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Management Options for Patients with GERD and Persistent Symptoms on Proton Pump Inhibitors: Recommendations from an Expert Panel

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Abstract

Background: The aim of this study was to assess expert gastroenterologists' opinion on treatment for distinct gastroesophageal reflux disease (GERD) profiles characterized by proton pump inhibitor (PPI) unresponsive symptoms.

Methods: Fourteen esophagologists applied the RAND/UCLA Appropriateness Method to hypothetical scenarios with previously demonstrated GERD (positive pH-metry or endoscopy) and persistent symptoms despite double-dose PPI therapy undergoing pH-impedance monitoring on therapy. *A priori* thresholds included: esophageal acid exposure (EAE) time >6.0%; symptom-reflux association: symptom index >50% and symptom association probability >95%; >80 reflux events; large hiatal hernia: >3cm. Primary outcomes were appropriateness of four invasive procedures (laparoscopic fundoplication, magnetic sphincter augmentation, transoral incisionless fundoplication, radiofrequency energy delivery) and preference for pharmacologic/behavioral therapy.

Results: Laparoscopic fundoplication was deemed appropriate for elevated EAE, and moderately appropriate for positive symptom-reflux association for regurgitation and a large hiatal hernia with normal EAE. Magnetic sphincter augmentation was deemed moderately appropriate for elevated EAE without a large hiatal hernia. Transoral incisionless fundoplication and radiofrequency energy delivery were not judged appropriate in any scenario.

Preference for non-invasive options was as follows: histamine-2 receptor antagonists for elevated EAE, transient lower esophageal sphincter relaxation inhibitors for elevated reflux episodes, and neuromodulation/behavioral therapy for positive symptom-reflux association.

Conclusion: For treatment of PPI unresponsive symptoms in proven GERD, expert esophagologists recommend invasive therapy only in the presence of abnormal reflux burden, with or without hiatal hernia, or regurgitation with positive symptom-reflux association and a large hiatus hernia. Non-invasive pharmacologic or behavioral therapies were preferred for all other scenarios.

Keywords

Refractory GERD; PPI non-response; LINX; EsophyX; Stretta

Introduction

Proton pump inhibitors (PPIs) are the mainstay pharmacologic treatment for gastroesophageal reflux disease (GERD). However, 10 to 40% of patients with GERD remain symptomatic despite PPI therapy.¹ Heterogeneous mechanisms may contribute to poor PPI response including a disrupted anti-reflux barrier, increased transient lower esophageal sphincter (LES) relaxations (TLESRs), reduced esophageal mucosal barrier function, impaired esophageal clearance and inadequate acid suppression.² Furthermore, reflux hypersensitivity and psychosocial factors may drive symptom perception regardless of whether or not excessive reflux burden is present.³⁻⁶

There is growing literature surrounding management options for the PPI non-responder population.⁷ Therapeutic strategies for refractory GERD include surgical approaches such as

magnetic sphincter augmentation and laparoscopic fundoplication, endoscopic approaches including transoral incisionless fundoplication and radiofrequency energy delivery to the LES⁷, pharmacologic neuromodulation, acid suppression, and TLESR inhibition, as well as cognitive behavioral therapy (CBT).⁸

Patients with previously demonstrated GERD and persistent symptoms despite PPI therapy often visit a gastroenterologist for physiologic testing and management. A nuanced understanding of both the literature and the patient's unique physiologic profile is critical to appropriate decision making, as inappropriate recommendations may compromise outcomes and patient safety. Thus, an evidence-based understanding of appropriate management options for patients with GERD and PPI unresponsive symptoms is needed. The objective of this initiative was to evaluate expert opinion, from a gastroenterology perspective, using a validated, prospective process, on the treatment of distinct GERD profiles characterized by PPI unresponsive symptoms.

Methods

Study Design

In this prospective study we employed the RAND/University of California, Los Angeles Appropriateness Method over six months (1/2017 to 6/2017) to assess the appropriateness of anti-reflux interventions.⁹

Fourteen esophagologists were invited to participate as expert panelists. Invitation criteria included leadership in the field of GERD, >20 peer-reviewed publications related to GERD, and prior involvement with GERD management consensus development. Northwestern REDCap was used to electronically distribute surveys and collect data.

Expert panelists participated in a three round process (moderator: RY). In round 1, panelists completed surveys regarding baseline characteristics and opinion on criteria for abnormal pH-impedance monitoring to be used in later polling. In round 2, panelists individually ranked the appropriateness of interventions for 9 distinct hypothetical patient scenarios described below. Prior to round 3 panelists received a literature review (bibliography in supplemental document). At the face-to-face round 3 meeting (May 2017, Chicago IL) panelists discussed each hypothetical patient scenario, round 2 results and the literature review, and re-ranked the appropriateness of intervention. In cases of 100% agreement, panelists provided performance thresholds, a minimum standard of performance below which the quality of care is considered suboptimal, to generate quality measures.

Hypothetical Patient

For each scenario, all hypothetical patients met the following baseline criteria: 1) persistent typical GERD symptoms of heartburn and/or regurgitation despite 8 weeks of double-dose PPI therapy, and 2) prior evidence of pathologic GERD evidenced by reflux esophagitis (Los Angeles Grade B or higher), Barrett's esophagus, and/or elevated esophageal acid exposure (EAE) on pH monitoring performed after withholding PPIs. In each scenario the hypothetical patient underwent pH-impedance monitoring on double-dose PPI therapy. Additionally, each hypothetical patient had a body mass index <35.0 kg/m², did not have

history of foregut surgery, and did not have any contraindications to potential anti-reflux interventions.

Nine patient profiles were considered based on multiple permutations of endoscopic and pH-impedance findings (see Table 1 & results for definitions): 1) elevated EAE with large hiatal hernia; 2) elevated EAE with small/absent hiatal hernia; 3) reflux sensitivity to heartburn with large hiatal hernia; 4) reflux sensitivity to regurgitation with large hiatal hernia; 5) reflux sensitivity to heartburn with small/absent hiatal hernia; 6) reflux sensitivity to regurgitation with small/absent hiatal hernia; 7) elevated reflux burden in absence of breakthrough acid or hypersensitivity with large hiatal hernia; 8) elevated reflux burden in absence of breakthrough acid or hypersensitivity with small/absent hiatal hernia; 9) negative testing.

Outcomes & Definitions:

The primary outcome was appropriateness of an intervention. An appropriate intervention is one in which the expected health benefit exceeds the expected negative consequences by a sufficiently wide margin that the procedure is worth doing, exclusive of cost.

The appropriateness of four invasive interventions (laparoscopic fundoplication, magnetic sphincter augmentation, transoral incisionless fundoplication, radiofrequency energy delivery) was ranked on a nine-point scale in which a score of 1 signified a definitely inappropriate intervention, 5 signified an uncertain/equivocal appropriate intervention, and 9 signified a definitely appropriate intervention. Final appropriateness was based on median rankings and the dispersion of rankings. Per RAND constructs, agreement was present when 80% or more of panelists' rankings fell in the same three point range: not appropriate (1–3), equivocal (4–6), or appropriate (7–9). If more than 20% of the rankings were in disparate categories this was indicative of disagreement.

The appropriateness of pharmacologic and behavioral interventions (histamine₂ receptor antagonist (H₂RA), TLESR inhibition, neuromodulation, and CBT) was assessed according to order of preference as 1st, 2nd, 3rd, or 4th choice, or not preferred. More than one intervention could be ranked as not preferred.

Results

Round 1: Baseline Characteristics & Definitions

All 14 invited esophagologists accepted the invitation and participated (mean age: 54.9±18.1 years, mean years in clinical practice: 25.9±10.8 years; 13 (93%) men) (Table 2).

In round 1, the majority of the expert panel selected the following thresholds as abnormal on pH-impedance monitoring performed on PPI therapy: EAE >6.0%, symptom-reflux association defined as symptom index >50% and symptom association probability >95%, and >80 reflux episodes (Table 1).⁴

Round 2 & 3: Ranking for Appropriateness of Interventions (Tables 3 & 4, Figure 1)

Permutations of patient profile and intervention yielded 56 hypothetical patient scenarios (36 related to invasive anti-reflux interventions, 20 related to non-invasive anti-reflux

interventions). Among the 36 hypothetical patient scenarios related to invasive anti-reflux interventions, the majority (69%) were ranked as inappropriate with >80% agreement, a minority (6%) were ranked as appropriate with >80% agreement, and the remaining 9 scenarios (25%) represented areas of <80% agreement or areas of overall disagreement. Overall rankings did not differ between Rounds 2 and 3 (Supplemental Tables).

Scenario 1) Breakthrough Acid with Large Hiatal Hernia: EAE>6.0%, hiatal hernia 3cm—Panelists unanimously agreed that Scenario 1 warrants referral for an anti-reflux intervention and assigned a mean performance benchmark of 95.0% to arrive at the following quality measure: *If a patient has abnormal EAE on a double-dose PPI and a large hiatal hernia, then additional anti-reflux measures should be pursued.*

All panelists agreed that laparoscopic fundoplication is an appropriate option for Scenario 1. While the majority agreed that magnetic sphincter augmentation with hiatal hernia repair may be appropriate for Scenario 1, some panelists did not rank magnetic sphincter augmentation as appropriate since it is not approved for use in hiatal hernia >3cm. Thus, magnetic sphincter augmentation was ranked as equivocal with disagreement. Both transoral incisionless fundoplication and radiofrequency energy delivery were ranked as inappropriate with >80% agreement in Scenario 1. Primary concerns related to the limited data for transoral incisionless fundoplication and radiofrequency energy delivery in the setting of a large hiatal hernia. These concerns and rankings for transoral incisionless fundoplication and radiofrequency energy delivery were reiterated in the subsequent hypothetical patient scenarios with a large hiatal hernia.

The order of preference for non-invasive options for Scenario 1 was: 1-H2RA and 2-TLESR inhibition; two experts felt that TLESR inhibition in the setting of a large hernia is less effective. A minority endorsed neuromodulation or CBT.

Scenario 2) Breakthrough Acid with Small/Absent Hiatal Hernia: EAE>6.0%, hiatal hernia<3cm—Panelists unanimously agreed that additional anti-reflux measures should be pursued for Scenario 2 and that laparoscopic fundoplication is appropriate. Seventy-seven percent agreed that magnetic sphincter augmentation is appropriate, transoral incisionless fundoplication was ranked as equivocal without agreement, and 92% agreed that radiofrequency energy delivery is inappropriate. Concerns surrounding transoral incisionless fundoplication and radiofrequency energy delivery were the lack of long-term data demonstrating sustained and consistent efficacy. The panel additionally noted that such a patient scenario was uncommon in daily practice.

Scenario 3) Reflux Sensitivity to Heartburn with Large Hiatal Hernia: EAE<6.0%, positive symptom-reflux association with heartburn, hiatal hernia 3cm—For Scenario 3 panelists disagreed as to whether additional anti-reflux measures should be pursued and whether laparoscopic fundoplication was inappropriate or equivocal. The majority agreed that transoral incisionless fundoplication, magnetic sphincter augmentation and radiofrequency energy delivery are inappropriate. Panelists asserted that post-intervention outcomes for reflux sensitivity with heartburn are poor.

Scenario 4) Reflux Sensitivity to Regurgitation with Large Hiatal Hernia: EAE<6.0%, positive symptom-reflux association with regurgitation, hiatal hernia 3cm—As opposed to Scenario 3, panelists agreed that additional anti-reflux measures should be pursued in this patient with regurgitation. The majority (69%) felt that laparoscopic fundoplication was appropriate whereas a minority (14%) felt that magnetic sphincter augmentation was appropriate. Transoral incisionless fundoplication and radiofrequency energy delivery were ranked as inappropriate with agreement for the reasons described in Scenarios 1 and 2.

The preference for non-invasive options for Scenario 3 and 4 combined was ordered as: 1-H2RA, 2-neuromodulation, 3-TLESR inhibition, and 4-CBT. In contrast to Scenarios 1 and 2, experts felt that there was a stronger indication to target visceral hypersensitivity and psychosocial factors through neuromodulation and CBT.

Scenario 5) Reflux Sensitivity to Heartburn with Small/Absent Hiatal Hernia: EAE<6.0%, positive symptom-reflux association with heartburn, hiatal hernia<3cm—Similar to Scenario 3, panelists disagreed as to whether anti-reflux measures should be pursued in this patient with heartburn. The majority agreed that transoral incisionless fundoplication, magnetic sphincter augmentation and radiofrequency energy delivery are inappropriate, and compared to Scenario 3, more panelists felt that laparoscopic fundoplication is inappropriate.

Scenario 6) Reflux Sensitivity to Regurgitation with Small/Absent Hiatal Hernia: EAE<6.0%, positive symptom-reflux association with regurgitation, hiatal hernia<3cm—As opposed to Scenario 4, fewer panelists felt that additional anti-reflux measures were warranted in the absence of a large hiatal hernia. Overall, all four invasive interventions were ranked as inappropriate.

The preference for non-invasive options for Scenario 5 and 6 was ordered as 1-CBT and 2-neuromodulation; 70% did not endorse H2RA.

Scenario 7) Elevated Reflux Burden with Large Hiatal Hernia: EAE<6.0%, negative symptom-reflux association, >80 reflux episodes, hiatal hernia 3cm—Half the panel felt that additional anti-reflux measures to restore the anti-reflux barrier and reduce reflux events were appropriate in Scenario 7. Laparoscopic fundoplication was ranked as equivocal with disagreement, while transoral incisionless fundoplication, magnetic sphincter augmentation and radiofrequency energy delivery were ranked as inappropriate with agreement for the reasons mentioned in Scenarios 1 and 2.

Scenario 8) Elevated Reflux Burden with Small/Absent Hiatal Hernia: EAE<6.0%, negative symptom-reflux association, >80 reflux episodes, hiatal hernia<3cm—The majority of the panel felt that additional anti-reflux measures should not be pursued in Scenario 8, and all four invasive interventions were ranked as inappropriate.

For both Scenarios 7 and 8 the preference for non-invasive treatment options was ordered as 1-TLESR inhibition, 2-neuromodulation and 3-CBT; many did not prefer H2RAs.

Scenario 9) Negative Testing: EAE<6.0%, negative symptom-reflux association, <80 reflux episodes—Panelists unanimously agreed that it is inappropriate to pursue additional anti-reflux measures for Scenario 9 and assigned a mean performance benchmark of 97.5% to arrive at the following quality measure: *If a patient has normal EAE on PPI therapy, negative symptom-reflux association, and a normal number of reflux events then additional anti-reflux measures should not be pursued.*

For Scenario 9 CBT and neuromodulation were the preferred non-invasive treatment options.

Discussion:

Patients previously diagnosed with GERD on the basis of endoscopy and/or pH monitoring that fail to improve with PPI therapy are not homogenous, and management needs to be personalized. Gastroenterologists must carefully select among treatment options based on underlying cause of symptoms, potential morbidity, likely therapeutic benefit, and durability. In this prospective three round process, 14 panelists ranked the appropriateness of four invasive anti-reflux options (laparoscopic fundoplication, magnetic sphincter augmentation, transoral incisionless fundoplication, radiofrequency energy delivery) and ranked their preference for pharmacologic and behavioral treatment options among hypothetical patient scenarios. In the majority of cases, an invasive anti-reflux intervention was ranked as an inappropriate option. In the case of breakthrough acid exposure, treatment recommendations aimed at restoring the anti-reflux barrier via laparoscopic fundoplication, with hernia repair if required, and possibly magnetic sphincter augmentation in the absence of a large hernia. When EAE was not elevated, most experts agreed that these patients fall on the spectrum of GERD and functional overlap, regardless of whether reflux sensitivity is present. In these cases, expert preference is to employ non-invasive strategies. An exception to this is the patient with reflux sensitivity to regurgitation symptoms and a large hiatal hernia, without breakthrough acid exposure, in which case experts would consider endorsing laparoscopic fundoplication. Radiofrequency energy delivery and transoral incisionless fundoplication were ranked as inappropriate options for most hypothetical scenarios.

For patients with previously demonstrated GERD and PPI unresponsive symptoms, a physiologic evaluation for elevated EAE despite PPI therapy is warranted. When EAE is elevated, laparoscopic fundoplication and magnetic sphincter augmentation are viable treatment options to restore anti-reflux barrier integrity, improve symptoms and reduce acid burden. While only laparoscopic fundoplication was ranked as appropriate when a large hernia is present, the majority of the panel was optimistic about magnetic sphincter augmentation and lack of available data was a main reason that the panel did not rank it as appropriate. As the literature evolves, we will need to revisit these rankings. For instance, a recent prospective multi-center study of 200 patients undergoing magnetic sphincter augmentation with repair of hernias >3cm reported significant post-operative improvement in quality of life and PPI discontinuation in 94% of patients.¹⁰ The expert panel did not

consider either invasive endoscopic option to be appropriate. Experts are reluctant to advocate for transoral incisionless fundoplication as the data suggest a decline in response rates over time.¹¹ With regard to radiofrequency energy delivery, the data are inconsistent; in some studies radiofrequency energy delivery did not outperform sham intervention in terms of acid exposure or LES pressure.¹² Nonetheless, experts are hopeful that effective endoscopic options will become available over time.

For patients with previously demonstrated GERD and PPI unresponsive symptoms but without elevated EAE on PPI therapy, visceral hypersensitivity and psychosocial factors often contribute to persistent symptoms.^{3, 5} In these scenarios, invasive anti-reflux procedures are unlikely to improve outcomes; instead, they risk increased morbidity, reduced quality of life and higher health care costs. Experts agree that neuromodulation and psychological approaches are first-line treatment options for reflux hypersensitivity and functional esophageal disorders. Tricyclic antidepressants and selective serotonin reuptake inhibitors have been shown to improve symptoms in functional chest pain and globus; one randomized controlled trial of patients with reflux hypersensitivity reported a significant improvement in symptomatic heartburn with citalopram.^{13, 14} Behavioral modification and relaxation therapy are also potentially effective. In a study of 9 patients with functional heartburn, esophageal-directed hypnotherapy was associated with significant improvements in symptoms, visceral anxiety and quality of life.¹⁵ In the setting of breakthrough acid exposure, or reflux hypersensitivity and a hiatal hernia, experts would trial bedtime H2RAs based on some data demonstrating a reduction in nocturnal acid breakthrough.⁸ Experts ranked TLESR inhibition as a first-line option in the case of elevated reflux burden. While supporting evidence is limited, a recent abstract reported reduced number of reflux episodes with baclofen compared to placebo in PPI unresponsive GERD.¹⁶

Current challenges in the field include the deficiency of high quality data and heterogeneity of study populations. Moving forward, standardized criteria, such as those applied to our hypothetical patients in this study, should be used to subtype PPI non-responsive GERD, allowing for more specific consideration of therapeutic options. Furthermore, research is needed to identify effective treatment options targeting alternative mechanisms of GERD, such as promotility agents to augment esophageal clearance and gastric emptying, and mechanisms to reduce bile acid reflux.

There are several limitations to this work. While we attempted to subtype the hypothetical patient according to pH-impedance results and presence of hernia, there are various factors that gastroenterologists must consider in real world practice including physiologic properties (i.e., gastric and esophageal motility patterns), endoscopic features on PPI (i.e., esophagitis), symptom presentations (i.e., atypical, extraesophageal) and patient characteristics (i.e., age, comorbidities, body mass index, personal preference, life expectancy, psychosocial factors). Also, these data represent one perspective, that of the gastroenterologist-esophagologist, and it is possible and maybe even likely that the therapeutic endoscopist or surgeon perspective may differ. Furthermore, when working with 14 esophageal experts potential conflicts of interest are unavoidable. To maintain transparency and reduce bias we reported industry support and personal practice patterns (Table 2).

In conclusion, a gastroenterologist should provide a personalized treatment approach for patients with previously demonstrated GERD and persistent symptoms despite double-dose PPI therapy undergoing pH-impedance monitoring on PPI therapy. Expert panel recommendation is: 1) Invasive therapy requires abnormal reflux burden in the form of elevated EAE (with or without a large hiatal hernia), or positive symptom-reflux association for regurgitation with large hiatal hernia (laparoscopic fundoplication for all three scenarios; magnetic sphincter augmentation for small/absent hiatal hernia), 2) Transoral incisionless fundoplication and radiofrequency energy delivery are not endorsed in any of the evaluated PPI unresponsive profiles, and 3) Overall, medical/behavioral therapies are preferred for the other scenarios.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

GERD	Gastroesophageal reflux disease
PPI	Proton pump inhibitor
LES	Lower esophageal sphincter
TLESR	Transient lower esophageal sphincter relaxation
CBT	Cognitive behavioral therapy
EAE	Esophageal acid exposure

References:

1. Baldi F PPI-Refractory GERD: an Intriguing, Probably Overestimated, Phenomenon. *Curr Gastroenterol Rep* 2015;17:451. [PubMed: 26122249]
2. Gyawali CP, Roman S, Bredenoord AJ, Fox M, Keller J, Pandolfino JE, Sifrim D, Tatum R, Yadlapati R, Savarino E, International GCWG. Classification of esophageal motor findings in gastro-esophageal reflux disease: Conclusions from an international consensus group. *Neurogastroenterol Motil* 2017;29.
3. Aziz Q, Fass R, Gyawali CP, Miwa H, Pandolfino JE, Zerbib F. Functional Esophageal Disorders. *Gastroenterology* 2016.
4. Roman S, Gyawali CP, Savarino E, Yadlapati R, Zerbib F, Wu J, Vela M, Tutuian R, Tatum R, Sifrim D, Keller J, Fox M, Pandolfino JE, Bredenoord AJ, group Gc. 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.
5. Yadlapati R, Tye M, Keefer L, Kahrilas PJ, Pandolfino JE. Psychosocial Distress and Quality of Life Impairment Are Associated With Symptom Severity in PPI Non-Responders With Normal Impedance-pH Profiles. *Am J Gastroenterol* 2017.

6. Hussain ZH, Henderson EE, Maradey-Romero C, George N, Fass R, Lacy BE. The Proton Pump Inhibitor Non-Responder: A Clinical Conundrum. *Clin Transl Gastroenterol* 2015;6:e115. [PubMed: 26448456]
7. Hillman L, Yadlapati R, Whitsett M, Thuluvath AJ, Berendsen MA, Pandolfino JE. Review of antireflux procedures for proton pump inhibitor nonresponsive gastroesophageal reflux disease. *Dis Esophagus* 2017;30:1–14.
8. Hillman L, Yadlapati R, Thuluvath AJ, Berendsen MA, Pandolfino JE. A review of medical therapy for proton pump inhibitor nonresponsive gastroesophageal reflux disease. *Dis Esophagus* 2017;30:1–15.
9. Fitch K, Aguilar MD, Burnand B, La Calle JR, Lazaro P, van het Loo M, McDonnell J, Vader J, Kahan JP. The RAND/UCLA Appropriateness Method User's Manual. Los Angeles, CA, 2001.
10. Buckley FP, 3rd, Bell RCW, Freeman K, Doggett S, Heidrick R. Favorable results from a prospective evaluation of 200 patients with large hiatal hernias undergoing LINX magnetic sphincter augmentation. *Surg Endosc* 2017.
11. Huang X, Chen S, Zhao H, Zeng X, Lian J, Tseng Y, Chen J. 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]
12. Fass R, Cahn F, Scotti DJ, Gregory DA. Systematic review and meta-analysis of controlled and prospective cohort efficacy studies of endoscopic radiofrequency for treatment of gastroesophageal reflux disease. *Surg Endosc* 2017.
13. Viazis N, Keyoglou A, Kanellopoulos AK, Karamanolis G, Vlachogiannakos J, Triantafyllou K, Ladas SD, Karamanolis DG. Selective serotonin reuptake inhibitors for the treatment of hypersensitive esophagus: a randomized, double-blind, placebo-controlled study. *Am J Gastroenterol* 2012;107:1662–7. [PubMed: 21625270]
14. Yamasaki T, Fass R. Reflux Hypersensitivity: A New Functional Esophageal Disorder. *J Neurogastroenterol Motil* 2017;23:495–503. [PubMed: 28992673]
15. Riehl ME, Pandolfino JE, Palsson OS, Keefer L. Feasibility and acceptability of esophageal-directed hypnotherapy for functional heartburn. *Dis Esophagus* 2016;29:490–6. [PubMed: 25824436]
16. Pauwels A, Boeckstaens V, Broers C, Iven J, Zhao D, Vanuytsel T, Tack J. A double-blind, placebo-controlled trial with baclofen for the treatment of refractory gastro-esophageal reflux disease. *Gastroenterology* 2017;152:S767.

What is Current Knowledge

1. Patients with GERD often do not derive complete symptom relief with PPI therapy
2. Surgical, endoscopic, pharmacologic and psychologic treatment options exist for PPI unresponsive GERD
3. Selection of anti-reflux management for PPI unresponsive GERD is controversial and complex

What is New Here

1. Management of PPI unresponsive GERD should be personalized based on physiology, symptoms, and patient preference
2. Invasive therapy (fundoplication or magnetic sphincter augmentation) is best reserved for patients with abnormal esophageal acid exposure, or patients suffering from regurgitation with a combination of a hiatal hernia and a positive symptom-reflux association
3. Neuromodulation or cognitive behavioral therapy are preferred therapies for reflux hypersensitivity
4. Transient lower esophageal sphincter relaxation inhibition is preferred for cases with excessive reflux episodes on reflux testing

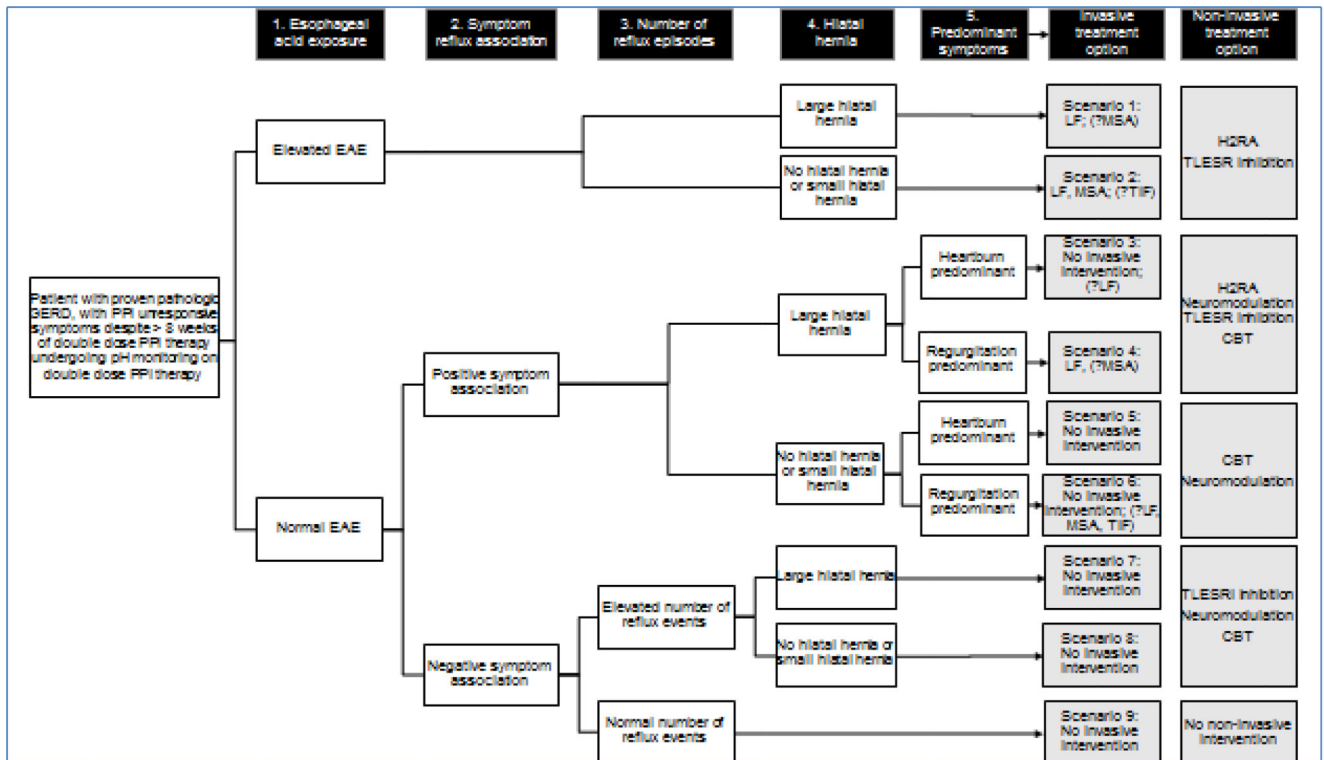


Figure 1. Personalized decision making flow chart based on pH-impedance monitoring results on PPI therapy. The decision points are ordered as: 1) Is esophageal acid exposure elevated?, 2) Is symptom association positive?, 2) Is there an elevated number of reflux events? Each decision point is further personalized on the basis of hiatal hernia. In the case of positive symptom association, the decision is further personalized on the type of predominant symptom (heartburn versus regurgitation). Proton pump inhibitor (PPI); Gastroesophageal reflux disease (GERD); Laparoscopic fundoplication (LF); Magnetic sphincter augmentation (MSA); Transoral incisionless fundoplication (TIF); Histamine2 receptor antagonist (H2RA); Transient lower esophageal sphincter relaxation (TLESR); Cognitive behavioral therapy (CBT).

Table 1.

Definition and Criteria for Physiologic Profiles

Scenario	Definition	Criteria per Round 1
Breakthrough acid	Elevated esophageal acid exposure time (% time pH < 4.0)	>6.0%
Large hiatal hernia	Size of hiatal hernia	>3cm
Reflux sensitivity	Positive symptom association (in absence of breakthrough acid)	Symptom index >50% and symptom association probability >95%
Elevated reflux burden	Elevated number of reflux events (in absence of reflux hypersensitivity & breakthrough acid)	>80

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Table 2.

Baseline Characteristics of Expert Panel

Characteristics	N=14
Age (years), mean (SD)	54.9 (18.1)
Number of years in practice, mean (SD)	25.9 (10.8)
Number of publications related to GERD, mean (SD)	97 (86)
Number of annual referrals by panelist, mean (SD)	
Laparoscopic fundoplication	7.0 (4.7)
Magnetic sphincter augmentation	3.2 (4.5)
Transoral incisionless fundoplication	0.0
Radiofrequency energy delivery	0.3 (0.6)
Radiofrequency energy delivery procedures performed annually, mean (SD)	0.0
Transoral incisionless fundoplication procedures performed annually, mean (SD)	0.1 (0.3)
Industry support from Torax, n (%)	
\$0	7 (50%)
\$1,000 to 10,000	6 (43%)
>\$10,000	1 (7%)
Industry support from Endogastric Solutions, n (%)	
\$0	12 (86%)
\$1,000 to 10,000	2 (14%)
>\$10,000	0 (0%)
Industry support from Mederi, n (%)	
\$0	12 (86%)
\$1,000 to 10,000	2 (14%)
>\$10,000	0
Support from proton pump inhibitor pharmaceutical industry, n (%)	
\$0	6 (43%)
\$1,000 to 10,000	5 (36%)
>\$10,000	3 (21%)

Table 3.

Final Ranking for Appropriateness

Hypothetical Patient Scenario	Ranking for appropriateness (% Agreement, Median (Min-Max))			
	LF	MSA	TIF	RFED
1) Breakthrough Acid, Large Hiatal Hernia	100%, 9 (7-9)	15%, 5 (1-7)	0%, 1 (1-5)	0%, 1 (1-2)
2) Breakthrough Acid, Small or No Hiatal Hernia	100%, 8 (7-9)	77%, 7 (3-9)	0%, 4 (1-6)	8%, 1 (1-8)
3) Reflux Sensitivity, Large Hiatal Hernia, Heartburn	8%, 4 (1-7)	0%, 1 (1-4)	0%, 1 (1-6)	0%, 1 (1-2)
4) Reflux Sensitivity, Large Hiatal Hernia, Regurgitation	69%, 7 (5-9)	8%, 3 (1-7)	0%, 2 (1-5)	0%, 1 (1-2)
5) Reflux Sensitivity, Small or No Hiatal Hernia, Heartburn	0%, 2 (1-5)	0%, 1 (1-6)	0%, 1 (1-4)	0%, 1 (1-2)
6) Reflux Sensitivity, Small or No Hiatal Hernia, Regurgitation	8%, 4 (1-7)	8%, 1 (1-8)	8%, 1 (1-7)	0%, 1 (1-4)
7) Elevated Reflux Burden, Large Hiatal Hernia	0%, 4 (1-6)	0%, 1 (1-4)	0%, 1 (1-4)	0%, 1 (1-2)
8) Elevated Reflux Burden, Small or No Hiatal Hernia	0%, 1 (1-4)	0%, 1 (1-4)	0%, 1 (1-5)	0%, 1 (1-2)
9) Absence of breakthrough acid, reflux hypersensitivity or elevated reflux burden	0%, 1 (1-1)	0%, 1 (1-1)	0%, 1 (1-1)	0%, 1 (1-1)

Data presented as % agreement, Median (Min-Max). Green cells represent agreement for appropriateness, blue cells represent majority agreement for appropriateness not meeting >80% criteria, gray cells represent disagreement, and red cells represent agreement for inappropriateness.

Laparoscopic fundoplication (LF); Magnetic sphincter augmentation (MSA); Transoral incisionless fundoplication (TIF); Radiofrequency energy delivery (RFED)

Table 4.

Expert Panelist Preference for Non-Invasive Anti-Reflux Interventions

Hypothetical Patient Scenario	Order of Expert Preference
Breakthrough Acid, Large Hiatal Hernia	1. H2RA (92% 1 st choice) 2. TLESR inhibition (77% 2 nd choice) 3. Neuromodulation (84% not preferred) 4. CBT (92% not preferred)
Breakthrough Acid, Small or No Hiatal Hernia	1. H2RA (85% 1 st choice) 2. TLESR inhibition (69% 2 nd choice) 3. Neuromodulation (62% not preferred) 4. CBT (62% not preferred)
Reflux Sensitivity, Large Hiatal Hernia	1. H2RA (38% 1 st choice) 2. Neuromodulation (38% 2 nd choice) 3. TLESR inhibition (46% 3 rd choice) 4. CBT (38% 4 th choice)
Reflux Sensitivity, Small or No Hiatal Hernia	1. CBT (8% 1 st choice) 2. Neuromodulation (46% 2 nd choice) 3. TLESR inhibition (39% not preferred) 4. H2RA (46% not preferred)
Elevated Reflux Burden, Large Hiatal Hernia	1. TLESR inhibition (46% 1 st choice) 2. Neuromodulation (31% 2 nd choice) 3. CBT (31% not preferred) 4. H2RA (70% not preferred)
Elevated Reflux Burden, Small or No Hiatal Hernia	1. TLESR inhibition (62% 1 st choice) 2. Neuromodulation (31% 2 nd choice) 3. CBT (31% 3 rd choice) 4. H2RA (70% not preferred)

Cognitive behavioral therapy (CBT); Histamine-2 receptor antagonist (H2RA), Transient lower esophageal sphincter relaxation (TLESR). Data in parenthesis indicates the preference option (1st, 2nd, 3rd, 4th or not preferred) with highest agreement among panel.