Approach to Refractory GERD

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CLINICAL PRACTICE UPDATE

AGA Clinical Practice Update on Functional Heartburn: Expert Review

Ronnie Fass,[1] Frank Zerbib,[2] and C. Prakash Gyawali[3]

Am J Gastroenterol 2022;117:27–56.

CME

ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease

Philip O. Katz, MD, MACG[1], Kerry B. Dunbar, MD, PhD[2,3], Felice H. Schnoll-Sussman, MD, FACG[1], Katarina B. Greer, MD, MS, FACG[4], Rena Yadlapati, MD, MSHS[5] and Stuart Jon Spechler, MD, FACG[6,7]

Recent advances in clinical practice

Updates to the modern diagnosis of GERD: Lyon consensus 2.0

Gyawali CP, *et al*. *Gut* 2024;**73**:361–371. doi:10.1136/gutjnl-2023-330616

- It has been suggested that up to 40% of patients treated with PPI will report persistent symptoms of heartburn and regurgitation, with negative effects on quality of life

Symptom presentations

- Heartburn (more likely to respond to PPIs)
- regurgitation
- extraesophageal symptoms.

Table 4. Potential mechanisms underlying symptoms suspected due to GERD but refractory to PPI therapy

Despite PPI therapy, abnormal acid reflux persists and is causing symptoms
There is reflux hypersensitivity, a condition in which PPIs have normalized esophageal acid exposure, but "physiologic" reflux episodes (acidic or nonacidic) nevertheless are strongly associated with and evoke symptoms
The symptoms are not due to GERD, but are caused by esophageal disorders other than GERD (e.g., EoE and achalasia)
The symptoms are not due to GERD, but are caused by nonesophageal disorders (e.g., gastroparesis, rumination, and heart disease)
The symptoms are functional (i.e., not because of GERD or any other identifiable histopathologic, motility, or structural abnormality).

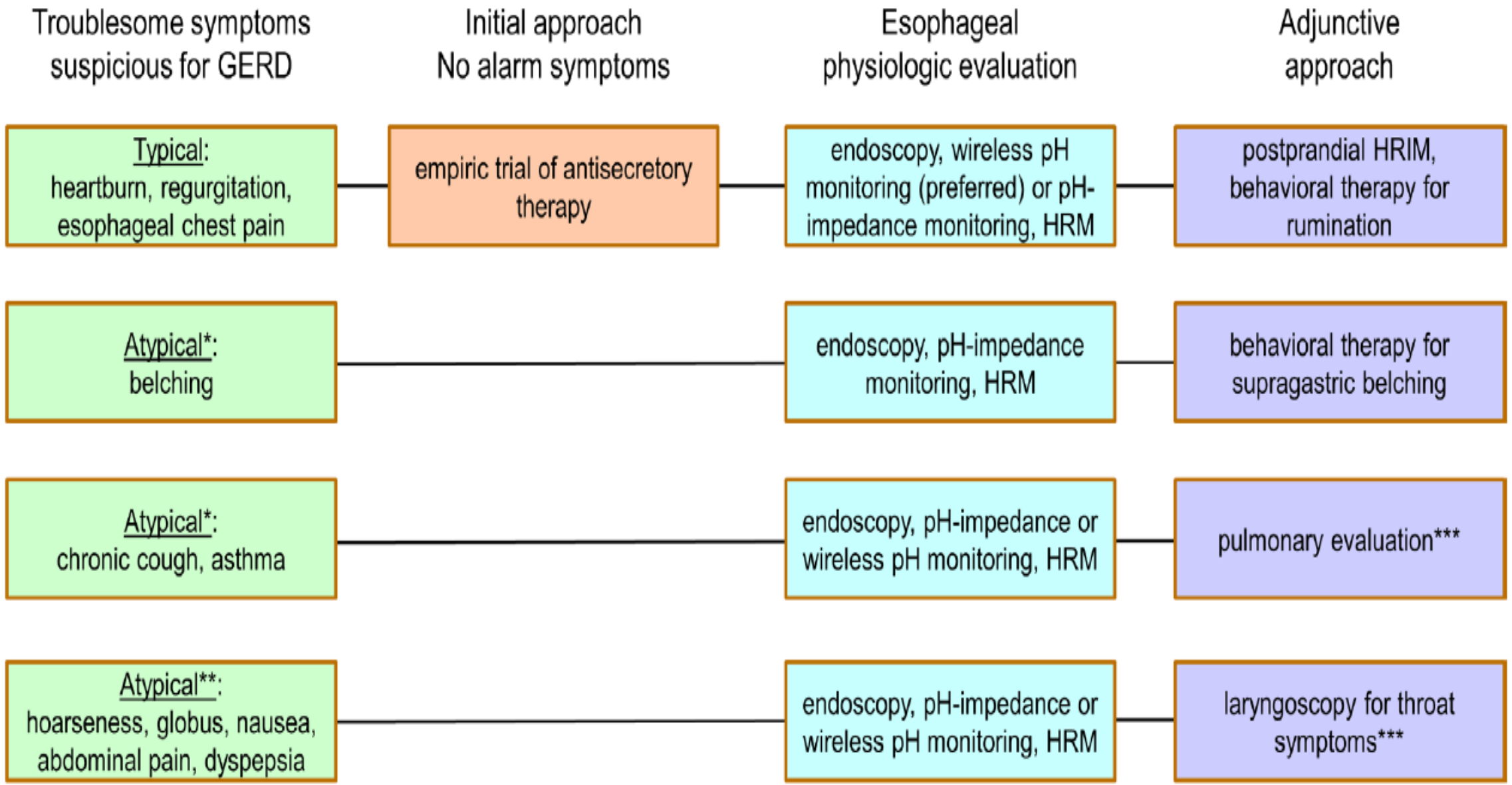
EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

- One group is patients with symptoms suspected to be GERD-related who have been empirically treated with a PPI (Unproven GERD)

- Group of patients have objective evidence of GERD, with endoscopic findings of erosive esophagitis or Barrett's esophagus and/or reflux testing showing abnormal esophageal acid exposure(Proven GERD)

Optimization of PPI Therapy

- Verifying compliance
- The PPI is taken 30 to 60 minutes before the first meal of the day and before the first and dinner meal
- Twice-daily PPI therapy is superior to once-daily double-dose PPI


Troublesome symptoms suspicious for GERD
Initial approach No alarm symptoms
Esophageal physiologic evaluation
Adjunctive approach
Typical: heartburn, regurgitation, esophageal chest pain
empiric trial of antisecretory therapy
endoscopy, wireless pH monitoring (preferred) or pH-impedance monitoring, HRM
postprandial HRIM, behavioral therapy for rumination
Atypical*: belching
endoscopy, pH-impedance monitoring, HRM
behavioral therapy for supragastric belching
Atypical*: chronic cough, asthma
endoscopy, pH-impedance or wireless pH monitoring, HRM
pulmonary evaluation***
Atypical**: hoarseness, globus, nausea, abdominal pain, dyspepsia
endoscopy, pH-impedance or wireless pH monitoring, HRM
laryngoscopy for throat symptoms***

Endoscopy

- Evaluate alternative diagnoses
- Identify evidence of GERD
- Performing endoscopy after a PPI holiday (2-4 weeks) might increase the yield for identifying erosive esophagitis or determine eosinophilic esophagitis.

- LA grades B, C and D esophagitis,
- biopsy proven Barrett’s esophagus and
- peptic stricture are conclusive for a diagnosis of GERD.

As many as 70% of symptomatic patients have endoscopically normal esophageal mucosa

- Histopathology has a low diagnostic yield, and only provides helpful clues to an underlying inflammatory mucosal disorder such as eosinophilic esophagitis

- Mucosal damage from reflux can lead to dilated intracellular spaces, (requires electron microscopy for optimal characterization)

Reflux monitoring

Wireless or Catheter based

- Wireless pH monitoring allows for up to 96 hours of pH monitoring, which can overcome day-to-day variation in reflux burden, and may guide PPI discontinuation if reflux is physiologic.

  Placed during index endoscopy ,provide highest diagnostic yield better patient tolerance

- Catheter based pH and pH-impedance monitoring requires HRM to localize the LES , and only provides a one-day assessment

Metrics

- The percent time distal esophageal pH is < 4.0 (AET)

Increasing AET correlates with increasing severity of esophagitis and increased length of intestinal metaplasia.

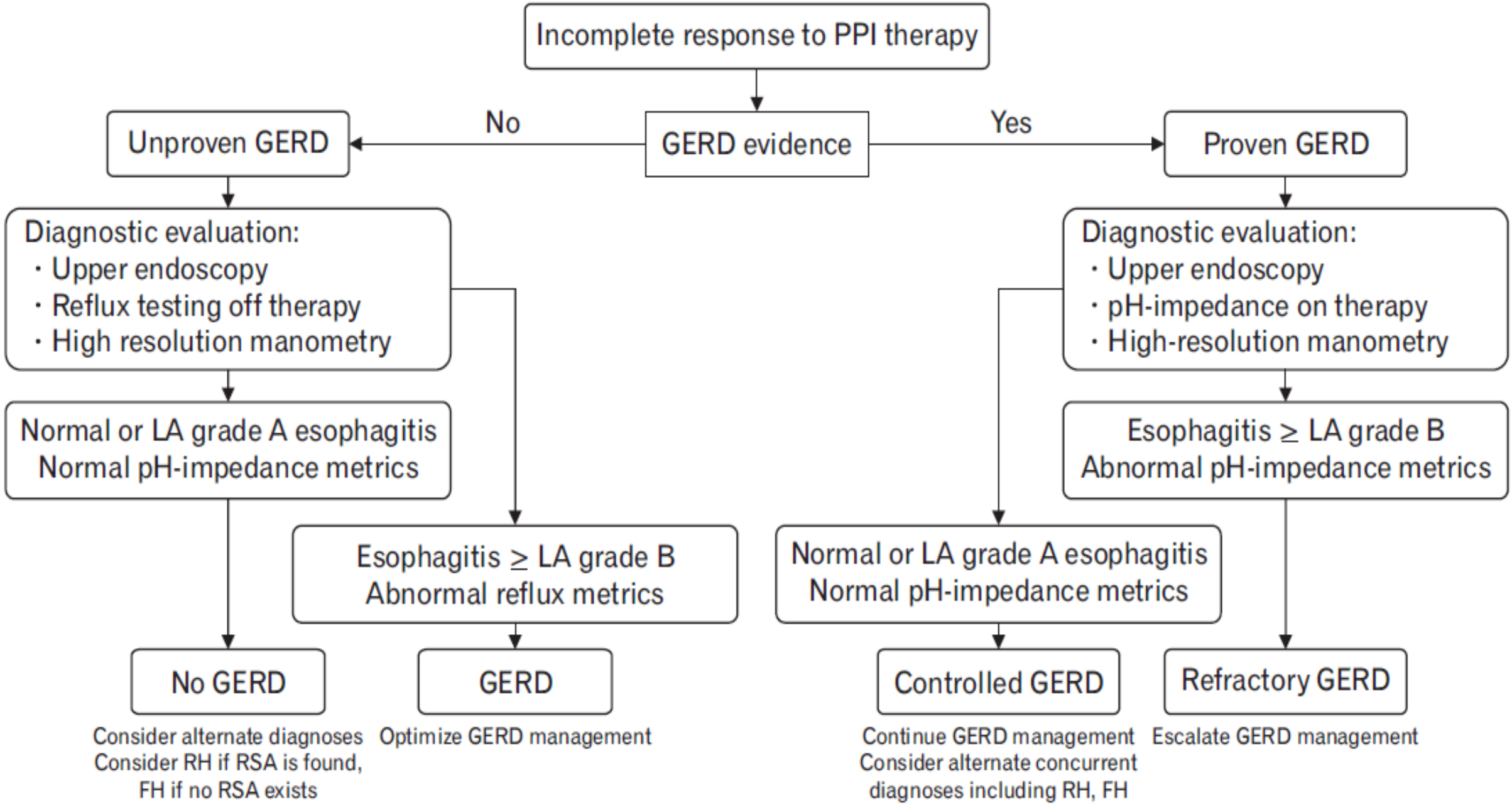
- Symptom correlation with reflux episodes (SI , SAP)

- PH-impedance distinguish ongoing acid reflux, weakly acidic, non-acidic reflux, adequate acid control but ongoing symptoms, assessment of baseline impedance, proximal extent of refluxate.

OFF Vs On PPI

- OFF PPIs if the diagnosis of GERD has not been established by a prior pH monitoring study or an endoscopy showing long-segment Barrett's esophagus or severe reflux esophagitis or for considering surgery.

- ON PPIs for patients with an established diagnosis of GERD whose symptoms have not responded adequately to twice-daily PPI therapy.


Incomplete response to PPI therapy
GERD evidence
No
Yes
Unproven GERD
Proven GERD
Diagnostic evaluation:
· Upper endoscopy
· Reflux testing off therapy
· High resolution manometry
Diagnostic evaluation:
· Upper endoscopy
· pH-impedance on therapy
· High-resolution manometry
Normal or LA grade A esophagitis
Normal pH-impedance metrics
Esophagitis ≥ LA grade B
Abnormal pH-impedance metrics
Esophagitis ≥ LA grade B
Abnormal reflux metrics
Normal or LA grade A esophagitis
Normal pH-impedance metrics
No GERD
GERD
Controlled GERD
Refractory GERD
Consider alternate diagnoses
Consider RH if RSA is found,
FH if no RSA exists
Optimize GERD management
Continue GERD management
Consider alternate concurrent
diagnoses including RH, FH
Escalate GERD management

Interpretation (Lyon consensus 2.0)

- AET < 4%, total reflux episodes < 40 ,mean nocturnal baseline impedance (MNBI) > 2500 ohms (Physiologic acid burden)

- AET > 6% and total reflux episodes > 80 (Conclusively abnormal)

- AET 4-6% and/or 40-80 total reflux episodes (Inconclusive)

Adjunctive evidence such as low MNBI, reflux-symptom association

Wireless pH monitoring

- AET<4.0% on all days of with negative reflux-symptom association excludes GERD.
- AET>6.0% for ≥2 days is diagnostic of GERD and supports treatment for GERD.
- AET<4.0% on all days with a positive reflux-symptom association meets criteria for reflux hypersensitivity.

- Total AET>6% off PPI (diagnostic of GERD)
- AET>4% and >80 reflux episodes/day on PPI (refractory GERD)
- *Baseline impedance of <1500 ohms (adjunctive evidence)*
- *>2500 ohms (evidence against pathological GERD)*
- normal MNBI and postreflux swallow-induced peristaltic wave index are additional supportive evidence

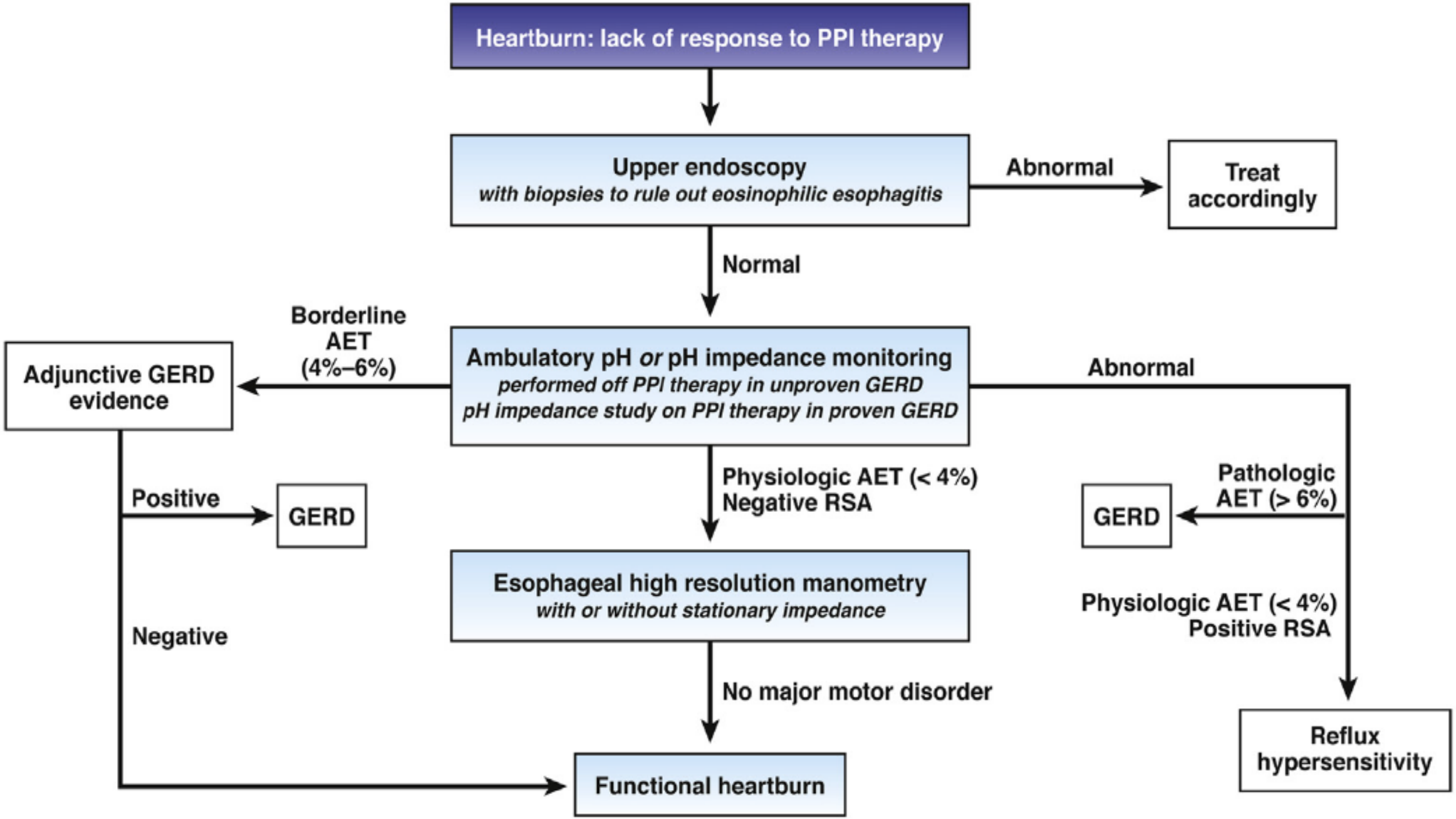
Symptom association

- In patients with normal AET, symptom index (SI), and symptom association probability (SAP) are used.
- SI is the proportion of symptoms that are reflux-related (positive if >50%).
- SAP is the probability that the observed temporal relationship between symptoms and reflux has not occurred by chance (positive if 95%).

- Functional heartburn can be reliably diagnosed in a patient with refractory heartburn, normal endoscopy, and AET, and negative SI and SAP.

PPIs have no therapeutic value in functional heartburn, the exception being proven GERD that overlaps with functional heartburn.

- Reflux hypersensitivity can be diagnosed if both SI and SAP are positive.


Heartburn: lack of response to PPI therapy
Upper endoscopy
with biopsies to rule out eosinophilic esophagitis
Abnormal
Treat accordingly
Normal
Borderline AET (4%–6%)
Adjunctive GERD evidence
Ambulatory pH or pH impedance monitoring
performed off PPI therapy in unproven GERD
pH impedance study on PPI therapy in proven GERD
Abnormal
Positive
GERD
Physiologic AET (< 4%)
Negative RSA
Pathologic AET (> 6%)
GERD
Esophageal high resolution manometry
with or without stationary impedance
Physiologic AET (< 4%)
Positive RSA
Negative
No major motor disorder
Functional heartburn
Reflux hypersensitivity

96 hour capsule based pH monitoring off PPI therapy in patients with persistent typical symptoms despite PPI treatment

- Patients with two or more days with AET >4 percent were unlikely to be able to stop PPIs.
- Those with a normal study on all four days were the group with the highest likelihood of being able to discontinue PPIs

Esophageal Manometry

- Accurate localization of the LES for placement of pH catheters

- Detect suboptimal EGJ barrier function, abnormal EGJ morphology based on degree of separation between the LES and crural diaphragm, and compromised esophageal body peristaltic function.

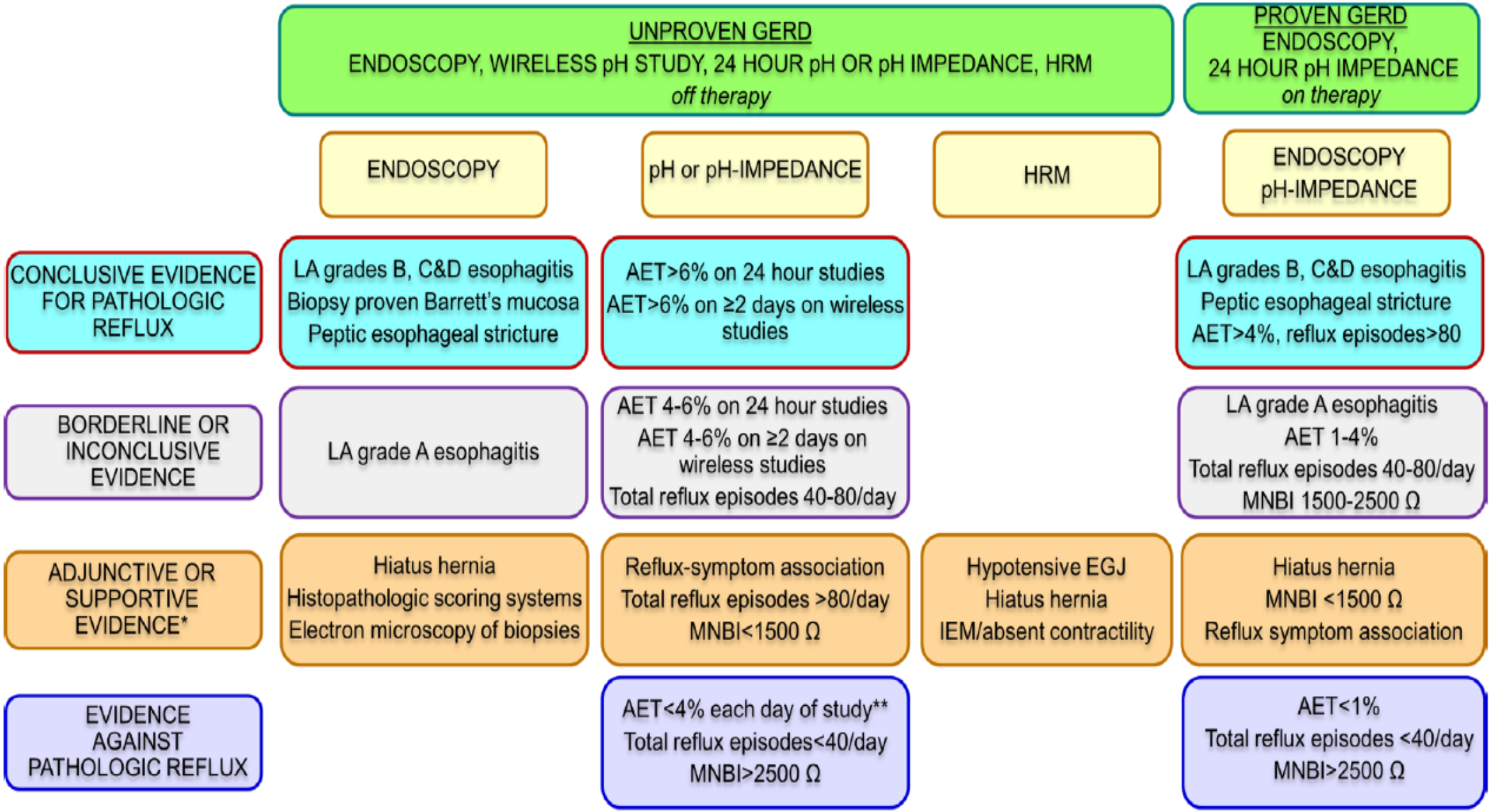
Esophageal Manometry

- Esophageal hypomotility (ineffective esophageal motility [IEM] and absent contractility) associate with increasing severity of GERD, hypothesized to be related to poor refluxate clearance, especially in the supine position.
- Peristaltic integrity , with increasing length of esophageal body peristaltic breaks (fragmented and failed peristalsis) associating better with abnormal AET in comparison to weak swallows.

Esophageal Manometry

- Achalasia (1-3% of refractory GERD)
- Esophageal spasm

- Rumination
- Supragastric belching


UNPROVEN GERD
ENDOSCOPY, WIRELESS pH STUDY, 24 HOUR pH OR pH IMPEDANCE, HRM
off therapy
PROVEN GERD
ENDOSCOPY,
24 HOUR pH IMPEDANCE
on therapy
ENDOSCOPY
pH or pH-IMPEDANCE
HRM
ENDOSCOPY
pH-IMPEDANCE
CONCLUSIVE EVIDENCE FOR PATHOLOGIC REFLUX
LA grades B, C&D esophagitis
Biopsy proven Barrett's mucosa
Peptic esophageal stricture
AET>6% on 24 hour studies
AET>6% on ≥2 days on wireless studies
LA grades B, C&D esophagitis
Peptic esophageal stricture
AET>4%, reflux episodes>80
BORDERLINE OR INCONCLUSIVE EVIDENCE
LA grade A esophagitis
AET 4-6% on 24 hour studies
AET 4-6% on ≥2 days on wireless studies
Total reflux episodes 40-80/day
LA grade A esophagitis
AET 1-4%
Total reflux episodes 40-80/day
MNBI 1500-2500 Ω
ADJUNCTIVE OR SUPPORTIVE EVIDENCE*
Hiatus hernia
Histopathologic scoring systems
Electron microscopy of biopsies
Reflux-symptom association
Total reflux episodes >80/day
MNBI<1500 Ω
Hypotensive EGJ
Hiatus hernia
IEM/absent contractility
Hiatus hernia
MNBI <1500 Ω
Reflux symptom association
EVIDENCE AGAINST PATHOLOGIC REFLUX
AET<4% each day of study**
Total reflux episodes<40/day
MNBI>2500 Ω
AET<1%
Total reflux episodes <40/day
MNBI>2500 Ω

When Should a Patient with GERD Be Referred for Surgery?

Clinically significant GERD	To control typical symptoms or severe esophagitis
Atypical GERD	when there is objective evidence to attribute such symptoms to reflux.
Medical treatment failure	Continued symptoms despite double-dose PPI for over six months should serve as a warning that symptoms may not be due to excess esophageal acid exposure. Such patients should be properly assessed before antireflux surgery.
Medication intolerance /Noncompliance/Prospect of lifelong medical therapy	Despite successful medical management, patients who are intolerant of, noncompliant with, or do not wish to continue lifelong medical therapy may opt for antireflux surgery due to quality of life considerations.

Surgical outcome

- Postoperative symptoms of dysphagia and gas bloating occur in 11 and 40 percent.
- Antireflux surgery has a failure rate of 10 to 15 percent.
- The main symptoms of operative failure are recurrent reflux symptoms and/or dysphagia.

- Approximately 5 to 10 percent of patients will need revisional surgery after laparoscopic fundoplication.

- 90 to 95 percent of adult patients are satisfied with the results of their surgery.

  (laparoscopic fundoplication performed by experienced operators)

Surgical versus medical therapy

- The comparison of controlled trials has identified mixed long-term results, with some studies finding comparable control of symptoms and others reporting better control by a fundoplication.

Surgical versus medical therapy

LOTUS trial

- Medical (esomeprazole) and surgical (standardized laparoscopic reflux procedure [LARS]) management provides similar five-year remission rates for controlling (GERD) symptoms.

- Patients who underwent LARS had a slightly lower estimated five-year remission rate compared with though treated medically (85 versus 92 percent); this difference was not statistically significant [98].

Surgical versus medical therapy

- Dysphagia, bloating, and flatulence were more common in patients treated with LARS.
- Acid regurgitation was less common.
- Patients who underwent LARS had lower residual 24 hour esophageal acid exposure than patients treated medically (Not significant)

Surgical versus medical therapy

A multicenter randomized trial (357 patients with greater than 12 months of GERD symptoms)

- Better control of GERD symptoms at five years following fundoplication.

The REFLUX trial (246 patients with five years of follow-up)

- patient undergoing a fundoplication were less likely to require antireflux medication at five years compared with patients managed by medical therapy alone (44 versus 82 percent).



Randomized Trial of Medical versus Surgical Treatment for Refractory Heartburn

- 366 patients with PPI-refractory heartburn who failed respond to a two-week course of double-dose omeprazole underwent a systematic workup including endoscopy, esophageal biopsy, esophageal manometry, and impedance-pH monitoring (on PPI therapy).

- Heartburn was PPI-refractory and reflux related in only 78 patients (21%).

- 42 (12%) HB was relieved with omeprazole BD with proper instructions,
- 70 (19%) were unwilling to complete the preoperative workup,
- 54 (15%) were excluded for miscellaneous reasons,
- 23 (6%) had non-GERD esophageal disorders such as EoE and achalasia,
- 99 (27%) had functional heartburn.

- 78 patients were randomly assigned to laparoscopic Nissen fundoplication or medical management.

- At one year, more patients who underwent surgery (67 percent) achieved a ≥50 percent decrease in GERD-health related QoL score compared with those who received medic treatments.

- Patients with esophageal visceral hypersensitivity responded to surgery as well as those with acid reflux.

- In conclusion, heartburn was both truly PPI-refractory and reflux-related in a minority of patients.

- In that highly selected group, laparoscopic Nissen fundoplication was significantly superior to medical therapy.

- Systematic workup including esophageal MII-pH monitoring can identify a subgroup of patients with PPI-refractory heartburn, who can have a response to antireflux surgery.

CME

ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease

Surgical and endoscopic options for GERD		
We recommend antireflux surgery performed by an experienced surgeon as an option for long-term treatment of patients with objective evidence of GERD. Those who have severe reflux esophagitis (LA grade C or D), large hiatal hernias, and/or persistent, troublesome GERD symptoms who are likely to benefit most from surgery.	Moderate	Strong
We recommend consideration of MSA as an alternative to laparoscopic fundoplication for patients with regurgitation who fail medical management.	Moderate	Strong
We recommend consideration of RYGB as an option to treat GERD in obese patients who are candidates for this procedure and who are willing to accept its risks and requirements for lifestyle alterations.	Low	Conditional

- Identifying patients with true refractory GERD is crucial because surgery (or endoscopic treatment) may truly be best in this group.

- Distinguish regurgitation from rumination, a functional disorder characterized by effortless food regurgitation during or soon after eating, typically with rechewing, reswallowing, or spitting out of the regurgitated material.

- Failure to respond to PPIs should be regarded as a red flag that GERD may not be the underlying cause.

- Patients who have the best response to antireflux surgery are those with typical GERD symptoms who respond well to PPIs.

- In summary, modern medical antireflux therapy and laparoscopic fundoplication seem to have similar efficacy in healing the symptoms and endoscopic signs of GERD.
- Surgery is not a permanent cure for GERD in all patients as it was once touted to be, and the operation occasionally can have severe adverse effects.
- Nevertheless, most patients obtain long-term benefit from fundoplication, and patient satisfaction with successful surgery seems to be greater than that for chronic medical therapy.

The major question for patients considering antireflux surgery is this:

- Does the.80% possibility of long-term freedom from PPIs and their attendant risks warrant the 4% risk of acute complications of fundoplication and its 17.7% risk of GERD recurrence?

