patient selection is crucial to obtain optimal results with the endoscopic treatments currently available. Morbidly obese patients and patients with a large hiatal hernia are best managed with an antireflux surgery (gastric bypass or laparoscopic Nissen fundoplication). Similarly, objective confirmation of reflux and exclusion of alternate causes of symptoms, such as motility disorders and eosinophilic esophagitis, are necessary to avoid dismal results. The evaluation of patients planned for endoscopic antireflux treatment should be standardized and should include esophagogastrosocopy, 24-hour pH study with or without

impedance measurement, and high-resolution manometry (Figure 2).

Gaps in Present Knowledge and the Future Directions of Endoscopic Antireflux Treatments

The body of evidence supporting the utility of endoscopic antireflux treatments is mounting. However, a few gaps still exist in the current understanding of our knowledge regarding these devices and techniques. First and foremost is the disparity between subjective and objective

improvement with the available endoscopic therapies. Although endoscopic antireflux modalities result in an impressive improvement in quality of life, the improvement in physiologic parameters such as LES pressure and esophageal acid exposure is not as robust as in laparoscopic fundoplication.²⁷ On the contrary, improvement in symptoms is not synonymous with improvement in esophageal acid exposure. This implies that the symptoms of GERD improve in the majority of patients despite persistence of reflux by pH studies. The significance of asymptomatic reflux is not well known and needs to be evaluated in long-term studies. Second, how these modalities fare with antireflux surgery is not well known. Randomized trials comparing endoscopic antireflux therapies and surgery are required before any conclusion can be drawn. Third, a significant proportion of patients receiving an endoscopic antireflux treatment resume PPIs on follow-up. Whether the resumption of PPIs is related to actual reflux needs to be studied to determine the true efficacy of endoscopic therapies. Resumption of PPIs may not be considered as failure in patients with an unimpaired quality of life and PPI refractoriness before the treatment. On the other hand, if the procedure was performed for unwillingness to continue PPIs, resumption of acid suppressive therapy is definitely a therapeutic failure. Fourth, quality evidence and long-term data are lacking for some of the endoscopic techniques that have been described in the literature. Endoscopic resection techniques have not been standardized, and, therefore, it is difficult to replicate the results. Finally, the optimal choice among the different endoscopic options currently available remains to be determined (Table 2). Several devices or techniques have undergone critical modifications to improve efficacy (eg, TIF) and minimize adverse events (eg, MUSE). It is likely that further modifications may make these devices more user-friendly.

Summary

The prevalence of GERD is increasing worldwide. The subset of patients with inadequate response to PPIs is substantial. Refractoriness to PPIs can be multifactorial; therefore, patients who are refractory to PPIs should undergo objective evaluation for the determination of the underlying mechanism of incomplete response. Endoscopic antireflux therapies made their appearance several decades ago. Although some modalities such as bulking agents and endoscopic suturing could not demonstrate efficacy and safety over time, other modalities such as RFA and TIF remained. However, some skepticism remains over their efficacy in the long run and improvement in objective parameters such as esophageal acid exposure. Proper selection of patients is paramount to achieve the

best results from endoscopic antireflux treatments. Endoscopic modalities can be a potential treatment alternative to antireflux surgery in a select group of patients.

The authors have no relevant conflicts of interest to disclose.

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