

Minimally Invasive and Novel Therapeutics (M.I.N.T.) in Foregut Disease
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Approach to Refractory GERD

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GERD- Symptoms

Typical

- Heartburn
- Acid/food regurgitation
- Intermittent dysphagia*

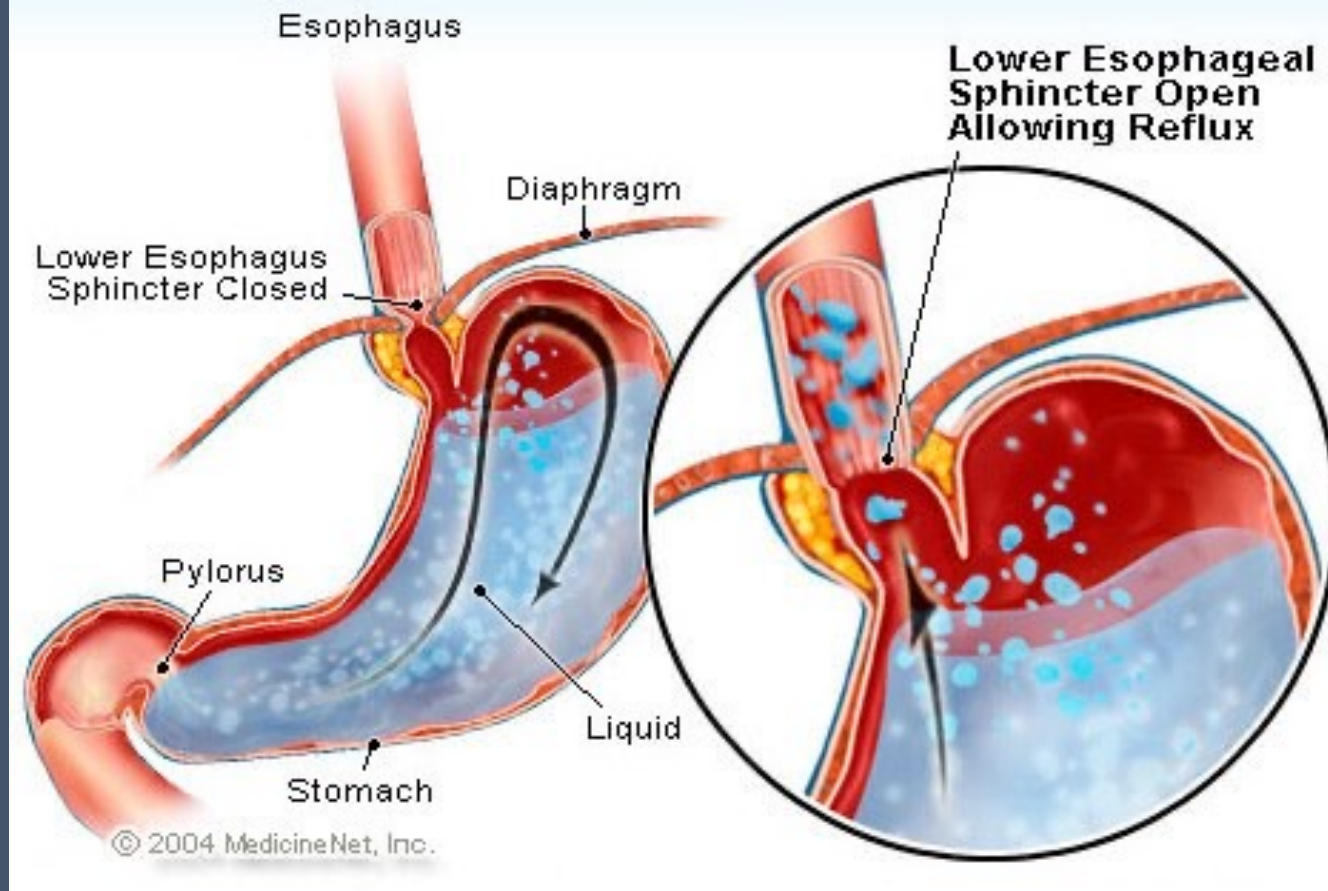
Atypical

- Cough*
- Hoarseness*
- Throat clearing*
- Post-nasal drip*
- Sore throat*
- Non-cardiac chest pain*



**Only once other causes have been excluded!
Do not presume this is due to GERD.*

Gastroesophageal Reflux



GERD-Facts

- Approximately 1/3 of patients have endoscopic abnormalities such as erosive esophagitis, Barrett's esophagus, peptic stricture or Schatzki ring.
- Hiatal hernias: most are asymptomatic (usually < 3cm- small). *Can* be a risk factor for GERD.
- Abnormal acid reflux is defined as a pH of LESS than 4 in the esophagus. Total acid exposure time is also important!

REFERENCES:

McPhee S. J., Papadakis M.A. & Rabow M.W. (2011). *Current Medical Diagnosis and Treatment*. 5th edition , McGraw Hill.

Yadlapati & DeLay. 2019. *Med Clin North Am*.



Refractory GERD

Defined as: The presence of persistent troublesome GERD symptoms and objective evidence of GERD despite optimized PPI therapy.

Yadlapati & DeLay. 2019. Med Clin North Am.



Case: 50 year old man with heartburn, acid regurgitation and dry cough...

- BMI 32
- PMH: HTN, DM Type II (A1C 7.0), Obesity, Anxiety
- PSH: none
- Allergies: none
- Medications: lisinopril 10 mg daily, Metformin 500 mg BID, citalopram 30 mg daily
- PCP started him on omeprazole 40 mg daily before breakfast with 50% improvement in symptoms



Table 1. Etiologies of Refractory GERD

Insufficient Acid Suppression or Increased Reflux
<ul style="list-style-type: none">• PPI compliance• PPI timing• CYP2C19 polymorphism• Weakly acidic reflux or nonacid reflux• Nocturnal acid breakthrough• Missed GERD• Acid pocket• Duodenogastroesophageal reflux
Functional Disorders
<ul style="list-style-type: none">• Functional heartburn or reflux hypersensitivity• Psychological comorbidities (including irritable bowel syndrome)
Alternative Diagnoses Unrelated to GERD
<ul style="list-style-type: none">• Zollinger-Ellison syndrome• Autoimmune skin conditions (eg, lichen planus)• Pill-induced esophagitis• Infectious esophagitis• Caustic esophagitis• Radiation-induced esophagitis• Eosinophilic esophagitis• Esophageal cancer• Achalasia• Gastroparesis• <i>Helicobacter pylori</i> carrier status• Rumination syndrome

CYP2C19, cytochrome P450 2C19; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

Source: Naik, Meyers & Vaezi. 2020. Gastroenterology & Hepatology



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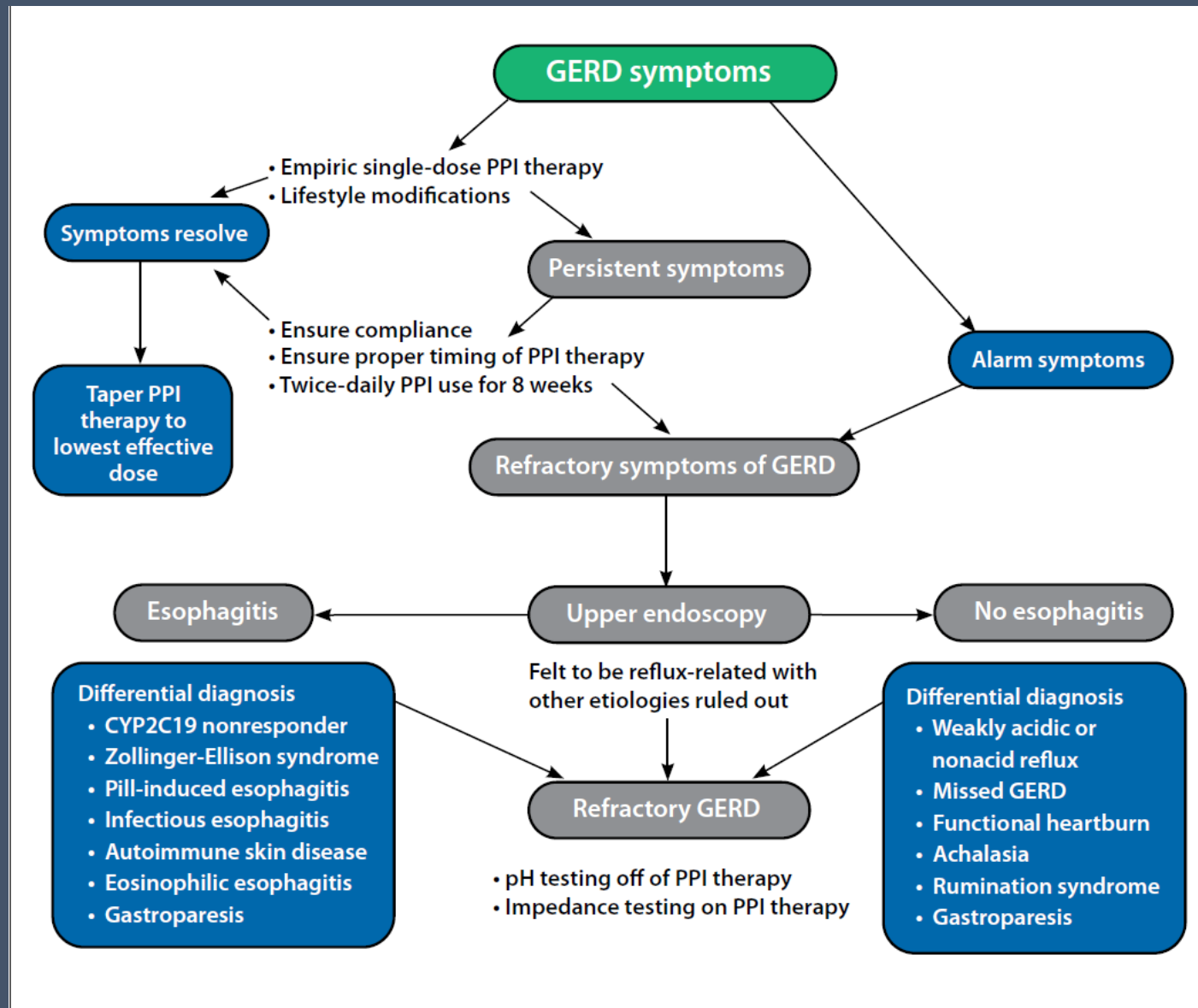
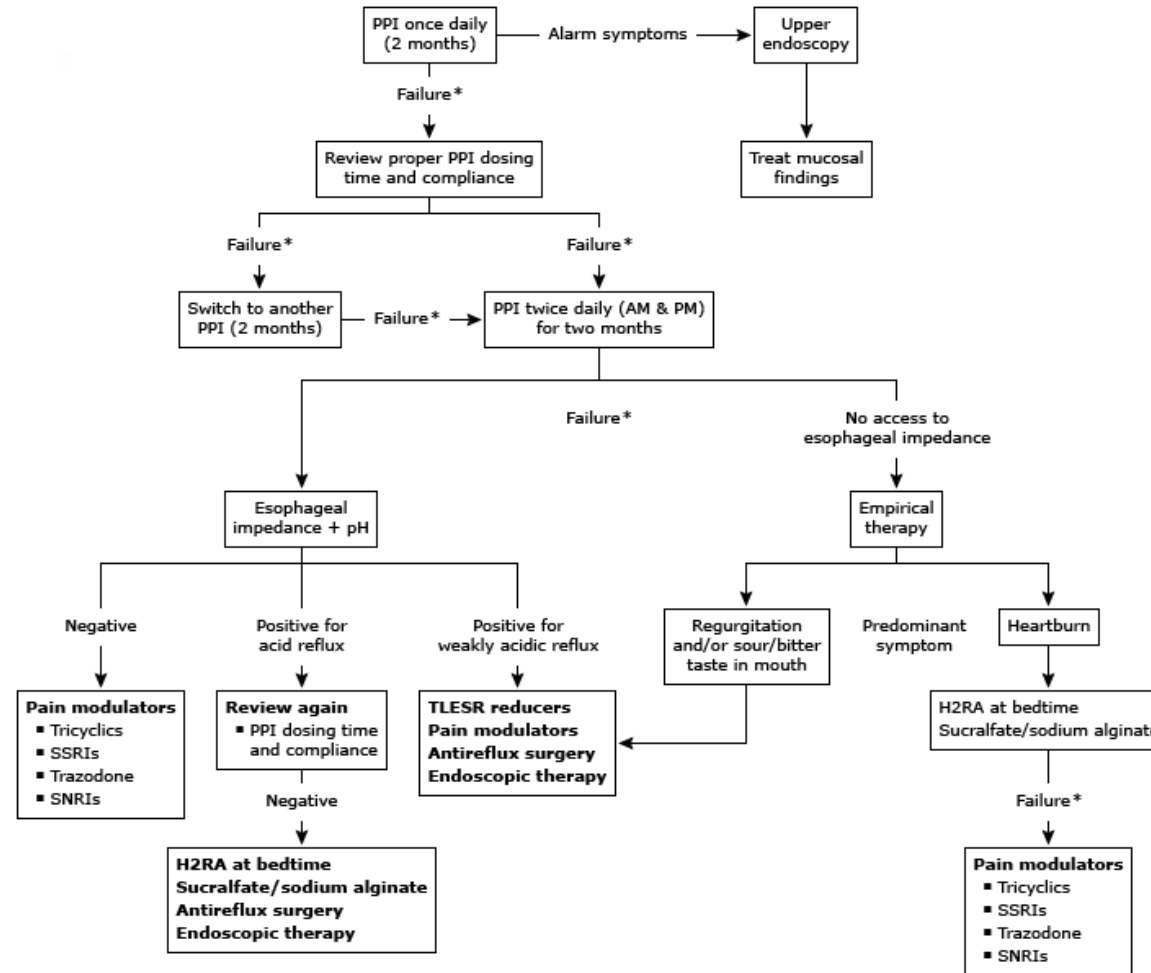


Figure. Management algorithm for refractory symptoms of GERD.

CYP2C19, cytochrome P450 2C19; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

Algorithm



Management algorithm of gastroesophageal reflux disease (GERD) patient who failed PPI once daily (complete or partial*).

PPI: proton pump inhibitor; SSRIs: selective serotonin reuptake inhibitors; SNRIs: serotonin-norepinephrine reuptake inhibitors; TLESR: transient lower esophageal sphincter relaxation; H2RA: histamine 2 receptor antagonist.

* Partial or incomplete relief of symptoms.

Original figure modified for this publication. Hershcovici T, Fass R. An algorithm for diagnosis and treatment of refractory GERD. *Best Pract Res Clin Gastroenterol* 2010; 24:923. Illustration used with the permission of Elsevier Inc. All rights reserved.



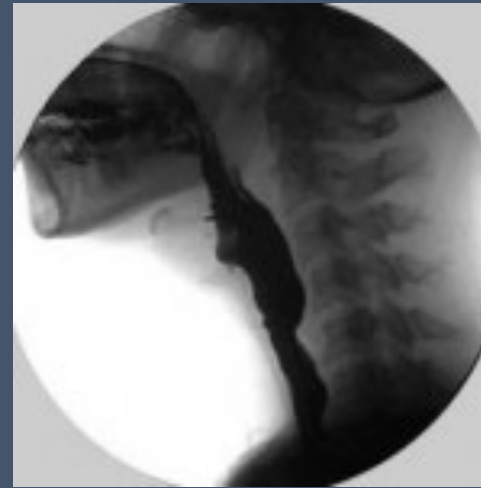
Dietary and Lifestyle Changes

- Low fat diet
- Limit carbonated drinks
- Small frequent meals
- Limit alcohol or remove completely
- Weight loss

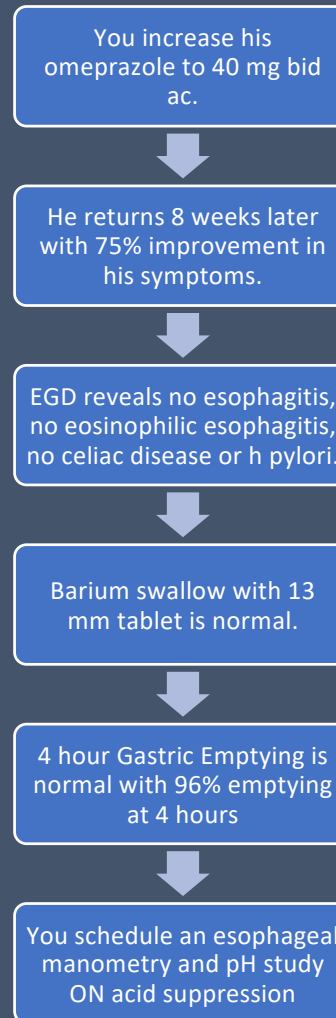


Testing to Consider

- Barium Swallow
- Upper Endoscopy
- Esophageal manometry
- Gastric Emptying Scan
- pH study – what kind?



Case: 50 year old man with heartburn, acid regurgitation and dry cough...



Yadlapati & DeLay.
2019. Med Clin North
Am.

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



Esophageal Manometry

LES parameters:

Mean basal LES pressure: 24.5 mmHg

Median integrated relaxation pressure (IRP): 14.7 mmHg consistent with normal LES relaxation

Esophageal body parameters:

% Peristaltic swallows (DCI > 100 mmHg*s*cm): 40%

% Ineffective swallows (DCI < 100 mmHg*s*cm): 60%

Ineffective swallows composed of:

% Failed swallows (DCI < 100 mmHg*s*cm): 33%

% Weak swallows (DCI > 100 mmHg*s*cm but less than 450 mmHg*s*cm): 27%

% Fragmented swallows (large break in isobaric contour with DCI > 450 mmHg*s*cm)(normal < 50%): 0%

% Premature contractions (swallows with distal latency ≤ 4.5 s and DCI > 450 mmHg*s*cm): 0%

Evidence of hypercontractile (jackhammer) esophagus (at least two swallows with DCI > 8000 mmHg*s*cm)? No

Evidence of elevated IRP in supine swallows that normalized in upright swallows? Yes

Impedance:

By impedance manometry, there was incomplete clearance of fluid boluses in 53% of wet swallows.

Multiple rapid swallow testing:

Normal response to multiple rapid swallow maneuver consisting of inhibition of esophageal peristalsis followed by a robust contraction response (normal).

Narrative:

Study consistent with normal LES relaxation and peristalsis.

PH study ON acid suppression: Scenario 1

PH PROBE ON Omeprazole 40 mg BID.:

In the proximal pH sensor in the proximal esophagus, total % time pH<4 was 2.8% (nl<1), upright 4.9% (nl<1.1), supine 0% (nl<0).

In the distal pH sensor in the distal esophagus, there were 15 acid reflux episodes noted (nl<50). Total % time pH<4 was 3% (nl<4.5), upright 5.2% (nl<6), supine 0% (nl<2).

DeMeester score: 11.4 (abnl >14.72)

IMPEDANCE:

Total amount of weakly acidic reflux episodes was 6 (nl<55); non acidic refluxes 0 (nl 2)

Impedance-based symptom association probability (SAP) for heartburn: 79.0 (Probability that symptom and reflux are not associated solely by chance, >95% is significant)

Mean nocturnal baseline impedance 2.32 kOhm which is normal.

Impression:

Normal acid exposure and reflux episode number while on Omeprazole 20 mg BID. No evidence of breakthrough GERD. Heartburn did not correlate with reflux events.

PH study ON acid suppression: Scenario 2

In the proximal pH sensor in the proximal esophagus, total % time pH<4 was 0% (nl<1), upright 0% (nl<1.1), supine 0% (nl<0).

In the distal pH sensor in the distal esophagus, there were 33 acid reflux episodes noted (nl<50). Total % time pH<4 was 1.3% (nl<4.5), upright 1.0% (nl<6), supine 2.5% (nl<2).

DeMeester score: 7.5 (abnl >14.72)

IMPEDANCE:

Total amount of weakly acidic reflux episodes was 170 (nl<55); non acidic refluxes 0 (nl 2)

Impedance-based symptom association probability (SAP) for heartburn: 74.8 (Probability that symptom and reflux are not associated solely by chance, >95% is significant)

Impression: There was a borderline increase in acid exposure while supine in the distal esophagus only; otherwise there was no increase in acid exposure in either the proximal or the distal esophagus. There was a significant increase in the number of weak acid refluxes. There were no non-acid refluxes. Symptoms of heartburn (reported 6 times) did not statistically correlate with reflux events. This study was performed while the patient was taking omeprazole 40 mg twice daily correctly.

What are Functional Gastrointestinal Disorders (FGIDs)?

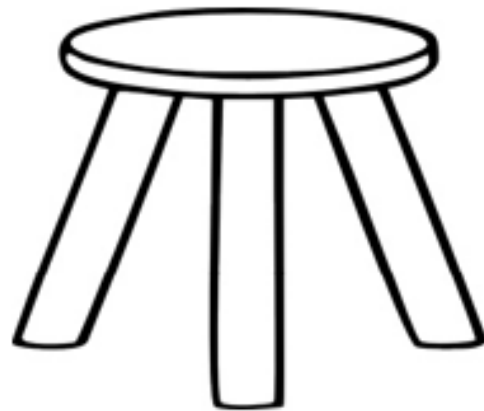
Functional GI Disorders

- According to the International Foundation for Gastrointestinal Disorders (IFFGD):
- “Functional GI and motility disorders ***generally cannot be diagnosed in a traditional way***. No inflammatory, infectious, or structural abnormality can be seen by commonly used examination, x-ray, or laboratory test.”
- “Problems occur when ***nerves or muscles*** in any portion of the digestive tract ***do not function in a coordinated fashion***, or when the ***sensitivity*** of the nerves of the intestines or the way in which the ***brain controls*** some of these functions ***is impaired***.”

CLINICAL
PEARL!!



Treatment of Functional GI Disorders



- Patient may need **3-legs of a stool** in order to address FGID symptoms
 - Pharmacotherapy
 - Complementary/ alternative medicine
 - Cognitive Behavior Therapies
- **Caveat:** hyperspecialized practice in a tertiary institution means I have a selection bias favoring patients with more severe symptoms
- Almost never have I told a patient with bothersome FGID that there was “nothing more than I can do,” but I do **work towards a mutually agreed upon treatment goal**

The Three Legged Stool – Fire Rescue Magazine

Functional Heartburn or Reflux Hypersensitivity

Medication options

Symptom/Concern	Medication	Potential Side Effects
Functional chest pain	Trazodone, venlafaxine, SSRI, TCA	Constipation, dry mouth, diarrhea, drowsy, mood changes, prolonged QTc. Caution, TCA and age >65
Globus	SSRI	Serotonin syndrome
Hypervigilance/symptom related anxiety	SSRI, SNRI, short-term clonazepam	Serotonin syndrome, diarrhea, mood changes, prolonged QTc, somnolence

Source:

Sobin, Heinrich, Drossman, 2017; Am Jour Gastro



Functional Heartburn or Reflux Hypersensitivity

Medications	Dosing
Trazodone	25 mg -150 mg qhs (12.5 mg qhs*)
TCAs (amitriptyline, nortriptyline, desipramine, imipramine)	25 mg – 150 mg qhs Liquid nortriptyline (can go as low as 2 mg)
SSRI (commonly used: citalopram, escitalopram)	Citalopram 10mg – 40 mg qd Escitalopram 5mg-20mg qd
SNRI (duloxetine, venlafaxine)	Duloxetine 30 mg -90 mg qd Venlafaxine 75 mg – 225 mg qd
Clonazepam	0.25 mg qd-bid

Source:

Sobin, Heinrich, Drossman, 2017; Am
Jour Gastro



Considering buspirone and gabapentin...

- Buspirone may be useful if patient has some anxiety. Some studies have suggested using this agent for ineffective esophageal motility. Generally start at 5 mg bid and increase to 15 mg bid as tolerated. (also TID dosing...)
- Gabapentin has been noted in some studies to be potentially helpful if patient has visceral hypersensitivity: (ie. Cough). Can start at liquid dose as low as 12.5 mg qhs or 25 mg qhs and increase to capsule form 100 mg qhs. Maximum dose 900 mg TID.
- Both agents are useful if patient is also experiencing functional dyspepsia/gastric accommodation problems/nausea and vomiting.
- Baclofen can be used for TLESR (Transient LES Relaxation)



Complementary or non-pharmacologic therapies and options

Beyond medications...

CBD marijuana

Acupuncture

Diaphragmatic
breathing exercises

Gut hypnotherapy,
Cognitive
Behavioral
Therapy, Reiki

Peppermint oil

Gaviscon liquid
(OTC)



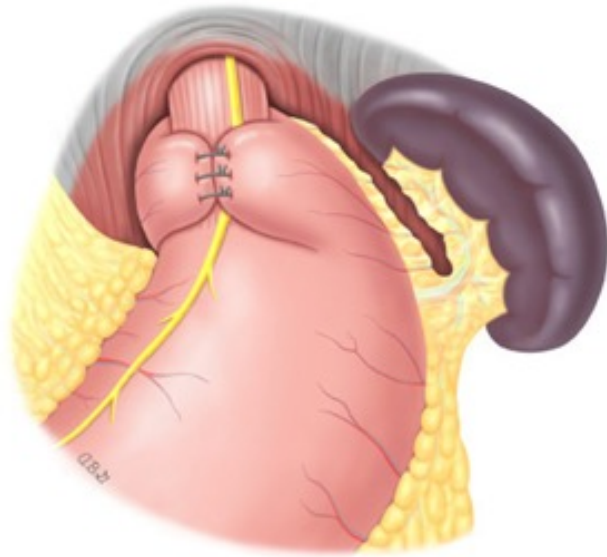
Scenario 3: Reflux is not well controlled on PPI...

Is Surgery an option?



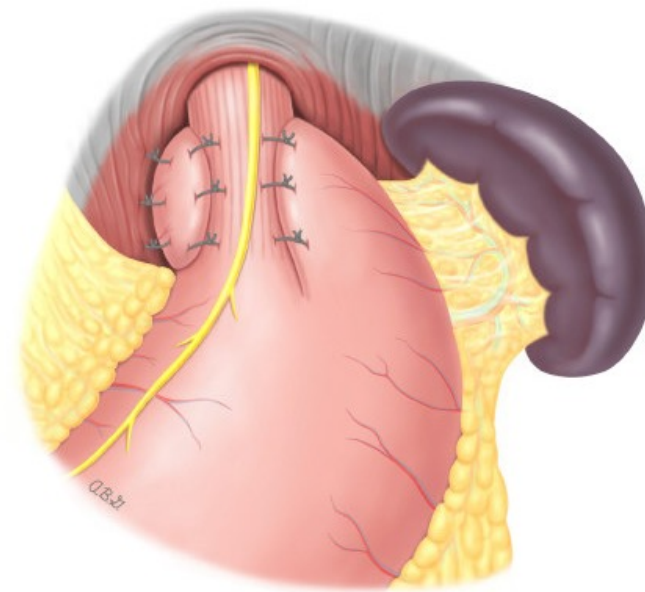
Types of fundoplication...

Nissen fundoplication



The Nissen fundoplication provides a 360° "wrap" or collar around the esophagus. Mobilization of the fundus is generally accomplished by dividing the short gastric vessels to the spleen.

Toupet fundoplication



The Toupet fundoplication is a partial fundoplication creating a collar of approximately 270° around the esophagus posteriorly.

Nissen Fundoplication

Criteria/ Qualifications:

- Well documented GERD.
- No swallowing disorders.
- BMI <32.
- Responsive to acid suppression.

Generally laparoscopic but may need to convert to open chest wall surgery if complications arise.

Potential complications

- Post operative swallowing problems
 - Surgical wrap failure
- Vagal nerve injury/hypersensitivity
 - Abdominal bloating



Magnetic Sphincter Augmentation



Figure 1. The LINX system is designed to help the LES resist opening to gastric pressure.



Figure 2. The LINX system is designed to expand to allow for normal swallowing.



Figure 3. Magnetic attraction of the device is designed to close the LES immediately after swallowing.

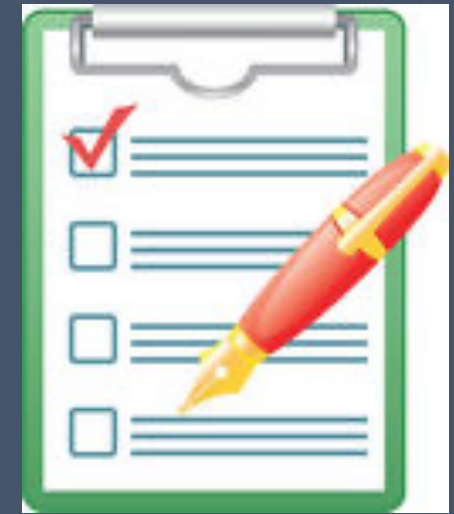


Reference: Torax Medical Devices, 2017

Magnetic Sphincter Augmentation

Criteria/ Qualifications:

- Well documented GERD.
- No swallowing disorders.
- Hiatal hernia < 2 cm in size.
- BMI <32.
- No prior esophageal/gastric surgery.
- No metal allergies. (Titanium, Stainless steel, nickel or ferrous material)
- Responsive to acid suppression.



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Potential complications

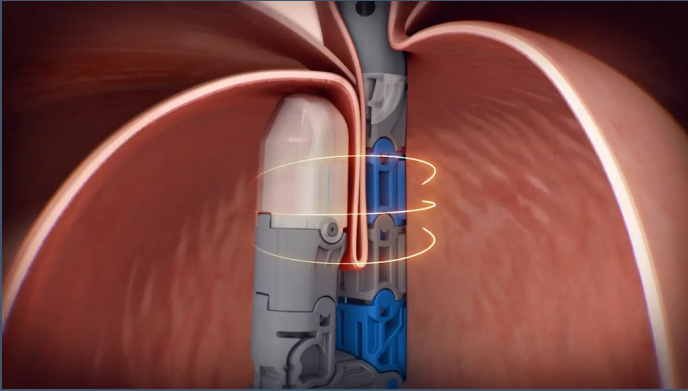
- Device erosion
- Post-operative swallowing problems
- Post-operative hypersensitivity.
- Not compatible with most MRI machines...
- Same concern with airport security.



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The safety and effectiveness of the LINX device has not been evaluated in patients with Barrett's esophagus or severe inflammation of the esophagus on upper endoscopy.

TIF Procedure



- Similar diagnostic/pretesting criteria as the LINX
- Hiatal hernia less than 3 cm
 - BMI <35. Ideally BMI < 32.
 - No previous gastric surgery.
 - Well documented GERD
 - No swallowing disorders.

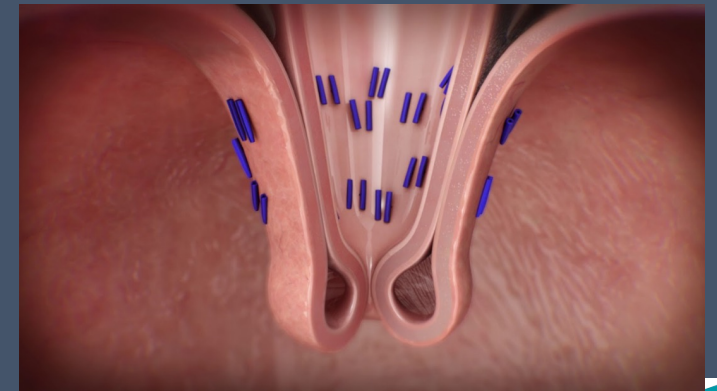


Photo Credit: <https://www.endogastricsolutions.com/tif-procedure/>

Post – Operatively

Inclusive for all procedures:

What to Expect:

- Liquid diet for a week after surgery.
- Soft diet for an additional several weeks.
- No heavy lifting! < 10 lbs.
- No strenuous activities.



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Clinical Pearls- Wrap Up

- ✓ Obtain detailed history of symptoms
- ✓ Obtain objective data
- ✓ Consider all possible differential diagnoses
- ✓ Ensure proper PPI timing
- ✓ Diet and lifestyle changes can provide added benefit
- ✓ Treatment can include several approaches
- ✓ Surgical intervention should be reserved for the appropriate candidate

