Esophageal and Gastric consideration for Solid-Organ Transplant: Dysmotility and Acid-suppression

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Annual Vanderbilt Transplant APP Symposium

VANDERBILT HEALTH

Disclosures

NIH Support

R01

R21

Consulting

Legal: Diabetic Therapy

Blueprints Medical

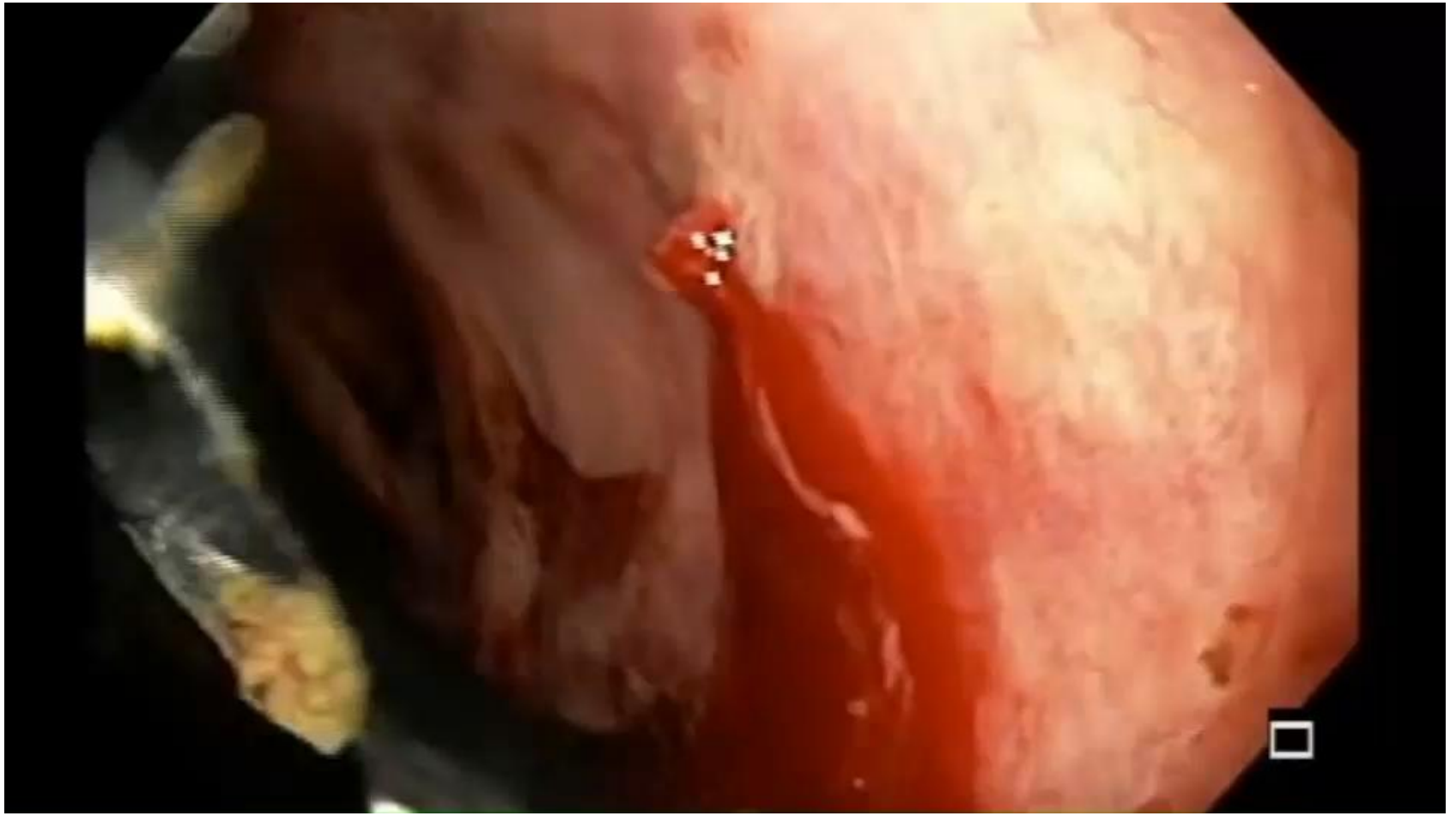
Sanofi/Regeneron

Medical Scientific Advisory Board

Esophageal Scleroderma

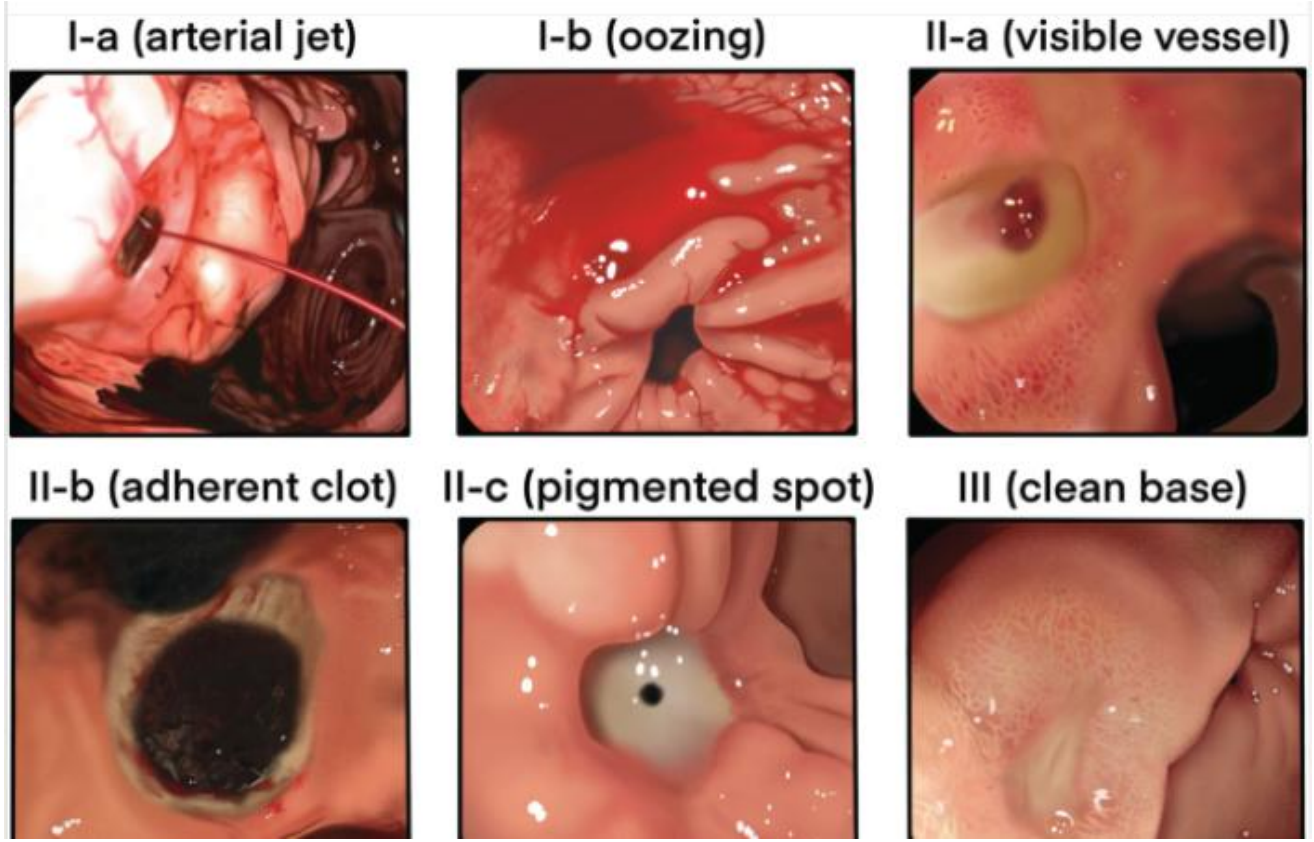
Vanderbilt Co-owns the patent for MiVU

You are called for a patient with anemia post transplant, what do you do?



Mucosal injury after Transplant

- Ulcerations
  - Peptic ulcers can be common
    - Risk factors:
      - Steroids
      - Stress response from surgery
      - Use of NSAIDS
      - Impairment of the native gastroduodenal cytoprotection due to AZA- or MMF-induced slowing of intestinal cell turnover



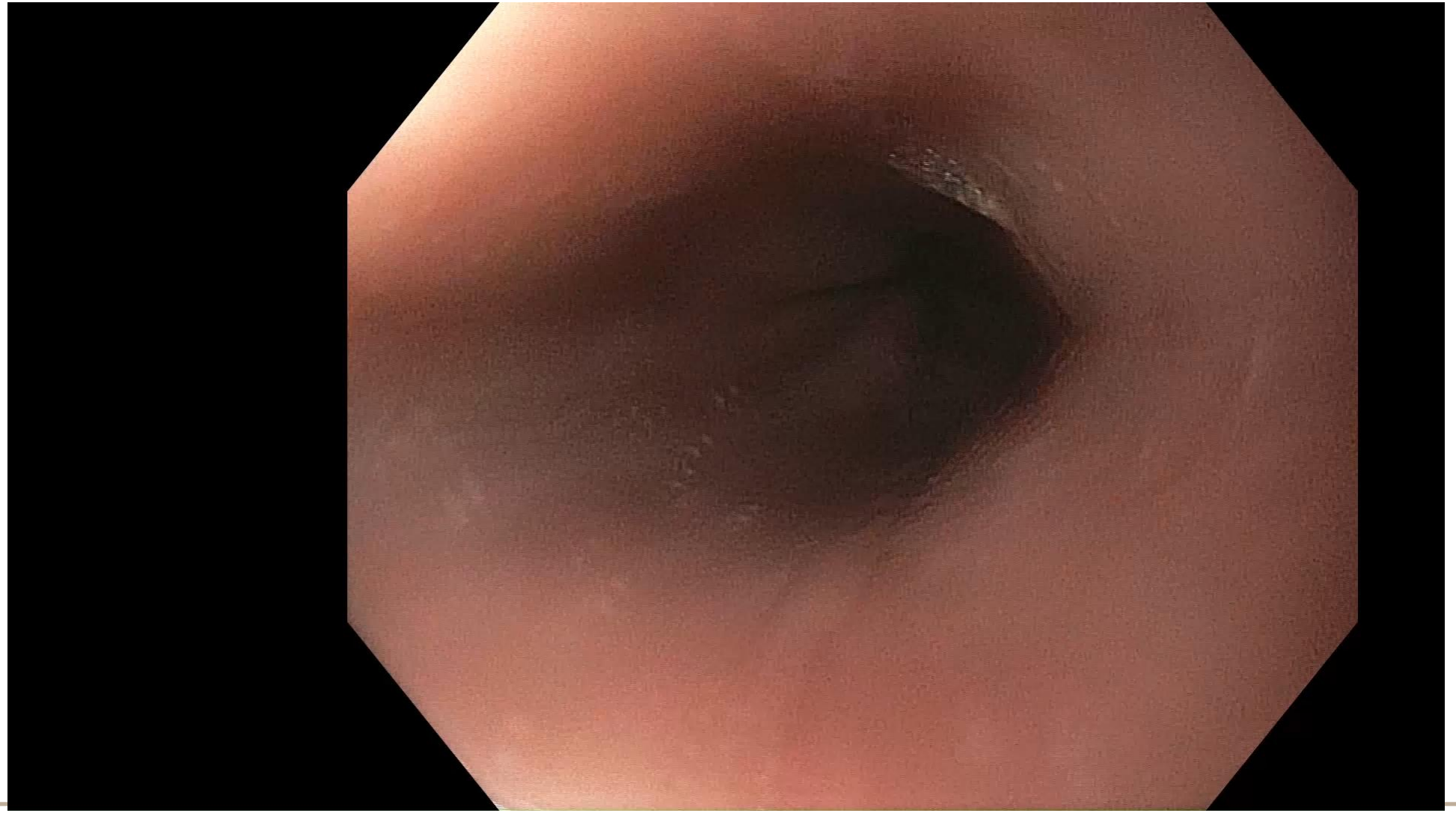
Mucosal injury after Transplant

- Ulcerations
  - Peptic ulcers can be common
    - Treatment
      - Proton Pump Inhibitors (omeprazole)
        - Be Careful with Hepatitis C Organ donor – prefer to avoid PPIs as able while on therapy for Hepatitis C treatment absorption
      - Anti-histamines (H2RA – famotidine)

5-year-old child post heart transplant prevents with feeding difficulty. He reports difficulty with swallowing his immunosuppression.

- Differential?
- Next step in management?

Patient given BID PPI, no improvement, referred for open access endoscopy. What is your next step?



Age	Preschoolers (≤3 years)[1-5]	School-Age Children (4-11 years)[1-5]	Adolescents and Adults (≥12 years)[1-5]
Common Signs & Symptoms	• Poor growth • Failure to thrive • Feeding concerns • Food refusal	• Abdominal pain • Vomiting • Regurgitation • Heartburn	• Dysphagia • Food impaction • Heartburn • Chest pain

Symptoms often progress from feeding difficulties in young children to dysphagia and food impaction in older children and adults[4]

Treat-to-Target in EoE: 2026

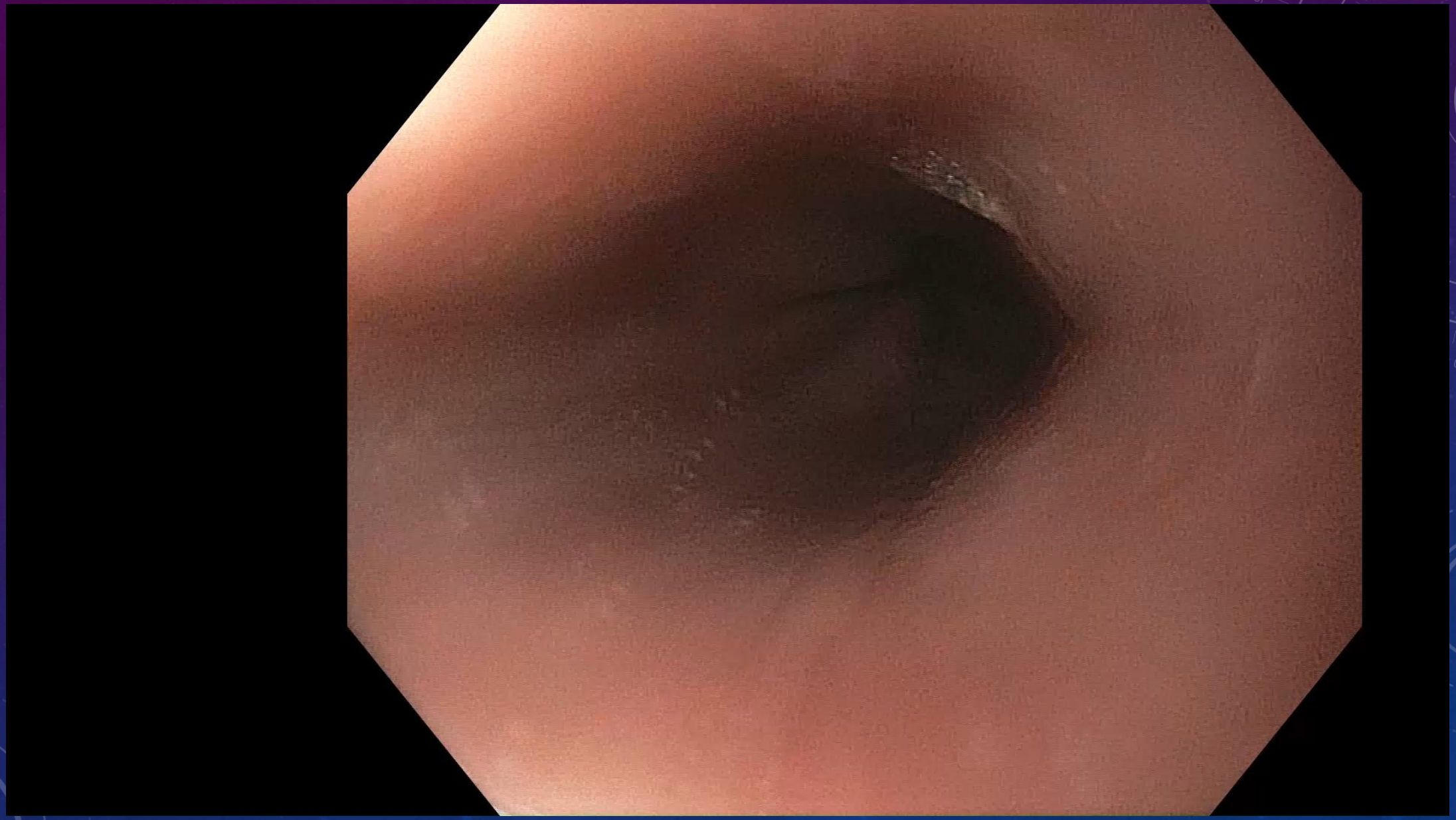
Optimal management should include objective measures of disease activity and not just symptoms

- **Symptoms**
  - Resolution of dysphagia without the need to modify or avoid food based on texture
- **Histopathology**
  - Resolution of esophageal eosinophilic inflammation
    - (<5-15 eos/hpf; EoE-HSS)
- **Endoscopy**
  - Improvement in inflammatory features and strictures
    - (Diameter > 15 mm ; EREFS overall score ≤ 2)

Management of EoE in 2026

- First line therapy for EoE can include PPI, topical steroids, dietary elimination, and dupilumab
- EoE is a chronic disease and maintenance therapy is needed to prevent fibrosis
- Esophageal dilation in addition to first-line therapy can help if ongoing dysphagia
- Biologic therapy is being positioned now
- Eosinophils can be in the stomach / duodenum / colon (EGID)
- In our pediatric group: Growth matters!

DILATION: EREFS AND PULL UP TECHNIQUE



62-year-old patient presents with need for urgent lung transplant listing. She reports chronic reflux and states she has been told she has a hiatal hernia.

- Next step in management?
- Does the hernia impact your plan for transplant?

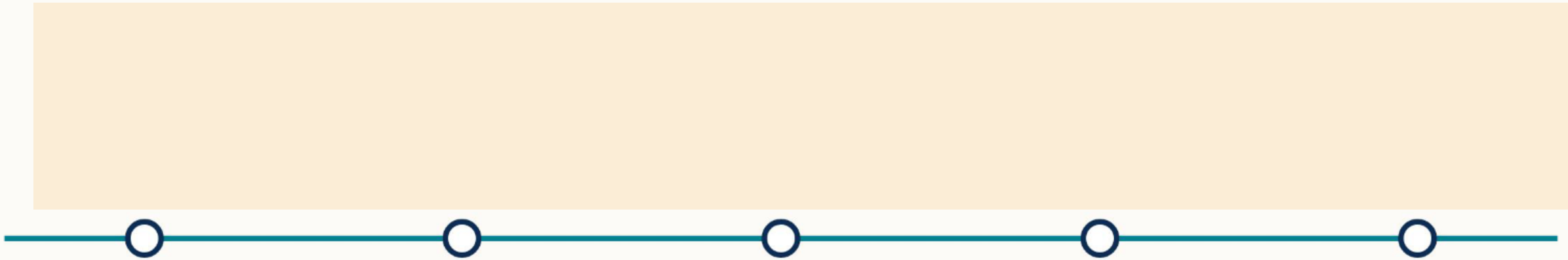
GERD testing

- Reflux testing
  - Ambulatory pH, Wireless pH capsule, pH with Impedance (MII-pH)
- Esophageal function testing:
  - High resolution manometry
- Limitation:
  - **Does not establish causality between esophageal disease and pulmonary microaspiration**

Esophageal Function Testing

- Weak swallows associated with early rehospitalization
- Increased risk of CLAD (rejection) with decreased esophageal clearance

The Recommended Clinical Pathway



1. Optimize

1) Evaluate lifestyle habits
2) Dietary changes
3) Increase PPI
4) Change to PCAB

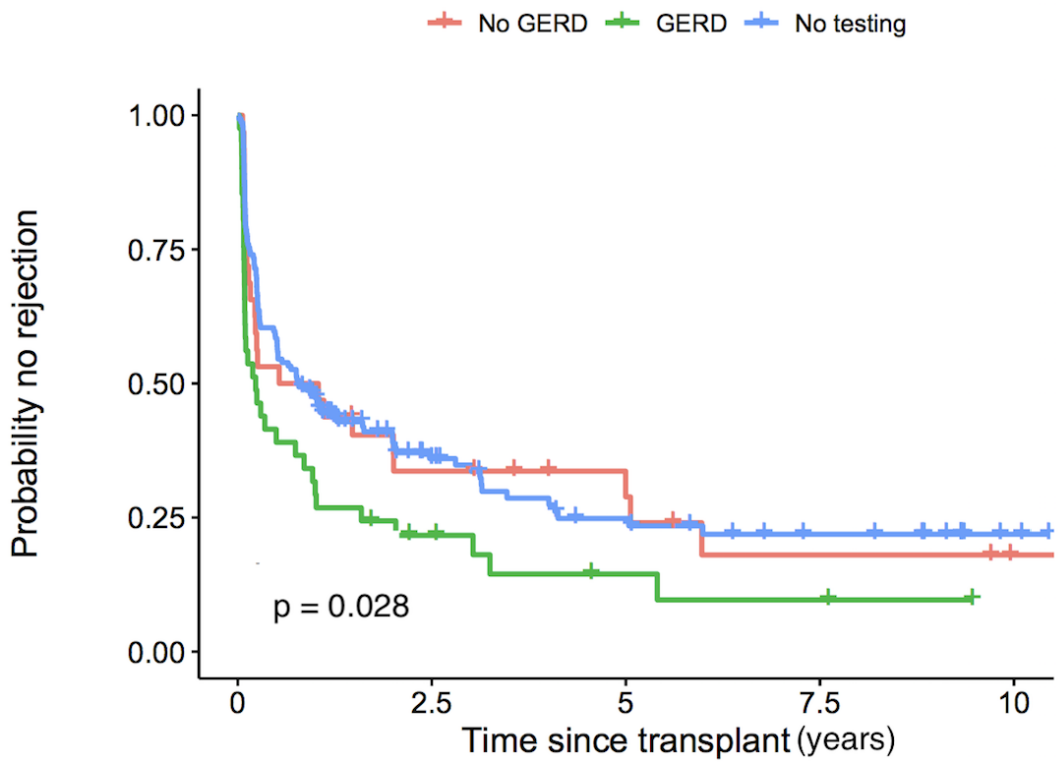
PPI and PCAB

	Omeprazole Equivalent
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

1) PPI
   a) Ensure Proper timing
   b) Ensure proper dosing
   c) Consider increasing dosing to help with enzymatic polymorphism

2) PCAB
   a) Vonoprazan
      i. Overcomes the enzymatic polymorphism
      ii. Potential option for refractory for reflux
      iii. H. pylori, Erosive Esophagitis, and NERD

Pre-Transplant GERD Predicts Acute Rejection in Lung Transplant



DDW 2021

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Transplant Hepatology

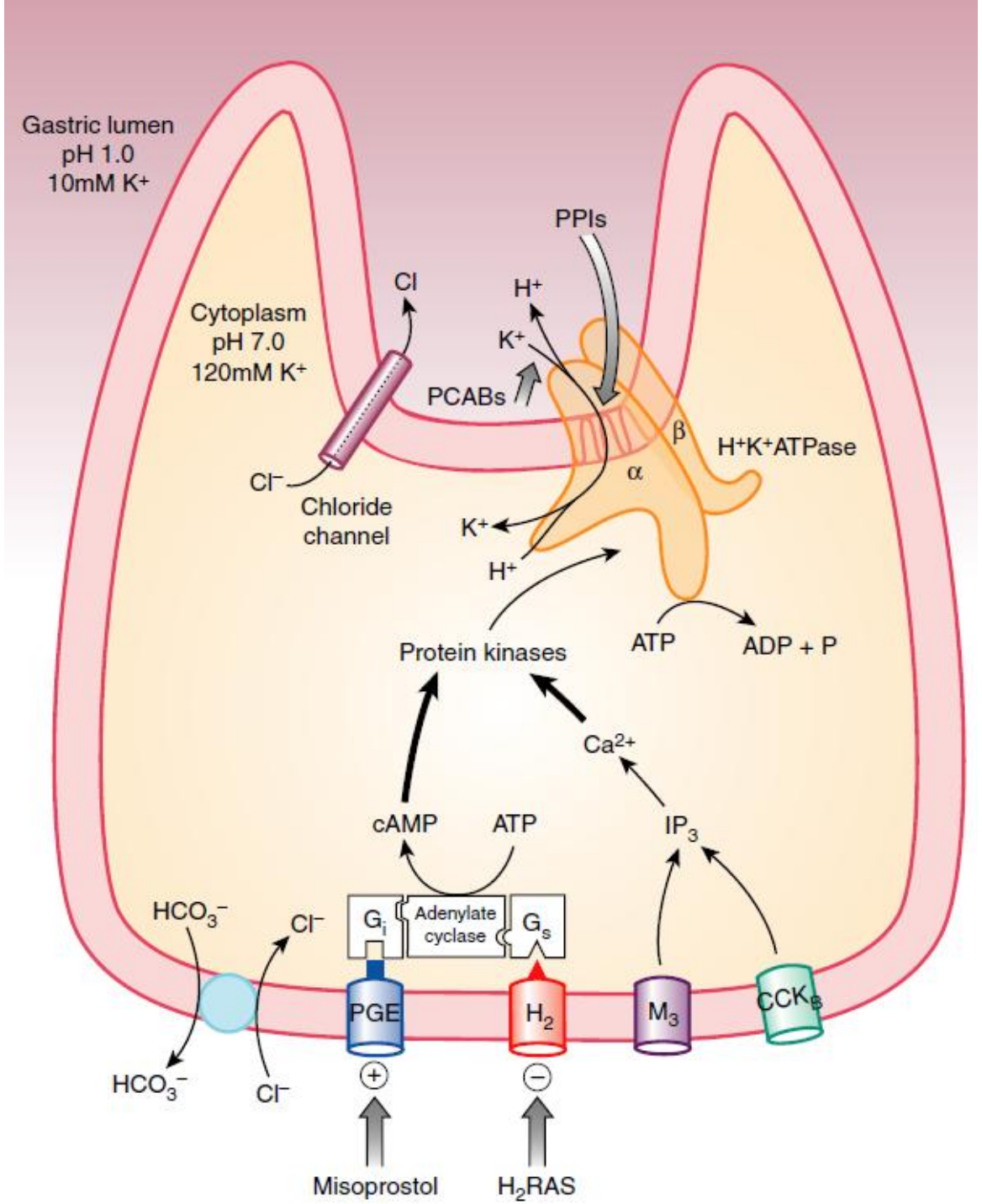
Reflux Testing in Lung Transplant

- pH parameters (AET) are associated with transplant outcomes
  - Acute Rejection
  - Chronic Rejection
  - 3-year survival

	Hazard Ratio for BOS	*P*
Increased AET	3.95 (1.19-13.1)	0.02
Elevated DeMeester	3.54 (1.09-11.6)	0.04
	Hazard ratio for CLAD	
Increased AET	3.05 (1.01-9.48)	0.05
Elevated DeMeester	2.78 (0.91-8.51)	0.07

AET indicates acid exposure time; BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction.

Acid-suppression



PPI Pharmacokinetics

- Only actively secreting parietal cells are affected by PPIs
  - *Fasting* - only ~5% of proton pumps actively secreting
  - *With meals* - 60-70% of proton pumps actively secreting
  - Food can affect bioavailability of some PPIs
  - Give PPIs 30-60 minutes before a meal
- PPIs have short half-life (~90 minutes)
  - Stomach constantly making new proton pumps
  - 3-5 days required to reach steady-state inhibition
- PPIs are metabolized primarily by CYP2C19
  - Polymorphisms in CYP2C19 gene among individuals affect rate of PPI metabolism

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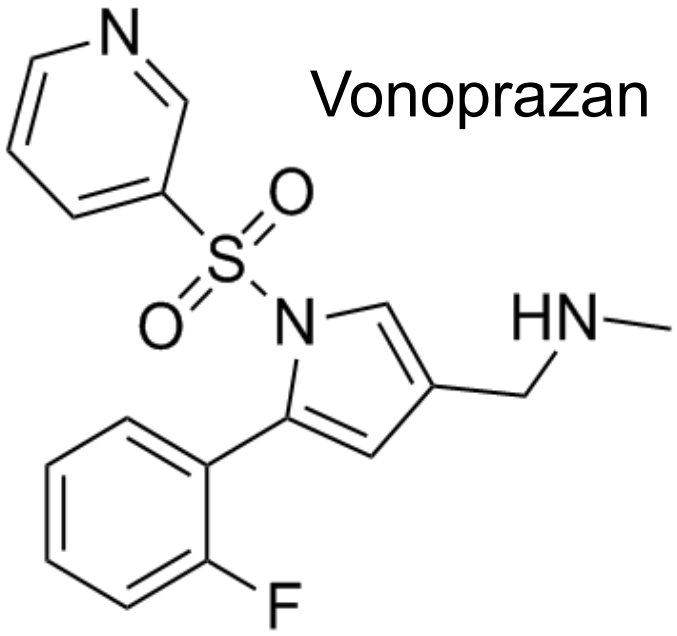
Potassium-Competitive Acid Blockers (P-CABs)

- The P-CAB vonoprazan has been used clinically in Japan since 2015.

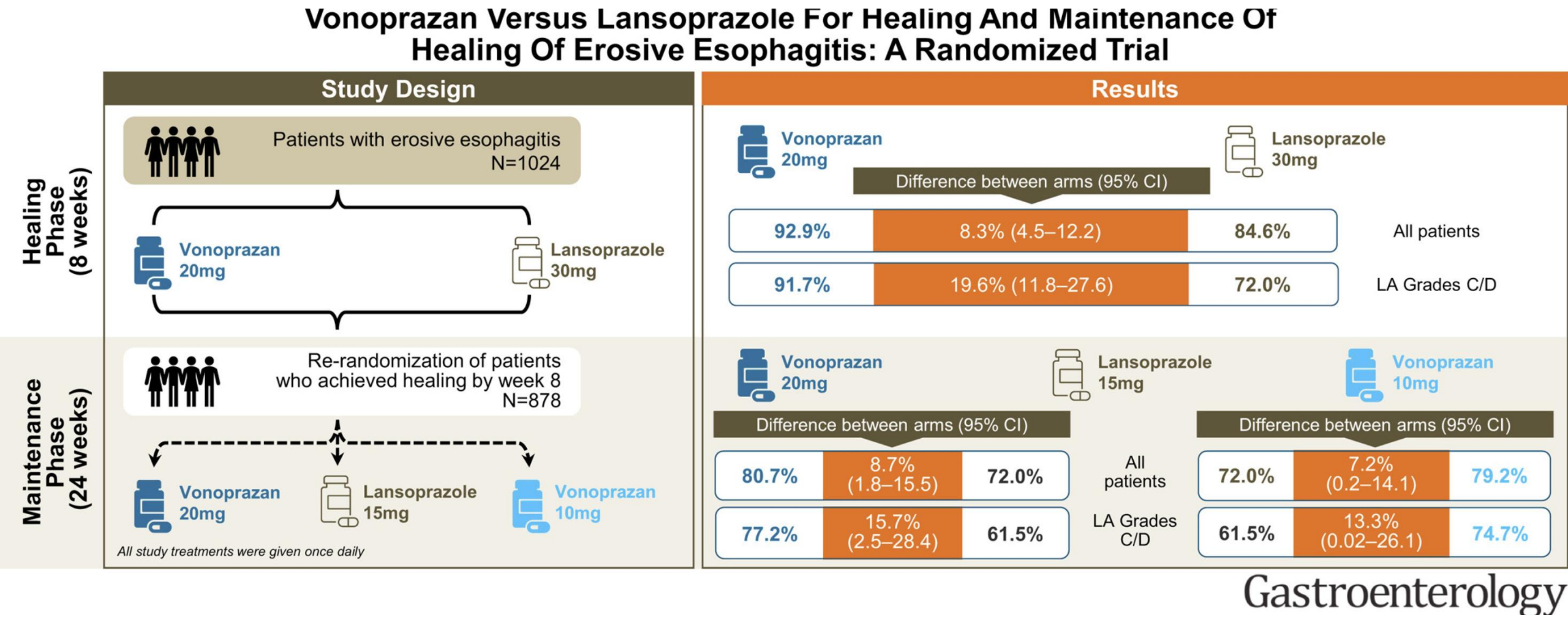


- P-CABs inhibit the H^+,K^+-ATPase (proton pump) of the parietal cell

P-CAB Pharmacologic Features

- P-CABs are acid stable
  - Do not require enteric coating
- P-CABs are active drugs, not prodrugs like PPIs
- P-CABs inhibit H^+,K^+-ATPase
  - Bind ionically (not covalently) to H^+,K^+-ATPase, preventing exchange of potassium ions for protons
  - Bind active and inactive proton pumps
    - No need to time dose around meals
- P-CABs have long half-life (7-8 hours for vonoprazan)
- P-CABs not metabolized primarily by CYP2C19

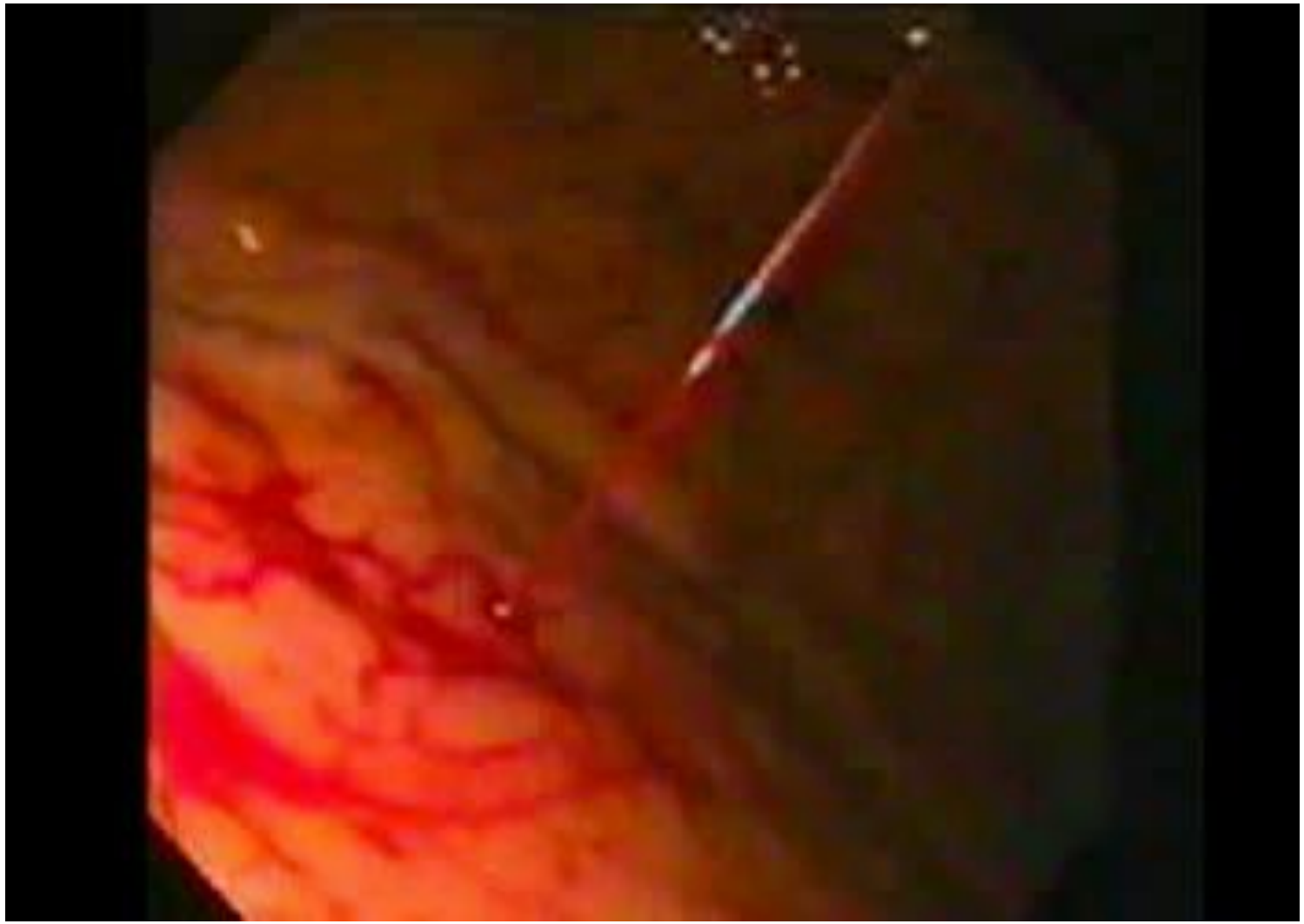
PPI and PCAB



Gastroenterology

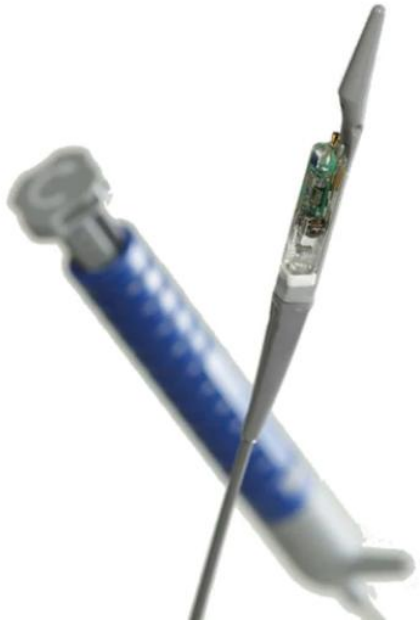
Laine, Gastroenterology, Volume 164, Issue 1 2023

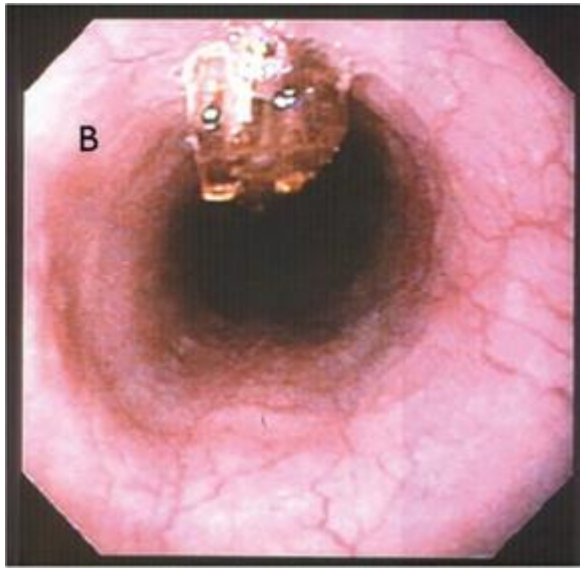
Is Acid Suppression Important?

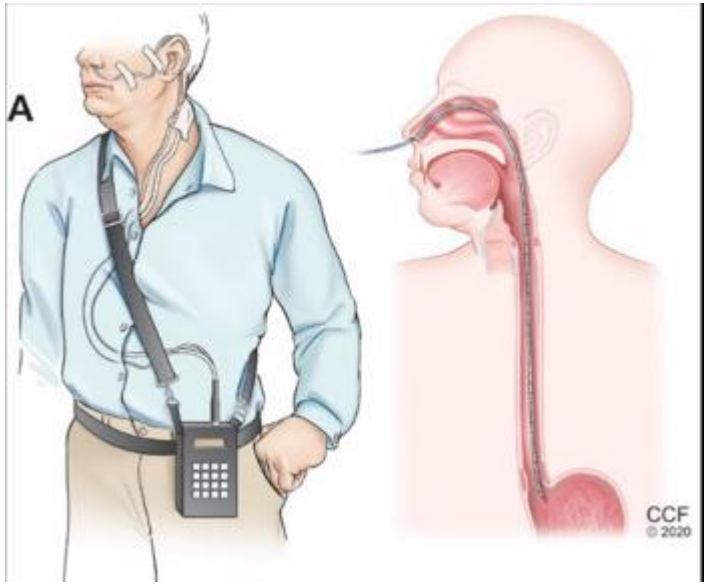


Reflux Monitoring

- Acid reflux testing
  - Wireless pH - Placed endoscopically during EGD
  - Transnasal pH monitoring
  - Off acid-suppression; often times post-lung transplant

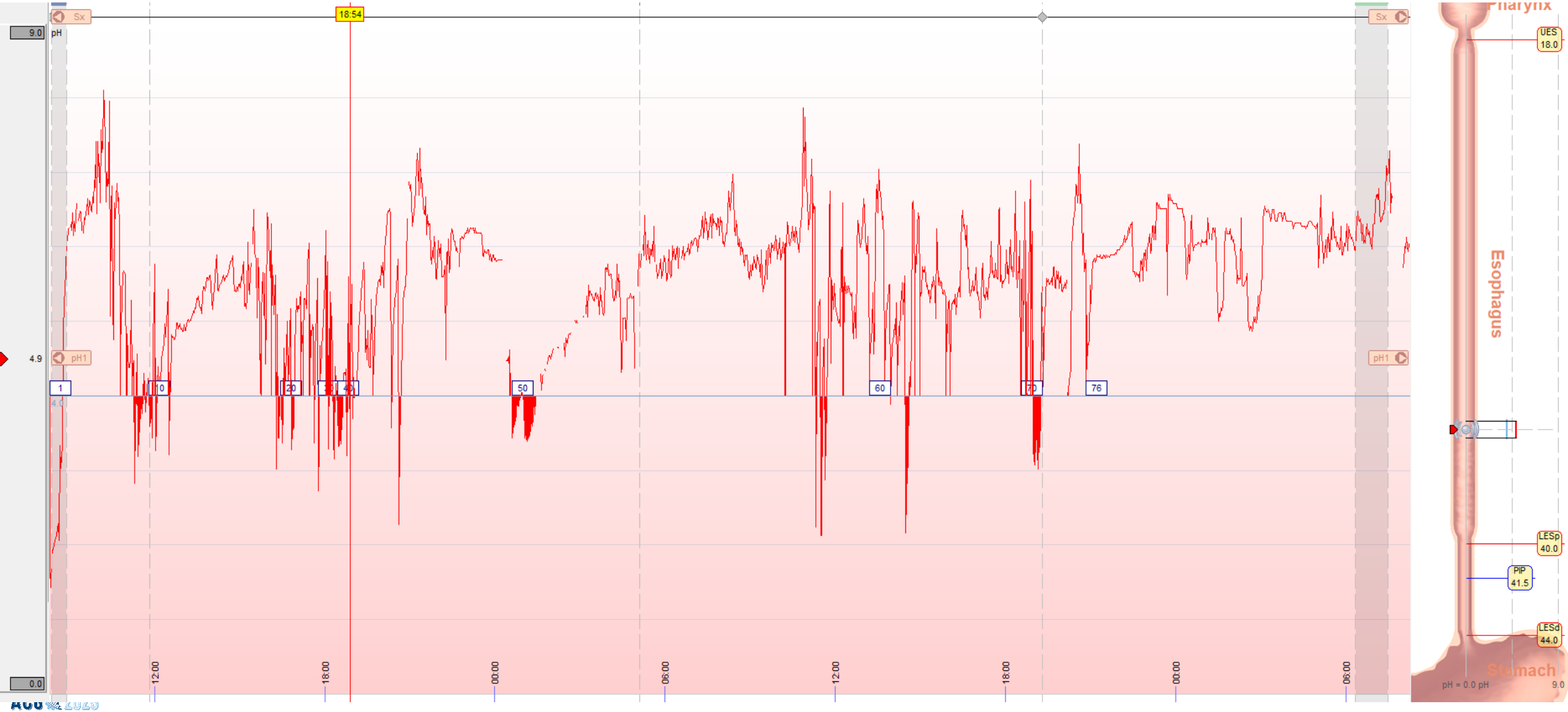






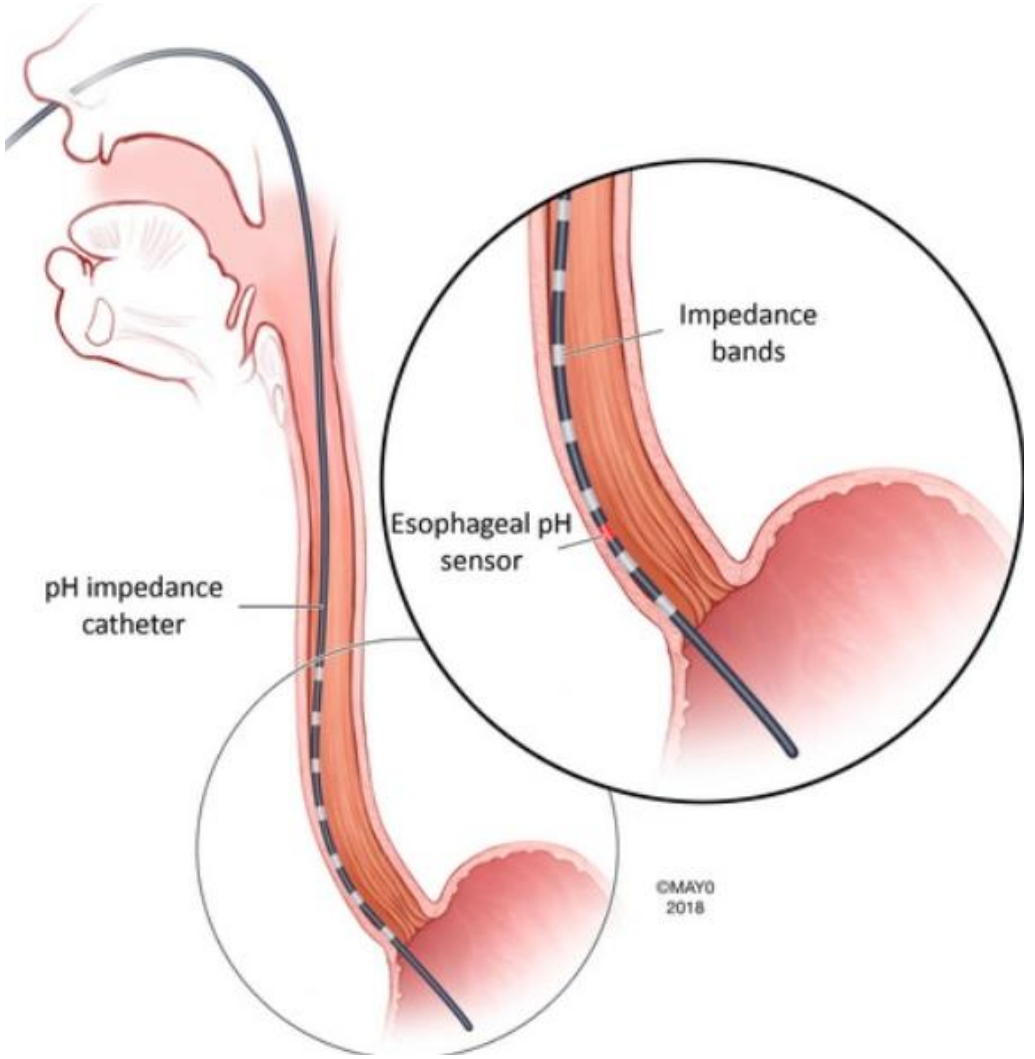
Young A, et al. Cleveland Clinic Journal of Medicine Apr 2020, 87 (4) 223-230
www.Medtronic.com

Ambulatory Reflux Monitoring



Impedance Monitoring

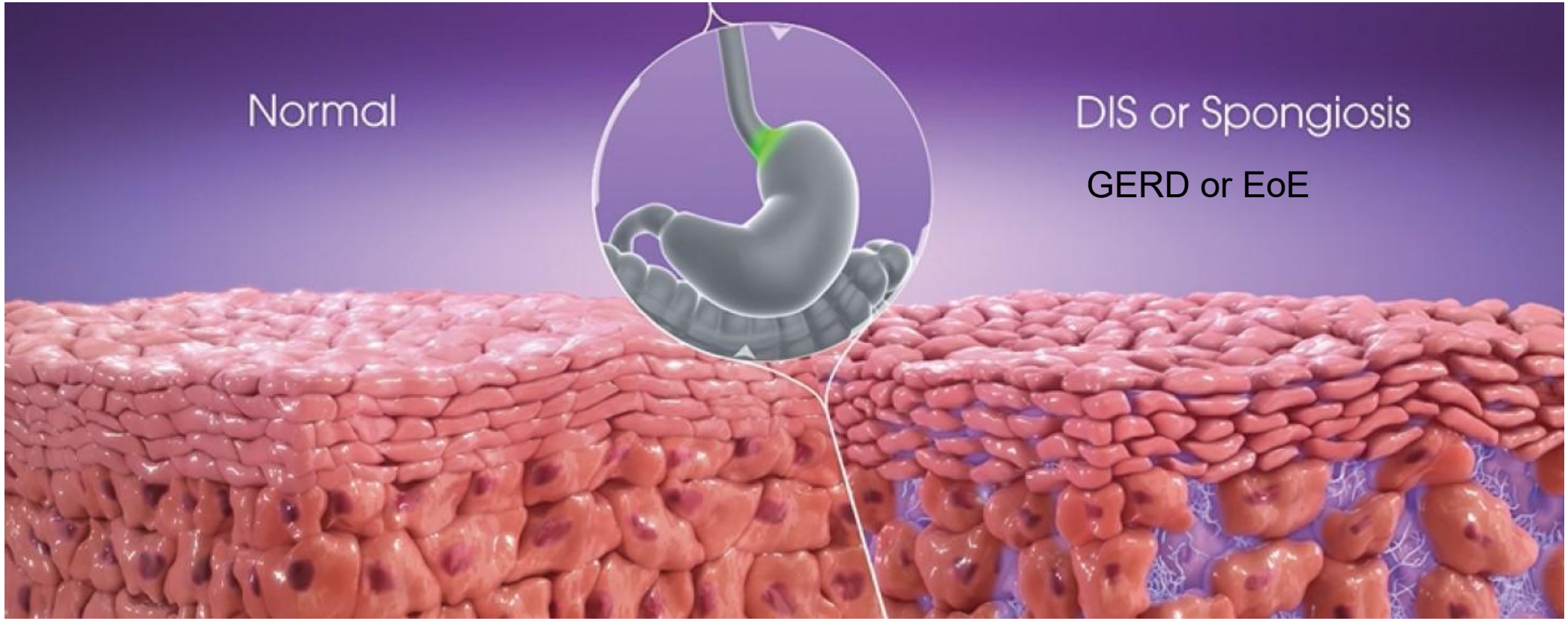
- Acid and non-acid testing
  - Impedance testing
  - Typically, **on therapy**; breakthrough symptoms
    - Despite adequate response to PPI, is there breakthrough symptoms of reflux leading to worsening lung dysfunction?



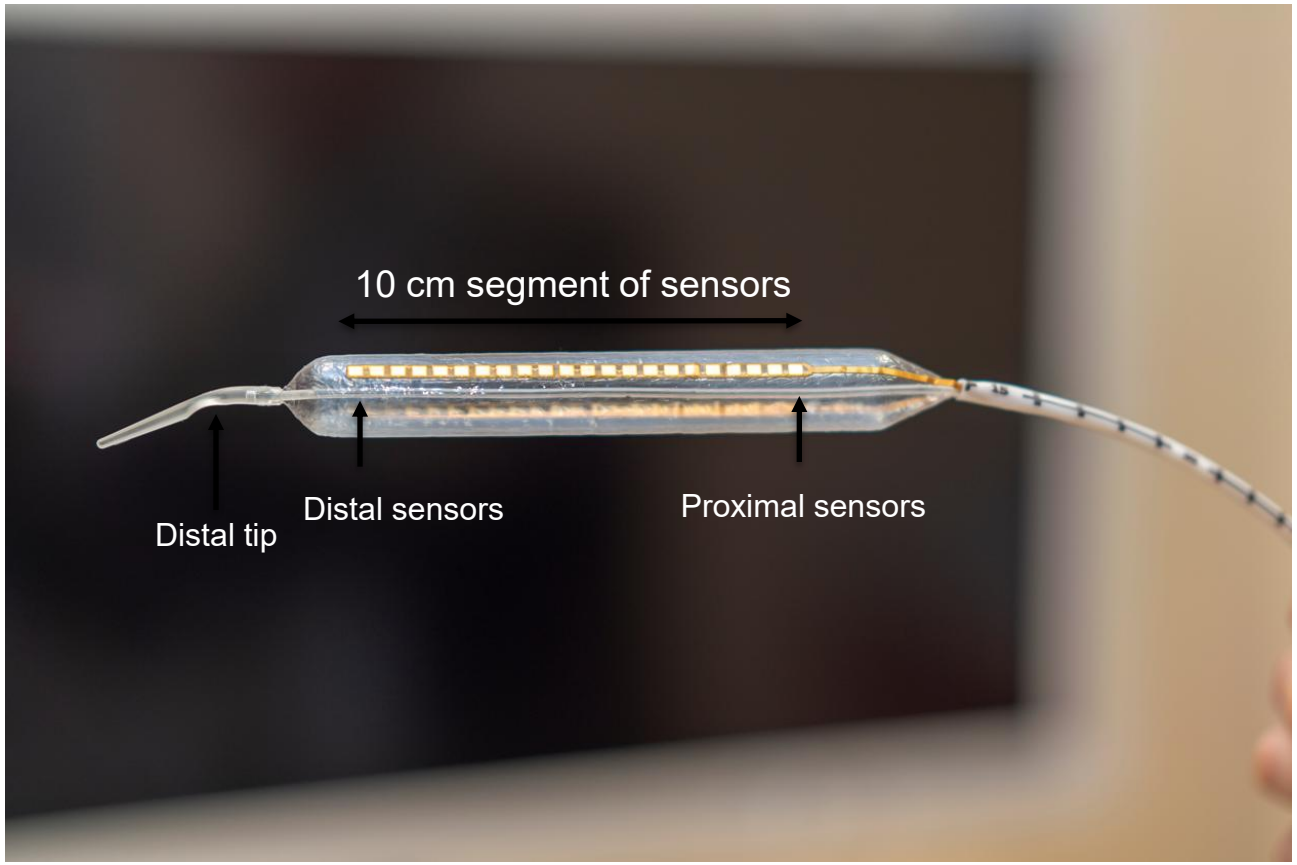
Blevins CH, et al. Neurogastroenterology and motility. 2018;30(10)

Mucosal integrity testing

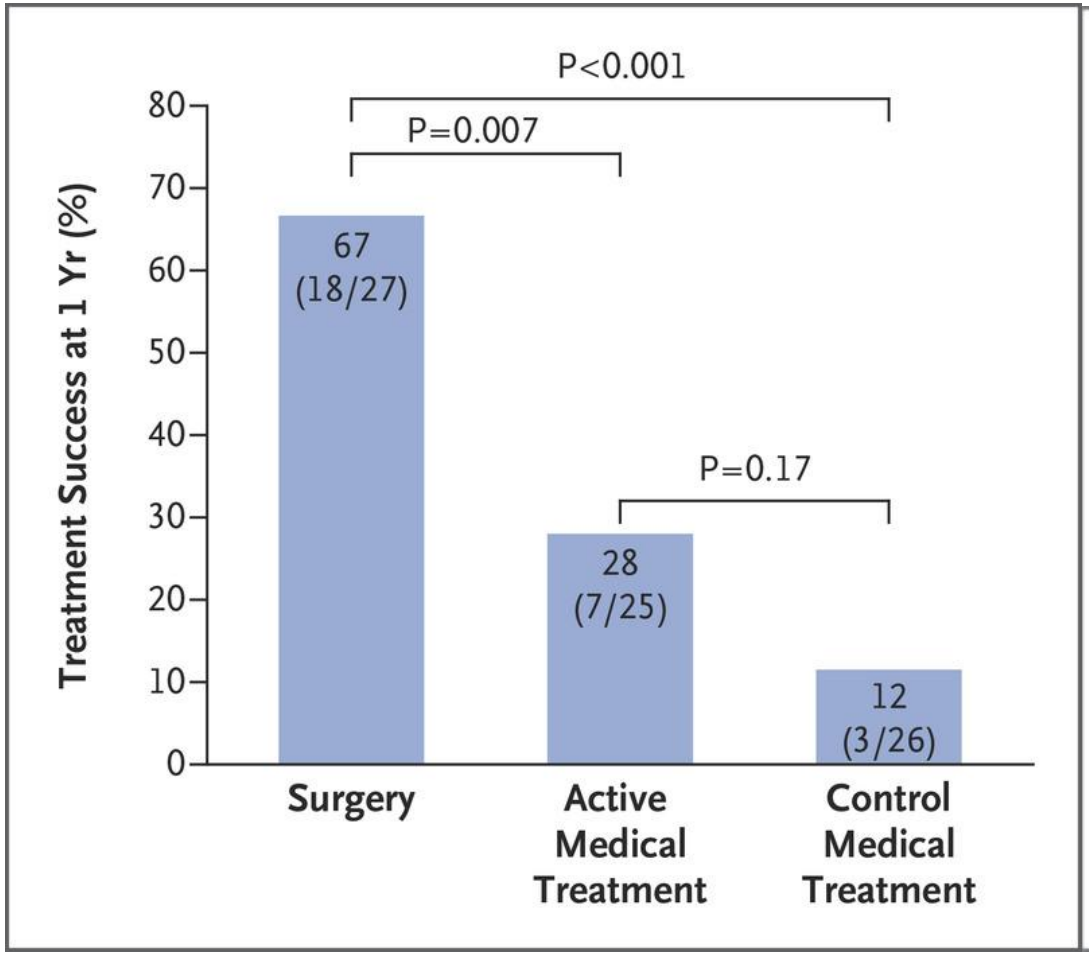
- Mucosal Integrity is affected by the presence of dilated intercellular spaces (DIS) which affects paracellular permeability.

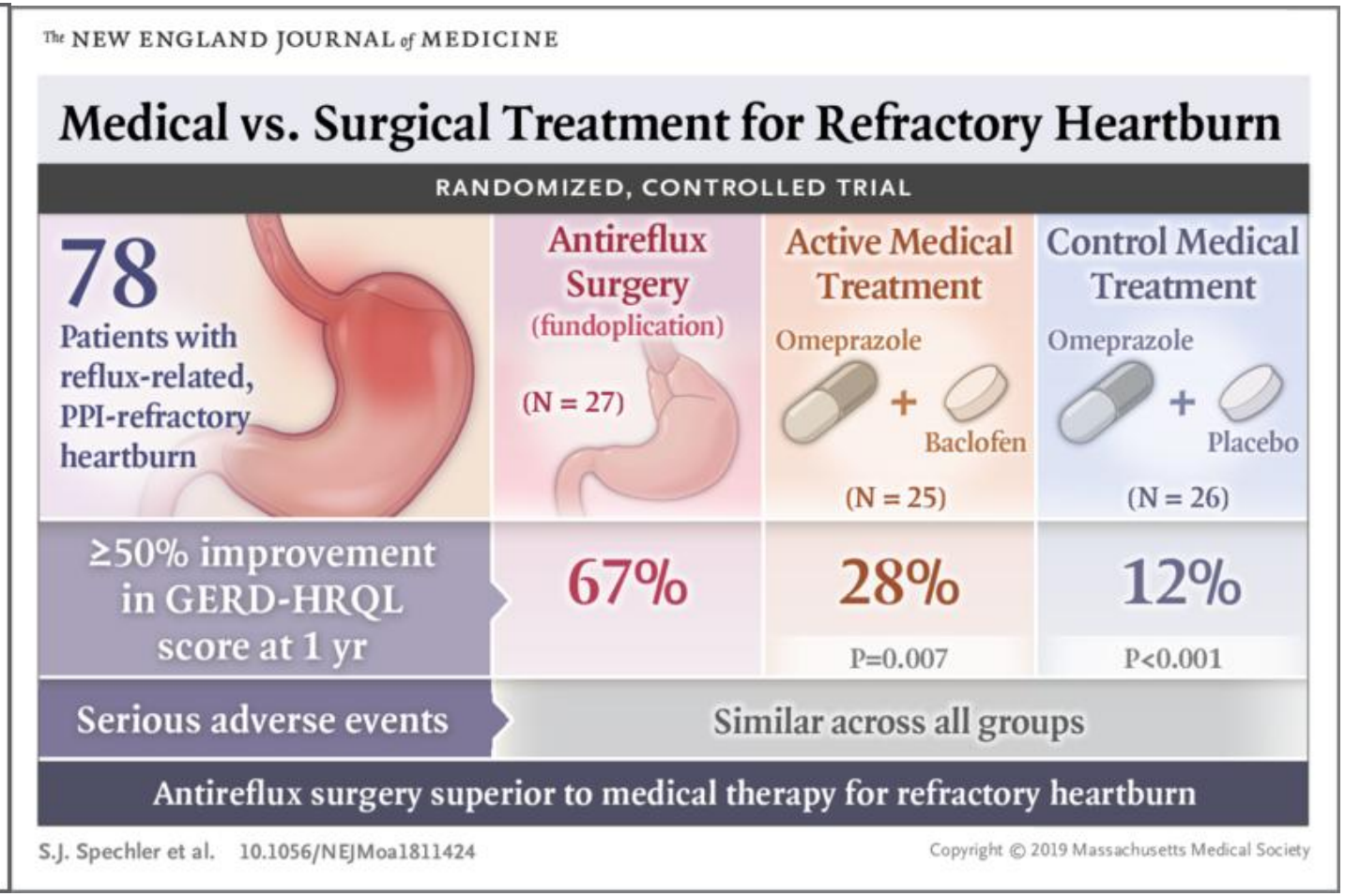


Mucosal integrity testing (GERD/EoE)



Laparoscopic Fundoplication

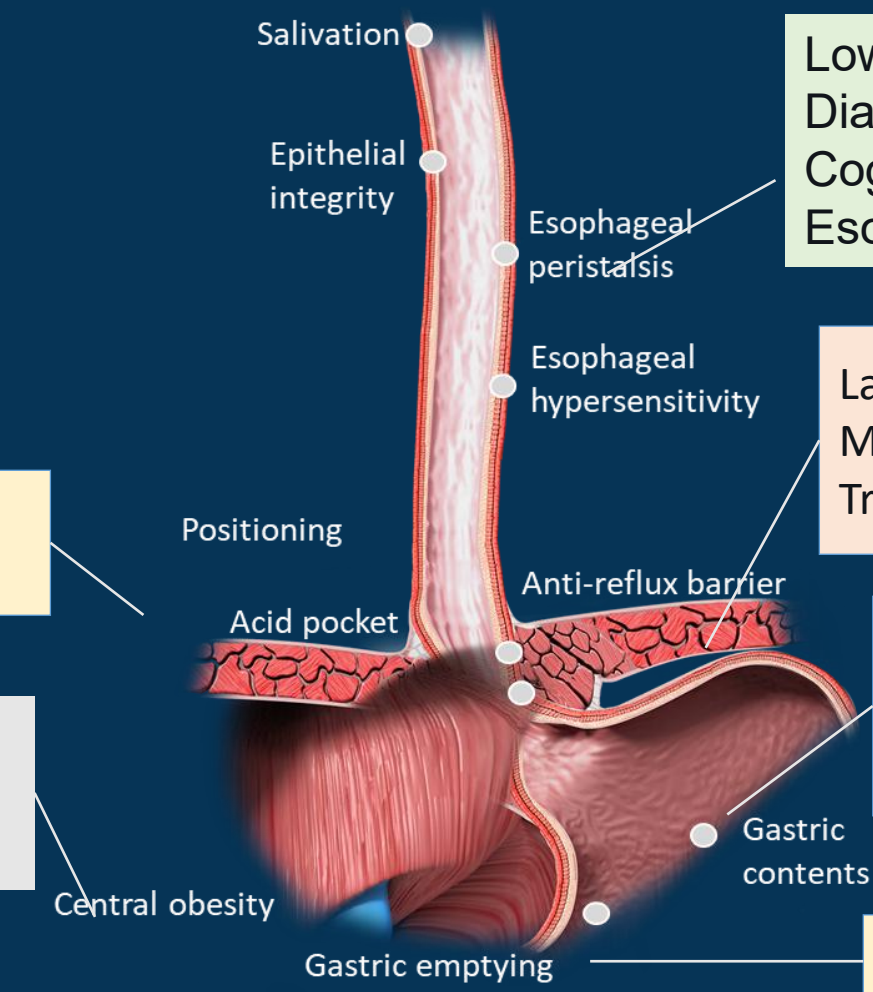




Side effects: dysphagia, gas-bloat syndrome, diarrhea

Spechler SJ et al. NEJM 2019;381:1513

Critical to Understand Mechanism of Symptom & Target Accordingly



Low dose anti-depressants
Diaphragmatic breathing
Cognitive behavioral therapy
Esophageal hypnotherapy

Lap fundoplication
Magnetic sphincter augmentation
Transoral incisionless fundoplication

Alginate antacid
GABA agonist

PPI
H2RA
PCABs

Weight loss
Dietary modifications
Head of bed elevation

Prokinetic

The Recommended Clinical Pathway

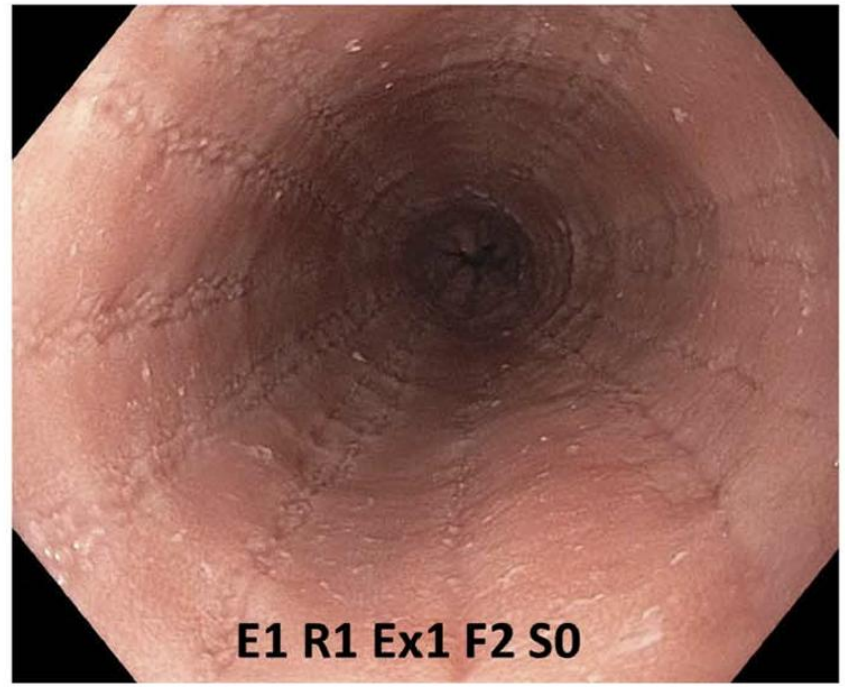
2. Endoscopy

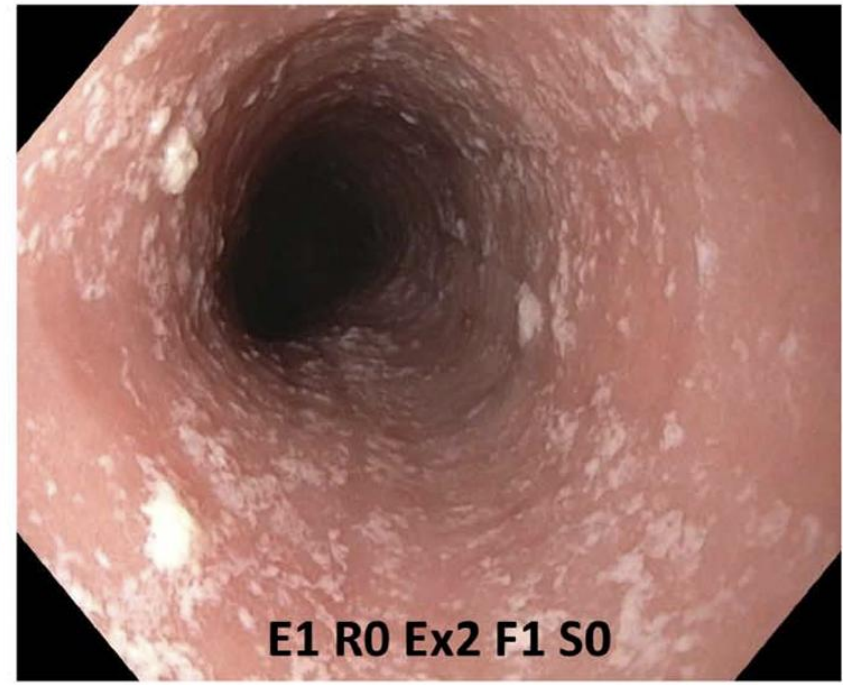
EGD: evaluate hiatus, peptic stricture, rule out EoE

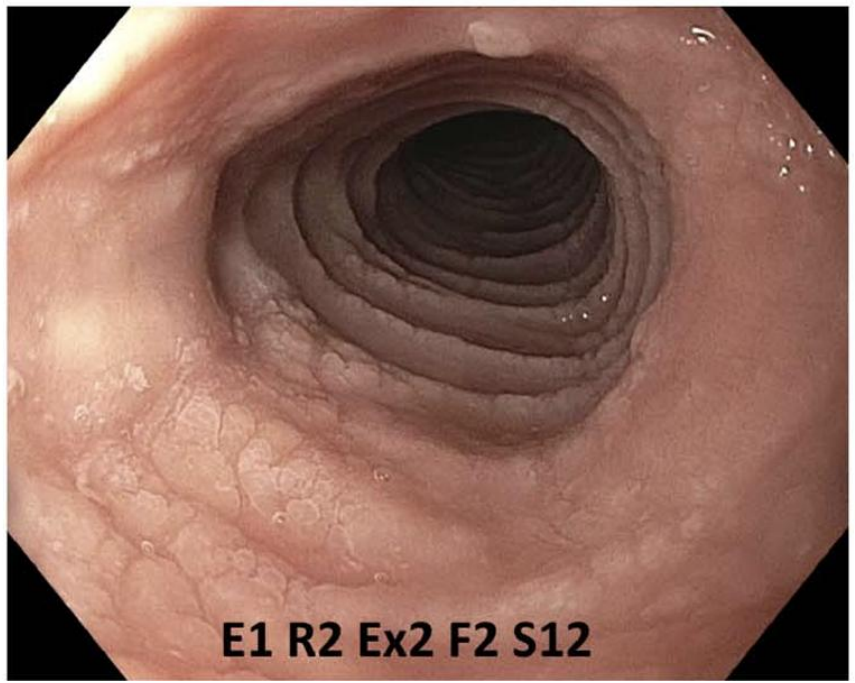
1. Optimize

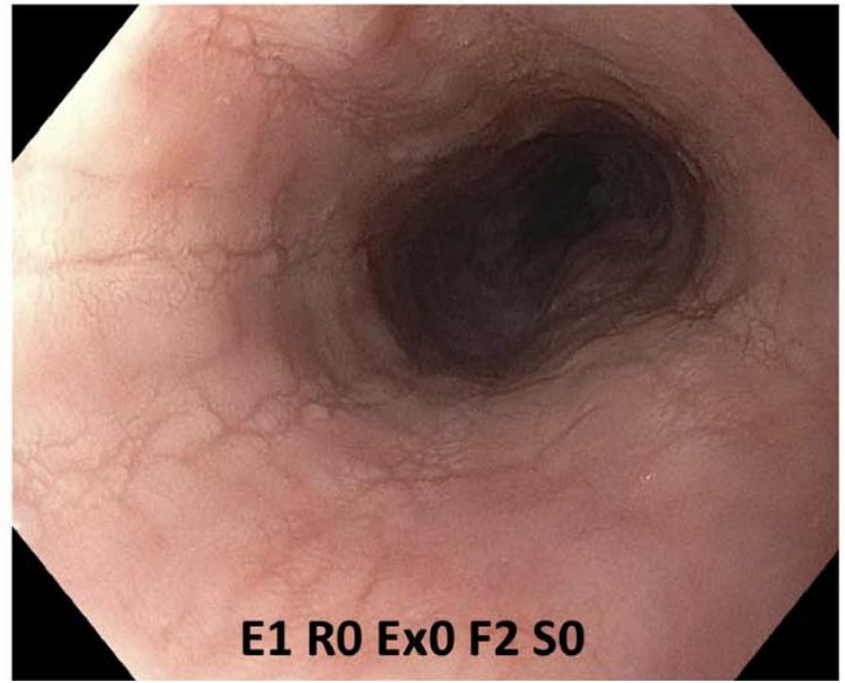
1) Evaluate lifestyle habits
2) Dietary changes
3) Increase PPI
4) Change to PCAB

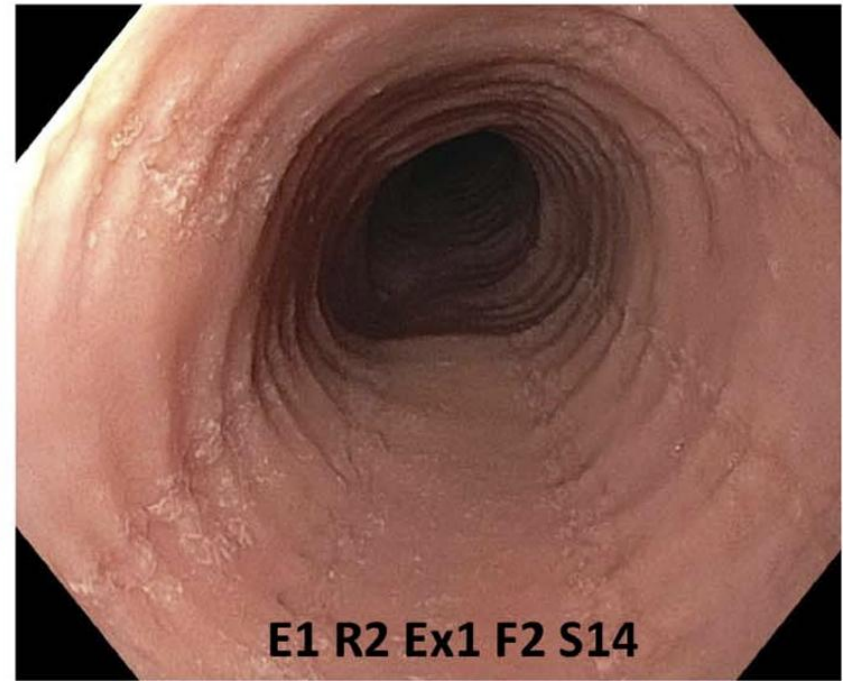
Finding	EREFS Scoring
Edema	1: Present (decreased vascularity)
Rings	1: Mild (ridges)
	2: Moderate (does not impede scope passage)
	3: Severe (standard scope does not pass)
Exudates	1: ≤ 10% of surface area
	2: >10% of surface area
Furrows	1: Mild
	2: Severe (with appreciable depth)
Stricture	1: Present; also estimate diameter in mm



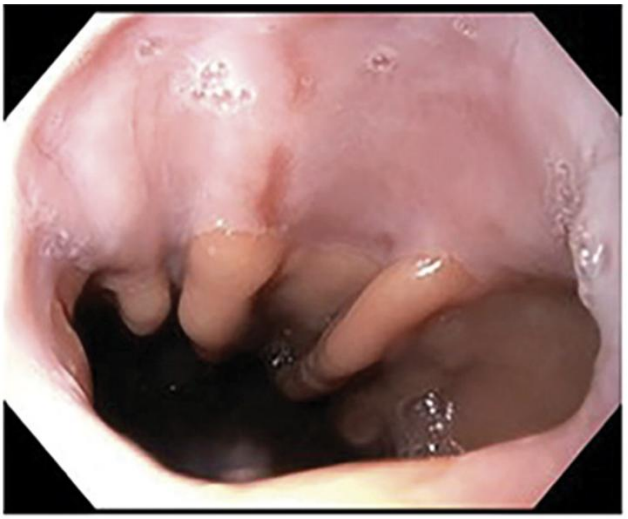






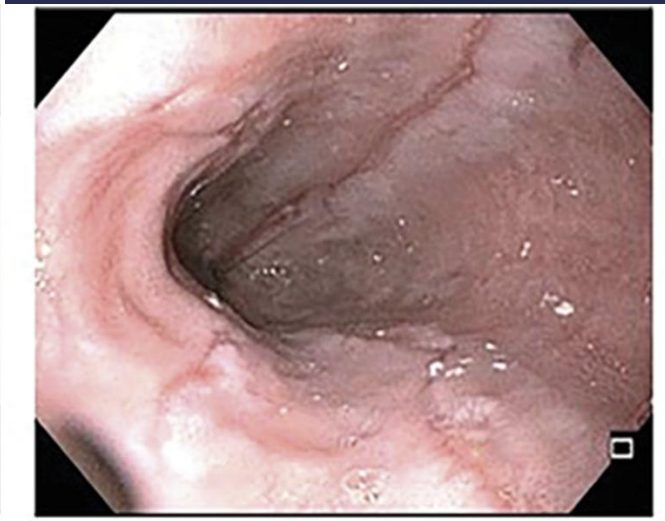


Endoscopy: Erosive Esophagitis



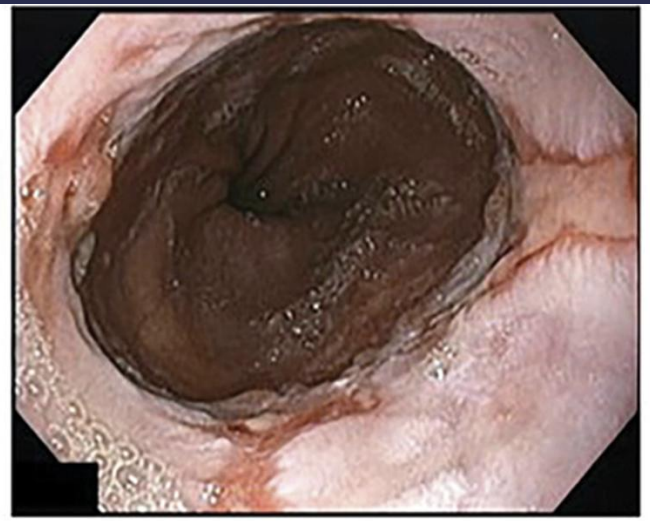
LA-A

≥1 mucosal break, ≤5 mm, does not extend between mucosal folds



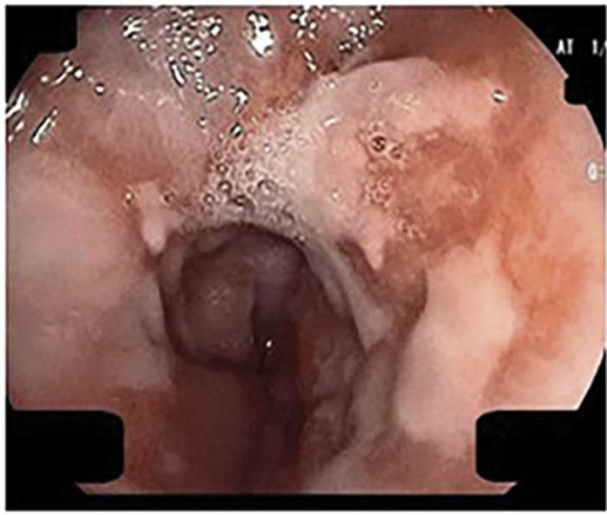
LA-B

≥1 mucosal break, >5 mm, does not extend between mucosal folds



LA-C

≥1 mucosal break, extends between mucosal folds, involves <75% of circumference

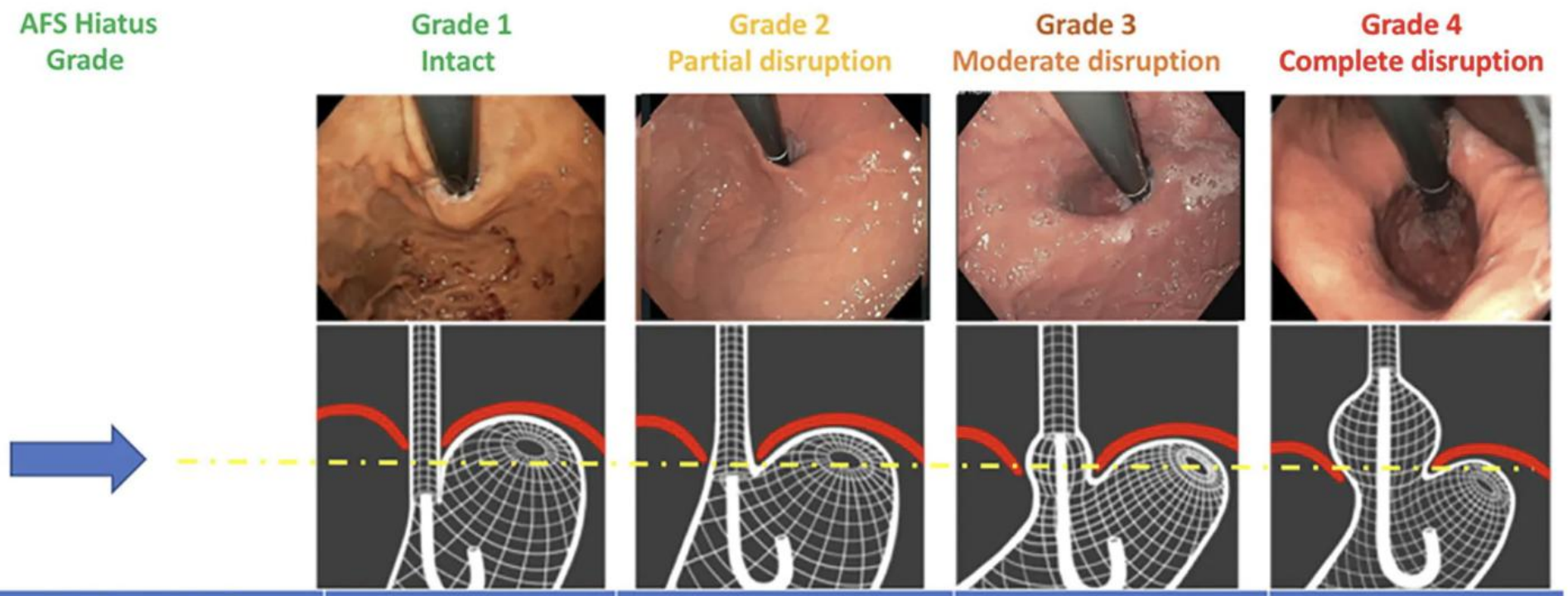


LA-D

≥1 mucosal break, involves >75% of circumference

Spechler, Clinical Gastroenterology and Hepatology, 2024; 22, 2526-2528.e1

Endoscopy: AFS Hiatus Grade



AFS Hiatus Grade	1	2	3	4
Hiatal axial Length, cm (L)	None (0 cm)	None (0 cm)	0-2 cm	>2 cm
Hiatal aperture, cm (D)	Snug to scope 1 cm	Loose 1-2 cm	Open 2-3 cm	Wide open >3 cm
Flap valve (F)	Present, full lip with Omega shape (F+)	Absent, thinning & flattening valve lip (F-)	Absent (F-)	Absent (F-)
LDF components	L0, D1, F+	L0, D1-2, F-	L0-2, D2-3, F-	L>2, D>3, F-

The Recommended Clinical Pathway

1. Optimize

1) Evaluate lifestyle habits
2) Dietary changes
3) Increase PPI
4) Change to PCAB

2. Endoscopy

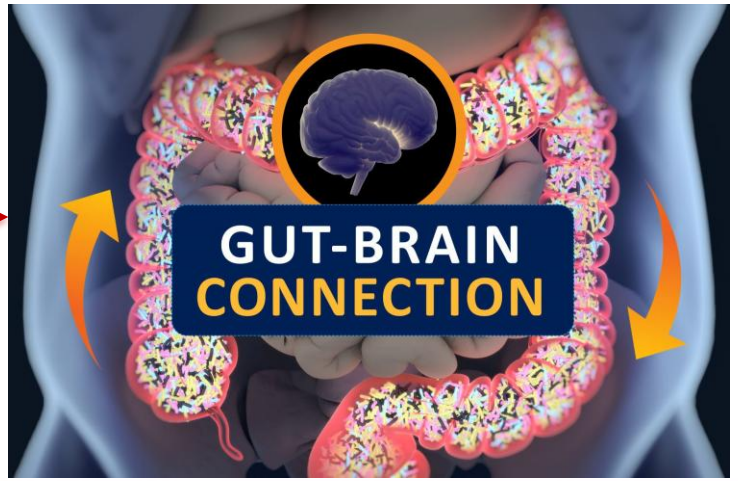
Perform EGD: evaluate hiatus, rule out EoE

3. Physiology

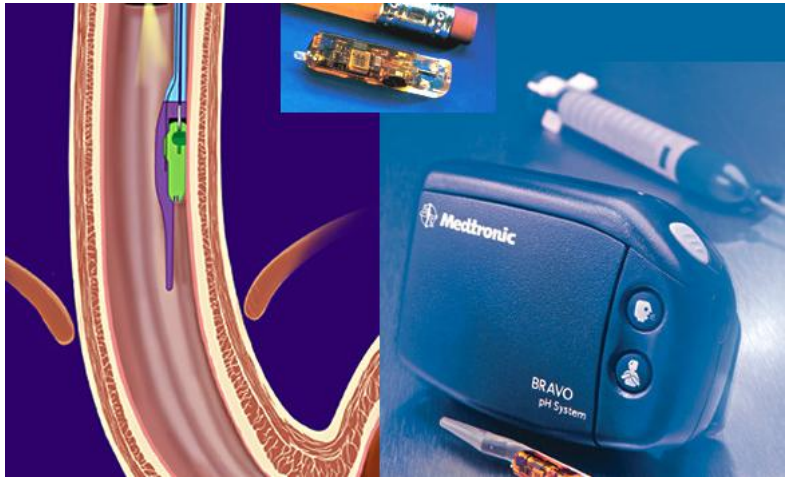
1) Ambulatory Reflux Testing
2) Mucosal Impedance/Integrity

Learn to phenotype

- Heartburn
  - Erosive Reflux disease (ERD)
  - Non-Erosive (NERD)
  - Reflux Hypersensitivity
  - Functional heartburn

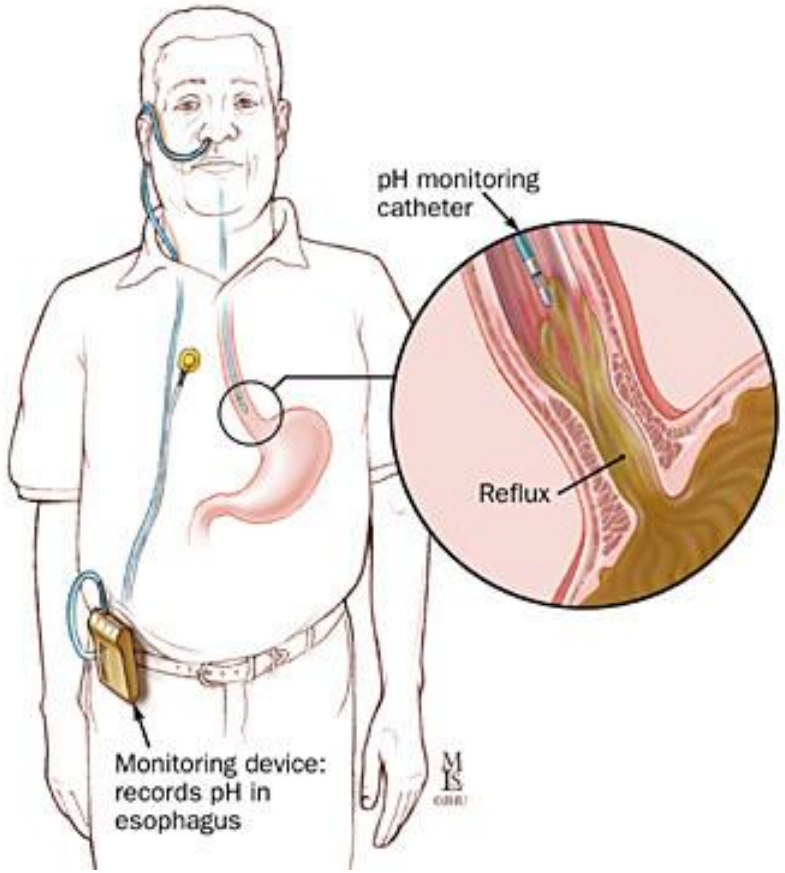


Diagnostic toolbox



Wireless pH monitoring
(48 to 96 hours)

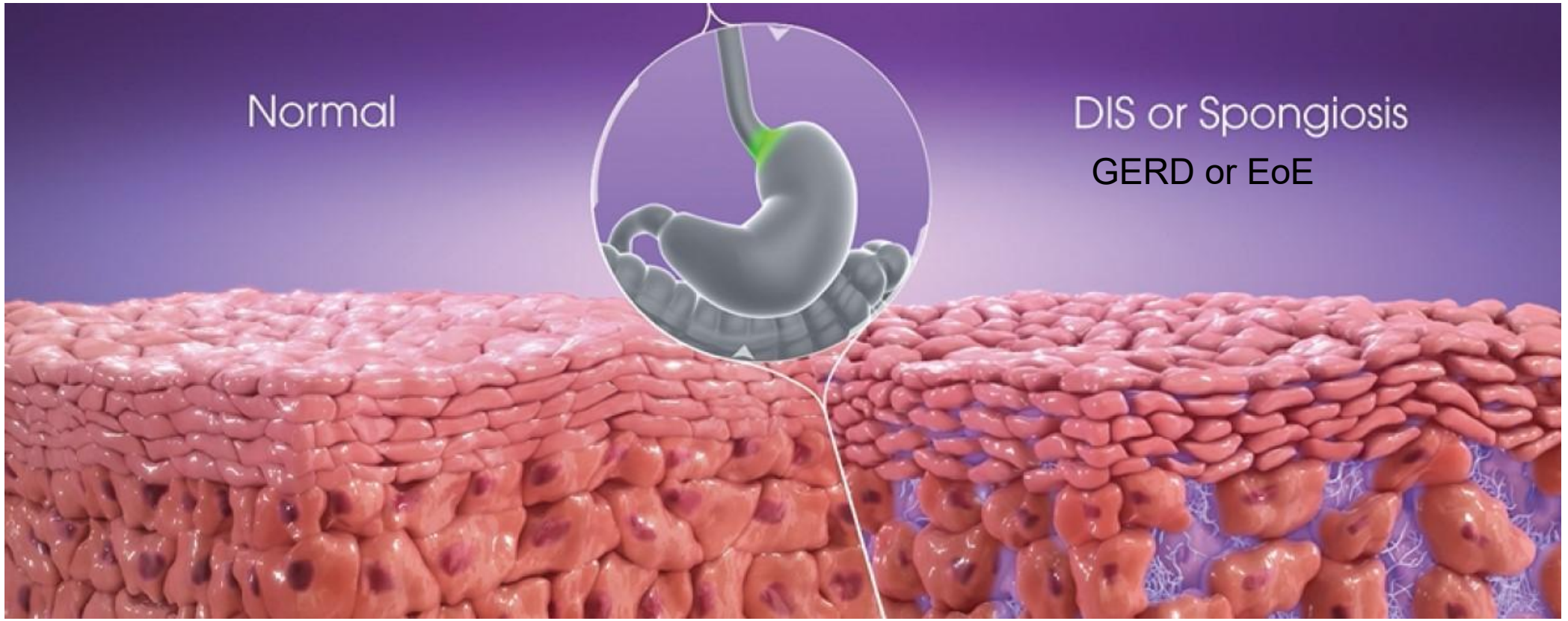
24-hour transnasal pH or
pH-impedance



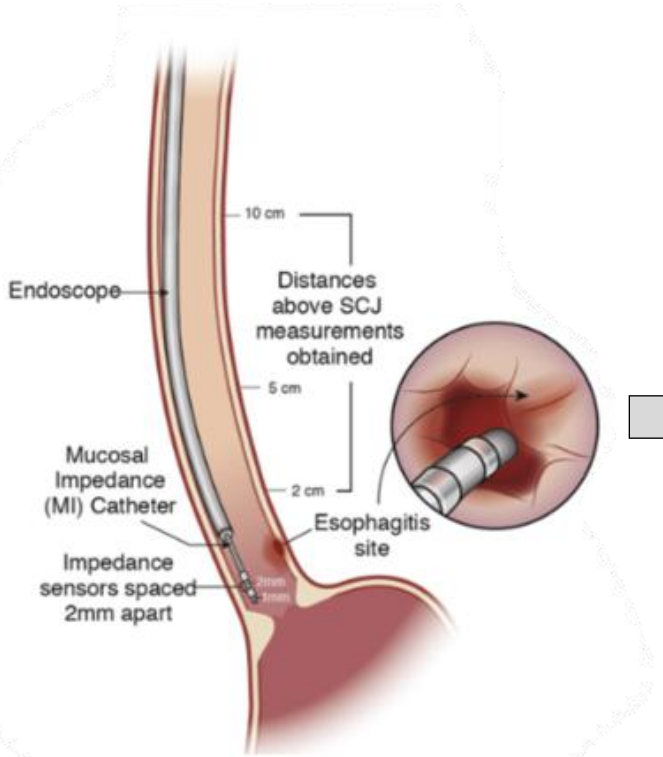
Mucosal integrity testing

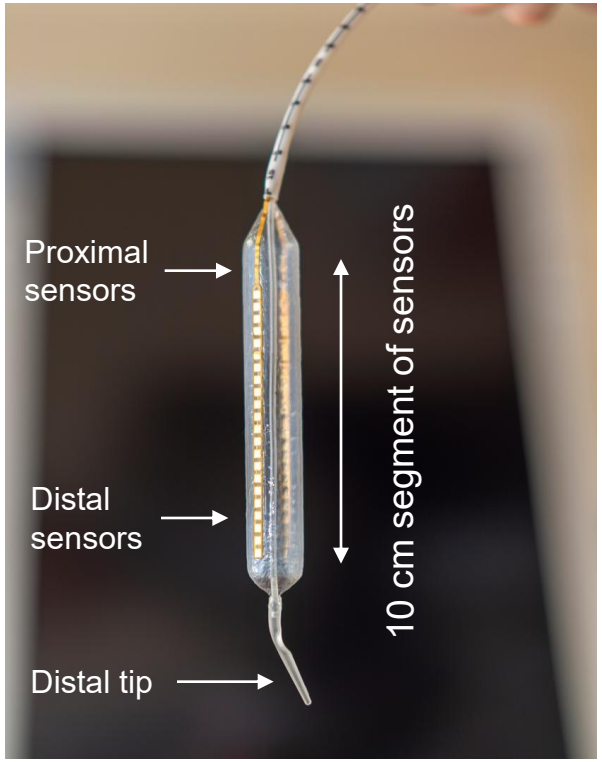
Mucosal Integrity is affected by the presence of dilated intercellular spaces (DIS) which affects paracellular permeability.

Normal MI allows real time detection of reflux/EoE versus functional heartburn

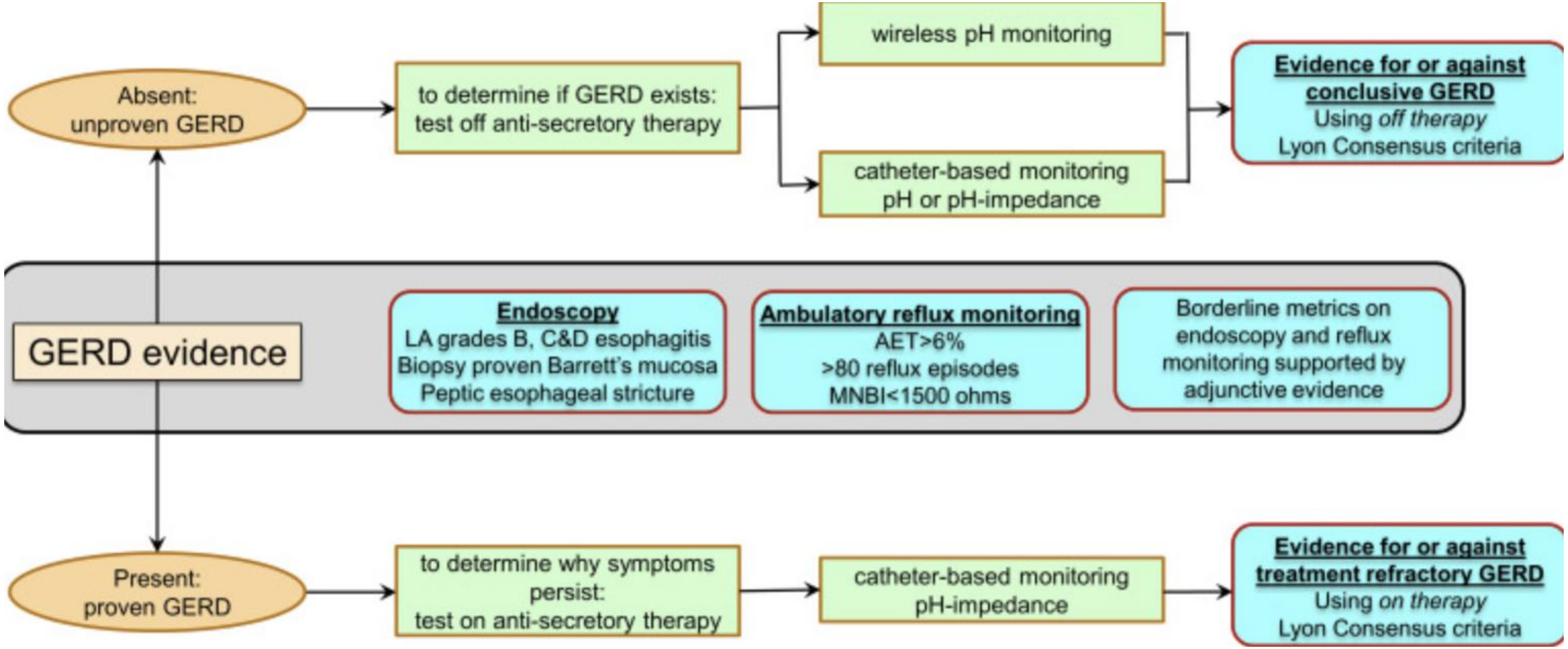


MUCOSAL INTEGRITY TESTING (MIT)





Lyon 2.0: Actionable GERD



Gyawali, C Prakash et al. *Gut* vol. 73,2 361-371. 5 Jan. 2024

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4) Change to PCAB

2. Endoscopy

Perform EGD: evaluate hiatus, rule out EoE

3. Physiology

1) Ambulatory Reflux Testing
2) Mucosal Impedance/Integrity

4. Motility

HRM: rule out achalasia

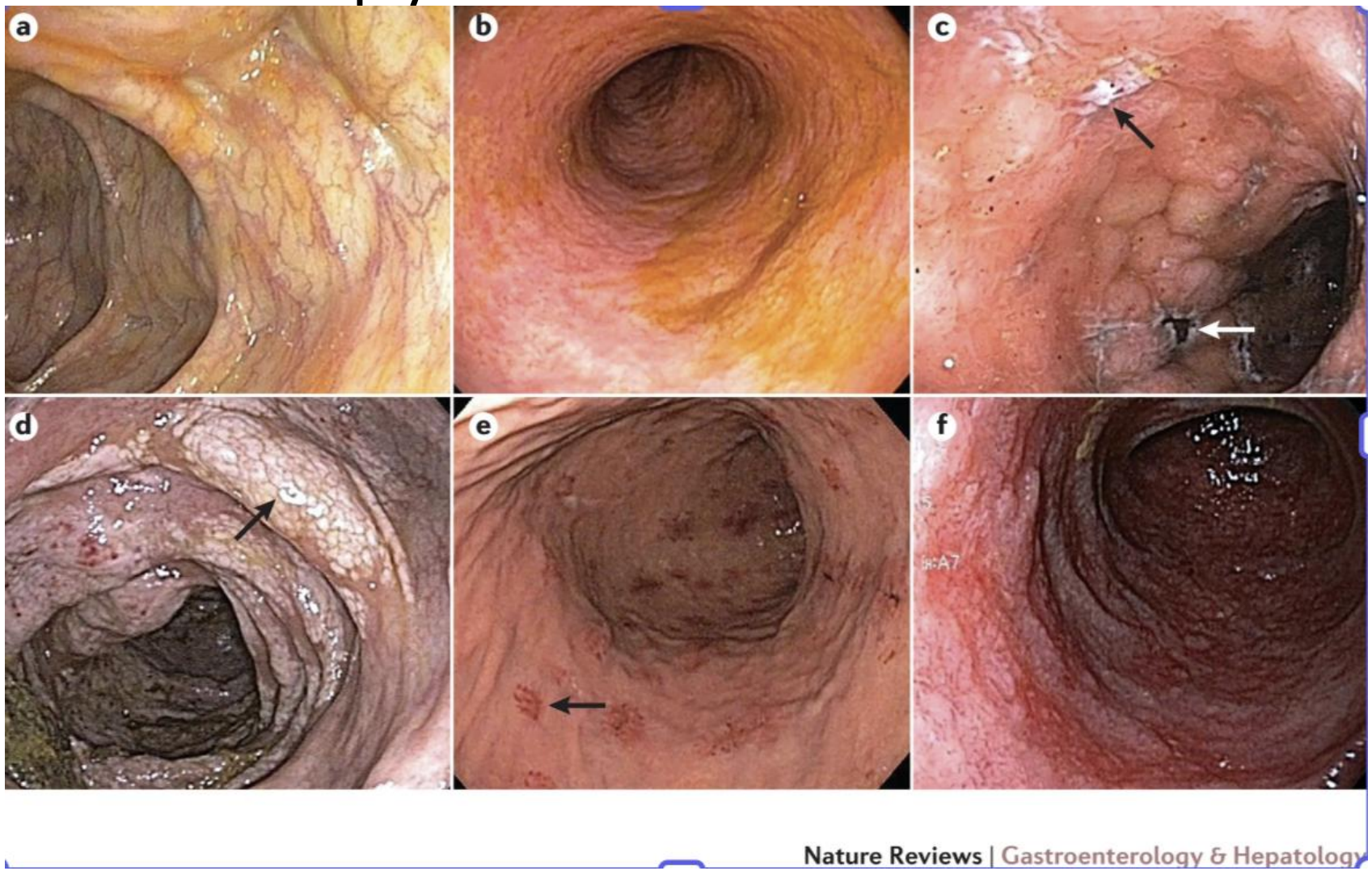
5. Decision

Shared Decision Making

49-year-old patient presents with 2 months of diarrhea and nausea and vomiting. Patient had an allogeneic haematopoietic stem cell transplantation (HSCT) 2.5 months ago

- Referral to GI for evaluation
- Next step in management?

EGD/Colonoscopy



Graft vs. Host Disease

- GVHD, a condition in which immune cells from the donor attack healthy recipient tissues.
- GVHD is defined histologically as the presence of gland apoptosis, not explained by other inflammatory or infectious etiologies.
- The gastrointestinal system is among the most common sites affected by acute GVHD, and severe manifestations of acute GVHD of the gut portends a poor prognosis in patients after HSCT.
- As reliable serum biomarkers have not yet been validated outside of clinical trials, endoscopic and histopathological evaluation continue to be utilized in diagnosis.
- Once a diagnosis of gastrointestinal acute GVHD is established, therapy with systemic corticosteroids is typically initiated, and non-responders can be treated with a wide range of second-line therapies.
- In addition to treating the underlying disease, the management of complications including profuse diarrhea, severe malnutrition and gastrointestinal bleeding is paramount.

Mucosal injury after Transplant

- Diarrhea
  - Medication related
    - Mycophenolate mofetil: MMF rates of diarrhea 1.9 times compared to AZA
    - MMF inhibition of colonic crypt cell division due to immune mediated mechanisms
    - Loss of normal villous structure in the duodenum
  - Dose manipulation, reduction of total dosage, or dose splitting can be helpful

61-year-old presents with 40-pound weight loss and night sweats. He is s/p heart transplant 11 years ago.

- CT A/P shows thickening of the distal duodenum
- Next steps of therapy?

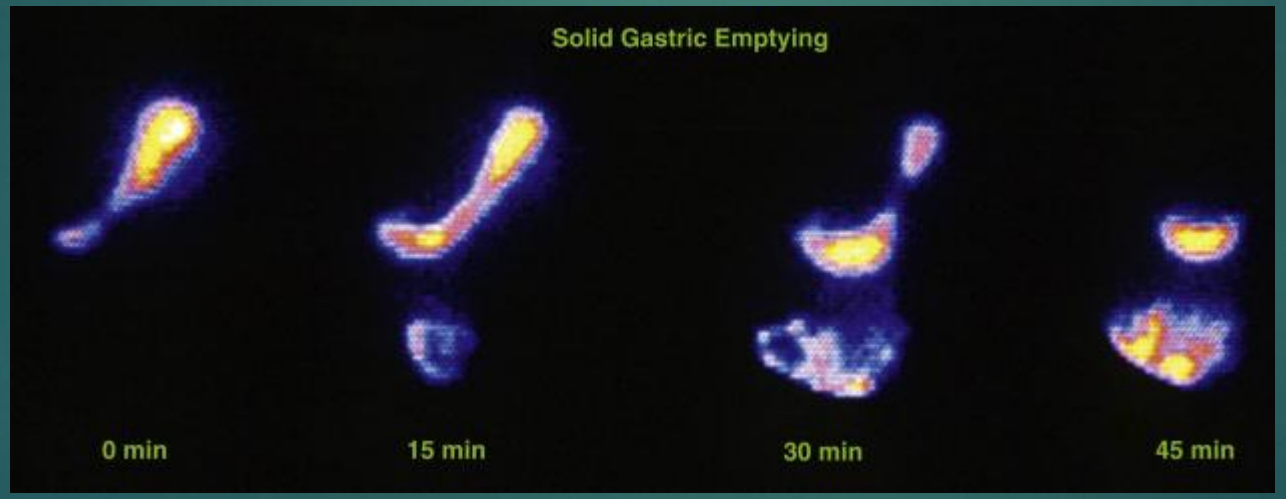
Malignancies

- Post-transplant lymphoproliferative disorder (PTLD)
  - Can involve GI tract in 10% of transplant recipients
  - Often, there are abnormal enlarged lymph nodes that are hard to biopsy
  - Driver is typically EBV
  - Biopsies are key
  - Therapy: lowering immunosuppression (or cessation) plus transplant ID

Patient:

56-year-old presents for consideration for heart-transplantation. Prior poorly controlled diabetes with nausea/vomiting. Patient reports he cannot eat solid food – ok to list for cardiac transplant?

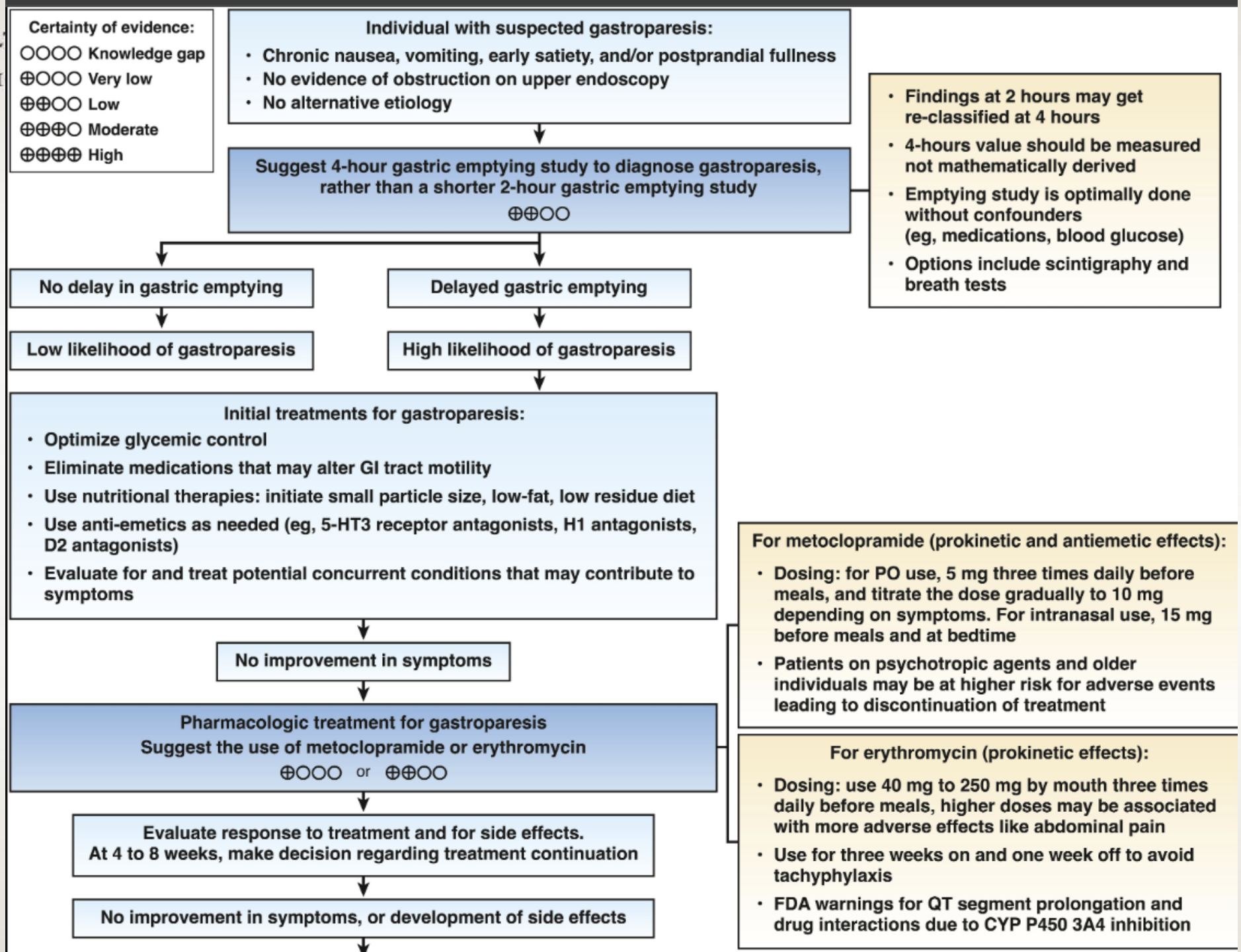
- EGD Normal – except retained food in the stomach
- Gastric emptying performed shows delayed motility – next steps?

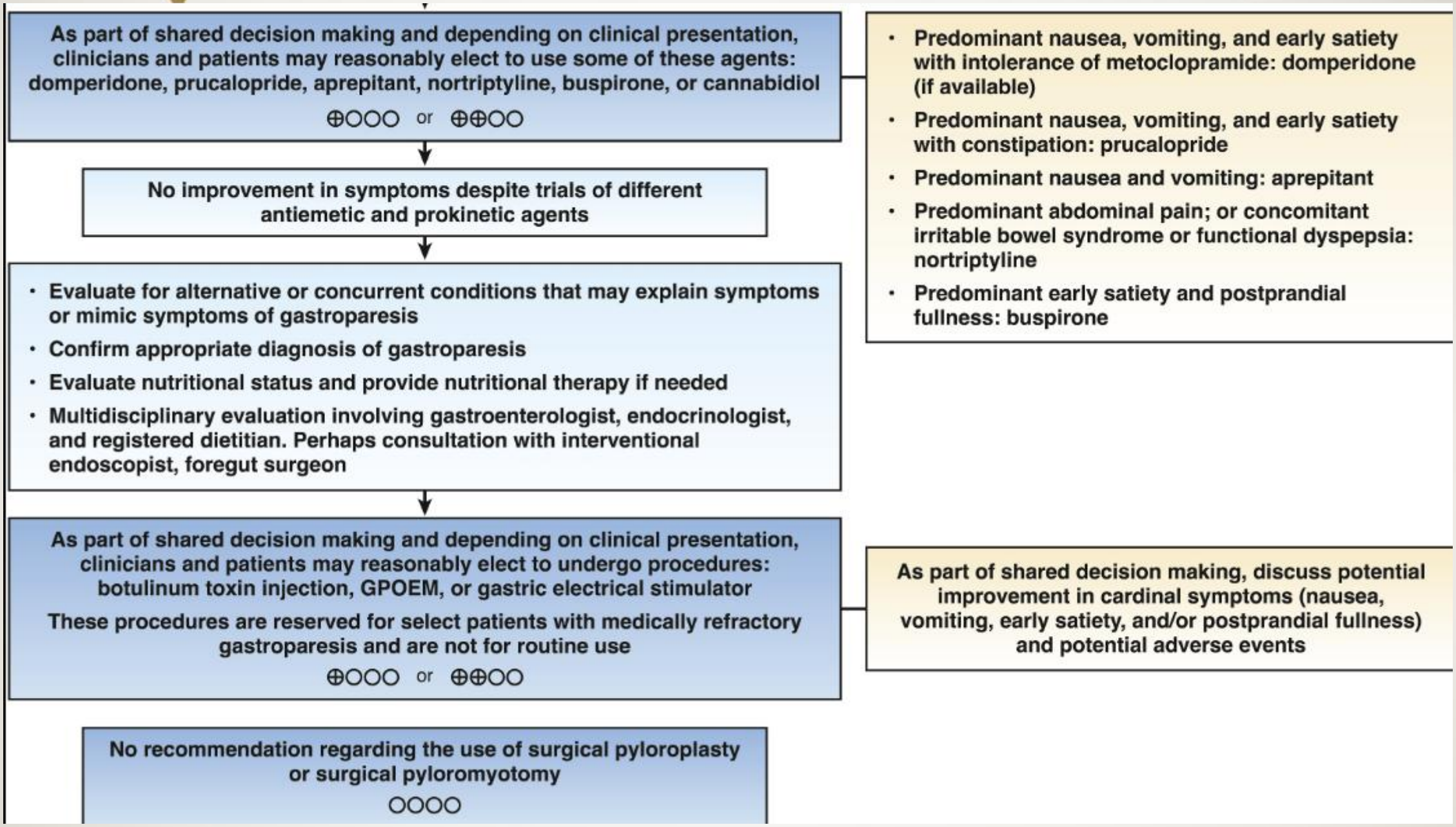


VANDERBILT UNIVERSITY MEDICAL CENTER

Gastroparesis

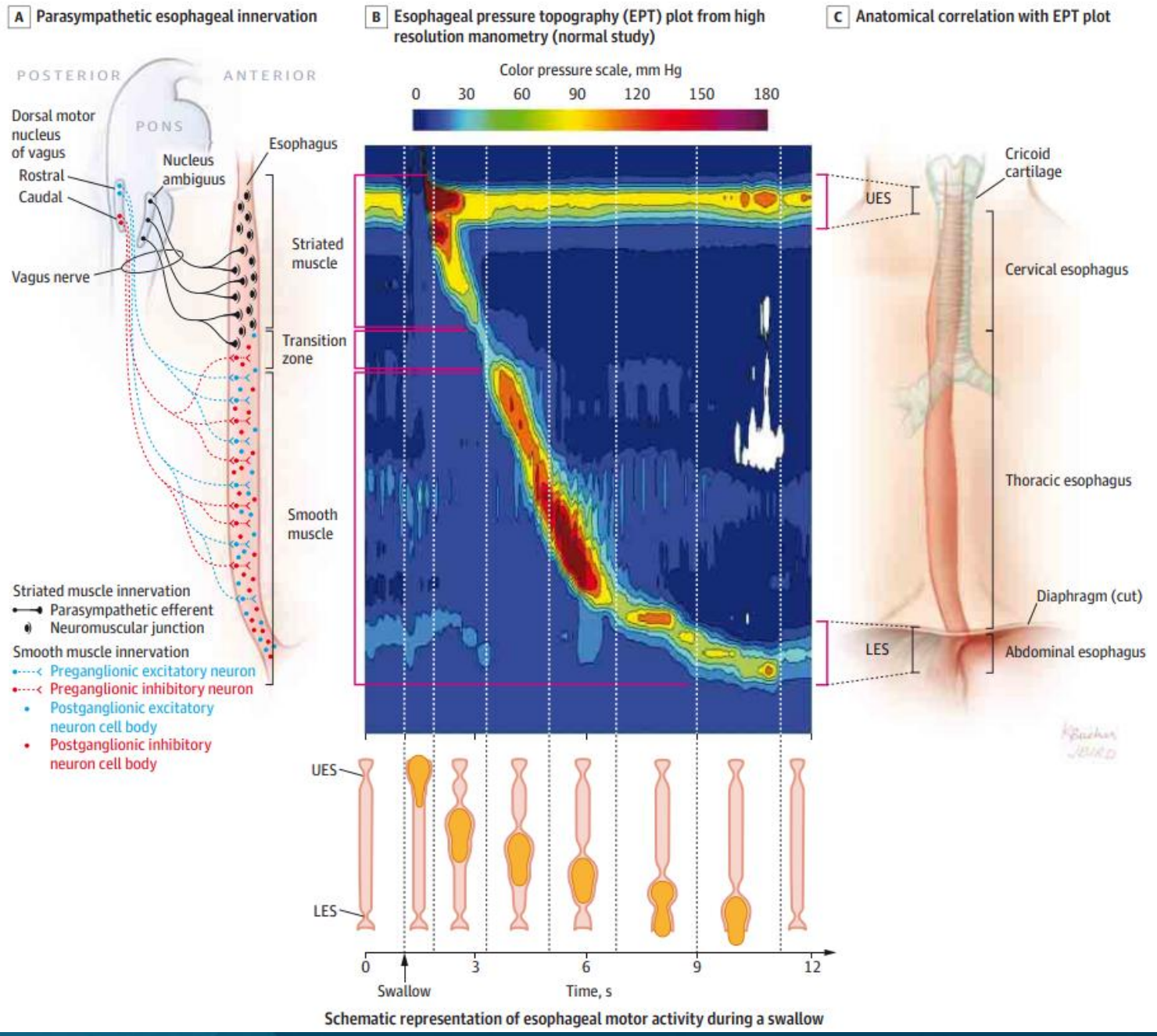
- Presentation: nausea, vomiting, fullness, “refractory reflux”
- Best test: gastric emptying test (off opiates)
- Treatment:
  - Dietary modification, Hydration and nutrition, Optimize glycemic control
  - Prokinetics
    - Metoclopramide – risk of tardive dyskinesia
    - Erythromycin – 2nd line
    - Domperidone – only available in Canada due to increase in cardiac arrythmias
  - Macrolide antibiotics
    - Erythromycin – inpatient, tachyphylaxis
    - 5HT4 agonist: Prucalopride (off-label) - (Cisapride – led to cardiac arrythmias and death)
  - Surgery
    - G-POEM
    - Surgical J tube (or G-J tube)


Certainty of evidence:
○○○○ Knowledge gap
⊕○○○ Very low
⊕⊕○○ Low
⊕⊕⊕○ Moderate
⊕⊕⊕⊕ High
Individual with suspected gastroparesis:
• Chronic nausea, vomiting, early satiety, and/or postprandial fullness
• No evidence of obstruction on upper endoscopy
• No alternative etiology
Suggest 4-hour gastric emptying study to diagnose gastroparesis, rather than a shorter 2-hour gastric emptying study
⊕⊕○○
• Findings at 2 hours may get re-classified at 4 hours
• 4-hours value should be measured not mathematically derived
• Emptying study is optimally done without confounders (eg, medications, blood glucose)
• Options include scintigraphy and breath tests
No delay in gastric emptying
Delayed gastric emptying
Low likelihood of gastroparesis
High likelihood of gastroparesis
Initial treatments for gastroparesis:
• Optimize glycemic control
• Eliminate medications that may alter GI tract motility
• Use nutritional therapies: initiate small particle size, low-fat, low residue diet
• Use anti-emetics as needed (eg, 5-HT3 receptor antagonists, H1 antagonists, D2 antagonists)
• Evaluate for and treat potential concurrent conditions that may contribute to symptoms
No improvement in symptoms
Pharmacologic treatment for gastroparesis
Suggest the use of metoclopramide or erythromycin
⊕○○○ or ⊕⊕○○
For metoclopramide (prokinetic and antiemetic effects):
• Dosing: for PO use, 5 mg three times daily before meals, and titrate the dose gradually to 10 mg depending on symptoms. For intranasal use, 15 mg before meals and at bedtime
• Patients on psychotropic agents and older individuals may be at higher risk for adverse events leading to discontinuation of treatment
For erythromycin (prokinetic effects):
• Dosing: use 40 mg to 250 mg by mouth three times daily before meals, higher doses may be associated with more adverse effects like abdominal pain
• Use for three weeks on and one week off to avoid tachyphylaxis
• FDA warnings for QT segment prolongation and drug interactions due to CYP P450 3A4 inhibition
Evaluate response to treatment and for side effects.
At 4 to 8 weeks, make decision regarding treatment continuation
No improvement in symptoms, or development of side effects


As part of shared decision making and depending on clinical presentation, clinicians and patients may reasonably elect to use some of these agents: domperidone, prucalopride, aprepitant, nortriptyline, buspirone, or cannabidiol
⊕○○○ or ⊕⊕○○
No improvement in symptoms despite trials of different antiemetic and prokinetic agents
• Evaluate for alternative or concurrent conditions that may explain symptoms or mimic symptoms of gastroparesis
• Confirm appropriate diagnosis of gastroparesis
• Evaluate nutritional status and provide nutritional therapy if needed
• Multidisciplinary evaluation involving gastroenterologist, endocrinologist, and registered dietitian. Perhaps consultation with interventional endoscopist, foregut surgeon
As part of shared decision making and depending on clinical presentation, clinicians and patients may reasonably elect to undergo procedures: botulinum toxin injection, GPOEM, or gastric electrical stimulator
These procedures are reserved for select patients with medically refractory gastroparesis and are not for routine use
⊕○○○ or ⊕⊕○○
No recommendation regarding the use of surgical pyloroplasty or surgical pyloromyotomy
○○○○
• Predominant nausea, vomiting, and early satiety with intolerance of metoclopramide: domperidone (if available)
• Predominant nausea, vomiting, and early satiety with constipation: prucalopride
• Predominant nausea and vomiting: aprepitant
• Predominant abdominal pain; or concomitant irritable bowel syndrome or functional dyspepsia: nortriptyline
• Predominant early satiety and postprandial fullness: buspirone
As part of shared decision making, discuss potential improvement in cardinal symptoms (nausea, vomiting, early satiety, and/or postprandial fullness) and potential adverse events

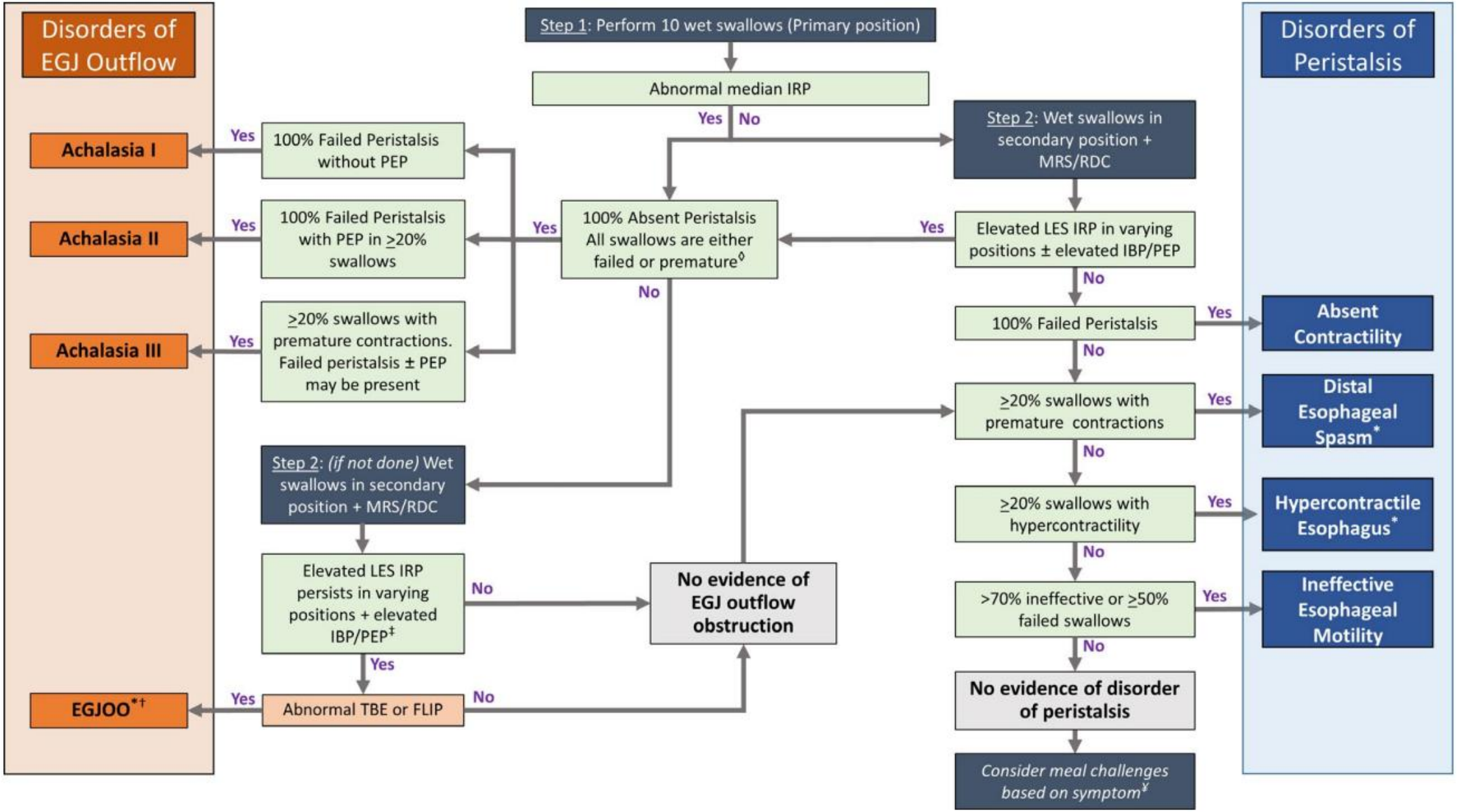
56-year-old person presents rapid dysphagia to solids and liquids. They were s/p kidney transplant 8 years ago

- Esophagram performed showing retention and concern for Achalasia



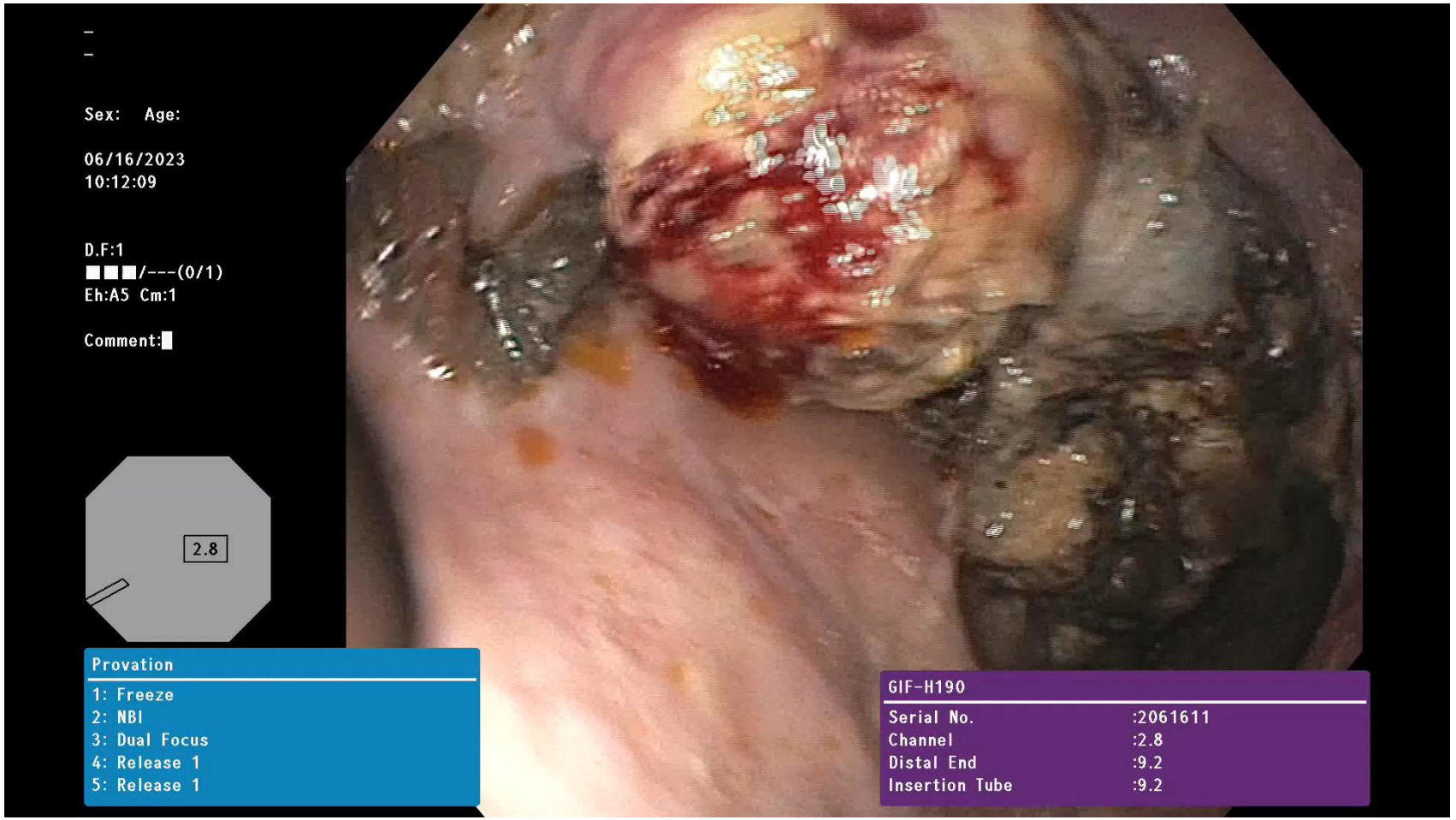
Schematic representation of esophageal motor activity during a swallow

Pandolfino, JAMA 2015

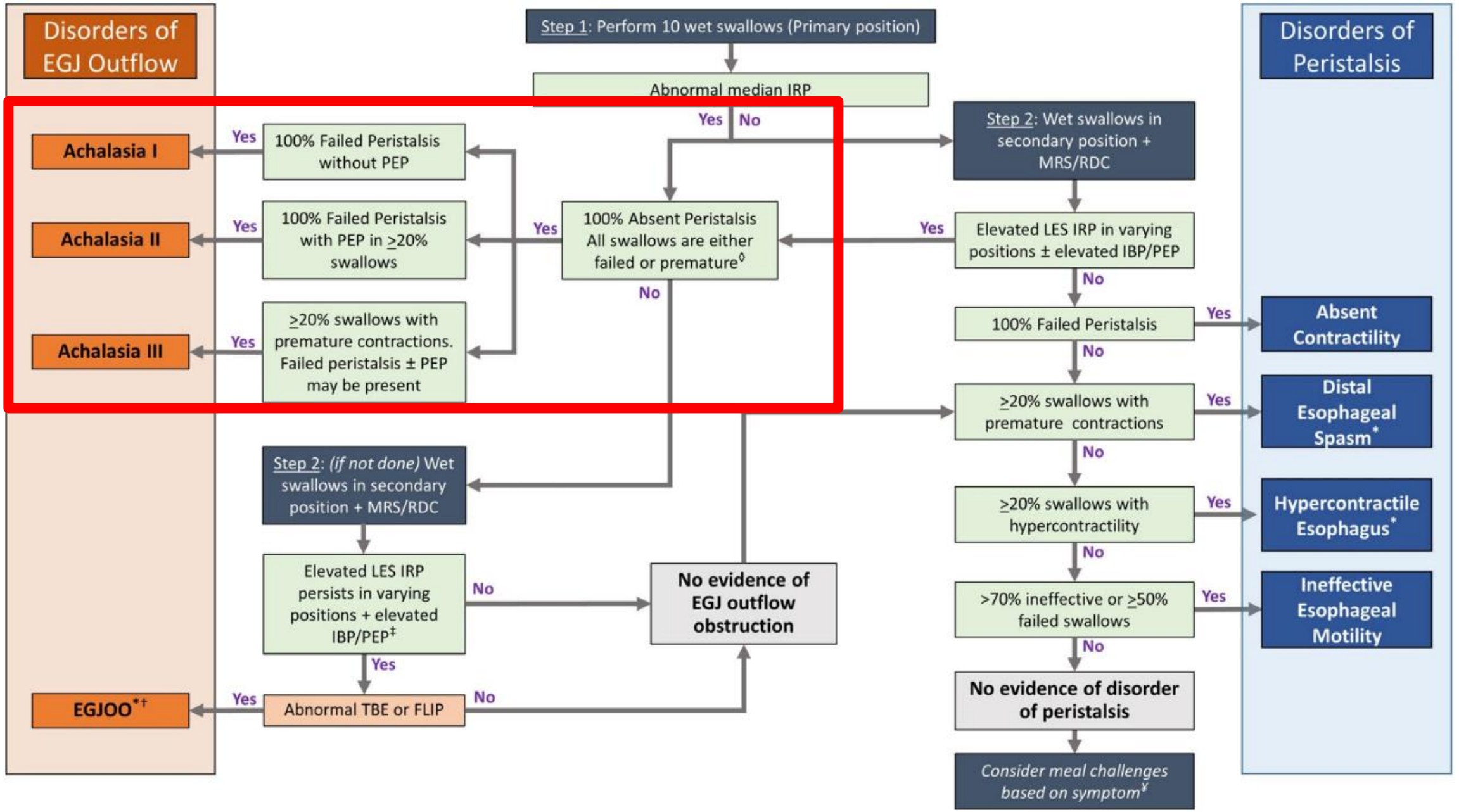


Yadlapati et al. ANMS 2021

Reports regurgitation and heartburn non-responsive to PPI



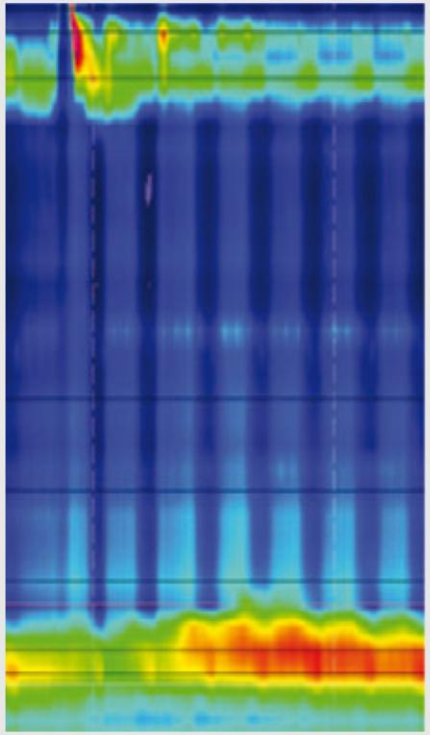
Chicago Classification 4.0: Achalasia



Achalasia:

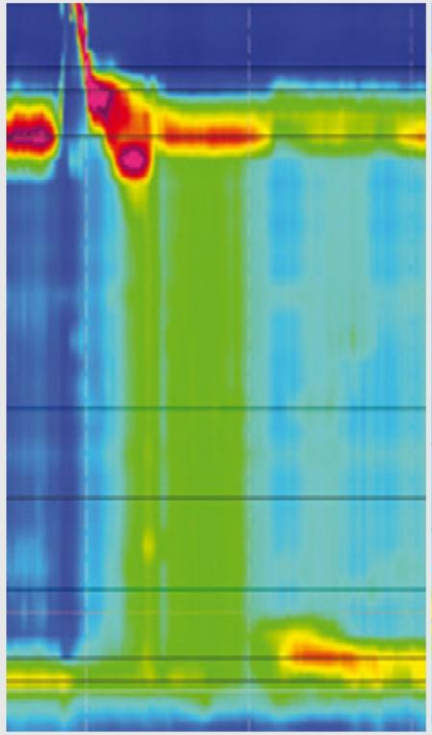
Elevated IRP and All swallows Failed

Type I Achalasia



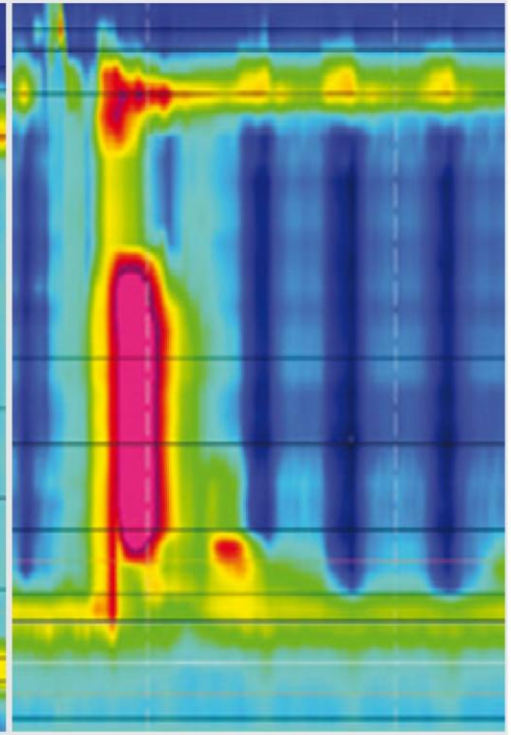
100% Failed Peristalsis

Type II Achalasia



≥ 20% Pan-esophageal pressurization

Type III Achalasia

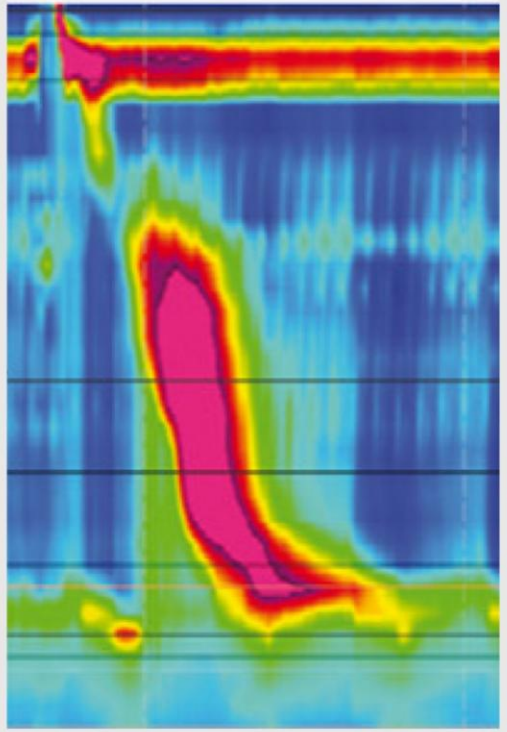


≥ 20% Premature or Spastic contractions

No Achalasia:

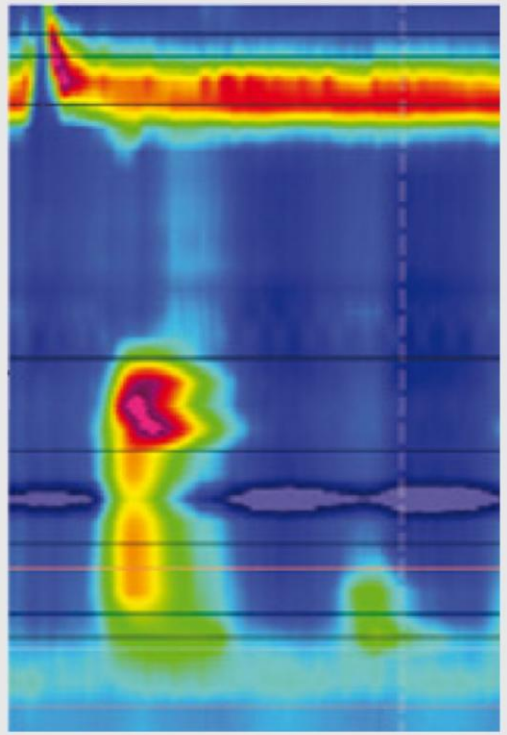
Normal IRP

Hypercontractile Esophagus



≥ 20% DCI >800

Diffuse Esophageal Spasm



≥ 20% Premature (DL <4.5 seconds) with DCI >450

Adopted from Patel D, Yadlapti R, Vaezi MF: Esophageal Motility Disorders: Current Approach to Diagnostics and Therapeutics. Gastroenterology, Volume 162, Issue 6, 1617 - 1634

Naik, Fass, Patel, Vaezi. Gastroenterology, 2026

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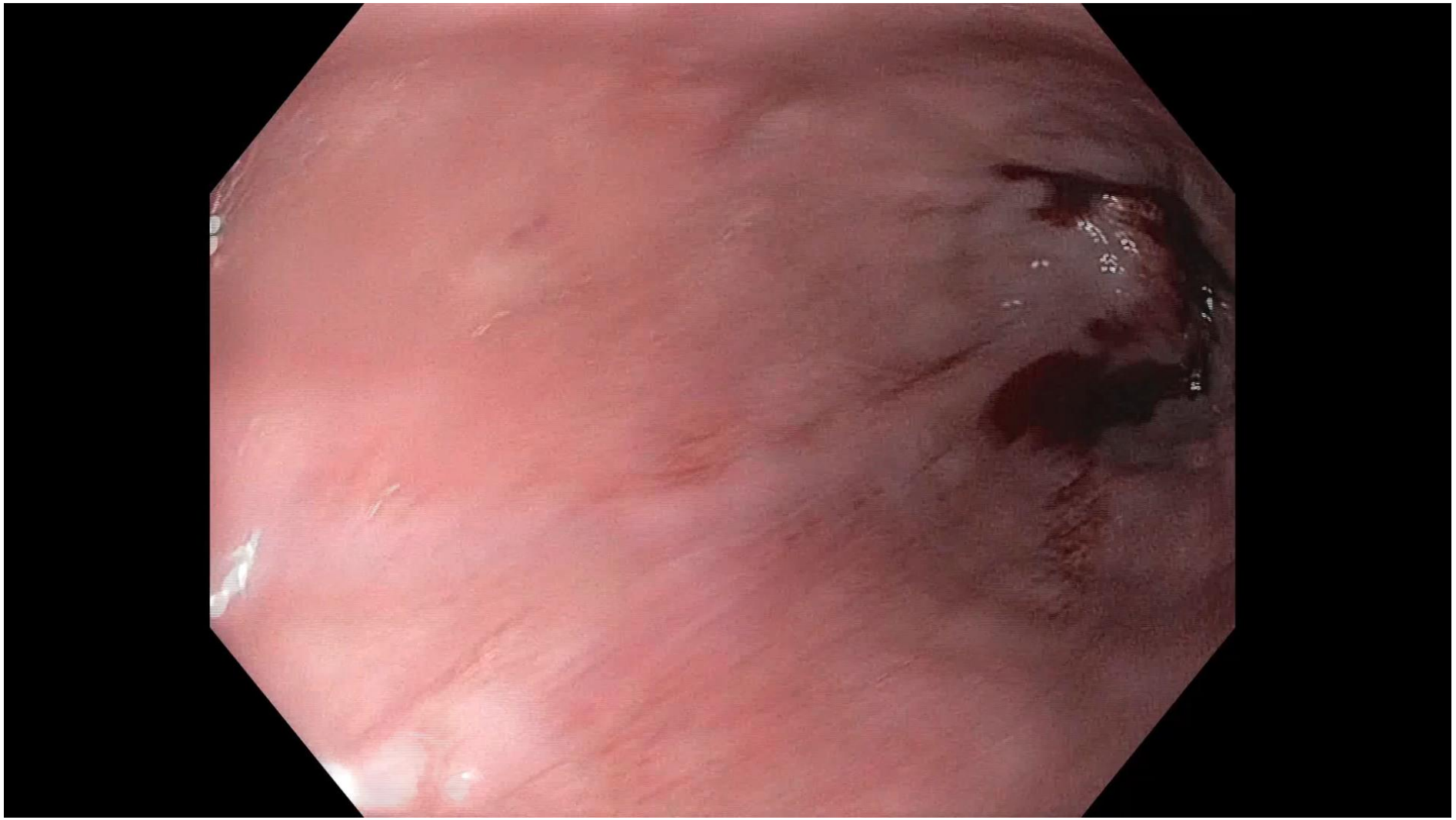
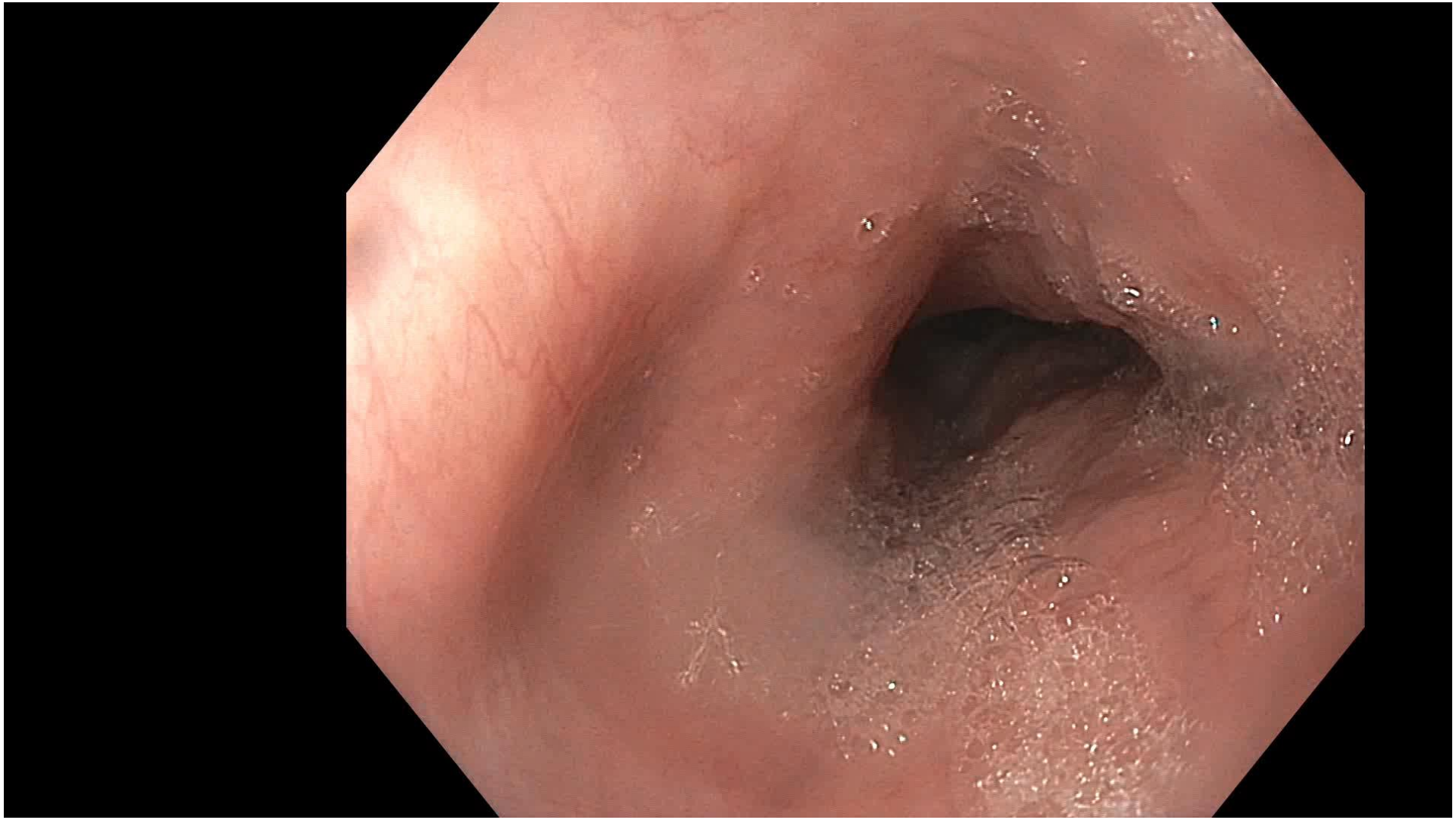


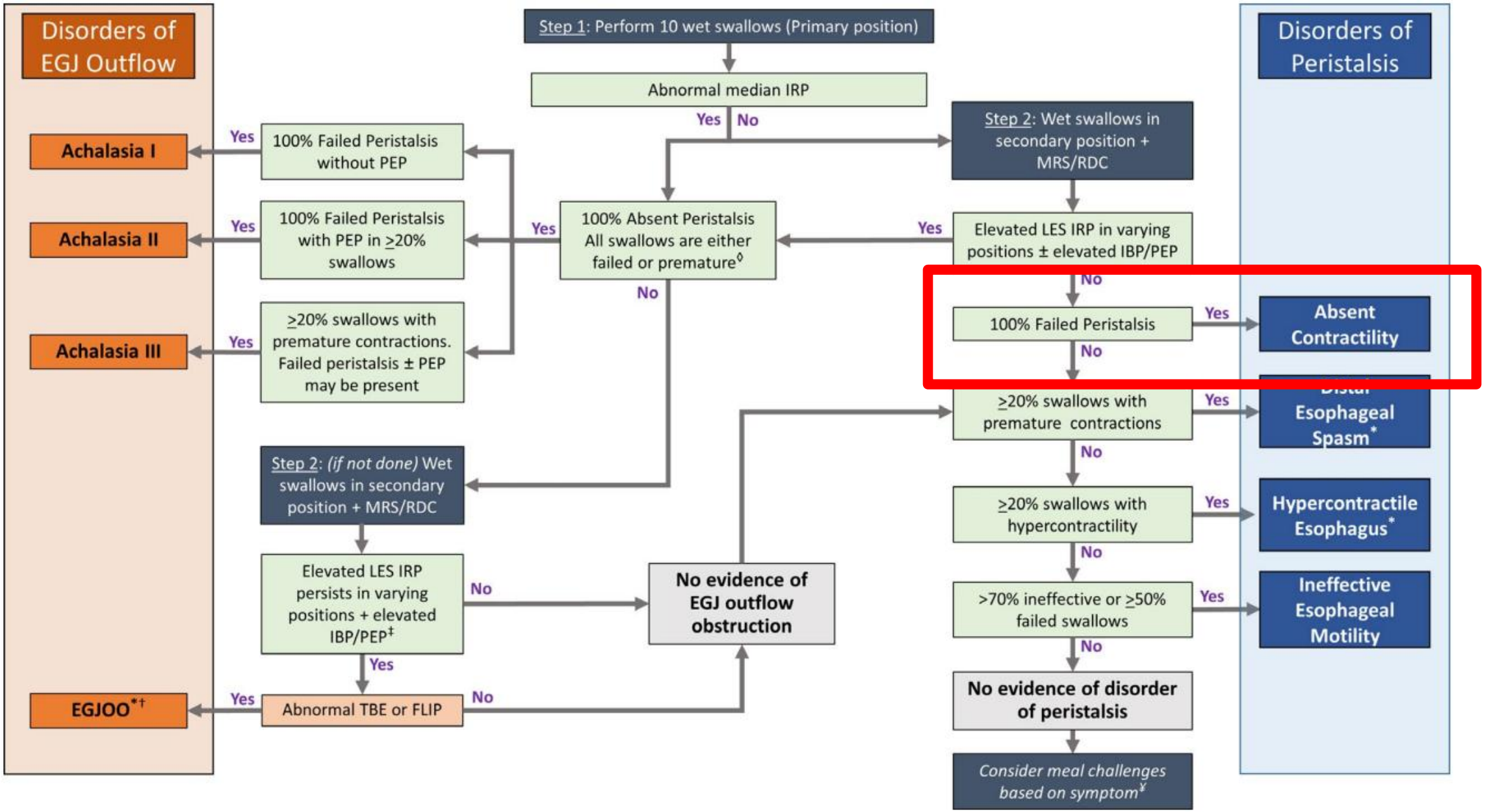
66-year-old person presents with rapid decline in lung function in need for heart and liver transplant

- They report dysphagia
- You perform an EGD which shows the following

What is the diagnosis?



Chicago Classification 4.0: Absent Contractility



Scleroderma

Work-up

ANA Profile

Extended Myositis Panel

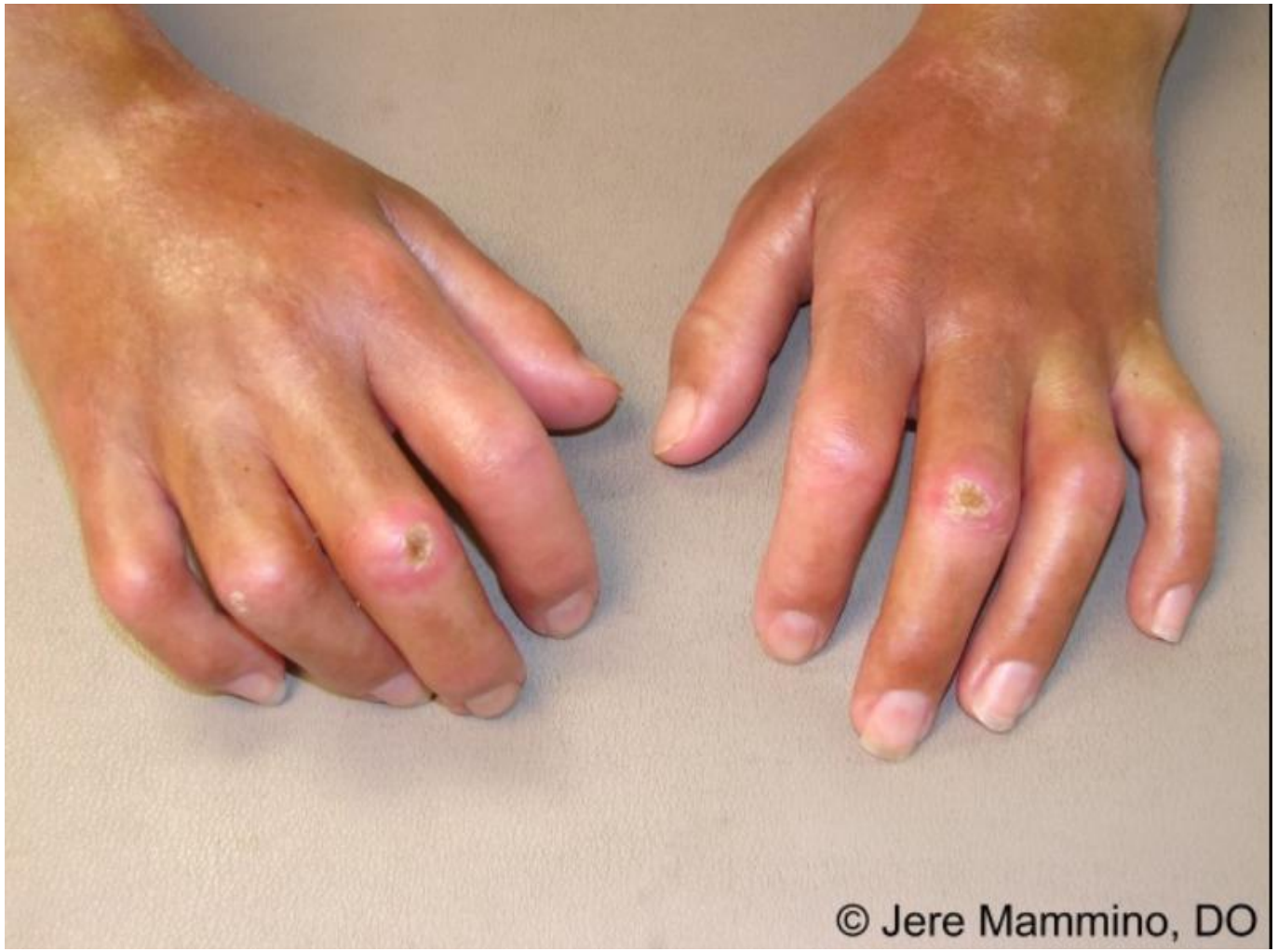
PE with nailfold exam

Differential

Scleroderma

Mixed Connective Tissue Disease

Myositis



Thank you

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VANDERBILT HEALTH