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Mini Review

Optimal Management of Erosive Esophagitis: An Evidence-based and Pragmatic Approach

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Abstract

Erosive Esophagitis (EE) is the most common complication of gastroesophageal reflux disease. Patients with EE can be asymptomatic or present with severe symptoms such as dysphagia and gastrointestinal bleeding. Approximately 10-15% of patients with EE have refractory disease. Optimal management of EE requires understanding its pathophysiology, clinical presentation, and available evaluation and treatment modalities. While pharmacologic treatment of EE is often successful, procedural options such as surgery and endoscopic therapy may be necessary. This article presents an evidence-based and pragmatic approach to the management of EE, the most common complication of gastroesophageal reflux disease.

Introduction

Gastroesophageal reflux disease (GERD) is the most common upper gastrointestinal issue encountered in clinical practice. Severe esophageal and extra-esophageal symptoms, as well as complications of GERD, are frequently observed. Up to 20% of patients with GERD develop serious esophageal complications, including erosive esophagitis (EE), Barrett's esophagus, esophageal stricture, and even esophageal adenocarcinoma.[1,2] EE is the most common complication of GERD, characterized by excessive reflux that leads to necrosis of the esophageal mucosa, erosions, ulcerations, and, in severe cases, hemorrhage.[3,4] EE should be differentiated from nonerosive reflux disease, in which no erosions are present. Patients with EE may present with heartburn, regurgitation, and more alarming symptoms, such as dysphagia and odynophagia.[2,4,5] While the majority of patients are successfully treated, up to 15% of patients with EE experience refractory disease and remain symptomatic without remission after eight weeks of proton pump inhibitor (PPI) therapy.[6,7] Given the multiple currently available medications, including the addition of potassium – competitive acid blockers (P-CABs) and the multiplicity of current and evolving endoscopic and surgical modalities for the treatment of EE, it was felt important to provide an approach for the treatment of EE to the practicing clinician. This article provides an evidence-based and pragmatic approach for the optimal management of EE, offering an overview of the current understanding of its pathophysiology, clinical presentation, and available evaluation and treatment modalities.

Keywords: Gastroesophageal reflux disease; GERD; GERD complications; Gastroesophageal reflux disease complications; Gastritis; Erosive gastritis.

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Pathogenesis

EE is most often caused by injury to the esophagus from gastric acid and pepsin, leading to symptoms and esophageal injury when pH is less than 4. Duodenogastric reflux of bile and medications may also cause injury in some cases.[1–3] As with GERD in general, several factors can contribute to the pathogenesis of EE, including a defective lower esophageal sphincter (LES), abnormal esophageal clearance due to the presence of a hiatal hernia, decreased amplitude of peristaltic contractions, increased frequency of nonpropulsive repetitive contractions, decreased salivary bicarbonate production, reduced salivary production, reduced esophageal mucosal resistance, and delayed gastric emptying.[5,7,8] Nocturnal acid secretion, associated with histamine release, plays an important role in nocturnal gastroesophageal reflux, which is linked to EE.[8–10]

Multiple medications and disease states can injure the esophageal mucosa and lead to EE, such as nitrates, calcium channel blockers, benzodiazepines, anticholinergics, and antidepressants.[11–13] Disease states such as obesity, cerebrovascular disease, diabetes mellitus, and Parkinson's disease can also affect the esophagus and are associated with EE.[14,15]

EE presents with visible endoscopic findings and histologic evidence of esophageal injury.[16] It typically presents with abnormally shaped or linear lesions in the distal esophagus.[17,18] Inflammation with cytokine release, neutrophils, eosinophils, lymphocytic infiltration, and surface necrosis are common features.[19,20]

Refractory EE can occur due to a variety of factors in addition to acidic or nonacidic gastroesophageal reflux. Factors related to

Table 1. Diagnostic tools in EE

Evaluation of mucosal injury	Evaluation of acid and non-acid reflux	Evaluation of esophageal motility
EGD – Best method for evaluation	96-h The Bravo pH testing	Esophageal manometry
Upper GI series – limited usefulness	24-h multichannel intraluminal impedance testing	

The Bravo™ calibration-free reflux testing system. GI, gastrointestinal; EGD, esophagogastroduodenoscopy; EE, erosive esophagitis.

poor compliance and adherence to medication guidelines, as well as the bioavailability of medications such as H2 receptor antagonists (H2RAs) and PPIs can promote EE. Certain medications can directly injure the esophageal mucosa, such as nonsteroidal anti-inflammatory drugs, potassium tablets, and bisphosphonates, leading to refractory disease. Reduced pain sensation in the elderly may contribute to increased acid injury with fewer symptoms.

Clinical presentation

In addition to heartburn and acid regurgitation, EE may present with globus sensation, water brash, belching, and nausea. Alarm symptoms that may indicate more serious disease include new onset of GERD in patients over 60 years of age, dysphagia, odynophagia, vomiting, anemia, unexplained weight loss, and gastrointestinal bleeding. These symptoms may be associated with other esophageal complications of GERD, such as Barrett's esophagus, esophageal stricture, and esophageal adenocarcinoma.[6–8]

Evaluation

Several diagnostic tests are available to evaluate patients with EE. Esophagogastroduodenoscopy (EGD) is necessary to make the diagnosis of EE.[4,6,8] Testing is especially important for patients with refractory disease or atypical symptoms, such as chest pain, ENT or pulmonary issues; alarm symptoms (e.g., dysphagia, odynophagia, unexplained weight loss, gastrointestinal hemorrhage, anemia); and for patients with EE prior to antireflux surgery (Table 1).[9,18,19]

Barium esophagram has limited use in GERD and no diagnostic utility in patients with EE.[2,4] EGD is superior because it provides direct visualization of the esophagus, allows for biopsy, and enables treatment in specific situations.[20,21]

EGD reveals the severity of esophagitis, which may not correlate with symptoms. It is required to detect EE and differentiate it from nonerosive reflux disease, in which no erosions are present. EGD can also evaluate other complications, such as Barrett's esophagus, esophageal stricture, esophageal adenocarcinoma, and GERD refractory to therapy. Additionally, EGD allows for biopsy to evaluate eosinophilic esophagitis, esophageal metaplasia, and dysplasia, and provides treatment for severe EE complications. For example, in patients with gastrointestinal hemorrhage, various techniques are available to control the hemorrhage during EGD. For patients with prolonged, severe EE and esophageal strictures, EGD allows for esophageal dilatation. EGD also offers ablative methods to treat Barrett's esophagus and can assess the Hill grade of the flap valve.

Several endoscopic grading methods assess the severity of EE, but the Los Angeles classification is the most widely used. It grades the severity of EE based on the extent of mucosal erosions, using four grades.[4,17,18] LA grade A esophagitis may be so mild that it requires confirmation via 96-h wireless pH testing or 24-h impedance-pH testing off acid suppression.[19,20] For EE patients with LA grades B, C, and D, pH testing off acid suppression is typically not required. However, in refractory EE patients with LA grades B, C, and D, 24-h impedance-pH testing on acid suppression is recommended to evaluate for acid and weak acid reflux.[2,4] In most patients with EE and LA grades B, C, or D, esophageal biopsies are not recommended. These patients should undergo repeat EGD in eight to twelve weeks after optimizing pharmacologic therapy to ensure healing of EE and rule out the presence of Barrett's esophagus.

Several methods are available to assess the degree of acid and non-acid reflux, as well as esophageal motility. These methods are primarily used for refractory EE patients and are not required for most EE cases. The evaluation of acid reflux is done by either 96-h The Bravo™ calibration-free reflux testing system by Medtronic or 24-h impedance-pH off acid suppression.[19,21]

Ambulatory pH monitoring using various techniques is helpful in EE patients with refractory disease or atypical symptoms to quantify the type and amount of gastroesophageal reflux. Multichannel intraluminal impedance with a pH sensor can detect pH episodes irrespective of the pH level.[22,23] Esophageal Bilitec detects the presence of bilirubin as a marker for bile reflux, but it is not widely available or recommended.[24–26]

High-resolution esophageal manometry is not required for the evaluation of most EE patients. However, it may be useful in refractory cases to detect esophageal motility disorders, such as achalasia, ensure proper placement of multichannel intraluminal impedance with pH sensor, and evaluate patients prior to antireflux surgery.[2,4,27]

Treatment

Pharmacologic therapy

The goals of EE treatment are to eliminate symptoms, heal EE, manage and/or prevent complications, and maintain remission. Most treatments are successful with lifestyle modifications and medication (Table 2).[2–4]

Lifestyle modification alone is not sufficient to control disease in most patients with EE. However, it should be encouraged as an adjunct to medication.[2,3] Medications such as nonsteroidal anti-inflammatory drugs, potassium tablets, bisphosphonates, beta-blockers, theophylline, and calcium channel blockers should be avoided or modified on an individual basis.[4,6,7]

Motility agents have limited success and are insufficient for

Table 2. Pharmacologic treatment

Medications
Antacids, motility agents, sucralfate, bile acid binders
H2RA agents
PPI agents
P-CAB agents

H2RA, histamine$_2$ (H_2) blockers; PPIs, proton pump inhibitors; P-CABs, potassium-competitive acid blockers.

Table 3. Endoscopic and surgical procedures

Endoscopic procedures	Surgical therapy	Newer endoscopic and surgical procedures
Stretta	Laparoscopic fundoplication	TIF
		MUSE
		LYNX
		LES-EST

LES-EST, lower esophageal sphincter electrical stimulation therapy; TIF, transoral incisionless fundoplication; MUSE, Medigus ultrasonic surgical stapler.

treating EE because they do not address the issue of acid reduction. Their use is only indicated for patients who have evidence of gastroparesis or poor esophageal clearance. These agents are also limited due to side effects, as seen with metoclopramide, and availability, such as with cisapride.[2,4,7,28,29]

Sucralfate is a mucosal-protecting agent effective in healing only low-grade EE and is recommended only for pregnant women with GERD.[4,30–33] Bile acid binders, such as cholestyramine and colesevelam, have not proven effective in EE.[2,4,7,13]

Acid reducing agents

Acid-reducing agents include antacids, H2RAs, PPIs, and potassium-competitive acid blockers (P-CABs).

Antacids have a limited role in treating GERD and little to no role in treating EE.[2,4]

H2RAs are useful in treating EE.[2,4,6] They are equally effective at equivalent doses, although higher than standard doses may be necessary in EE.[7,34,35]

PPIs are very effective for treating EE. PPIs provide excellent acid suppression and effective symptom relief. PPI agents are equally effective for EE.[2–4] For refractory disease, once-daily PPI therapy may be insufficient, and increasing the dose to twice-daily may be necessary. There is a significant risk of acid rebound upon cessation of therapy, so a tapering regimen must be followed to avoid symptom recurrence and disease flare. Maintenance therapy is often necessary for patients with LA grades C and D.[7,36,37]

Although PPIs are effective for treating EE, up to 15% of patients may be refractory to treatment, without full remission after eight weeks. Optimizing PPI therapy can help patients who are refractory to standard therapy.[2–5,7] Optimization involves proper dosing, 30 minutes before a meal. For those who remain refractory, switching to another PPI may be beneficial.[30,31] In refractory patients, double-dose therapy using a PPI twice daily before breakfast and dinner may improve symptoms. Adding an H2RA at night to twice-daily PPI therapy has been shown to reduce nocturnal acid breakthrough and GERD symptoms. However, tachyphylaxis of H2RAs may limit their utility in refractory EE. The addition of prokinetics to a PPI offers no benefit in EE.[32,36]

P-CABs are a new and significant addition to the treatment of EE. These weak bases are protonated and concentrate in the acid-secreting canaliculi of the parietal cells. Unlike PPIs, P-CABs competitively inhibit potassium-stimulated dephosphorylation and acid secretion by binding reversibly to the E2P form of the H+/K+-ATPase proton pump. P-CABs can bind both active and inactive proton pumps, so acid suppression is independent of de novo pump synthesis. P-CABs elevate intragastric pH more rapidly and provide the same degree of acid blockade as PPIs.[38,39]Acid suppression is not unnecessarily prolonged, potentially decreasing the risk of acid rebound upon cessation of therapy.[40,41] Vonoprazan fumarate is available in the US and is highly effective for treating EE.[42–46] Tegoprazan is another P-CAB approved outside the US and is also effective for treating EE.[47–49]

Since relapses are common in patients with EE, optimal management often requires long-term maintenance therapy. With proper monitoring and dosing, long-term treatment remains safe.

Potential complications of prolonged acid suppressive agents

A full discussion of the effects of prolonged acid suppression is beyond the scope of this review. However, prolonged acid suppression can affect B12, iron, and calcium absorption, bacterial proliferation, and drug metabolism.[50,51] Osteoporosis and bone fractures are potential concerns reported with PPIs, H2RAs, and P-CABs.[52] Bacteria can proliferate, leading to community-acquired pneumonia and gastrointestinal infections, such as Clostridium difficile-associated colitis, which have been associated with PPIs, H2RAs, and P-CABs.[53] These agents may also affect the absorption and metabolism of some drugs through the P-450 CYP2C19 and P-450 3A4 pathways.[2,4,6] Nevertheless, these agents are safe and effective for the long-term management of EE.[36,54]

Treatment of EE in pregnancy

H2RAs and PPIs are probably safe for pregnant and lactating females. P-CABs are not safe for pregnant or lactating females. Several studies have shown no significant difference in major congenital birth defects, spontaneous abortions, or preterm delivery in women exposed to H2RAs and PPIs during pregnancy. All H2RAs are FDA category B, and all PPIs are FDA category B, except for omeprazole, which is FDA category C.[55,56]

Procedural therapy

Most EE patients can be successfully managed with medical therapy. However, optimal management may require invasive surgical or endoscopic treatments in some cases (Table 3).

Surgery

Laparoscopic fundoplication

Anti-reflux surgery is an option for selected patients with EE who are refractory to therapy or unable to tolerate or comply with long-term pharmacotherapy. Surgery is primarily effective for patients who have refractory disease with either a partial or complete response to PPI therapy. Surgical outcomes are superior to medical therapy for patients with typical symptoms or objective evidence of acid reflux and good presurgical compliance with antireflux medications. Complications of laparoscopic fundoplication include dyspepsia, dysphagia, and gas bloat syndrome, with a potential for recurrent symptoms. Surgical candidates should undergo

a complete preoperative evaluation, including a thorough assessment of symptoms, EGD, esophageal manometry, pH testing, and gastric emptying studies prior to surgery.[57,58]

Endoscopic procedures

Stretta procedure

The Stretta procedure uses radiofrequency energy to the LES to increase basal pressure and reduce LES compliance.[59,60] Success is limited, and studies show no significant benefit over placebo.[60,61]

Newer endoscopic and surgical procedures

Newer surgical and endoscopic invasive methods of treatment are evolving for the management of EE, especially in refractory patients (Table 3).[62]

Transoral incisionless fundoplication (TIF)

TIF is an endoscopic procedure performed using the EsophyX device for endoscopic fundoplication. The effectiveness of TIF is similar to laparoscopic Nissen fundoplication and more effective than high-dose PPI therapy, at least at six-month follow-up. TIF can be considered for patients with a hiatal hernia less than 2 cm and Hill grade I/II.[63,64]

Magnetic augmentation device (LINX)

The LINX device is a magnetic augmentation device surgically positioned around the lower esophageal sphincter. It appears to be safe and efficacious and may be useful for refractory patients.[65]

Lower esophageal sphincter electrical stimulation therapy ((LES- EST)

Lower esophageal, sphincter, electrical stimulation therapy (LES-EST) is a new procedure that uses an implantable pulse generator with an external programmer to generate electrical stimulation, increasing the resting LES pressure. It seems to be safe and effective for EE, but further evaluation is needed.[66,67]

Medigus ultrasonic surgical stapler (MUSE)

MUSE is a procedure that creates a transoral fundoplication using a surgical stapler with video and ultrasound guidance. Further evaluation of this device is needed.[68,69]

Optimal management of EE

Esophagogastroduodenoscopy (EGD) is required to document EE, evaluate patients with refractory symptoms, and screen for more serious complications in patients with significant risk factors.

In EE, step-down therapy optimizes treatment (Fig. 1). The step-down therapy starts with PPIs or P-CABs to control EE and gradually reduces the potency of therapy until breakthrough symptoms develop. A PPI or P-CAB should be used daily for eight weeks. If improvement is noted, acid suppression can be reduced by lowering the dose of the PPI or P-CAB or switching to an H2RA. Optimizing PPI therapy is crucial for patients on PPI therapy who are refractory to standard treatment, and proper dosing 30 minutes prior to a meal is important. For those who remain refractory to PPI therapy, consideration should be given to switching the PPI or trying double-dose therapy, using a PPI agent twice daily before breakfast and dinner to improve symptoms. PPIs and P-CABs should only be administered on-demand for mild EE. On demand therapy is not recommended for more severe EE (LA grade C and D). PPIs and P-CABs provide endoscopic healing rates of EE in up to 86% of patients.

Patients with severe EE (LA grades C and D) on initial endoscopy should undergo a follow-up endoscopy after an eight-week course of PPI therapy to assess healing and rule out Barrett's esophagus.

In patients with refractory EE, ambulatory pH monitoring, multichannel intraluminal impedance with pH sensor, and esophageal manometry are useful for ruling out esophageal motility disorders and evaluating peristaltic function prior to antireflux surgery.

Patients with EE most often require maintenance acid suppression with a PPI or P-CAB due to recurrent disease and the potential for complications when medication is decreased or discontinued. PPIs and P-CABs should be prescribed at the lowest dose for the shortest duration. For patients on PPIs for longer than six months, the PPI dose should be tapered before discontinuation. H2RAs may be used for mild or intermittent symptoms in EE.

Surgery and endoscopic therapy should be considered for refractory patients or those on long-term treatment with PPIs or P-CABs who need to discontinue the medications. Laparoscopic fundoplication can be useful for selected patients with EE who are refractory to therapy or unable to tolerate or comply with long-term pharmacotherapy. Outcomes from surgical therapy are superior to medical therapy in patients with objective evidence of acid reflux and good presurgical compliance with medical therapy. Surgical candidates should undergo a complete preoperative evaluation, including a thorough assessment of symptoms, EGD, esophageal manometry, pH testing, and gastric emptying studies prior to surgery.

Other surgical and endoscopic invasive methods of EE treatment, especially for refractory patients, are evolving. The Stretta procedure remains controversial at best. TIF has similar effectiveness to laparoscopic Nissen fundoplication and may be considered for patients with a hiatal hernia less than 2 cm and Hill grade I/II. The LINX device appears to be safe and efficacious and may be useful for refractory patients. LES Electrical Stimulation Therapy is a new procedure that appears to be safe and effective for EE, but further evaluation is needed. MUSE is another procedure that requires further evaluation to establish its role in EE management.

In pregnant patients, EGD to confirm the diagnosis of EE is unnecessary. It should only be performed if there is a strong indication and should be postponed until the second trimester if possible. In the management of pregnant patients with EE, sucralfate, H2RAs, and PPIs can be used in consultation with the obstetrician.

Areas for future investigation of EE

Several areas of future investigation for EE relate to motility and reduction in inflammation. There is a need for a safe and effective motility agent to improve LES tone and esophagogastric motility. There is a need for a safe and effective acid-reducing agent with prolonged activity, that can reduce acid throughout the day and effectively treat nighttime reflux but avoid the long-term complications of acid-reducing agents. Additionally, there is a need for an agent that can safely reduce inflammation directly and prevent mucosal damage in EE. Further evaluation and development of surgical and endoscopic invasive methods of EE treatment are necessary.

Conclusions

There are many currently available medications and many current and evolving endoscopic and surgical modalities for the treatment of EE available for the treatment of EE by the practicing clinician. An evidence-based and pragmatic approach to management can provide optimal treatment of EE. Treatment of EE is most often

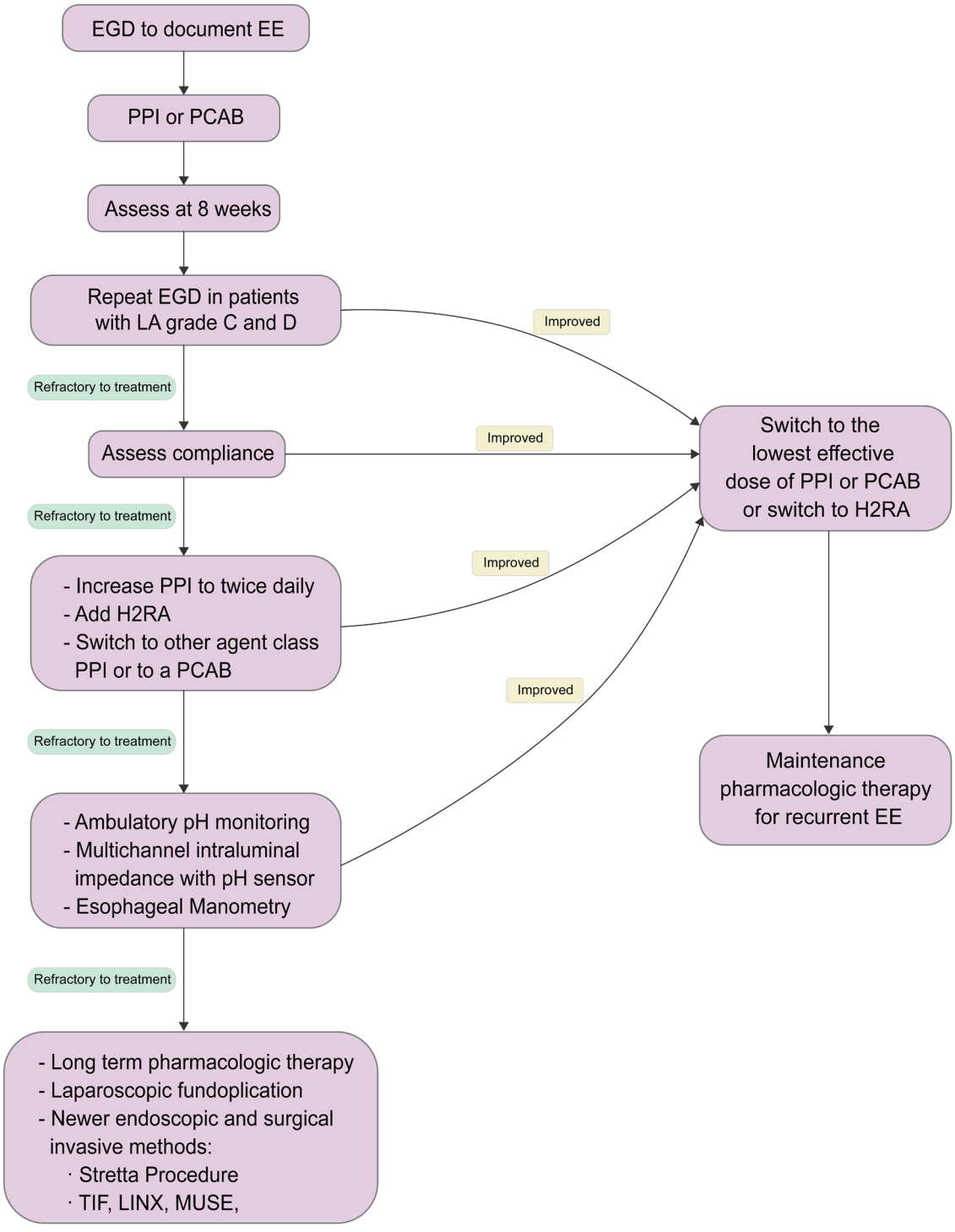

Fig. 1. EE step-down therapy starts with a PPI or P-CAB daily for eight weeks. If improvement is noted, acid suppression should be decreased to a lower dose of PPI or P-CAB or switched to an H2RA. Patients with LA grades C and D on initial endoscopy should undergo a follow-up endoscopy after an eight-week course of therapy to assess healing and rule out Barrett's esophagus. In refractory EE patients, further evaluation is recommended. Patients with EE most often require maintenance acid suppression with a PPI or P-CAB because recurrent disease and potential complications when medication is decreased or discontinued are common. PPIs and P-CABs should be prescribed at the lowest dose for the shortest duration. Surgery and endoscopic therapy should be considered in refractory patients or those on long-term treatment with PPIs or P-CABs if unable to discontinue medication. EGD, esophagogastroduodenoscopy; EE, erosive esophagitis; PPI, proton pump inhibitor; P-CAB, potassium-competitive acid blocker; LA grade, Los Angeles grade; H2RA, H2 receptor antagonist; TIF, transoral incisionless fundoplication; LINX, magnetic augmentation device; MUSE, Medigus ultrasonic surgical stapler; LES, lower esophageal sphincter electrical stimulation therapy.

successful with pharmacologic methods, especially with the use of PPIs and P-CABs. Procedural therapeutic options are evolving, including surgery and endoscopic therapy, and may be considered in refractory cases.

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Conflict of interest

The author reports no conflicts of interest in this work.

Author contributions

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