Personalized Management of GERD and the Risk/Benefits of PPI and PCABs

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Disclosure

Advisory Board: Ethicon Endosurgery; Medtronic; Phathom; Sandhill/Diversatek

Consultant: Ethicon Endosurgery; Laborie; Medtronic; Phathom; Sandhill/Diversatek

Patent Royalties: Laborie

Research Grant: Medtronic; Sandhill/Diversatek

Speaker's Bureau: Ethicon Endosurgery; Phathom

Stocks: Medtronic

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Learning Objectives

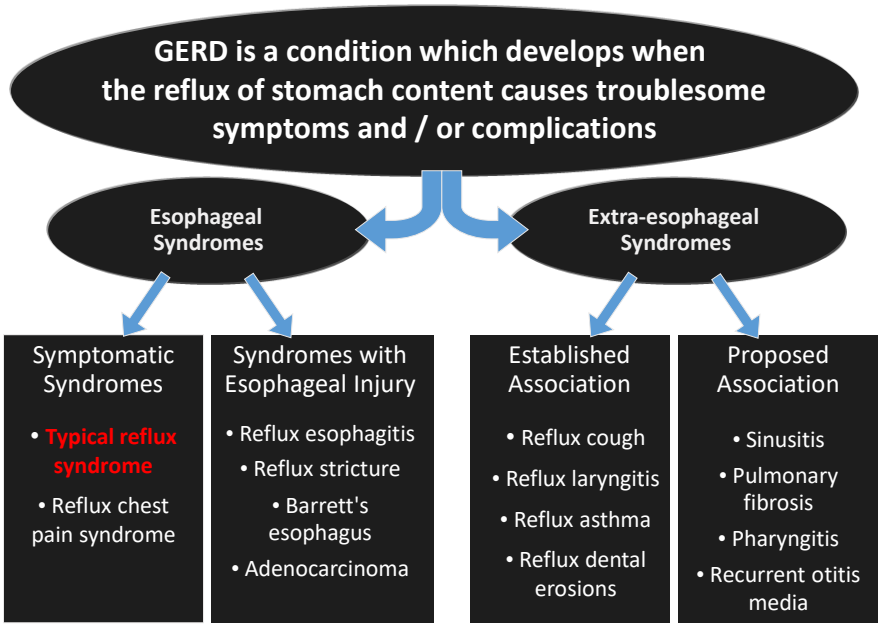
To be able to:

1. phenotype GERD into clinically relevant categories that can inform therapy.
2. determine which therapy will have the most targeted effect.
3. take people off of inappropriate PPI therapy.

Personalized Medicine: GERD

Case:

- 42-year-old male with heartburn and chest discomfort for approximately 6 months.
  - Originally seen by his PCP- referred for exercise stress echocardiogram and cardiac CT – **both negative**.
  - Current ROS
    - 15 lb weight gain, no trouble swallowing, no evidence of GI bleeding
  - Management:
    - Started on omeprazole 20 mg- mild response
    - Increased to 20 mg twice a day- about 20% better
    - Tried on pantoprazole 40 mg twice a day- no change
    - Switched to dexlansoprazole 60mg twice a day- 20% better
- 6 months later finally referred to GI
- 7 months later- Endoscopy was negative
- 8 months later- Reflux testing ?



Vakil N et al. Am J Gastroenterol 2006;101:1900

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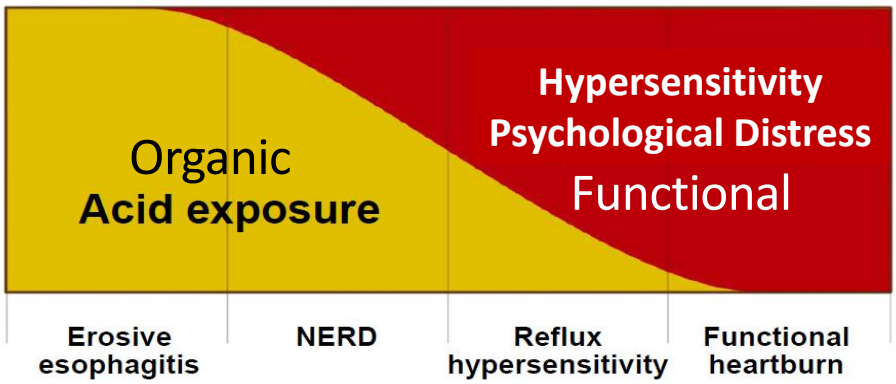
GERD Dogma: Organic versus Functional

Roles of acid exposure and esophageal hypersensitivity in overlapping GERD and functional esophageal syndromes. Acid exposure and response to proton pump inhibitors decreases from erosive esophagitis to functional heartburn while esophageal hypersensitivity increases across the same spectrum.
(Adapted from Galmiche et al, UEG Journal 2013)



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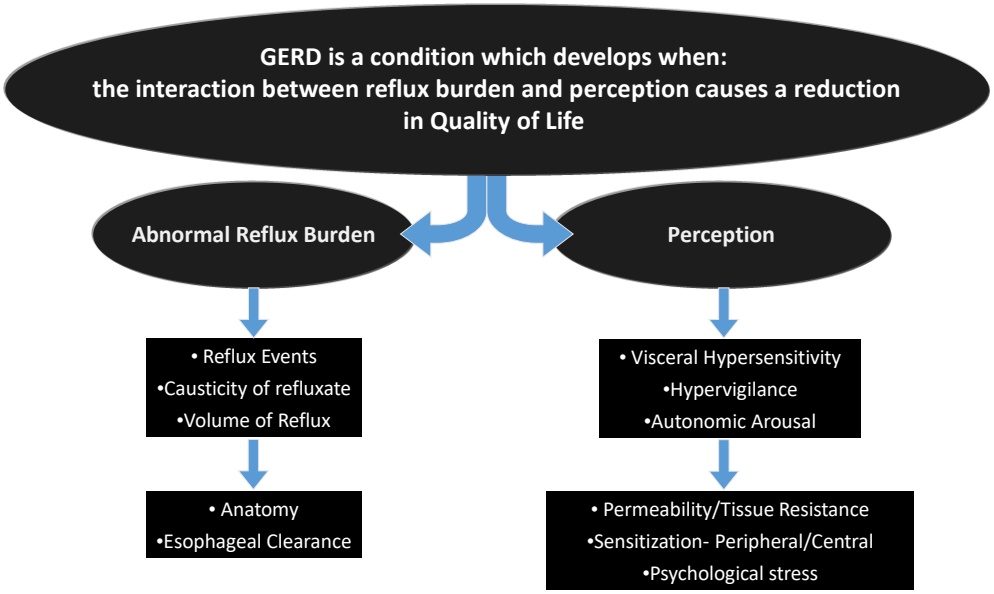
Flawed Dogma of Model of Functional and Organic GERD

- **Esophageal hypervigilance is as important than anatomy and physiology**
- We studied 286 patients undergoing pH monitoring at Northwestern Medicine and assessed the relationship between QOL/Symptom severity and reflux burden and markers of psychological stress.
  - Health related quality of life measured by the NEQOL was not associated with total Bravo ($r = -0.13$, $p = .051$) or pH impedance ($r = -0.10$, $p = .108$) acid events.
  - However, elevations in hypervigilance and symptom-specific anxiety using the EHAS strongly associated with decreased HrQOL ($r = -0.73$, $p < .001$).

Guadagnoli et al. Neurogastroenterol Motil 2021 Jan 11;e14081

7

Pathogenesis of GERD



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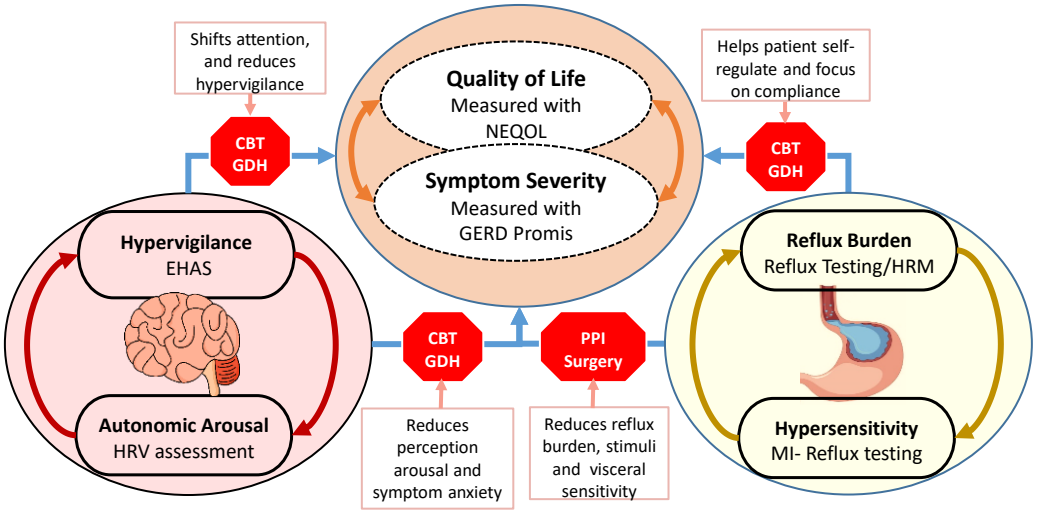
Conceptual Model of the Psycho-Physiologic Model of GERD



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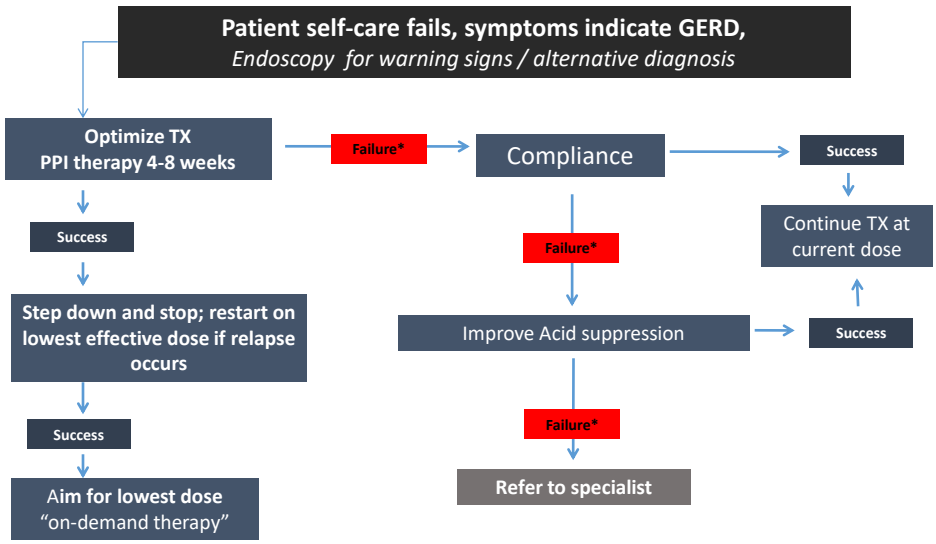
Treating Reflux Disorders: Current Model



* Always consider alternative diagnosis when treatment failure occurs

Modified :Tytgat GN, et al. *Aliment Pharmacol Ther*. 2008;27:249-256.

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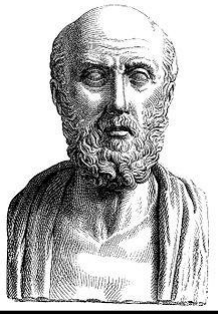
Personalized Medicine: GERD

- **Personalized medicine:** is a medical approach that separates patients into different groups—with medical decisions, practices, interventions and/or products being tailored to the individual patient based on their predicted response or risk of disease

- Optimal GERD management should be determined by an analysis of important patient centered foci and specific defects in function.
  - ***Symptoms***
  - ***Response to medicine***
  - ***Anatomy***
  - ***Physiology***
  - ***Psychosocial stressors***



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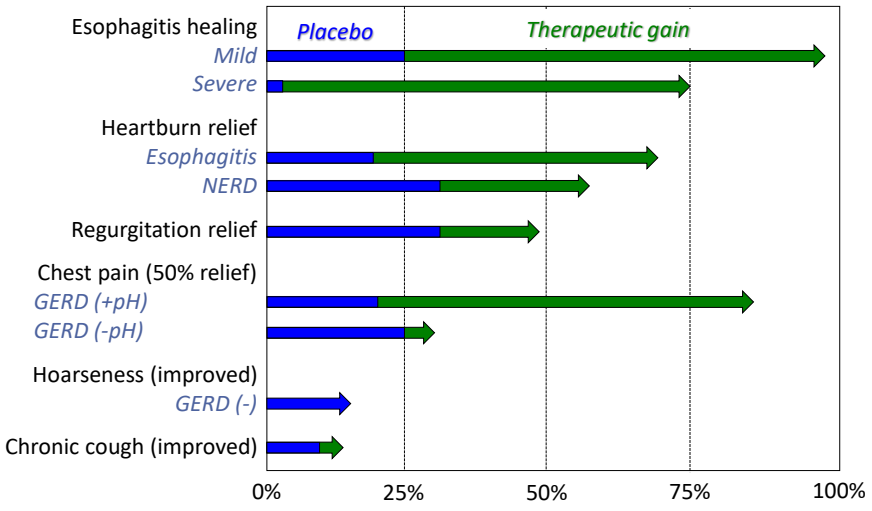
PPI Efficacy for Potential Manifestations of GERD

Estimates Based on Available RCT Data



- Kahrilas PJ...Response of regurgitation to PPI therapy in clinical trials of GERD. AJG, 2011;106(8):1419-25;

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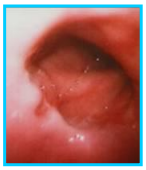
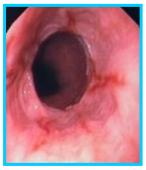
The Los Angeles Classification System for Esophagitis
The "Flap Valve" Concept of EGJ Disruption

Los Angeles Grade A



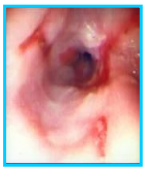
One or more mucosal breaks no longer than 5 mm, not bridging the tops of mucosal folds

Los Angeles Grade B



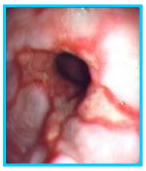
One or more mucosal breaks longer than 5 mm, not bridging the tops of mucosal folds

Los Angeles Grade C



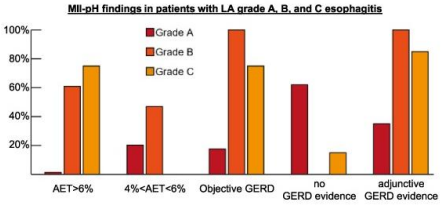
One or more mucosal breaks bridging the tops of mucosal folds involving <75% of the circumference

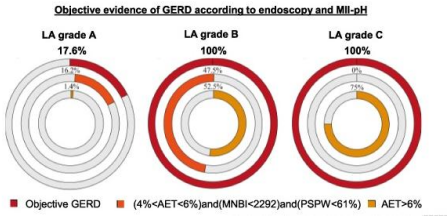
Los Angeles Grade D



One or more mucosal breaks bridging the tops of mucosal folds involving >75% of the circumference

Lundell LR, et al. *Gut*. 1999;45:172–180.
Armstrong D, et al. *Gastroenterology.* 1996;111:85–92.





Hill LD, et al. Gastrointest Endosc 1996;44:541-547

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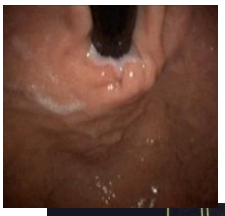
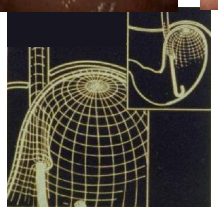
The "Flap Valve" Concept of EGJ Disruption

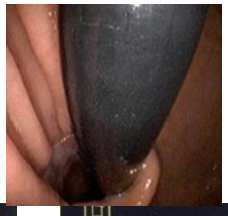
Grade I

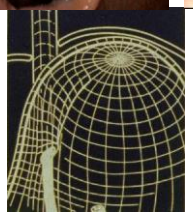




Normal ridge of tissue closely approximated to the scope

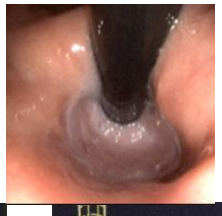
Grade II

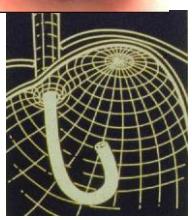




Ridge is slightly less well defined and opens with respiration

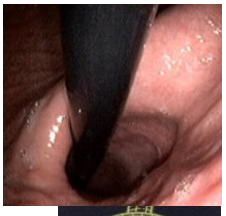
Grade III

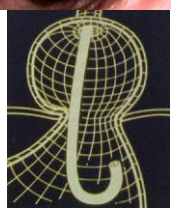




Ridge is effaced and the hiatus is patulous

Grade IV





Hiatus is wide open at all times and displaced axially

Hill LD, et al. Gastrointest Endosc 1996;44:541-547

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Personalized Medicine: GERD

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  - Originally seen by his PCP- referred for exercise stress echocardiogram and cardiac CT – **both negative**.
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- 6 months later finally referred to GI
- 7 months later- Endoscopy was negative
- 8 months later- Reflux testing ?

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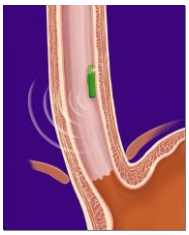
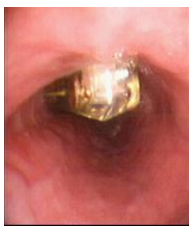
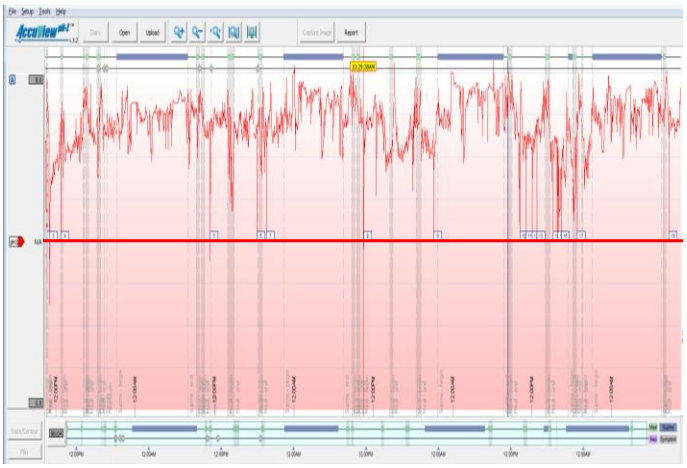
Phenotyping PPI Non-responders:

Low Pre-test Probability of Refractory GERD

Wireless Reflux Testing System: pH Testing







Pandolfino et al. Am J Gastroenterol. 2003 Apr;98(4):740-9

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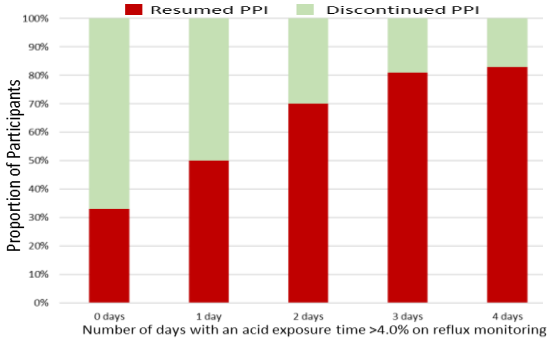
NIDDK GERD Study

Effectiveness of Physiologic Testing in PPI Non-Responders.

- 100 patients with refractory GERD underwent 4 day wireless pH testing
  - **Patients underwent a structured PPI withdrawal [3 weeks] to determine who could stop PPI therapy**
- Wireless pH testing provides important information regarding stratification of PPI therapy and should direct treatment.
  - **29 patients could stop PPI therapy based on acid exposure data**
  - **71 patients should potentially continue PPI therapy based on acid exposure data**



Yadlapati, Gastroenterology. 2020 Sep 16:S0016-5085(20)35161-1.

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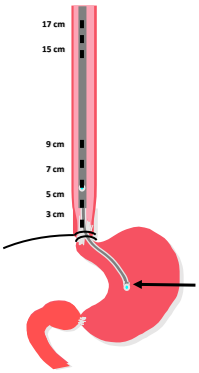
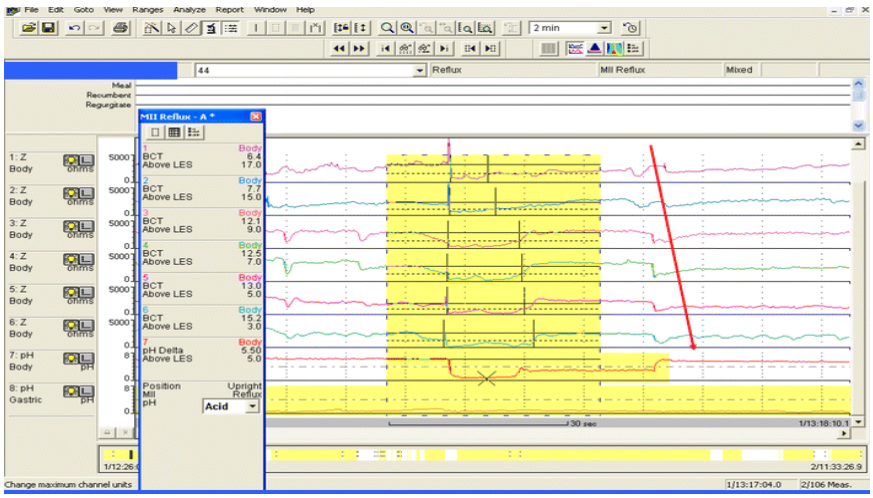
Phenotyping PPI Non-responders:

High Pre-test Probability of Refractory GERD

pH-impedance Monitoring





Pandolfino JE, Vela, MF. Gastrointest Endosc. 2009 Apr;69(4):917-30,

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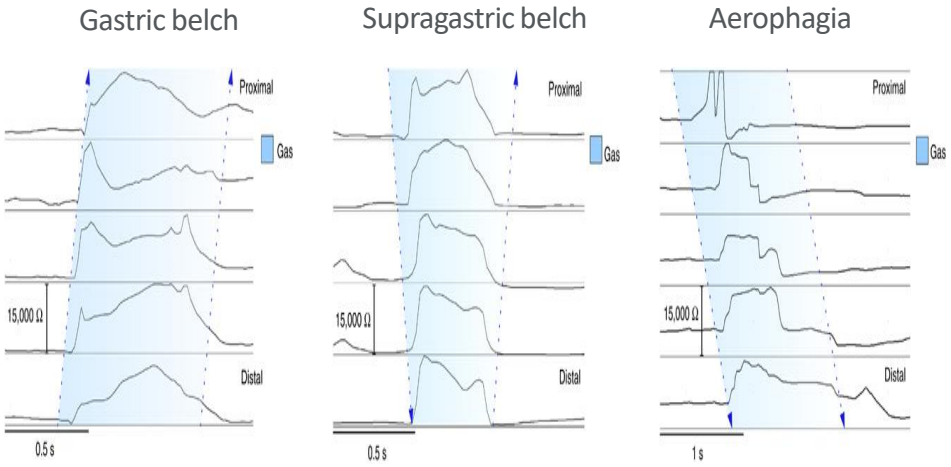
Belching

Impedance Can Distinguish from Gastric from Supragastric Belching



Kessing et al. Am J Gastroenterol 2014; 109:1196–1203

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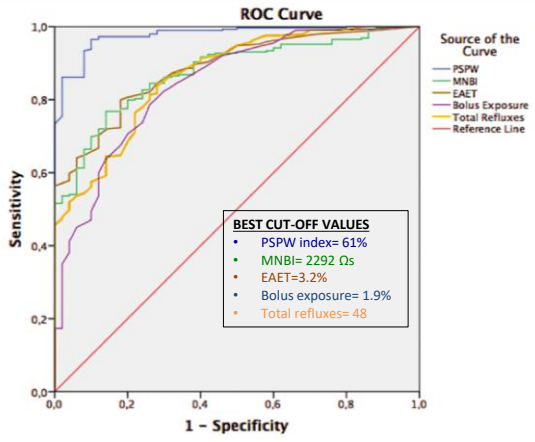
Phenotyping PPI Non-responders:

High Pre-test Probability of Refractory GERD

pH-impedance Monitoring



Analyses of the Post-reflux Swallow-induced Peristaltic Wave Index and Nocturnal Baseline Impedance Parameters Increase the Diagnostic Yield of Impedance-pH Monitoring of Patients With Reflux Disease

Marzio Frazzoni,* Edoardo Savarino,‡ Nicola de Bortoli,§ Irene Martinucci,§ Manuele Furnari,‖ Leonardo Frazzoni,* Vincenzo Giorgio Mirante,* Helga Bertani,* Santino Marchi,§ Rita Conigliaro,* and Vincenzo Savarino‖

Baseline Impedance in GERD diagnosis

	Acc	Sens	Spec	PPV	NPV
ERD (n=68)	89%	91%	86%	90%	88%
NERD (n=221)	75%	72%	86%	96%	41%
pH-positive NERD (n=118)	86%	86%	86%	94%	73%
pH-negative NERD (n=103)	66%	56%	86%	89%	49%
pH-negative, SAP/SI+ NERD (n=65)	67%	52%	86%	83%	58%
pH-negative, SAP/SI- NERD (n=38)	76%	63%	86%	77%	75%

PSPW index in GERD diagnosis

	Acc	Sens	Spec	PPV	NPV
ERD (n=68)	97%	100%	92%	94%	100%
NERD (n=221)	89%	89%	92%	98%	65%
pH-positive NERD (n=118)	97%	99%	92%	97%	98%
pH-negative NERD (n=103)	82%	77%	92%	95%	66%
pH-negative, SAP/SI+ NERD (n=65)	86%	82%	92%	93%	79%
pH-negative, SAP/SI- NERD (n=38)	82%	68%	92%	87%	79%

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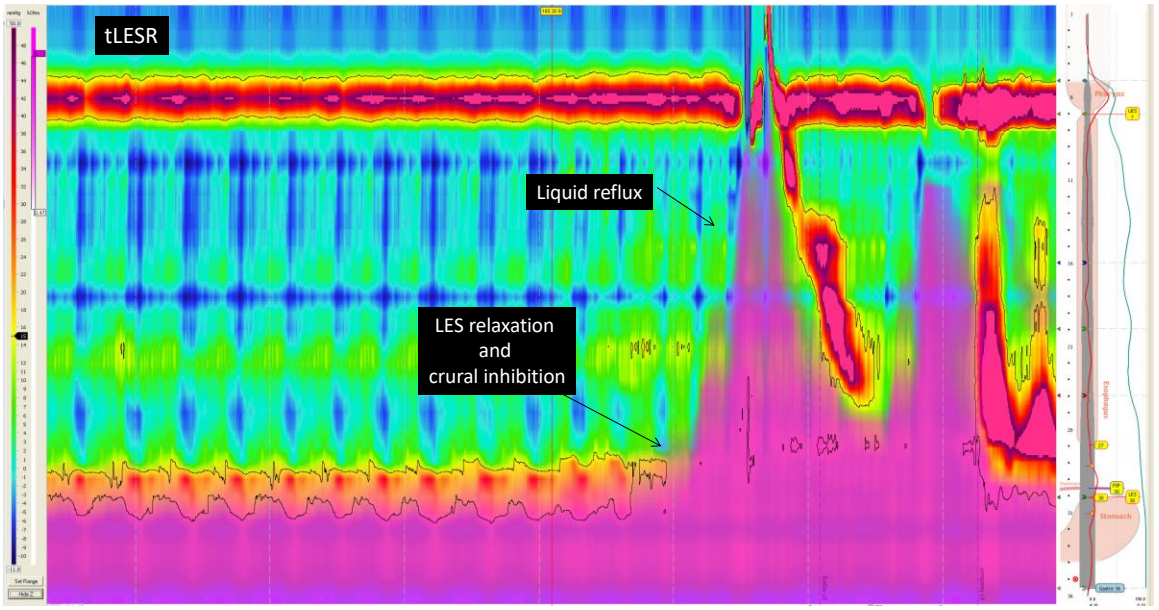
HRIM with Post-prandial Challenge



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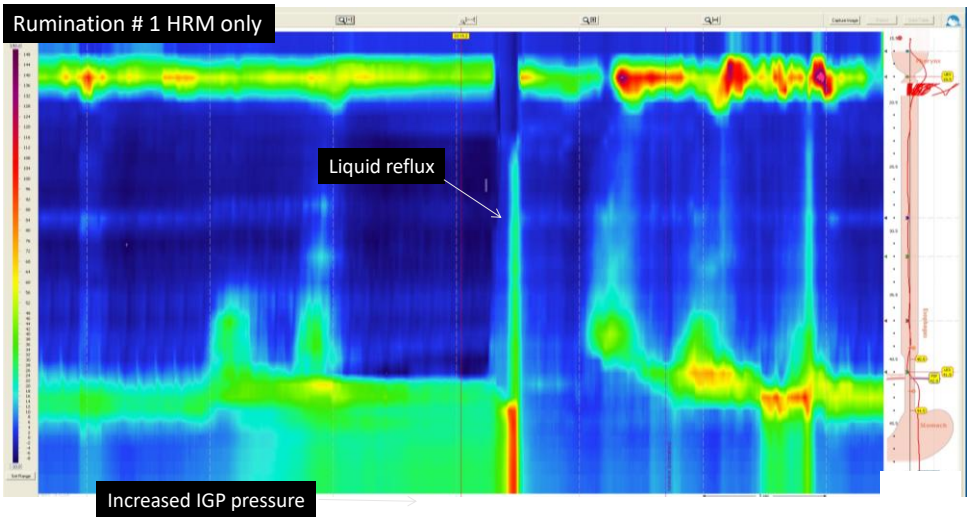
HRIM with Post-prandial Challenge: Alternative Diagnosis



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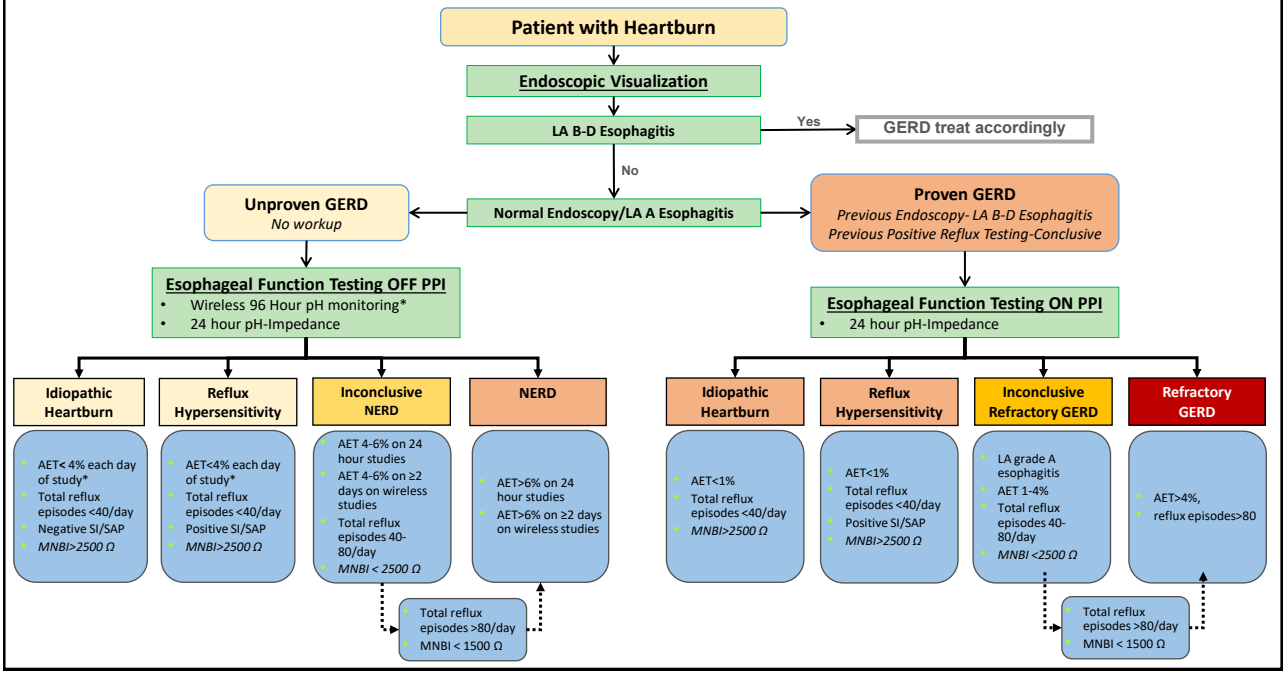
Heartburn Diagnostic Algorithm: Previous Figure 4- Now Combined with Lyon Table



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Management of Patients with Proven GERD and Refractory Symptoms (Heartburn, Regurgitation and Chest Pain)
Based on Wireless Monitoring and 24 Hour pH-impedance Testing

Assuming positive wireless off PPI/ LA B or greater Esophagitis and a Negative HRIM for Rumination and EMD

24 Hour pH-Impedance ON PPI
HRIM if not done to rule out Rumination/EMD

FUNCTIONAL OVERLAP
AET < 2.0/ RE < 40
Negative SRA

1. Do not refer for Surgery- if **Borderline Reflux** OFF medication
2. Continue PPI
3. CBT or GDH if not attempted
4. Neuromodulator if not attempted

- Patients with hernia > 3 cm and **Definitive GERD** OFF medication can be referred for surgical consultation if no response to non-surgical approaches. Patient should be counseled on lower likelihood of response.

BORDERLINE REFRACTORY GERD
not meeting Refractory GERD
Functional Overlap Criteria

1. Continue PPI at high dose
2. CBT/GDH/Neuromodulator if not attempted
3. ***Consider non-surgical/endoscopic approaches in patients without a significant hernia, obesity and poor esophageal motility.***

Precision approach based on pattern of reflux in patients with GEFV I-III.
- Belching
  - TIF, Baclofen, SLP-supragastric
- Poor Clearance based on PSPW- IEM
  - Promotility
- Increased mucosal permeability (MI / MNBI)
  - Alginates/bioadhesives
- Hypotensive EGJ and GEFV I-II
  - TIF

- Patients with GEFV IV-hernia > 3 cm and **Definitive GERD** OFF medication can be referred for surgical consultation if no response to non-surgical approaches.

DEFINITIVE REFRACTORY GERD
EGD: > Los Angeles B esophagitis
AET > 4.0%:

1. Acid suppression failure
2. Surgical Consultation
3. Esophageal physiologic testing [HRIM to assess (endoscopic/surgical) candidacy and for alternative diagnoses
4. Consider gastric emptying study
5. Consider esophagram for patients with large hernias and to assess bolus clearance.

Precision approach based on presence of hernia, obesity and poor esophageal and gastric motility.
- Hernia > 3 cm- GEFV IV
  - Partial Fundoplication/ MSA
- Obesity (BMI > 40)
  - Can consider bariatric surgery (GBP)
- Poor motility
  - Consider partial fundoplication after discussing risks and benefits.

PPI proton pump inhibitor, **HRM** high-resolution manometry, **EHAS** Esophageal Hypervigilance and Anxiety Scale, **NM** Neuromodulator, **HRV** heart rate variability, **CBT** Cognitive Behavioral Therapy, **GDH** Gut Directed Hypnotherapy, **AET** acid exposure time, **RE** reflux events, **TIF** transoral incisionless fundoplication, **NF** Nissen Fundoplication, **MSA** Magnetic sphincter Augmentation, **SLP** speech language pathologist. **FVG** Flap Valve grade

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Most of the Emphasis of Therapy Has Focused on Escalating Acid Suppression and Reducing Reflux Events

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Lifestyle Modification and Diet

Recommendation	Target Population
Smoking cessation	Smokers
Weight reduction	Body mass index (BMI) >25
Avoid alcohol consumption	Alcohol related symptoms
Avoid eating 3hrs before bed	Night time symptoms
Head of bed elevation	Night time symptoms
Smaller more frequent meals	Postprandial symptoms

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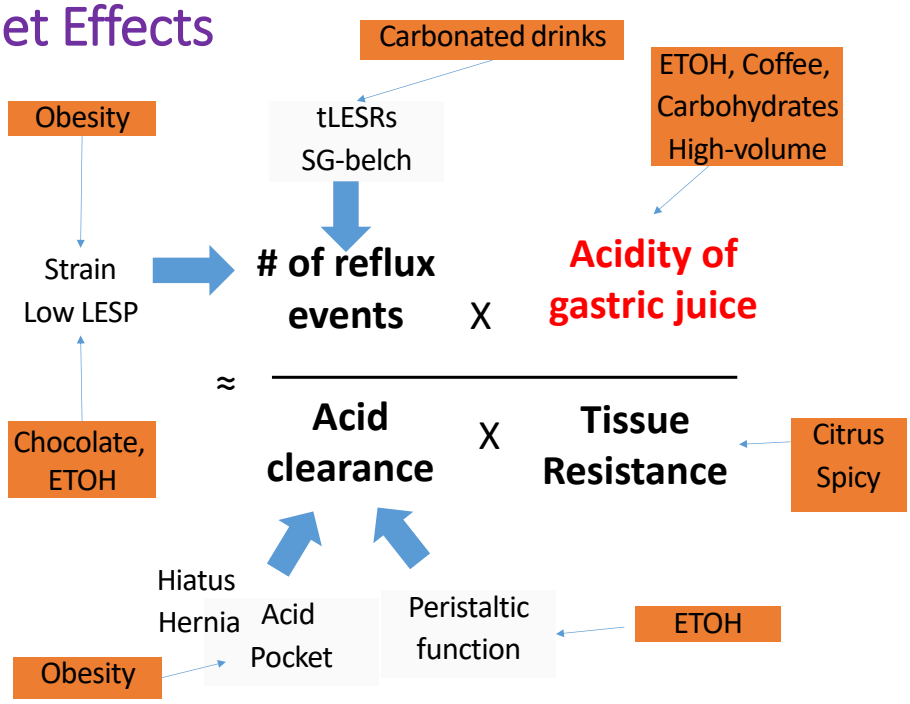
Diet Effects



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Relative Potency of PPIs

Table 1. Potency of PPIs Based on OE

Drug at lowest available dosage	OE
Pantoprazole 20 mg	4.5 mg
Lansoprazole 15 mg	13.5 mg
Omeprazole 20 mg	20 mg
Esomeprazole 20 mg	32 mg
Rabeprazole 20 mg	36 mg

NOTE. PPIs are listed in order of increasing potency.[17]

OE, omeprazole equivalent; PPIs, proton pump inhibitors.

- *I switch PPI non-responders with true refractory reflux to Rabeprazole due to the preferential metabolism and potency.*
- *I switch patients to pantoprazole if they can't tolerate other PPI therapy and they want to be on a low dose.*

Graham et al. Clin Gastroenterol Hepatol. 2018 Jun;16(6):800-808

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Management of GERD in 2026

- About 50-60% of patients with GERD do well on a PPI and it is a safe and effective therapy.
  - We should make every attempt to reduce their risks and educate the patient on the risk benefit.
  - Should be on the lowest effective dose.
- PPI therapy is safe.

- Take home comments on PPI risks.

- Long-term PPI use likely increases some risks (SIBO, B12 deficiency, hypomagnesemia). These are either exceedingly rare or idiosyncratic, or are treatable and reversible.
- Patients with cirrhosis may be at increased risk of SBP (if +ascites) or HE with long-term PPI use. The indication for PPI use should be carefully considered in this population.
- Data supporting the risks of CV events, dementia, CKD, calcium & iron deficiency is of low quality and/or conflicting and should not alter current PPI management.

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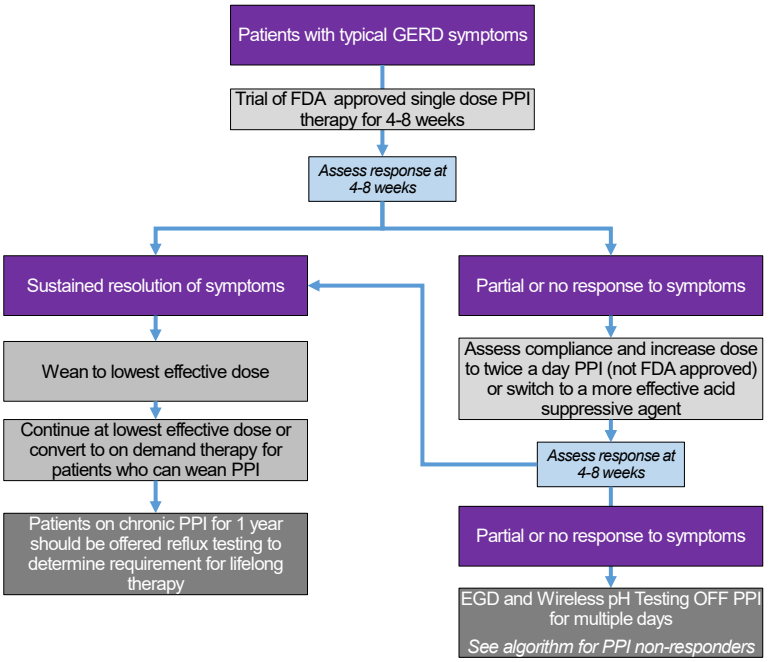
Utilization of PPI Therapy in GERD



30

Management of GERD in 2026

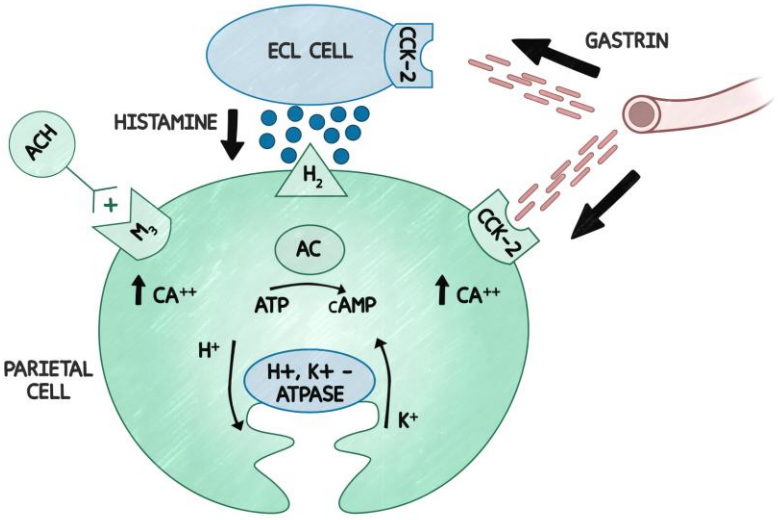
- About 50-60% of patients with GERD do well on a PPI and it is a safe and effective therapy.
  - We should make every attempt to reduce their risks and educate the patient on the risk benefit.
  - Should be on the lowest effective dose.
  - Most interventions can not guarantee PPI withdrawal with many patients ending up back on PPI.
  - PCABs- Vonoprazan- FDA Approved

However, 40-50% of patients are not satisfied with PPI therapy or have some intolerance.

- Headache
- Change in bowel habits
- Dyspepsia

31

Acid Secretion by the Gastric Parietal Cell



- Diagram from Feldman M, et al. Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 11th ed. Elsevier; 2020.

32

PPI Pharmacologic Features That Limit Speed of Onset and Acid Inhibiting Efficacy

PPIs are vulnerable to degradation by gastric acid

Enteric coating protects them from acid but delays absorption

PPIs are prodrugs

Must be activated by gastric acid to bind covalently to proton pumps

Only actively secreting parietal cells affected by PPIs

Fasting: only ≈5% of proton pumps actively secreting
With meals: 60% to 70% of proton pumps actively secreting

Short plasma half-life (2 to 3 hours)

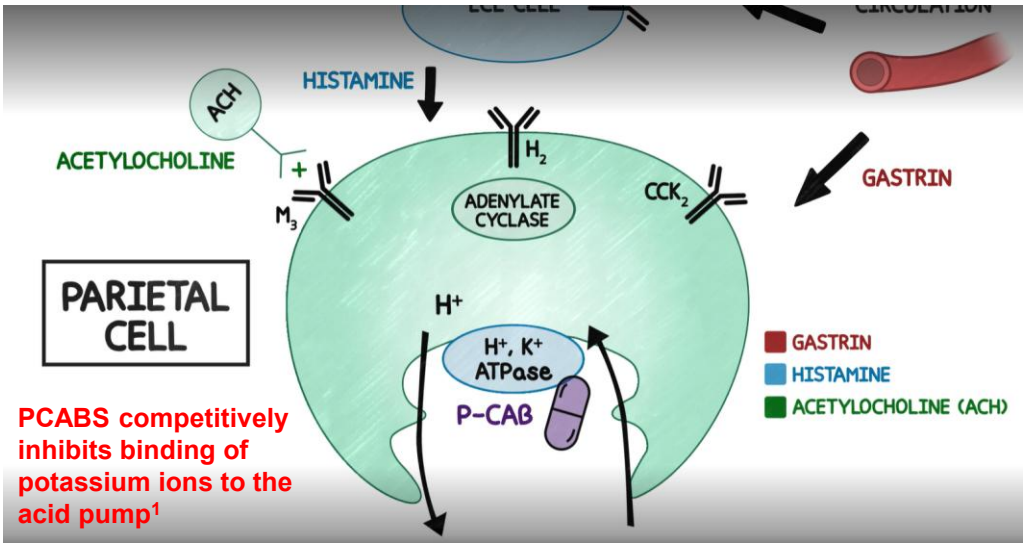
Stomach constantly making new proton pumps (25% replaced in 24 hours)
Repeated administration required

Individual variability in rate of metabolism by CYP2C19

- Kinoshita Y, et al. J Neurogastroenterol Motil. 2018;24:182-196.

33

Potassium-Competitive Acid Blockers (P-CABs) Compete with Potassium for Binding to H+,K+-ATPase



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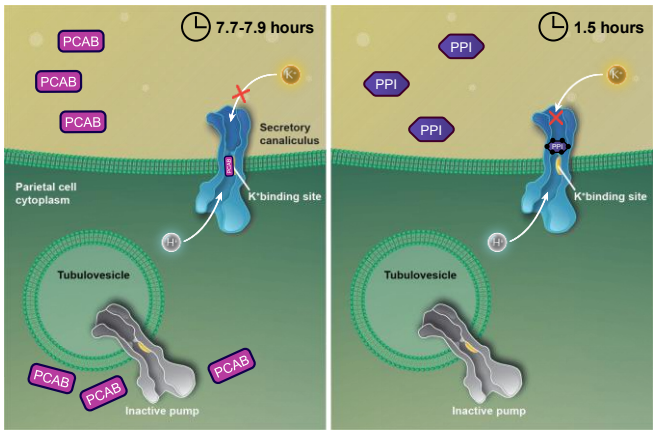
Mechanism of Action
Potassium-Competitive Acid Blocker (PCAB)



Reused from Laine L et al. *Am J Gastroenterol.* 2022;117:1158-1161.[3]

VONOPRAZAN has a half-life of 7-8 hours

1- may selectively concentrate in both resting and stimulated parietal cells[1]

2- does not require acid for activation and can be taken with or without food[1,2]

3- long half-life of VONOPRAZAN may contribute to its ability to provide durable acid suppression[1,3]

[a]7.7 hours with 10-mg dose and 7.9 hours with 20-mg dose.
PCAB = potassium-competitive acid blocker; PPI = proton pump inhibitor.
1. Prescribing Information. Phathom Pharmaceuticals, Inc.; 2024. **2.**. Prescribing Information. Takeda Pharmaceuticals America, Inc.; 2022. **3.** Laine L et al. *Am J Gastroenterol.* 2022;117:1158–1161.

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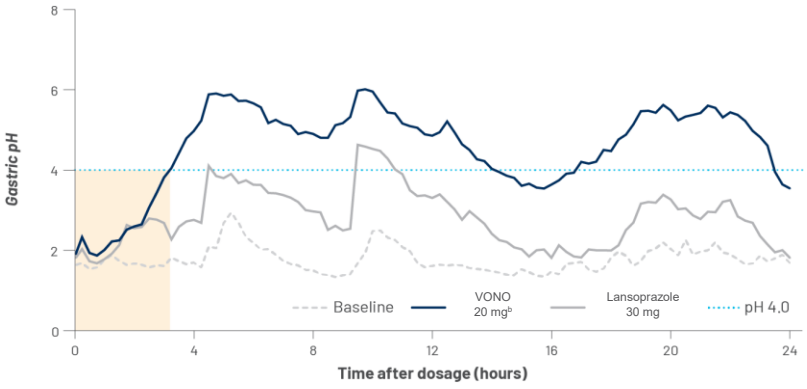
Rapid, Potent, and Durable Acid Suppression

In a phase 1, open-label, crossover study with 44 healthy volunteers receiving VOQUEZNA 20 mg once daily,

VONOPRAZAN has been shown to provide rapid, potent, and durable acid suppression[a]



Reused from Laine L et al. *Am J Gastroenterol.* 2022;117:1158-1161.

Rapid

Increased pH within 2-3 hours, reaching pH >4 within 4 hours

The clinical significance of quantitative differences in mean intragastric pH has not been established.

[a]Healthy volunteers were randomized to 7 days of vonoprazan 20 mg QD, followed by lansoprazole 30 mg QD, or the reverse, separated by a ≥7-day washout. Subjects fasted and received study drug each morning. On Days 1 and 7 of each 7-day period, breakfast was held, and subjects received standardized meals at 4 and 9 hours post-dose, and a snack at 12 hours post-dose. [b]20 mg daily is the approved dose for healing of Erosive GERD. Approved dose for maintenance of healing of Erosive GERD and Non-Erosive GERD is 10 mg once daily.
QD = once daily.
Laine L et al. *Am J Gastroenterol.* 2022;117:1158–1161.

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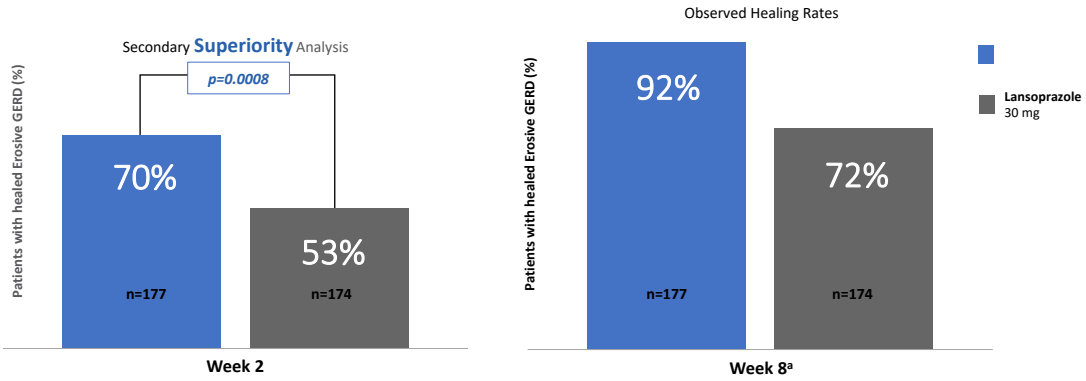
Phase 3 Trial of Vonoprazan vs Lansoprazole in US and European Patients with EE: Maintenance Phase

Complete Healing in Grades C/D[1,2]



VONOPRAZAN [a]Healing was assessed at Week 2 and Week 8. If endoscopic healing was confirmed at Week 2, the patient entered the maintenance phase. If endoscopic healing was not confirmed at Week 2, the patient continued to receive randomized treatment until Week 8.

- Lane L, et al. Presented at: Digestive Disease Week 2022; May 21-24, 2022; San Diego, California. Presentation 883-- *Gastroenterology*. 2023;164:61–71.

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Medical Management of Refractory Reflux

Patients with Abnormal Reflux Burden [reflux exposure/ increased events]

- **Reduce reflux events- increased number of reflux events- Belching/Cough**
  - Reflux inhibition- Baclofen- Not FDA Approved
- **Promotility-** Not FDA Approved
  - **Esophageal Clearance**
    - Poor evidence
  - **Poor Gastric Emptying**
    - Metoclopramide
    - Domperidone
    - Prucalopride

38

GERD: Data to Support a Precision Approach

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 17, 2019 VOL. 381 NO. 16

Randomized Trial of Medical versus Surgical Treatment for Refractory Heartburn

S.J. Spechler, J.G. Hunter, K.M. Jones, R. Lee, B.R. Smith, H. Mashimo, V.M. Sanchez, K.B. Dunbar, T.H. Pham, U.K. Murthy, T. Kim, C.S. Jackson, J.M. Wallen, E.C. von Rosenvinge, J.P. Pearl, L. Laine, A.W. Kim, A.M. Kaz, R.P. Tatum, Z.F. Gellad, S. Lagoo-Deenadayalan, J.H. Rubenstein, A.A. Ghaferi, W.-K. Lo, R.S. Fernando, B.S. Chan, S.C. Paski, D. Provenzale, D.O. Castell, D. Lieberman, R.F. Souza, W.D. Chey, S.R. Warren, A. Davis-Karim, S.D. Melton, R.M. Genta, T. Serpi,* K. Biswas, and G.D. Huang

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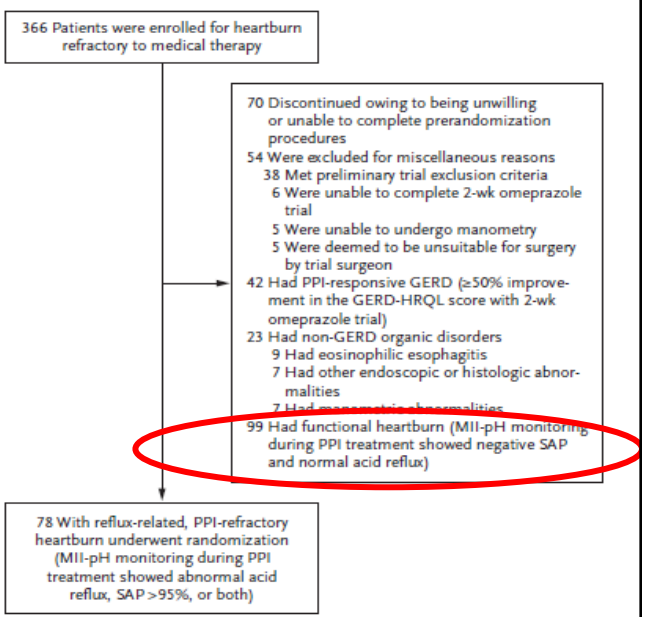
VA Randomized Trial in Refractory GERD

- Very difficult study that had to change design and sample size due to poor recruitment.
- Initially powered for approximately 390 patients- only enrolled 78 total.

- ***A LARGE PROPORTION OF PATIENTS DID NOT HAVE GERD OR WERE PPI RESPONSIVE ONCE COMPLIANCE WAS CHECKED***



Spechler SJ, et al. Randomized trial of medical versus surgical treatment of refractory heartburn. *N Engl J Med.* 2019;381:1513–1523

40

VA Randomized Trial in Refractory GERD

LIMITATIONS

- Small numbers and patients were not blinded to surgery [difficult to do].
- Anatomy- how many had hernia-GEFV.
- Limited data on regurgitation and which scores contributed to improvements in the GERD-HRQL improvement.
- Used two medications with very limited data to support efficacy
  - Baclofen- belching
  - TCA- Functional HB
  - Would have used rabeprazole or dex-lansoprazole

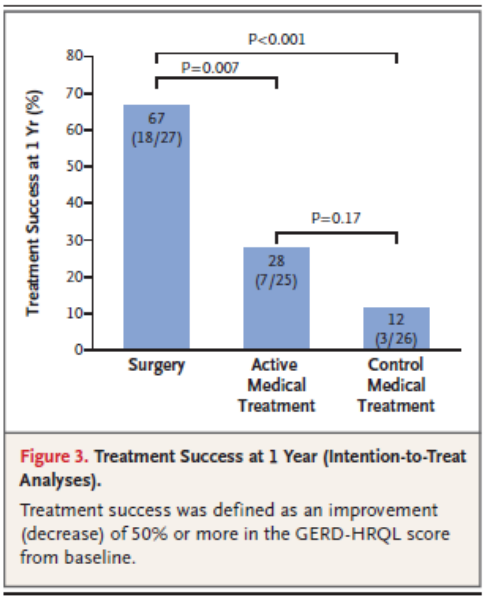


Figure 3. Treatment Success at 1 Year (Intention-to-Treat Analyses).

Treatment success was defined as an improvement (decrease) of 50% or more in the GERD-HRQL score from baseline.

Spechler SJ, et al. Randomized trial of medical versus surgical treatment of refractory heartburn. *N Engl J Med.* 2019;381:1513–1523

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The Dissatisfied Fundoplication Patient

Rates of Complications and Adverse Events

Primary Fundoplication	
Complication	Reported Rates
Primary Fundoplication	NIS database 2010 n=18,780
Acute post-operative complications (within 30 days)	4.1% [1] (n=769)
30-day surgical mortality	0.1 to 0.2% [1, 2] (n=19 to 38)
Infection	1.1% [1] (n=207)
Bleeding	0.9% [1] (n=169)
Esophageal perforation	0.9% [1] (n=169)
Acute post-operative dysphagia	50%[3, 4] (n=9,390)
Failure of fundoplication: Wrap herniation, Pouch formation, Paraoesophageal herniation	2 to 23% [1 5] (n=376 to 4319)
Post-fundoplication stenosis	10% (n=1878)
Post-fundoplication dilation rate	2.8% [5] (n=530)
Gas-bloat syndrome	10 to 32% [5 6, 7] (n=1878 to 6010)
Esophageal dysmotility, Chest pain, Diarrhea	18% to 33%[8, 9] (n=3380 to 6197)

Complications of Antireflux Surgery. Yadlapati R, Hungness ES, Pandolfino JE.Am J Gastroenterol. 2018 Aug;113(8):1137-1147. doi: 10.1038/s41395-018-0115-7. Epub 2018 Jun 14

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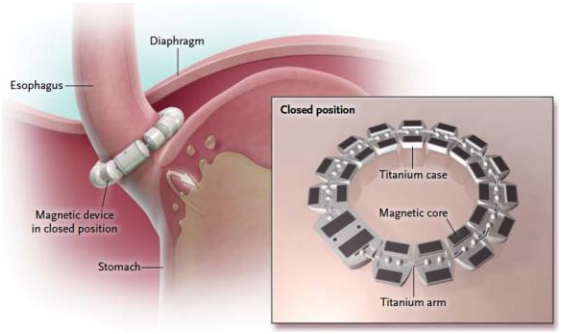
Magnetic Sphincter Augmentation:
Some Inherent Benefits Not Offered by LNF

- **Pros:**
- No alterations to gastric anatomy
- Standardized device/procedure
- Normal LES function
- Removable



Cons:
Implant, erosions and dysphagia.

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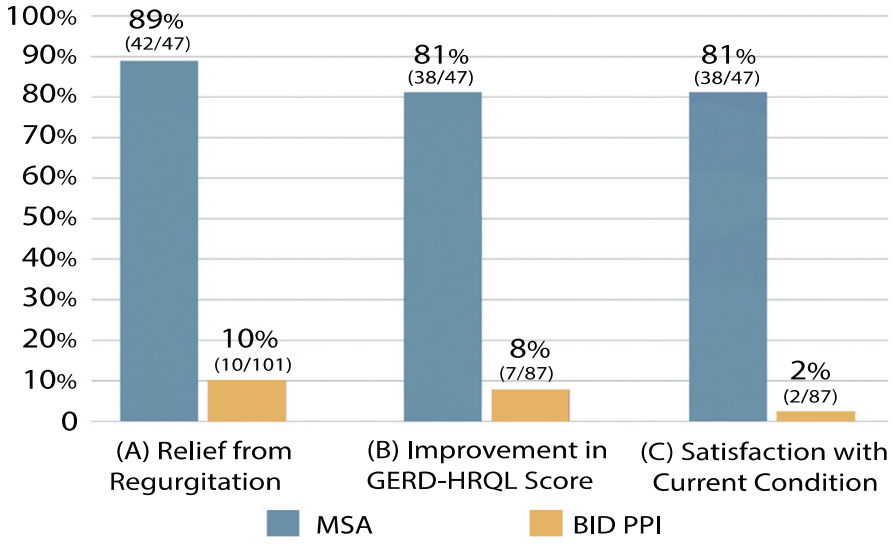
Caliber Results - Overview



Magnetic Sphincter Augmentation Superior to Proton Pump Inhibitors for Regurgitation in a 1-Year Randomized Trial.
Bell R et al. Clin Gastroenterol Hepatol. 2020 Jul;18(8):1736-1743.e2. doi: 10.1016/j.cgh.2019.08.056. Epub 2019 Sep 10.

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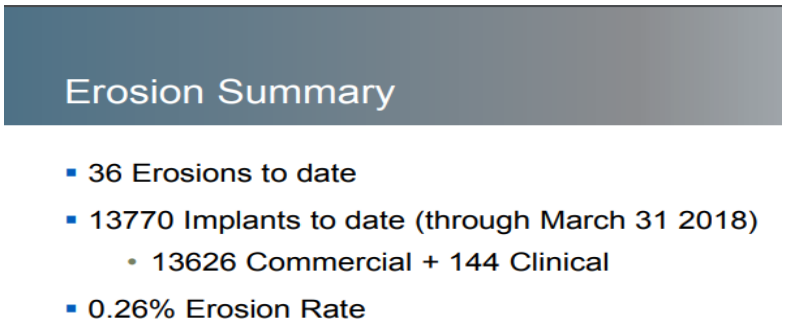
Caliber Safety - Overview

- Fifteen patients (32%) in the MSA arm reported dysphagia, rated
  - mild in 9 (19%),
  - moderate in 4 (9%), and
  - severe in 2 (4%).
- This was transient (minimal or resolved by 6 months) in 13 patients and was ongoing in 2 (4%). One rated moderate, and 1 rated severe.



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Bell R et al. Clin Gastroenterol Hepatol. 2020 Jul;18(8):1736-1743.e2. doi: 10.1016/j.cgh.2019.08.056. Epub 2019 Sep 10.

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TIF Procedure: Endoscopic Retroflex View….

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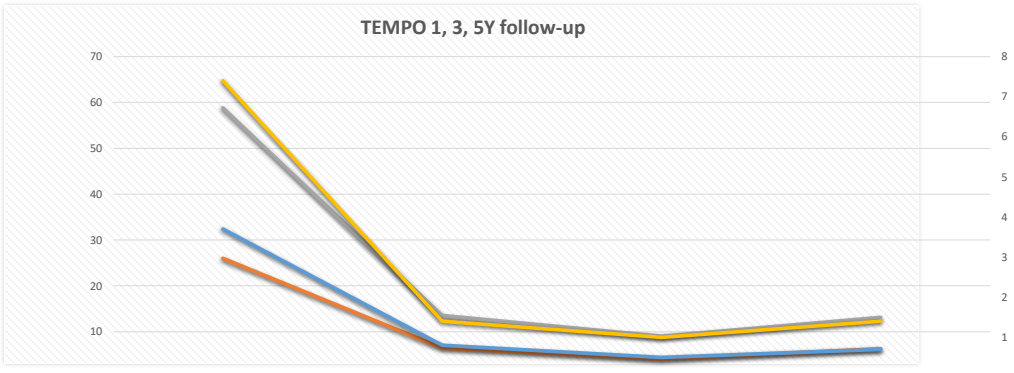
TEMPO 5 Year Durability: TIF 2.0 Procedure Pre & Post Off PPI

Reference: Trad, et al.; Surg Innov. 2018 Feb 6

All symptoms improved significantly post-TIF procedure, and scores at 1Y, 3Y and 5Y showed no clinically statistical difference



	Screening	1Y	3Y	5Y
GERD-HRQL	32.8	7.1	5	6.8
RSI	26	6.4	4	6.3
Regurgitation (from RDQ)	3.7	0.6	0.5	0.7
RDQ	3.7	0.8	0.5	0.7

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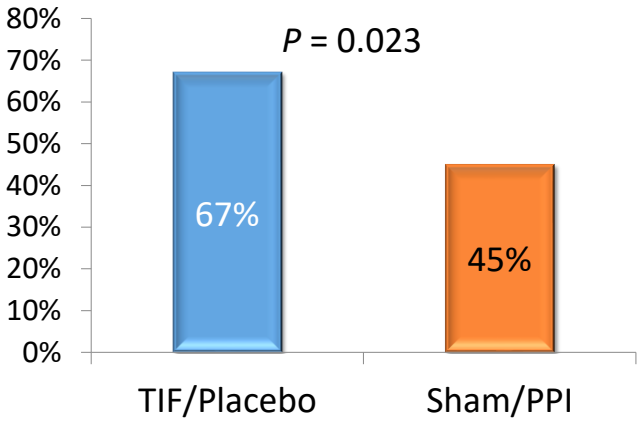
Endoscopic Therapies for GERD
Transoral Incisionless Fundoplication

- **RESPECT- Primary endpoint of troublesome regurgitation**



Reference: Hunter, et al. Gastroenterology. 2015 Feb;148(1):324-33.

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Personalized Medicine: GERD

Case:

- 42 year old male with heartburn and chest discomfort for approximately 6 months.
  - Originally seen by his PCP- referred for exercise stress echocardiogram and cardiac CT – **both negative**.
  - Current ROS
    - 15 lb weight gain, no trouble swallowing, no evidence of GI bleeding
  - Management:
    - Started on omeprazole 20 mg- mild response
    - Increased to 20 mg twice a day- about 20% better
    - Tried on pantoprazole 40 mg twice a day- no change
    - Switched to dexlansoprazole 60mg twice a day- 20% better
- 6 months later finally referred to GI
- 7 months later- Endoscopy was negative
- 8 months later- Reflux testing – Negative
- 9 months later – Manometry is Normal- Diagnosis Functional Heartburn

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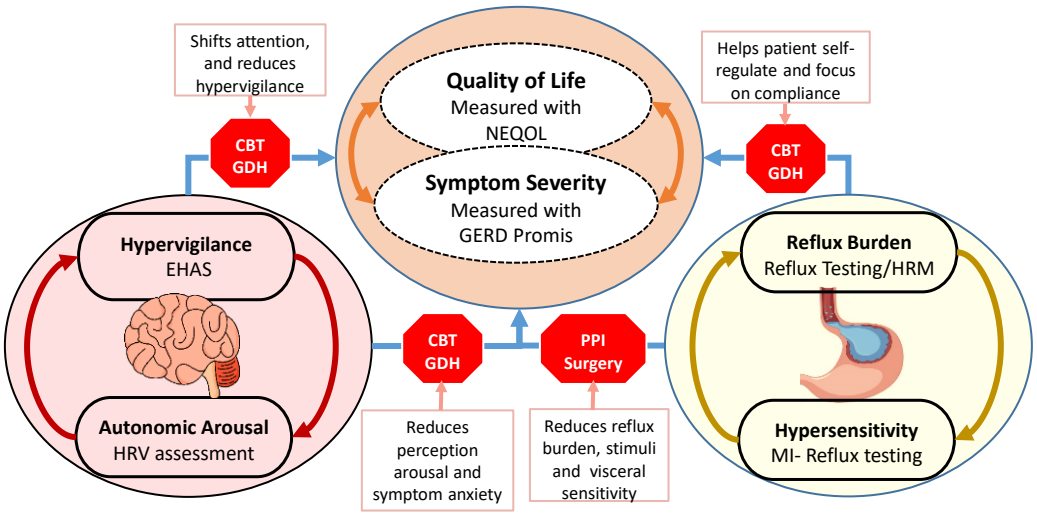
Conceptual Model of the Psycho-Physiologic Model of GERD



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Medical Management
NOT FDA APPROVED

Table. Antidepressants With the Best Evidence to Support
Their Use in a Specific Esophageal Disorder With a Functional Component

Esophageal disorder	Medication Class	Dose
Functional chest pain	Imipramine TCA	25–50 mg[a]
	Sertraline SSRI	50–200 mg[a]
	Venlafaxine SNRI	75 mg
Hypersensitive esophagus	Citalopram SSRI	20 mg
Refractory GERD	Fluoxetine SSRI	20 mg
Globus	Amitriptyline TCA	25 mg

**GERD, gastroesophageal reflux disease; SNRI, serotonin-norepinephrine reuptake inhibitors.*
[a]*Escalating dose*
Editorial- CGH 2014: Maradey-Romero & Fass

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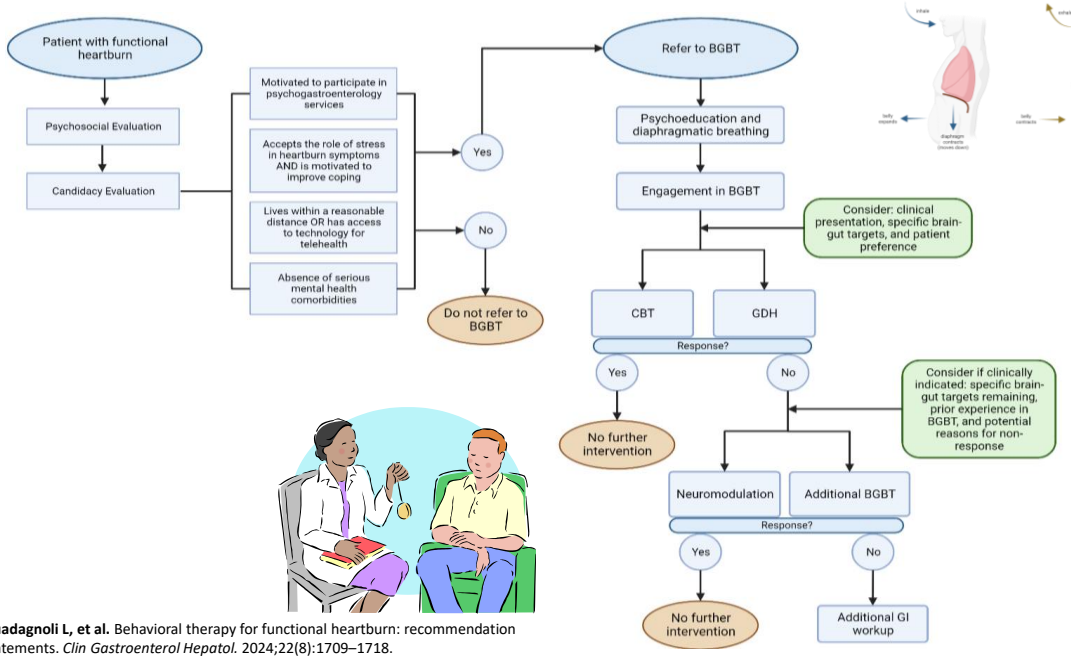
Behavioral Medicine in GERD



Guadagnoli L, et al. Behavioral therapy for functional heartburn: recommendation statements. *Clin Gastroenterol Hepatol.* 2024;22(8):1709–1718.

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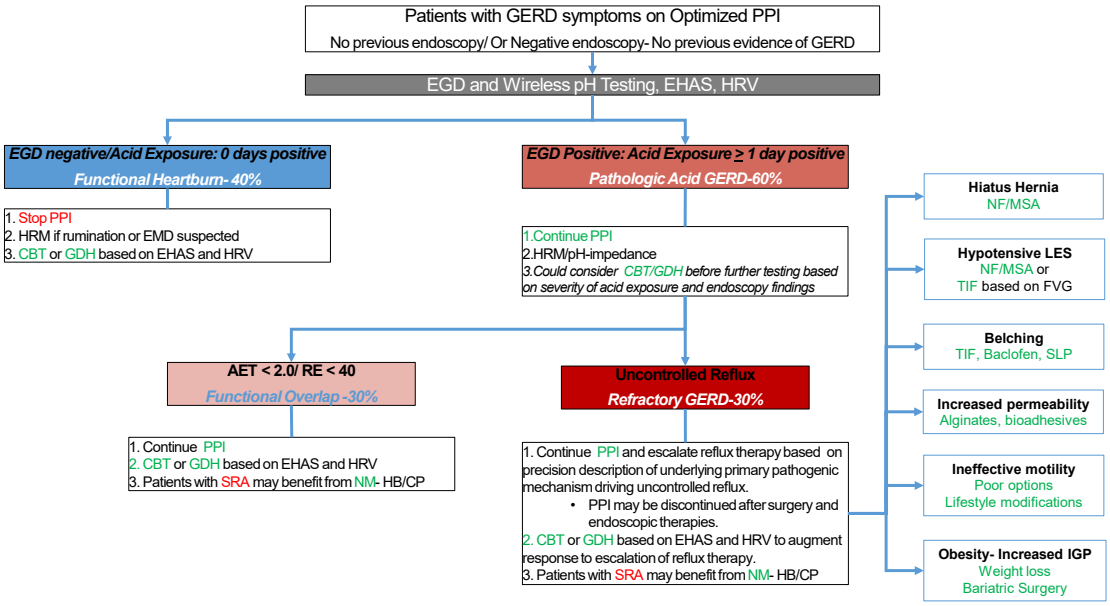
Evolving Psycho-Physiologic GERD Model Developed for Clinical Practice



PPI proton pump inhibitor, **HRM** high-resolution manometry, **EHAS** Esophageal Hypervigilance and Anxiety Scale, **NM** Neuromodulator, **HRV** heart rate variability, **CBT** Cognitive Behavioral Therapy, **GDH** Gut Directed Hypnotherapy, **AET** acid exposure time, **RE** reflux events, **TIF** transoral incisionless fundoplication, **NF** Nissen Fundoplication, **MSA** Magnetic sphincter Augmentation, **SLP** speech language pathologist. **FVG** Flap Valve grade

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Management of GERD in 2026

- The majority of patients can be effectively managed in the community practice setting using endoscopy, wireless pH testing and PPI use based on degree of acid suppression.
- However, 40-50% of patients are not satisfied with PPI therapy or have some intolerance.
  - *These patients will likely require more sophisticated testing and this may warrant referral to a reflux center of excellence.*
- Patients can be further phenotyped using HRIM and pH-impedance and treatment can be personalized based on patient input and various predictors of outcome:
  - *Anatomy*
  - *BMI- GLP-1s*
  - *Pattern and type of reflux mechanism*

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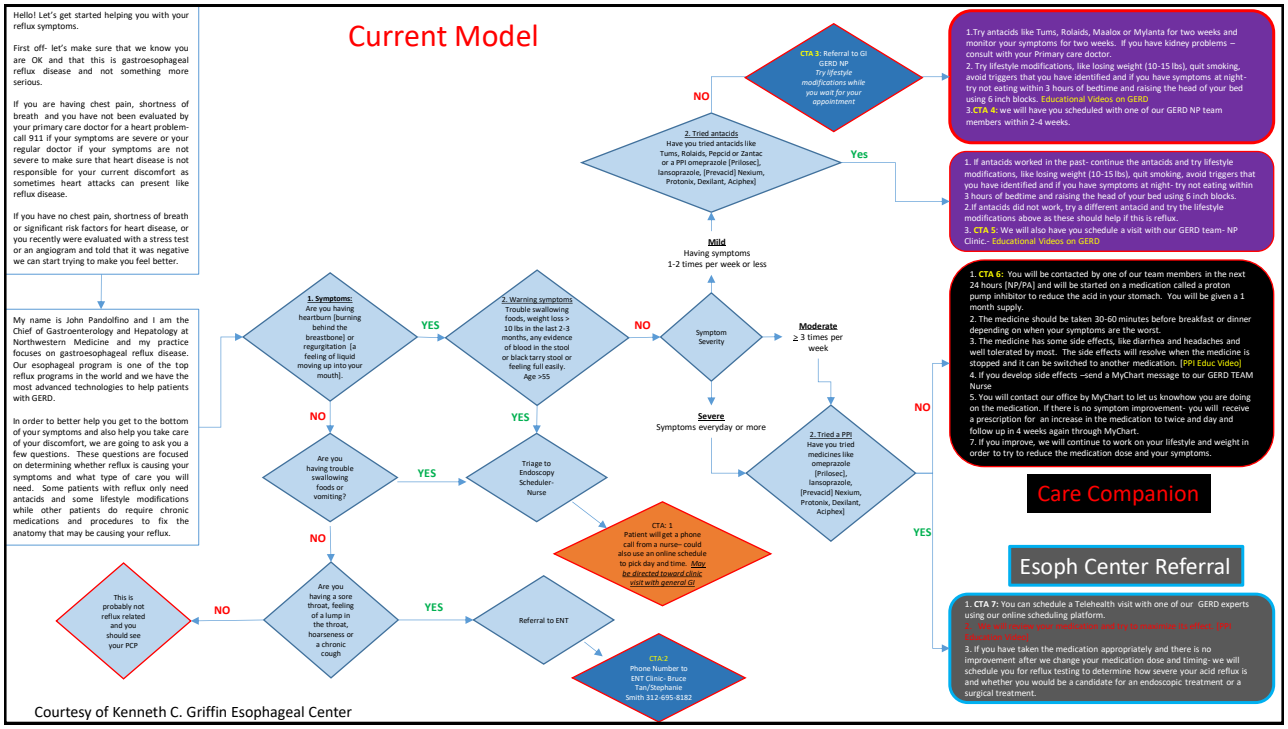

Courtesy of Kenneth C. Griffin Esophageal Center

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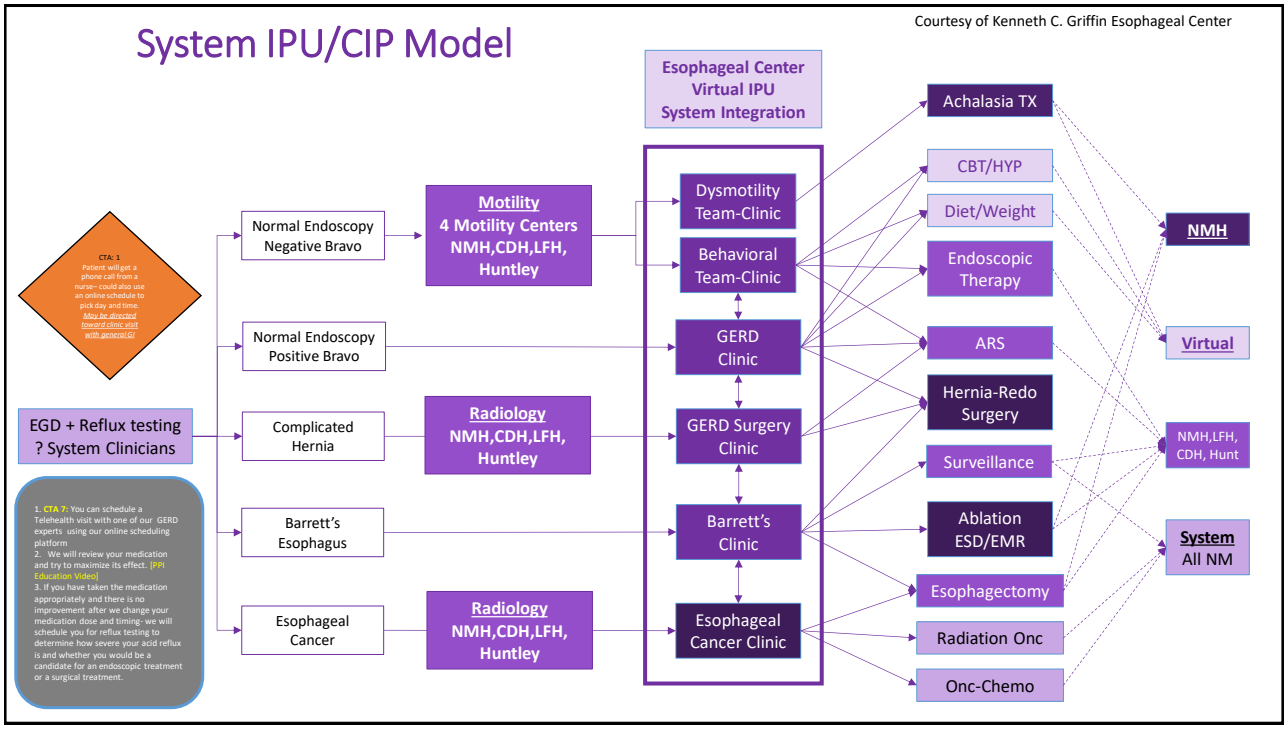

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What Is the Best Approach to Diagnosing GERD in Patients Not Responding to PPI Therapy?

A. Endoscopy
B. Wireless pH monitoring over 96 hours off PPI
C. Wireless pH monitoring over 96 hours on PPI
D. 24-hour pH-impedance testing off PPI
E. 24-hour pH-impedance testing on PPI

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