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PPI Refractory Gastroesophageal Reflux Disease

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Introduction

Gastroesophageal reflux disease (GERD) is among the most common conditions seen in ambulatory clinics and its disease burden continues to rise, with most recent studies reporting an 18 to 28% prevalence of GERD among North Americans.[1, 2] Proton pump inhibitor (PPI) therapy is the mainstay pharmacologic management for GERD, although up to 40% of patients with suspected GERD derive inadequate symptom relief with PPI.[3] While patients with PPI non-response may not have true GERD to begin with, a subset of PPI non-responders will have PPI refractory GERD. The management strategies for refractory GERD expand beyond PPIs to include other pharmacologic or invasive interventions. Since mechanisms of PPI refractory GERD are varied, the choice of management strategy should be personalized to the patient's needs and mechanistic dysfunction. This article will review the definition, mechanisms, and management options for PPI refractory GERD.

Definition of PPI Refractory GERD

PPI refractory GERD is defined as the presence of persistent troublesome GERD symptoms and objective evidence of GERD despite optimized PPI therapy (Figure 1). Generally, an optimized PPI trial consists of double dose PPI therapy over at least eight weeks.[4] Data supporting the optimal duration and dose of a PPI trial mostly derives from studies assessing healing in erosive esophagitis which demonstrated higher rates of endoscopic healing of erosive esophagitis and heartburn symptom resolution with double dose PPI compared to single dose[5], and lower symptom relapse following eight weeks of PPI therapy compared with four weeks of therapy.[6] At present, the US Food and Drug Administration (FDA) recommends single dose PPI use over 4 to 8 weeks for GERD.[7] Professional societies such as the American College of Gastroenterology and the American Gastroenterological

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Association recommend escalating to double dose PPI if erosive esophagitis persists or symptoms are only partially controlled on single dose PPI.[8, 9]

Partial PPI response, according to the Montreal Consensus, is presence of mild heartburn and/or regurgitation on three or more days/week despite at least four weeks of PPI.[10] When assessing for symptom response it is essential to ensure correct medication administration and that PPIs are being taken 30 to 60 minutes prior to a meal, as up to 54% of patients take PPIs incorrectly.[11, 12] Furthermore, at the onset of treatment providers should review treatment expectations and assist with goal setting. An aligned goal should be to reduce symptoms to a tolerable level and optimize quality of life, with the shared understanding that complete resolution is rarely achieved.[13]

Objective Diagnosis of PPI Refractory GERD—In the setting of persistent troublesome symptoms despite an appropriate PPI trial, the next step is to evaluate for objective evidence of GERD. Esophageal pH monitoring is the gold standard, and choice of testing modality depends on the pre-test likelihood of GERD. If objective GERD has not been previously diagnosed and/or there is a low suspicion of pathologic GERD, initial testing should be performed off PPI therapy with either wireless or catheter-based pH systems to evaluate for baseline GERD.[14] Not infrequently, pH testing in these scenarios is negative for GERD and helps to guide the evaluation and management away from GERD. However, in patients previously diagnosed with pathologic GERD (e.g., Los Angeles Grade C or D esophagitis, peptic stricture, Barrett's esophagus, or pathologic acid exposure off PPI on esophageal pH monitoring) the diagnostic evaluation begins with esophageal pH-impedance monitoring on PPI therapy to assess not only for PPI refractory acid exposure, but also excessive burden of non-acidic or weakly acidic contents.[14] According to the GERD Consensus Group, esophageal acid exposure time greater than 6% on PPI is consistent with PPI refractory GERD. When acid exposure time is borderline (4 to 6%), the group recommends consideration of further complimentary metrics (Figure 2).

Mechanisms of PPI Refractory GERD

Pathologic GERD typically requires compromise to one or more protective systems which exist to prevent gastroesophageal reflux, as well as an enhanced reflux physiology (Table 1).

Anti-reflux Barrier—The anti-reflux barrier is a high-pressure zone comprised of the LES attached to the crural diaphragm via the phreno-esophageal ligament and functions to prevent gastroesophageal reflux. Reduced integrity of the anti-reflux barrier, either by way of a hypotonic resting LES and/or axial displacement of the LES and crural diaphragm (hiatal hernia), can lead to increased reflux burden and acid exposure (Case example in Figure 3).[15, 16]

Reduced Esophageal Clearance—Delays in esophageal acid and bolus clearance are also associated with pathological acid reflux.[17] Primary peristalsis is the principal mechanism of reflux clearance.[18] In addition, volume distention induces secondary peristalsis and salivation assists with esophageal clearance.[19, 20] Reduced esophageal

clearance can occur with impaired esophageal peristalsis, in the setting of a hiatal hernia with re-refluxing of bolus, and impaired salivation.[21]

Epithelial Tissue Resistance—Barrier function of the esophageal mucosa is maintained by cell to cell junctions and works to prevent toxic substances from compromising the mucosal integrity.[22] Biopsies in patients with erosive and non-erosive reflux disease show evidence of microscopic esophagitis: necrosis, erosions, eosinophilic/neutrophilic infiltrate, basal cell hyperplasia, elongation of papillae, or dilation of intercellular spaces.[23] Therefore, reduced mucosal integrity is a potential mechanism of PPI refractory GERD. Mucosal impedance is an emerging field of study to examine electrical conductivity and mucosal integrity of the esophagus. A lower baseline mucosal impedance is associated with increased acid exposure and dilated intracellular spaces and seems to differentiate patients with objective GERD from other disease states.[24, 25]

Delayed gastric emptying—Slowed gastric emptying may also contribute to PPI refractory GERD through increased gastric distension and initiation of reflux events via TLESRs.[26] In one study, use of a prokinetic agent that accelerates gastric emptying prior to pH-impedance and manometry testing significantly reduced acid exposure time and acid clearance time.[27] However, in the absence of delayed gastric emptying, the data generally does not demonstrate reliable symptom improvement in PPI refractory GERD with adjunctive use of promotility agents (i.e., metoclopramide, prucalopride, and domperidone).[28, 29]

Physiologic Mechanisms of Reflux—TLESRs, prolonged relaxations in the LES associated with inhibition of the crural diaphragm that occur in response to gastric distention in the absence of a swallow, are the primary mechanism of initiating reflux in the context of an intact EGJ, (Figure 4).[29–32] When the LES is hypotensive, reflux can occur with a rise in intragastric pressure (strain-induced) or without a rise in intragastric pressure (free-reflux). Furthermore, gastric contents and esophageal bolus can re-reflux when hiatal hernia is present.

Pharmacologic Management of PPI Refractory GERD

CYP Independent PPIs—The mainstay of treatment for GERD is PPIs. Among different PPIs, there are variations in drug metabolism that can alter plasma levels.[33] Genetic polymorphisms of the CYP isoenzyme CYP2C19 in the liver affect drug levels of PPIs that are dependent on CYP2C19 for metabolism.[34] A patient with a rapid metabolizer genotype of CYP2C19 may have lower plasma levels of PPI, reducing effective acid suppression.[35] Use of specific PPIs that do not rely exclusively on CYP2C19 metabolism (i.e., rabeprazole and esomeprazole) in rapid metabolizers can increase acid suppression, improve symptom response, and improve rates of healing and remission of erosive esophagitis.[32, 36] Therefore, switching therapy from CYP dependent PPIs to more CYP independent PPIs in partial PPI responders may be a reasonable first step.[32, 37]

H2 Receptor Antagonists—H2 receptor antagonists (H2RAs) can be utilized to help reduce nighttime heartburn in conjunction with double dose PPI.[32, 38] Although there is

controversy regarding whether H2RAs help to decrease nocturnal acid breakthrough, studies have shown that in patients on both double dose PPI and nightly H2RAs, nighttime reflux symptoms are improved and sleep is less disturbed.[38] Tolerance to H2RAs has been suggested, however, and the benefit of adding H2RAs may wane over time.[39]

Potassium Competitive Acid Blockers—Potassium-competitive acid blockers (P-CABs), such as vonoprazan, competitively inhibit proton pumps and are currently approved in Japan for the treatment of peptic ulcer disease, healing of reflux esophagitis, and eradication of Helicobacter Pylori infection.[40, 41] Compared to PPIs, P-CABs have a higher potency, longer duration of action, and ability to block both inactive and active proton pumps.[32] Multiple retrospective studies have shown a symptomatic improvement in PPI-refractory GERD[42], and vonoprazan was found to be non-inferior to lansoprazole for treatment of erosive esophagitis.[43]

GABA-Agonists—GABA-agonists, such as Baclofen, have been shown to decrease the number of TLESR events and reduce heartburn and regurgitation symptoms in PPI refractory GERD when compared to placebo.[44] Potential side effects of GABA agonists, including CNS depression, should be considered when selecting patients to start therapy.

Alginate Antacids—Alginate antacids, such as Gaviscon, may be effective in controlling post-prandial heartburn and regurgitation.[28, 45] When exposed to gastric acid, alginates precipitate and form a floating raft to function as a physical barrier between gastric contents and the LES.[46, 47] The low side effect profile and unique mechanism of action make alginate antacids a helpful adjunct to partial PPI response.[47]

Invasive Management of PPI Refractory GERD

Laparoscopic Fundoplication—Laparoscopic fundoplication involves hernia repair with repositioning of the LES in the intraabdominal cavity and creation of a one-way flap valve in order to reduce reflux events.[48–50] Success rates of laparoscopic fundoplication range from 67% to 95% and are highly dependent on surgical expertise, adequate preoperative evaluation, and appropriate patient selection.[51–53] Nissen fundoplication is a total 360 degree fundoplication following crural closure. In the setting of impaired esophageal peristaltic reserve at baseline, partial wraps, such a 270 degree posterior fundoplication (Toupet) or a 180 degree anterior fundoplication (Dor), may be preferred to reduce post-fundoplication dysphagia.[54] Since the EGJ is a complex anatomical area subject to a multitude of mechanical stresses, the durability of a fundoplication may weaken over time resulting in hiatal herniation proximal to the wrap and/or slippage of the fundoplication.[55–57] Furthermore, tight fundoplications may result in dysphagia and other obstructive symptoms.[3, 24, 29] In fact, up to 30% of patients will develop a prolonged structural complication following fundoplication. Additionally, symptoms such as gas-bloat syndrome, chest pain, and diarrhea following fundoplication are common.[58, 59]

Magnetic Sphincter Augmentation—Magnetic sphincter augmentation is a new procedure using the LINX device FDA approved for treatment of PPI refractory GERD.[60] This laparoscopic procedure entails placing a magnetic bead device around the LES to

augment EGJ pressure through magnetic attraction. In a multi-center trial of 100 patients, the prevalence of esophagitis after LINX decreased by 28%[61] and in a prospective study of 200 patients undergoing magnetic sphincter augmentation and repair of large hernias > 3 cm, outcomes included post-operative improvement in quality of life.[62] The most common side effect of magnetic sphincter augmentation is dysphagia, and the rate of device migration and esophageal erosion is approximately 0.15%.[63]

Roux-en-Y Gastric Bypass—Obesity is a major risk factor for failure of laparoscopic fundoplication,[64] and procedures such as Roux-en-Y gastric bypass have been studied to treat both GERD and obesity. At three year follow-up of 55 patients with morbid obesity undergoing Roux-en-Y gastric bypass, reflux symptoms improved and incidence of esophagitis decreased.[65] Thus in the setting of morbid obesity, obesity with related comorbidity, or fundoplication failure, Roux-en-Y gastric bypass should be considered for PPI refractory GERD.

Transoral Incisionless Fundoplication—Transoral incisionless fundoplication is an endoluminal procedure that aims to reduce hiatal hernia size, restore the physical barrier of the LES, and prevent reflux of gastric contents.[66] In this procedure, a plication device is inserted to first reduce the hiatal hernia, and then create a mechanical valve by way of a partial fundoplication.[66, 67] In a meta-analysis, transoral incisionless fundoplication did not outperform surgical fundoplication with regards to reduction in esophagitis and increase in LES pressure.[66, 68] The rate of serious adverse outcomes, including GI perforation and bleeding, was 2.4%.[69]

Radiofrequency Energy Delivery to the LES—The Stretta procedure is another minimally-invasive treatment with a low adverse event rate (<1%) aimed at improving the barrier function of the EGJ through endoscopic administration of radiofrequency energy to the LES.[70] Studies have shown a significant improvement in symptoms and decreased PPI use with the Stretta procedure. [70–76] Nonetheless, concerns of limited post-procedural durability surround both transoral incisionless fundoplication and radiofrequency energy delivery.

Summary

Diagnosis of PPI refractory GERD requires the presence of troublesome symptoms and objective evidence of ongoing pathologic GERD despite PPI optimization. pH-impedance monitoring on PPI therapy is the standard method to objectively document PPI refractory GERD. Alternate causes of PPI non-response are common and should be ruled out to avoid misdiagnosis and mismanagement. Mechanisms of PPI refractory GERD vary and include a dysfunction of protective systems (e.g., anti-reflux barrier, esophageal clearance, epithelial resistance) and enhanced reflux physiology (e.g., TLESR episodes, hypotensive LES with free-or strain induced reflux, re-reflux with hiatal hernia).

As such, management of PPI refractory GERD should be tailored to mechanism, patient profile, and patient preference, as possible. It is reasonable to switch PPIs from CYP dependent to less CYP dependent PPIs (e.g., rabeprazole, esomeprazole). H2RAs may be an

option for patients reporting nighttime symptoms and/or in the setting of breakthrough nocturnal acid exposure. P-CABs seem to be a promising pharmacologic option for acid related erosive disease, however are not currently available in the US. GABA agonists such as Baclofen may be tried in PPI refractory GERD, particularly in patients exhibiting TLESRs, an elevated number of reflux events, and regurgitation; GABA agonists may not be as effective in the setting of hiatal hernia. Alginate-antacids carry a favorable safety profile and may be an effective adjunct to PPI.

When non-invasive treatment options fail, invasive anti-reflux options should be considered. Once again, confirmation of objective PPI refractory GERD is essential as surgical and endoscopic anti-reflux interventions are associated with risks, and outcomes are dependent on appropriate patient selection. The gold standard anti-reflux surgery remains laparoscopic fundoplication in the form of a complete or partial wrap. Other interventions include laparoscopic magnetic sphincter augmentation, endoscopic transoral incisionless fundoplication, or endoscopic radiofrequency energy delivery to the LES. Selection of anti-reflux intervention requires a discussion of risks and long-term efficacy and durability with the patient.

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References

1. El-Serag HB, Sweet S, Winchester CC, et al. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 2014;63:871–80. [PubMed: 23853213]
2. Peery AF, Crockett SD, Barritt AS, et al. Burden of Gastrointestinal, Liver, and Pancreatic Diseases in the United States. Gastroenterology 2015;149:1731–1741.e3. [PubMed: 26327134]
3. Kahrilas PJ, Boeckxstaens G, Smout AJ. Management of the patient with incomplete response to PPI therapy. Best Pract Res Clin Gastroenterol 2013;27:401–14. [PubMed: 23998978]
4. Yadlapati R, Vaezi MF, Vela MF, et al. Management options for patients with GERD and persistent symptoms on proton pump inhibitors: recommendations from an expert panel. Am J Gastroenterol 2018.
5. Kinoshita Y, Hongo M. Efficacy of twice-daily rabeprazole for reflux esophagitis patients refractory to standard once-daily administration of PPI: the Japan-based TWICE study. Am J Gastroenterol 2012;107:522–30. [PubMed: 22433921]
6. Hsu PI, Lu CL, Wu DC, et al. Eight weeks of esomeprazole therapy reduces symptom relapse, compared with 4 weeks, in patients with Los Angeles grade A or B erosive esophagitis. Clin Gastroenterol Hepatol 2015;13:859–66.e1. [PubMed: 25245625]
7. Bonavina L, Saino GI, Bona D, et al. Magnetic augmentation of the lower esophageal sphincter: results of a feasibility clinical trial. J Gastrointest Surg 2008;12:2133–40. [PubMed: 18846406]
8. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol 2013;108:308–28; quiz 329. [PubMed: 23419381]
9. Kahrilas PJ, Shaheen NJ, Vaezi MF, et al. American Gastroenterological Association Medical Position Statement on the management of gastroesophageal reflux disease. Gastroenterology 2008;135:1383–1391, 1391 e1–5. [PubMed: 18789939]
10. Vakil N, Niklasson A, Denison H, et al. Symptom profile in partial responders to a proton pump inhibitor compared with treatment-naive patients with gastroesophageal reflux disease: a post hoc analysis of two study populations. BMC Gastroenterol 2014;14:177. [PubMed: 25304129]

11. Gunaratnam NT, Jessup TP, Inadomi J, et al. Sub-optimal proton pump inhibitor dosing is prevalent in patients with poorly controlled gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2006;23:1473–7. [PubMed: 16669962]
12. Wolfe MM, Sachs G. Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. Gastroenterology 2000;118:S9–31. [PubMed: 10868896]
13. Dean BB, Gano AD, Jr, Knight K, et al. Effectiveness of proton pump inhibitors in nonerosive reflux disease. Clin Gastroenterol Hepatol 2004;2:656–64. [PubMed: 15290657]
14. Roman S, Gyawali CP, Savarino E, et al. Ambulatory reflux monitoring for diagnosis of gastro-esophageal reflux disease: Update of the Porto consensus and recommendations from an international consensus group. Neurogastroenterol Motil 2017;29:1–15.
15. Gyawali CP, Roman S, Bredenoord AJ, et al. Classification of esophageal motor findings in gastro-esophageal reflux disease: Conclusions from an international consensus group. Neurogastroenterol Motil 2017;29.
16. Herregods TV, Bredenoord AJ, Smout AJ. Pathophysiology of gastroesophageal reflux disease: new understanding in a new era. Neurogastroenterol Motil 2015;27:1202–13. [PubMed: 26053301]
17. Bredenoord AJ, Hemmink GJ, Smout AJ. Relationship between gastro-oesophageal reflux pattern and severity of mucosal damage. Neurogastroenterol Motil 2009;21:807–12. [PubMed: 19374635]
18. Anggiansah A, Taylor G, Bright N, et al. Primary peristalsis is the major acid clearance mechanism in reflux patients. Gut 1994;35:1536–42. [PubMed: 7828968]
19. Kahrilas PJ, Bredenoord AJ, Fox M, et al. The Chicago Classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil 2015;27:160–74. [PubMed: 25469569]
20. Reddy CA, Patel A, Gyawali CP. Impact of symptom burden and health-related quality of life (HRQOL) on esophageal motor diagnoses. Neurogastroenterol Motil 2017;29.
21. Tack J, Pandolfino JE. Pathophysiology of Gastroesophageal Reflux Disease. Gastroenterology 2018; 154:277–288. [PubMed: 29037470]
22. Dellon ES, Shaheen NJ. Persistent reflux symptoms in the proton pump inhibitor era: the changing face of gastroesophageal reflux disease. Gastroenterology 2010;139:7–13.e3. [PubMed: 20493864]
23. Tobey NA, Hosseini SS, Argote CM, et al. Dilated intercellular spaces and shunt permeability in nonerosive acid-damaged esophageal epithelium. Am J Gastroenterol 2004;99:13–22. [PubMed: 14687135]
24. Kandulski A, Weigt J, Caro C, et al. Esophageal intraluminal baseline impedance differentiates gastroesophageal reflux disease from functional heartburn. Clin Gastroenterol Hepatol 2015;13:1075–81. [PubMed: 25496815]
25. Ates F, Yuksel ES, Higginbotham T, et al. Mucosal impedance discriminates GERD from non-GERD conditions. Gastroenterology 2015;148:334–43. [PubMed: 25448923]
26. Emerenziani S, Sifrim D. Gastroesophageal reflux and gastric emptying, revisited. Curr Gastroenterol Rep 2005;7:190–5. [PubMed: 15913477]
27. Kessing BF, Smout AJ, Bennink RJ, et al. Prucalopride decreases esophageal acid exposure and accelerates gastric emptying in healthy subjects. Neurogastroenterol Motil 2014;26:1079–86. [PubMed: 24891067]
28. Gyawali CP, Fass R. Management of Gastroesophageal Reflux Disease. Gastroenterology 2018;154:302–318. [PubMed: 28827081]
29. Ren LH, Chen WX, Qian LJ, et al. Addition of prokinetics to PPI therapy in gastroesophageal reflux disease: a meta-analysis. World J Gastroenterol 2014;20:2412–9. [PubMed: 24605040]
30. Sifrim D, Castell D, Dent J, et al. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. Gut 2004;53:1024–1031. [PubMed: 15194656]
31. Roman S, Holloway R, Keller J, et al. Validation of criteria for the definition of transient lower esophageal sphincter relaxations using high-resolution manometry. Neurogastroenterol Motil 2017;29.

32. Hillman L, Yadlapati R, Thuluvath AJ, et al. A review of medical therapy for proton pump inhibitor nonresponsive gastroesophageal reflux disease. Dis Esophagus 2017;30:1–15.
33. Sagar M, Tybring G, Dahl ML, et al. Effects of omeprazole on intragastric pH and plasma gastrin are dependent on the CYP2C19 polymorphism. Gastroenterology;119:670–676. [PubMed: 10982760]
34. Ishizaki T, Horai Y. Review article: cytochrome P450 and the metabolism of proton pump inhibitors--emphasis on rabeprazole. Aliment Pharmacol Ther 1999;13 Suppl 3:27–36. [PubMed: 10209682]
35. Furuta T, Ohashi K, Kosuge K, et al. CYP2C19 genotype status and effect of omeprazole on intragastric pH in humans. Clin Pharmacol Ther 1999;65:552–61. [PubMed: 10340921]
36. Schwab M, Klotz U, Hofmann U, et al. Esomeprazole-induced healing of gastroesophageal reflux disease is unrelated to the genotype of CYP2C19: evidence from clinical and pharmacokinetic data. Clin Pharmacol Ther 2005;78:627–34. [PubMed: 16338278]
37. Zendehdel N, Biramijamal F, Hossein-Nezhad A, et al. Role of cytochrome P450 2C19 genetic polymorphisms in the therapeutic efficacy of omeprazole in Iranian patients with erosive reflux esophagitis. Arch Iran Med 2010;13:406–12. [PubMed: 20804307]
38. Rackoff A, Agrawal A, Hila A, et al. Histamine-2 receptor antagonists at night improve gastroesophageal reflux disease symptoms for patients on proton pump inhibitor therapy. Dis Esophagus 2005;18:370–3. [PubMed: 16336606]
39. Fackler WK, Ours TM, Vaezi MF, et al. Long-term effect of H2RA therapy on nocturnal gastric acid breakthrough. Gastroenterology 2002;122:625–32. [PubMed: 11874994]
40. Yamashita H, Kanamori A, Kano C, et al. The Effects of Switching to Vonoprazan, a Novel Potassium-Competitive Acid Blocker, on Gastric Acidity and Reflux Patterns in Patients with Erosive Esophagitis Refractory to Proton Pump Inhibitors. Digestion 2017;96:52–59. [PubMed: 28662503]
41. Graham DY, Dore MP. Update on the Use of Vonoprazan: A Competitive Acid Blocker. Gastroenterology 2018;154:462–466. [PubMed: 29337157]
42. Shinozaki S, Osawa H, Hayashi Y, et al. Vonoprazan 10 mg daily is effective for the treatment of patients with proton pump inhibitor-resistant gastroesophageal reflux disease. Biomed Rep 2017;7:231–235. [PubMed: 28894571]
43. Ashida K, Sakurai Y, Hori T, et al. Randomised clinical trial: vonoprazan, a novel potassium-competitive acid blocker, vs. lansoprazole for the healing of erosive oesophagitis. Aliment Pharmacol Ther 2016;43:240–51. [PubMed: 26559637]
44. Abbasinazari M, Panahi Y, Mortazavi SA, et al. Effect of a Combination of Omeprazole Plus Sustained Release Baclofen Versus Omeprazole Alone on Symptoms of Patients with Gastroesophageal Reflux Disease (GERD). Iran J Pharm Res 2014;13:1221–6. [PubMed: 25587310]
45. Rohof WO, Bennink RJ, Smout AJPM, et al. An Alginate-Antacid Formulation Localizes to the Acid Pocket to Reduce Acid Reflux in Patients With Gastroesophageal Reflux Disease. Clinical Gastroenterology and Hepatology;11:1585–1591.
46. Zentilin P, Dulbecco P, Savarino E, et al. An evaluation of the antireflux properties of sodium alginate by means of combined multichannel intraluminal impedance and pH-metry. Aliment Pharmacol Ther 2005;21:29–34. [PubMed: 15644042]
47. Mandel KG, Daggy BP, Brodie DA, et al. Review article: alginate-raft formulations in the treatment of heartburn and acid reflux. Aliment Pharmacol Ther 2000;14:669–90. [PubMed: 10848650]
48. Dallemagne B, Weerts JM, Jehaes C, et al. Laparoscopic Nissen fundoplication: preliminary report. Surg Laparosc Endosc 1991;1:138–43. [PubMed: 1669393]
49. Geagea T Laparoscopic Nissen's fundoplication: preliminary report on ten cases. Surg Endosc 1991;5:170–3. [PubMed: 1839573]
50. Dallemagne B, Weerts J, Markiewicz S, et al. Clinical results of laparoscopic fundoplication at ten years after surgery. Surg Endosc 2006;20:159–65. [PubMed: 16333553]

51. Jobe BA, Richter JE, Hoppo T, et al. Preoperative diagnostic workup before antireflux surgery: an evidence and experience-based consensus of the Esophageal Diagnostic Advisory Panel. J Am Coll Surg 2013;217:586–97. [PubMed: 23973101]
52. Fernando HC. Endoscopic fundoplication: patient selection and technique. J Vis Surg 2017;3:121. [PubMed: 29078681]
53. Moore M, Afaneh C, Benhuri D, et al. Gastroesophageal reflux disease: A review of surgical decision making. World J Gastrointest Surg 2016;8:77–83. [PubMed: 26843915]
54. Jobe BA, Kahrilas PJ, Vernon AH, et al. Endoscopic appraisal of the gastroesophageal valve after antireflux surgery. Am J Gastroenterol 2004;99:233–43. [PubMed: 15046210]
55. Richter JE. Let the patient beware: the evolving truth about laparoscopic antireflux surgery. Am J Med 2003;114:71–3. [PubMed: 12543294]
56. Hinder RA, Libbey JS, Gorecki P, et al. Antireflux surgery. Indications, preoperative evaluation, and outcome. Gastroenterol Clin North Am 1999;28:987–1005, viii. [PubMed: 10695013]
57. Horgan S, Pohl D, Bogetti D, et al. Failed antireflux surgery: what have we learned from reoperations? Arch Surg 1999;134:809–15; discussion 815–7. [PubMed: 10443802]
58. Swanstrom L, Wayne R. Spectrum of gastrointestinal symptoms after laparoscopic fundoplication. Am J Surg 1994;167:538–41. [PubMed: 8185044]
59. Lundell L Complications after anti-reflux surgery. Best Pract Res Clin Gastroenterol 2004;18:935–45. [PubMed: 15494287]
60. Summary of Safety and Effectiveness Data: LINX Reflux Management System. In: FDA, ed, 2012.
61. Azagury D, Morton J. Surgical Anti-Reflux Options Beyond Fundoplication. Curr Gastroenterol Rep 2017;19:35. [PubMed: 28725999]
62. Buckley FP, 3rd, Bell RCW, Freeman K, et al. Favorable results from a prospective evaluation of 200 patients with large hiatal hernias undergoing LINX magnetic sphincter augmentation. Surg Endosc 2018;32:1762–1768. [PubMed: 28936790]
63. Smith CD, Ganz RA, Lipham JC, et al. Lower Esophageal Sphincter Augmentation for Gastroesophageal Reflux Disease: The Safety of a Modern Implant. J Laparoendosc Adv Surg Tech A 2017;27:586–591. [PubMed: 28430558]
64. Perez AR, Moncure AC, Rattner DW. Obesity adversely affects the outcome of antireflux operations. Surg Endosc 2001;15:986–9. [PubMed: 11443428]
65. Madalosso CA, Gurski RR, Callegari-Jacques SM, et al. The Impact of Gastric Bypass on Gastroesophageal Reflux Disease in Morbidly Obese Patients. Ann Surg 2016;263:110–6. [PubMed: 25607766]
66. Richter JE, Kumar A, Lipka S, et al. Efficacy of Laparoscopic Nissen Fundoplication vs Transoral Incisionless Fundoplication or Proton Pump Inhibitors in Patients With Gastroesophageal Reflux Disease: A Systematic Review and Network Meta-analysis. Gastroenterology 2018.
67. Hakansson B, Montgomery M, Cadiere GB, et al. Randomised clinical trial: transoral incisionless fundoplication vs. sham intervention to control chronic GERD. Aliment Pharmacol Ther 2015;42:1261–70. [PubMed: 26463242]
68. Trad KS, Barnes WE, Prevou ER, et al. The TEMPO Trial at 5 Years: Transoral Fundoplication (TIF 2.0) Is Safe, Durable, and Cost-effective. Surg Innov 2018:1553350618755214.
69. Huang X, Chen S, Zhao H, et al. Efficacy of transoral incisionless fundoplication (TIF) for the treatment of GERD: a systematic review with meta-analysis. Surg Endosc 2017;31:1032–1044. [PubMed: 27495332]
70. Franciosa M, Mashimo H. Stretta radiofrequency treatment for GERD: a safe and effective modality. Am J Gastroenterol 2013;108:1654–5. [PubMed: 24091508]
71. Kim MS, Dent J, Holloway RH, et al. Radiofrequency energy delivery to the gastric cardia inhibits triggering of transient lower esophageal sphincter relaxation in a canine model. Gastroenterology; 118:A860.
72. Arts J, Bisschops R, Blondeau K, et al. A double-blind sham-controlled study of the effect of radiofrequency energy on symptoms and distensibility of the gastro-esophageal junction in GERD. Am J Gastroenterol 2012;107:222–30. [PubMed: 22108449]

73. Arts J, Sifrim D, Rutgeerts P, et al. Influence of radiofrequency energy delivery at the gastroesophageal junction (the Stretta procedure) on symptoms, acid exposure, and esophageal sensitivity to acid perfusion in gastroesophagal reflux disease. Dig Dis Sci 2007;52:2170–7. [PubMed: 17436101]

74. Triadafilopoulos G, DiBaise JK, Nostrant TT, et al. The Stretta procedure for the treatment of GERD: 6 and 12 month follow-up of the U.S. open label trial. Gastrointest Endosc 2002;55:149–56. [PubMed: 11818914]

75. Sifrim D, Zerbib F. Diagnosis and management of patients with reflux symptoms refractory to proton pump inhibitors. Gut 2012;61:1340–54. [PubMed: 22684483]

76. Fass R, Cahn F, Scotti DJ, et al. Systematic review and meta-analysis of controlled and prospective cohort efficacy studies of endoscopic radiofrequency for treatment of gastroesophageal reflux disease. Surg Endosc 2017;31:4865–4882. [PubMed: 28233093]

Synopsis:

Proton pump inhibitor (PPI) refractory gastroesophageal reflux disease (GERD) is defined by the presence of troublesome GERD symptoms despite PPI optimization for at least 8 weeks in the setting of ongoing documented pathologic gastroesophageal reflux. PPI refractory GERD arises from a dysfunction in protective systems to prevent reflux, as well as propagation of physiologic reflux events. Treatment for PPI refractory GERD includes pharmacologic options such as addition of histamine-2 receptor antagonists, alginate antacids, and GABA agonists. Invasive management strategies include surgery such as laparoscopic fundoplication, magnetic sphincter augmentation, and Roux-en-Y gastric bypass, and endoluminal therapies such as transoral incisionless fundoplication and radiofrequency energy delivery.

Key Points:

- Proton pump inhibitor (PPI) refractory gastroesophageal reflux disease (GERD) occurs when troublesome symptoms and elevated acid exposure and/or reflux burden persist despite an optimized PPI trial.
- PPI refractory GERD arises from dysfunction of physiologic lines of defense (e.g., anti-reflux barrier, reflux clearance, epithelial tissue resistance) and propagation of reflux mechanisms (e.g., transient lower esophageal sphincter relaxations, hernia re-reflux, hypotensive lower esophageal sphincter).
- Pharmacologic options for PPI refractory GERD include switching to a less CYP2C19 dependent PPI, adding H2 receptor antagonists at night, using alginate-based antacids, and trialing GABA agonists.
- Surgical options for PPI refractory GERD include laparoscopic fundoplication, magnetic sphincter augmentation, and Roux-en-Y gastric bypass, particularly in the setting of morbid obesity.
- Transoral incisionless fundoplication and radiofrequency energy delivery to the LES are endoluminal interventional options for PPI refractory GERD.

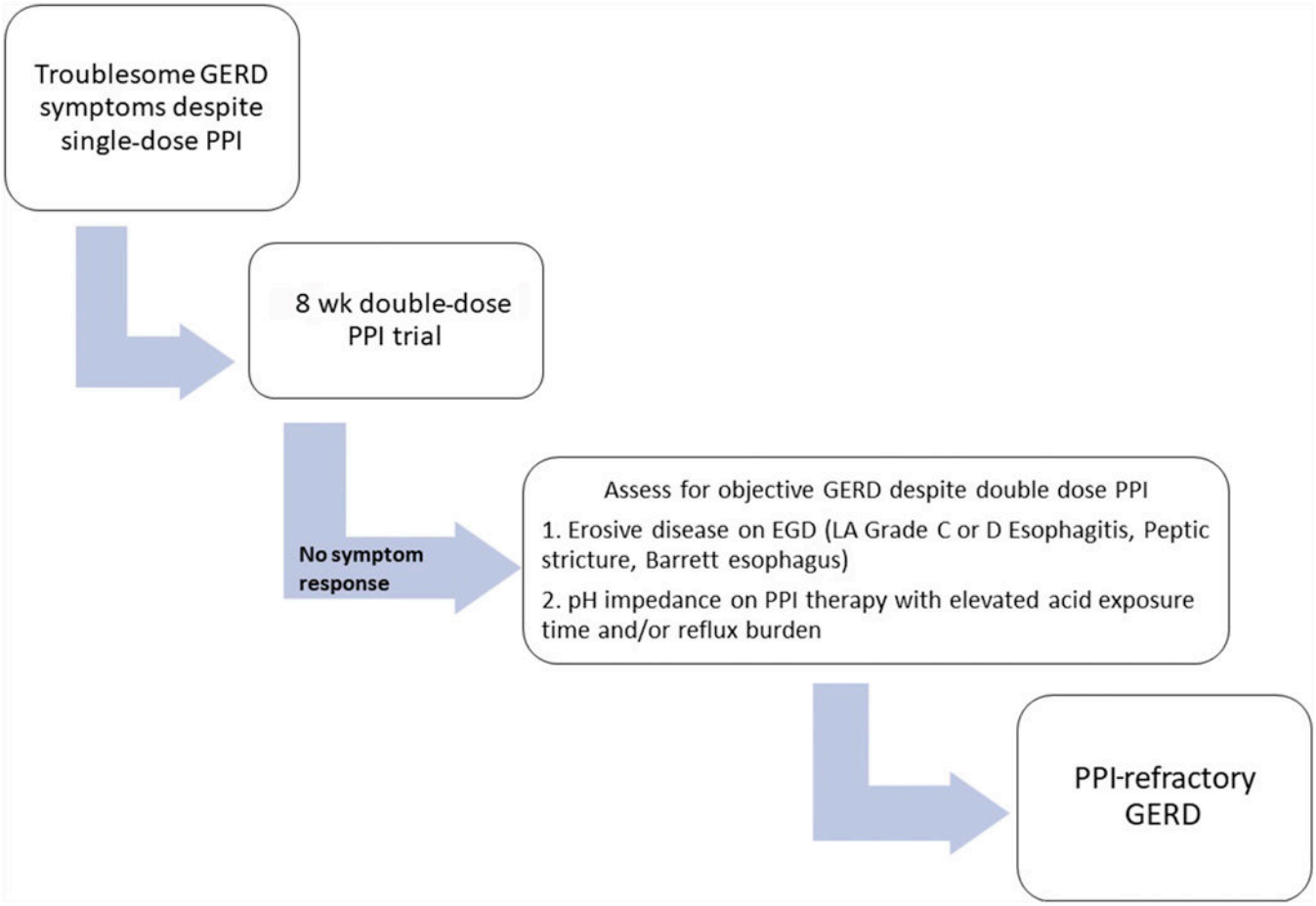

Figure 1.
Arriving at a diagnosis of PPI refractory GERD.

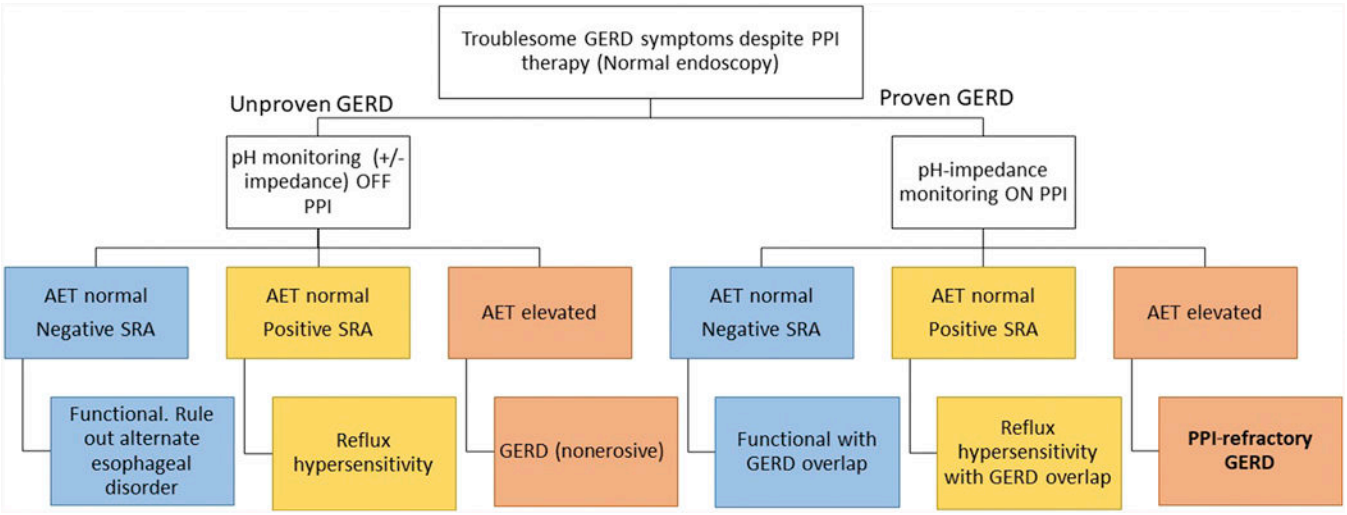

Figure 2.
Role of pH testing to identify etiologies of PPI non-response.

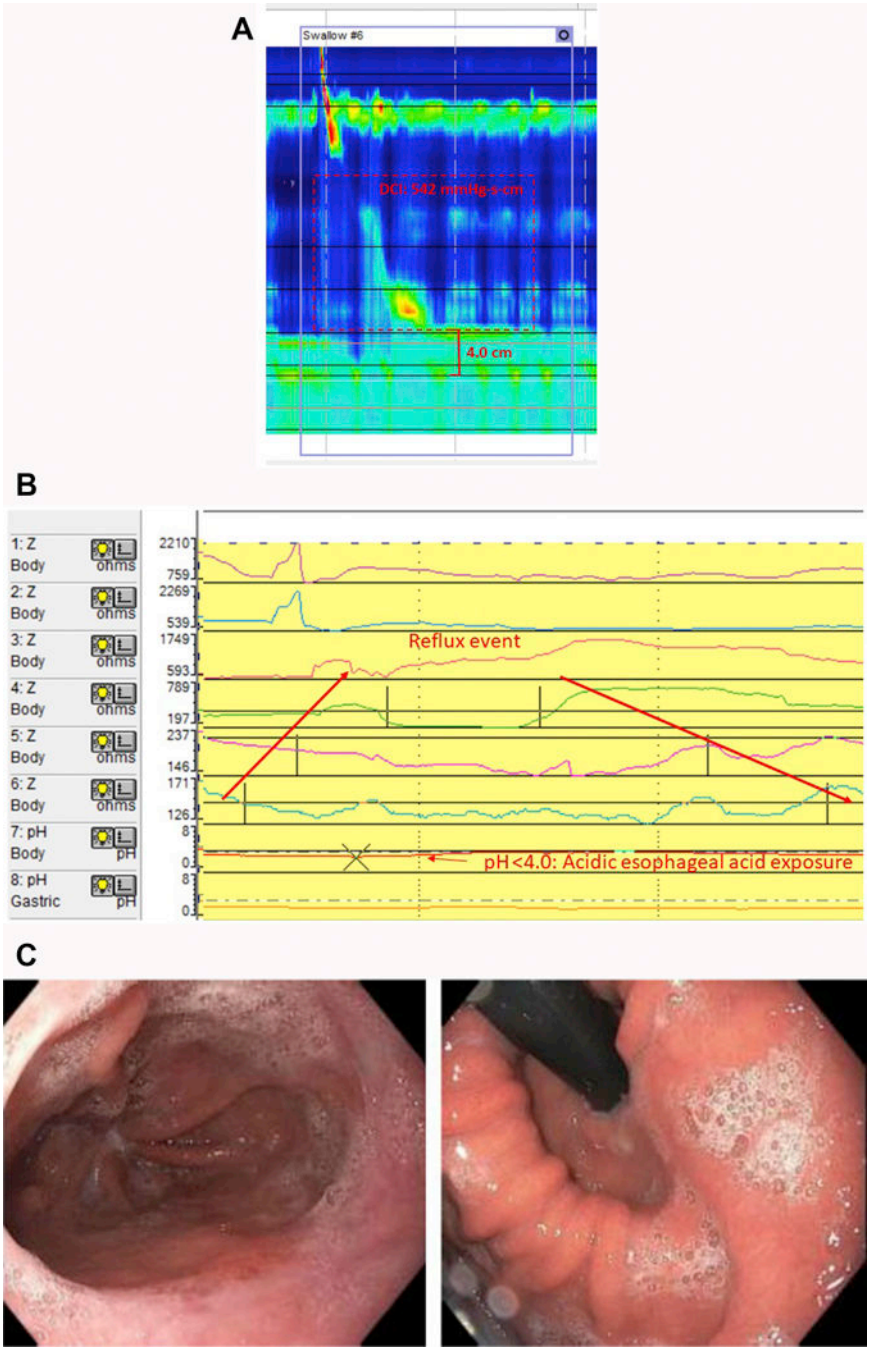

Figure 3.

Example of a patient with troublesome regurgitation and heartburn despite optimized PPI therapy for 8 weeks, and a positive wireless pH study performed off PPI previously, who on evaluation was noted to have a 4.0cm hiatal hernia and pathologic gastroesophageal reflux. Patient underwent a hernia repair and magnetic sphincter augmentation. (A) Image depicts high-resolution esophageal manometry study with a 4cm separation between her LES and crural diaphragm, with borderline intact peristaltic contractility. (B) Image depicts pH impedance on PPI testing with pathologic acid exposure and elevated number of reflux

events. (C) Image demonstrates endoscopic view in forward view and retroflexion of separation between the crural diaphragm and lower esophageal sphincter.

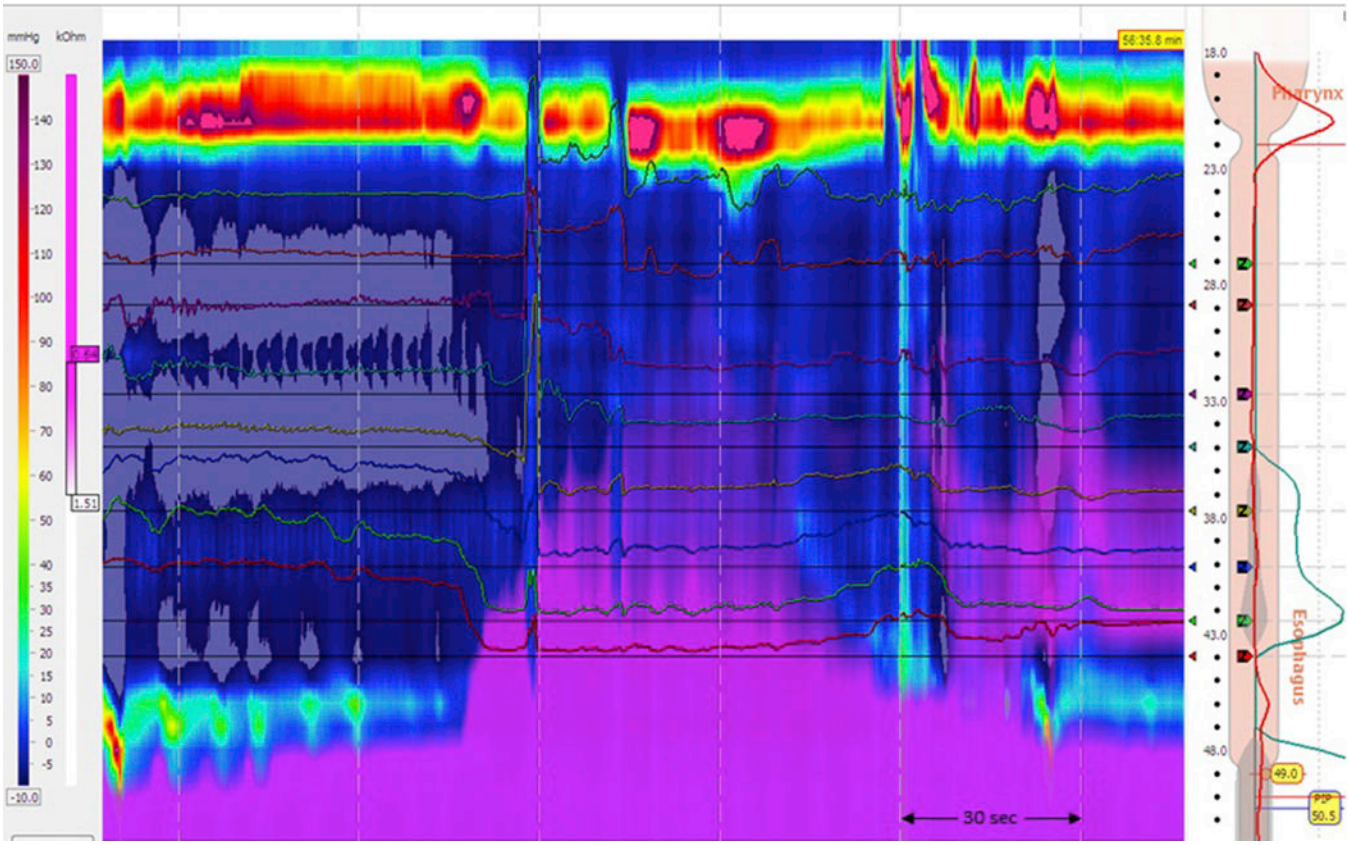

Figure 4.

Example of a transient lower esophageal sphincter relaxation (TLESR) with reflux episode. First there is inhibition of the crural diaphragm and the lower esophageal sphincter relaxes for more than 10 seconds and this is accompanied by a gastroesophageal reflux episode.

Table 1:

Diagnostic testing and management options based on pathophysiologic mechanism of refractory GERD

Pathophysiologic Mechanism	Presenting Symptoms	Diagnostic Testing	Potential Treatment Options
Increased TLESR	Regurgitation, heartburn, chest pain	Post-prandial highresolution esophageal manometry	GABA agonist
Hiatal hernia	Regurgitation, heartburn, chest pain	Barium esophagram; Upper GI endoscopy; High-resolution esophageal manometry	Hernia repair
Hypotensive LES	Regurgitation, heartburn, chest pain	High-resolution esophageal manometry	Surgical/endoluminal restoration
Reduced esophageal contractility	Dysphagia	High-resolution esophageal manometry	Limited options Consider muscarinic receptor agonist
Increased mucosal permeability	Heartburn	Mucosal impedance testing (investigational); pH impedance testing	
Persistent esophageal acid exposure on double dose PPI	Heartburn, chest pain	pH impedance testing on PPI	H2RA Consider switching to a CYP independent PPI
Delayed gastric emptying	Regurgitation, heartburn, chest pain	Gastric emptying study; Upper GI series with small bowel follow through	Roux-en-Y gastric bypass