

Diarrhea, GERD, and Rejection: GI Issues after Transplantation

Rishi D. Naik, MD, MSCI, FACG

Assistant Professor of Medicine

Associate Program Director for VUMC GI Fellowship

Department of Esophageal Diseases



2025 Vanderbilt Transplant APP Symposium



Disclosures

- Paid Consultant
 - Ellodi (Trial Design), Completed
 - Renexxion (Trial Design, Therapeutics), Completed
 - Sanofi/Regeneron: Consultant
- Grant Funding
 - R01 (NIH) - Achalasia

Outline

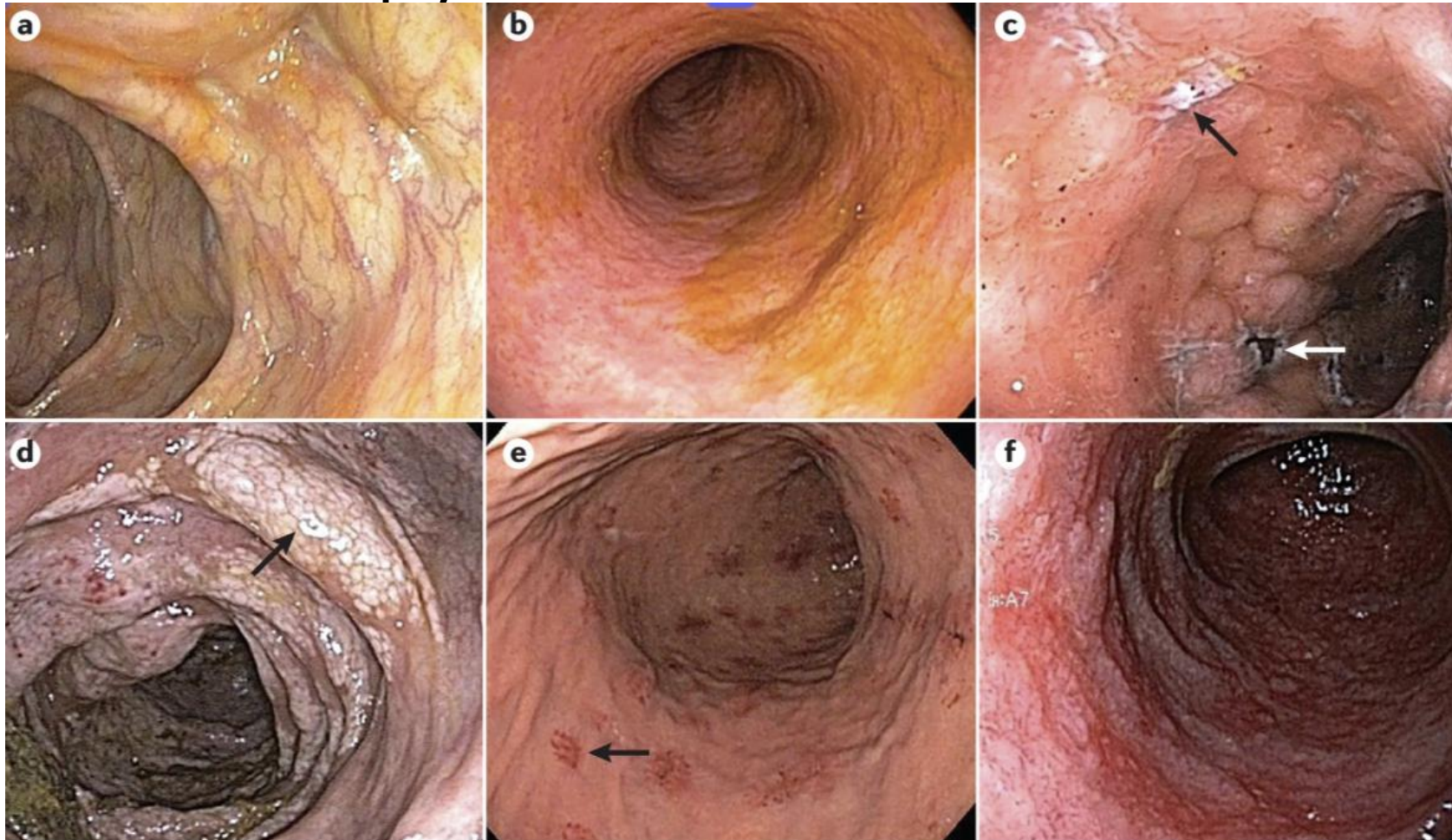
- Diarrhea
- GERD
- Updates to Gastroparesis
- GI Bleeding



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

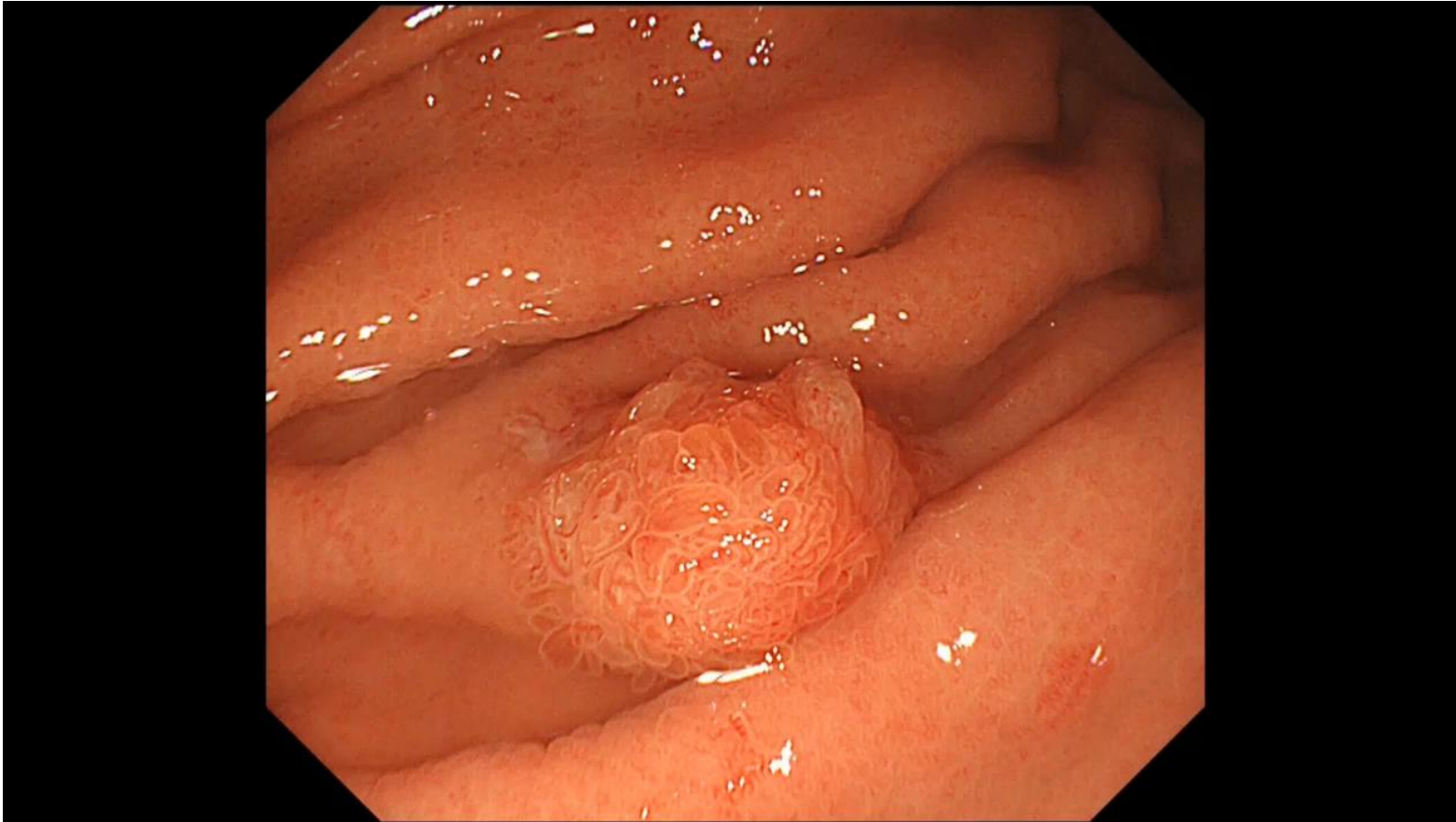


Nature Reviews | Gastroenterology & Hepatology

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 diarrhoea, severe malnutrition and gastrointestinal bleeding is paramount.

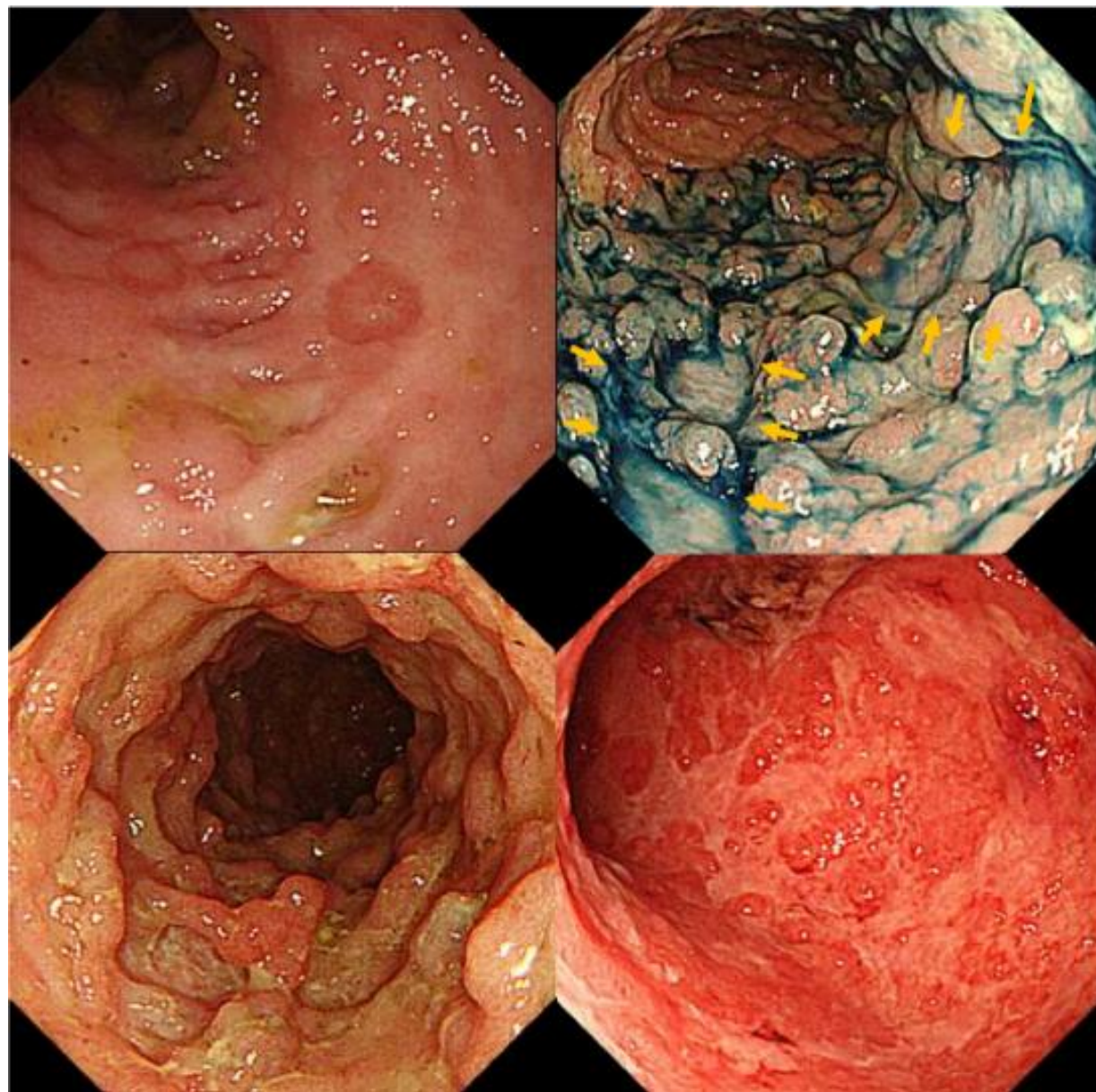
2025 Image Quality in GI





72- year old patients presents with worsening abdominal pain, diarrhea and night-time fevers.

- Lung Transplant 1 year ago
- CT abdomen shows colonic thickening
- Next step in therapy?



Infections after Transplant

- Viral Infections

- Cytomegalovirus (CMV)
- Herpes Virus

- Fungal Infections

- Candida

Infections after Transplant

- Bacterial Infections
 - C. Difficile (recurrent antibiotics)
 - Helicobacter Pylori
- Parasitic Infections
 - *Strongyloides stercoralis*

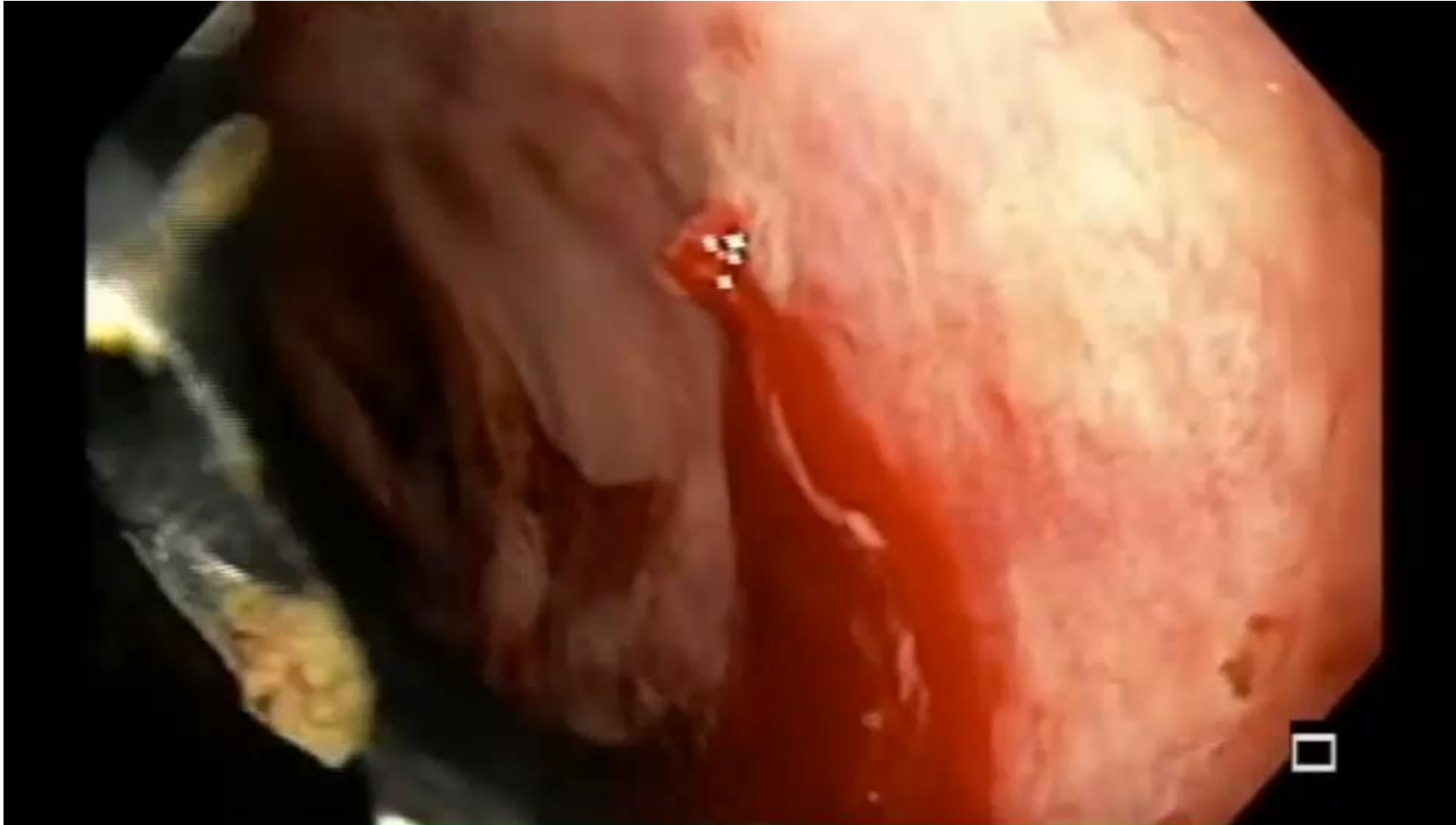
57-year-old patient presents with 3 months of chronic diarrhea. Infectious studies are normal. He has a history of small bowel transplant and is on MMF

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

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

Mucosal injury after Transplant



Mucosal injury after Transplant

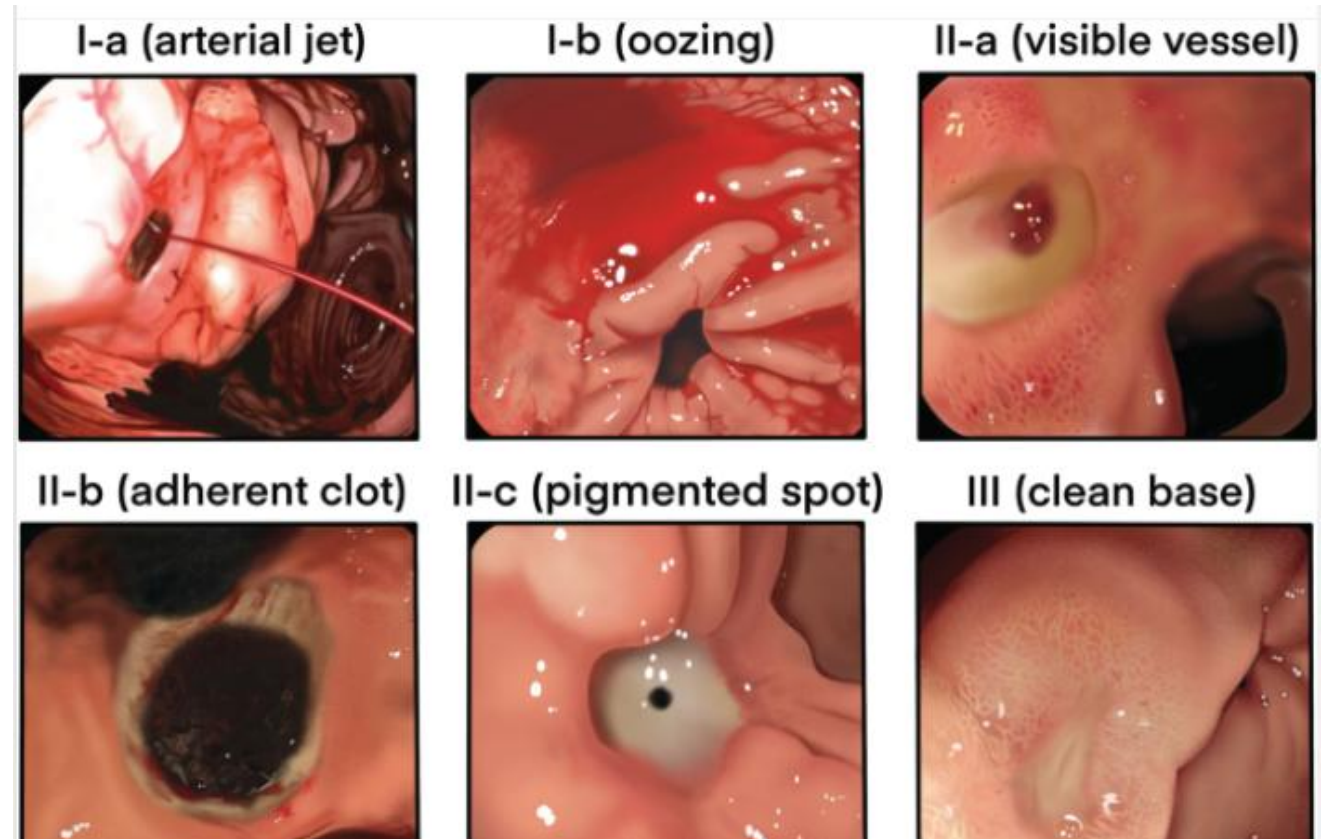
- Ulcerations

- 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)



49-year-old s/p kidney transplant
presents with diarrhea with
worsening pain in their left lower
quadrant

- WBC is 19k
- CT performed which shows thickening of the left colon, outpouchings of the colon, and concern for contained perforation.
- Next steps?

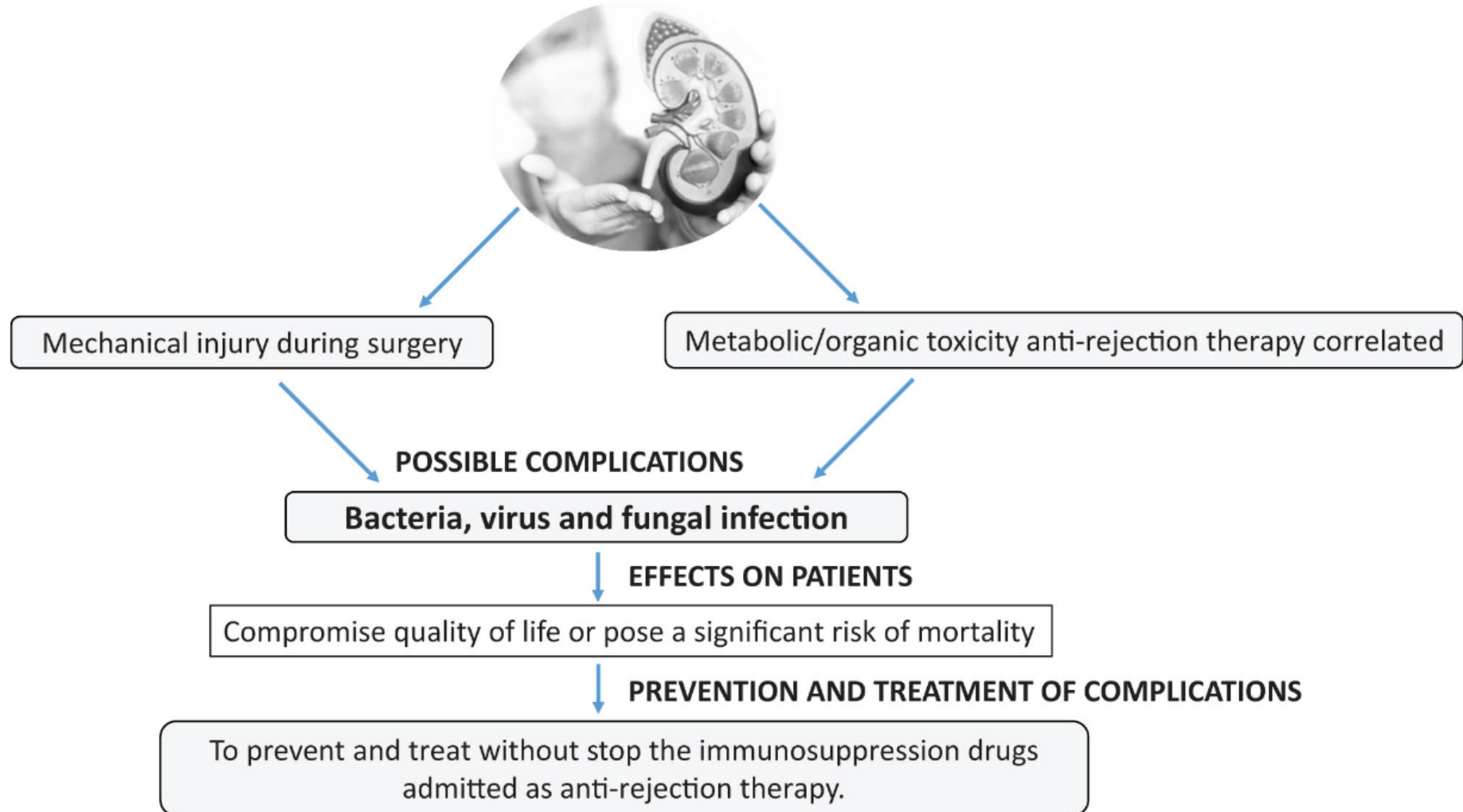
Diverticular Disease

- Diverticulosis vs. Diverticulitis (infection) vs. Diverticular bleed
 - Common, especially after renal transplant
 - Medications which slow motility (including GLP1-RA)
 - In 1186 renal transplant patients at Vanderbilt, pre-transplantation colonoscopies were ineffective in predicting post-transplant colonic complications
 - Polycystic kidney disease have higher risk of diverticulitis/complications

Diverticular Disease

- Diverticulosis vs. Diverticulitis (infection) vs. Diverticular bleed
 - Treatment
 - High fiber
 - Stop offending agents that cause constipation
 - For uncomplicated diverticulitis – recommend colonoscopy in 2 months to ensure no underlying malignancy
 - For non-transplant patients, uncomplicated diverticulitis can be managed without antibiotics, for immunosuppressed patients, threshold is lower to treat given immunosuppression

Gastrointestinal complications in kidney transplantation

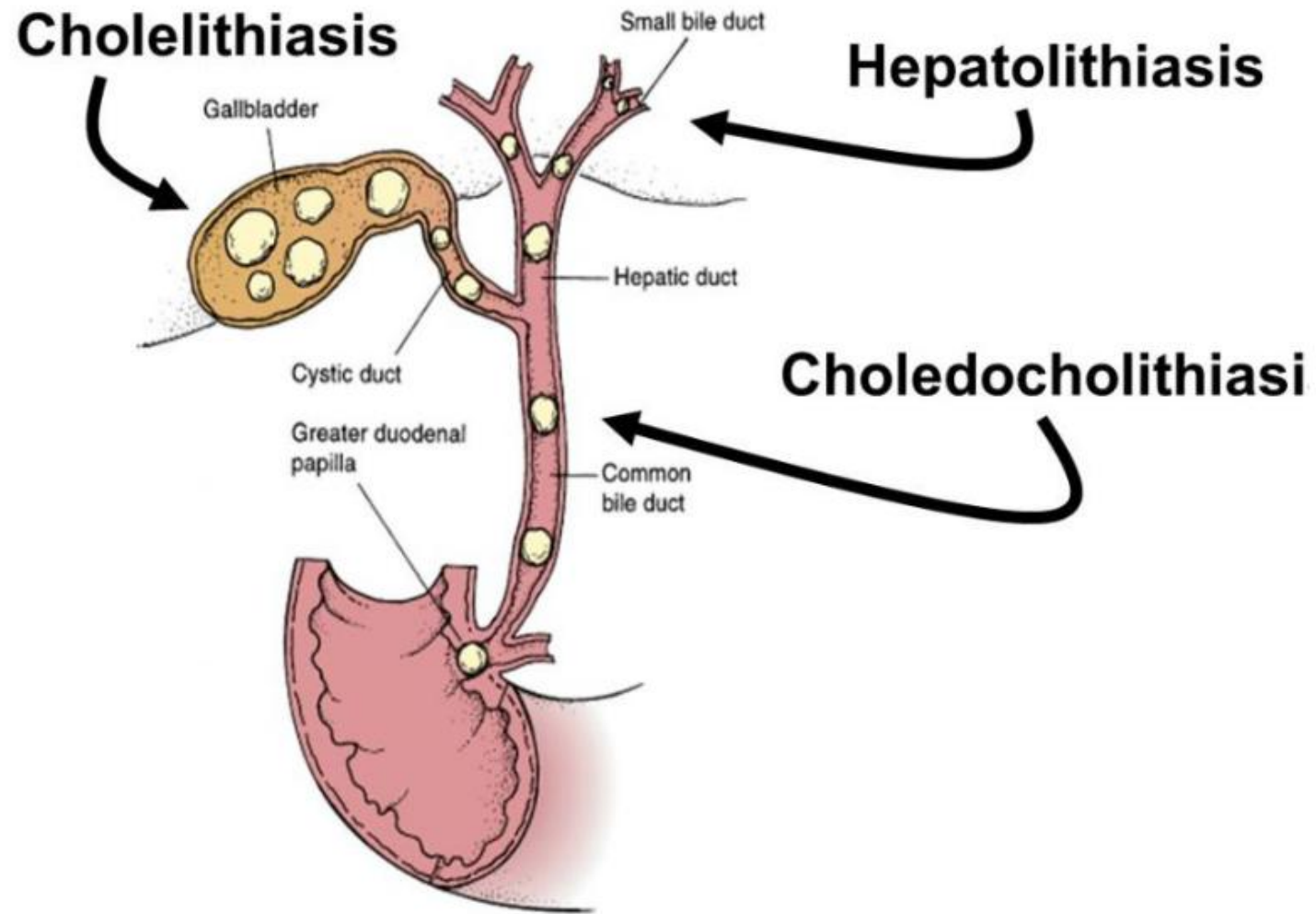




64-year-old presents with diarrhea and pain in the right upper quadrant. They are s/p kidney transplant 5 years ago.

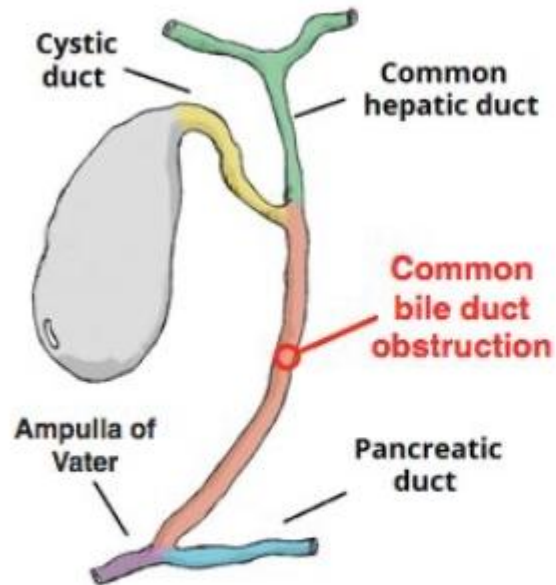
- WBC is 17k
- RUQ U/S shows thickened gallbladder with a common bile duct of 1.8cm
- Next steps?

Biliary Tract Diseases



Biliary Tract Diseases

Bacterial infection in a patient with biliary obstruction



▲ Charcot's Triad

Fever
Abdominal pain
Jaundice

◆ Reynolds pentad

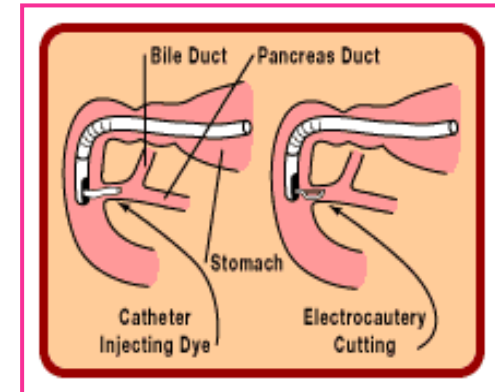
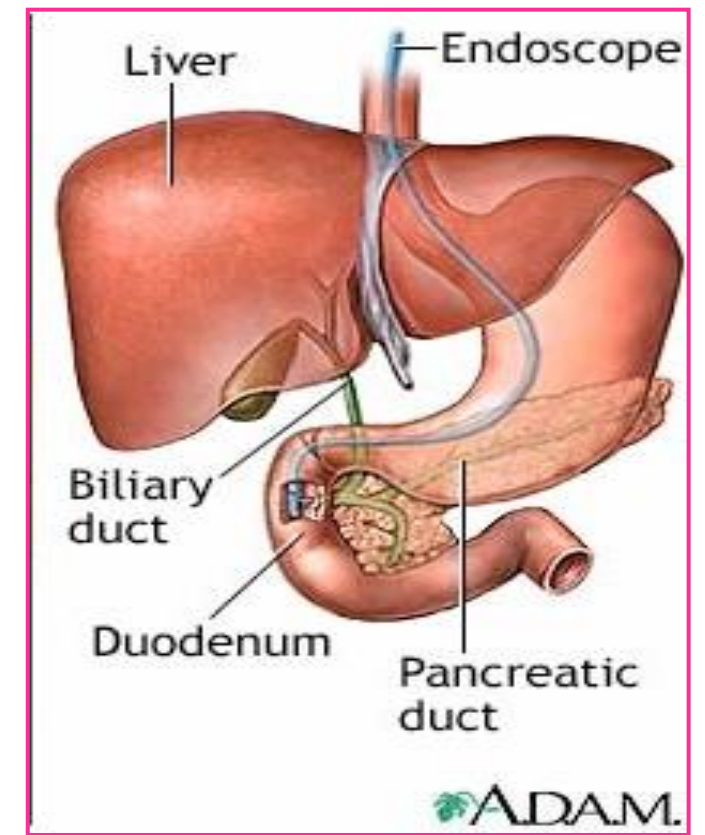
Fever
Abdominal pain
Jaundice
+
Confusion
Hypotension

Management

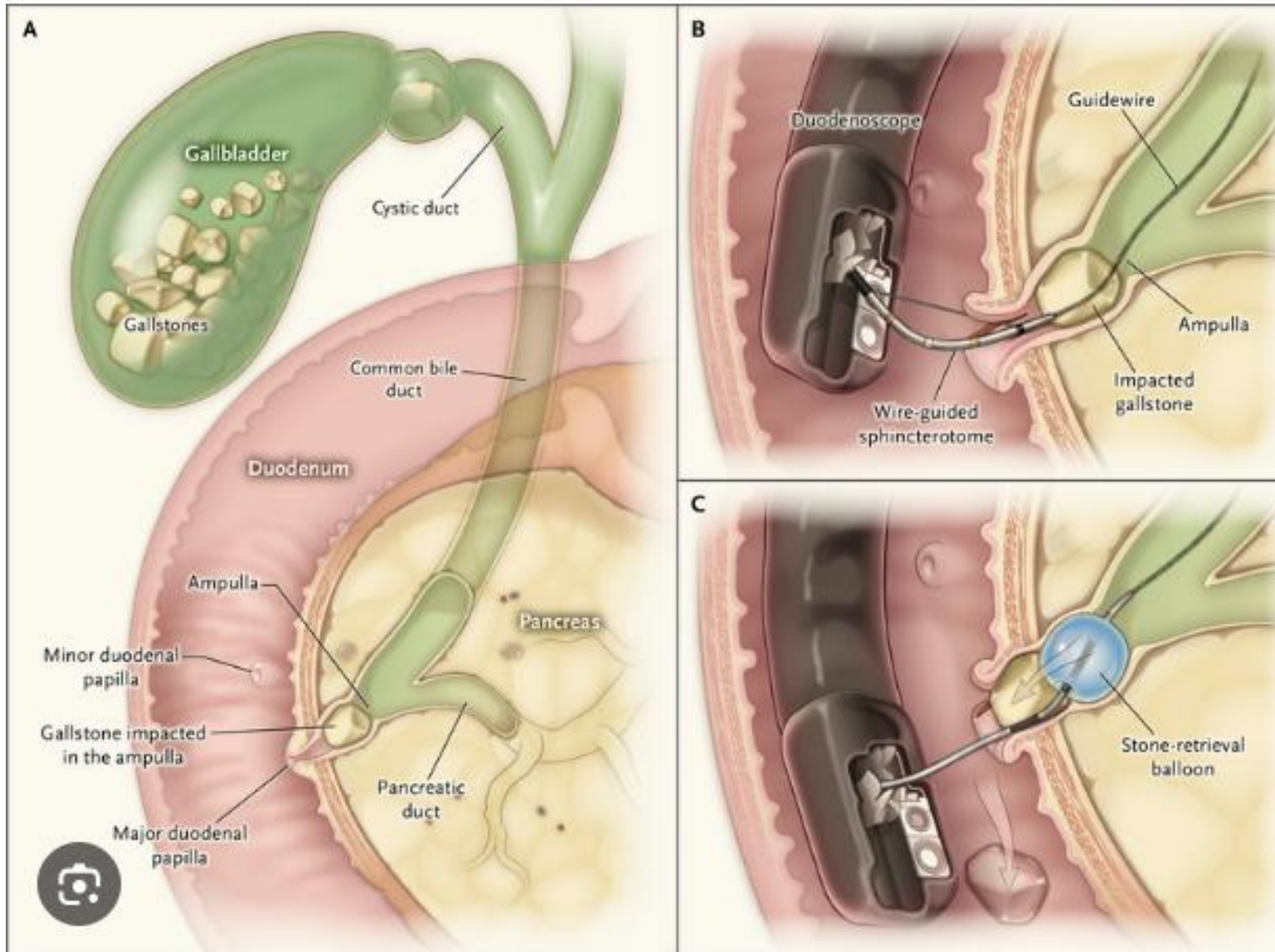
- Broad-spectrum antibiotics (e.g. Ampicillin-sulbactam)
- Biliary drainage (e.g. ERCP)

Biliary Tract Diseases

- **E**ndoscopic **R**etrograde **C**holangio**P**ancreatography
 - A way to study bile/panc ducts
 - Can also biopsy, stent, remove stones, sphincterotomy, etc.
- Risks
 - Pancreatitis (contrast, injury)
 - Perforation or bleeding
- MRI (MRCP) can image also



Biliary Tract Diseases





42-year-old presents with PSC
presents with worsening RUQ
pain. They are 3 days post liver
transplant.

- Liver function tests are AST >1000, ALT >1000
- Patient is altered
- Next best step?

Hepatic Artery Thrombosis

- HAT – serious vascular complication after liver transplantations
 - Obtain STAT RUQ U/S with dopplers
 - If identified, recommend urgent transplantation to prevent biliary sepsis

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

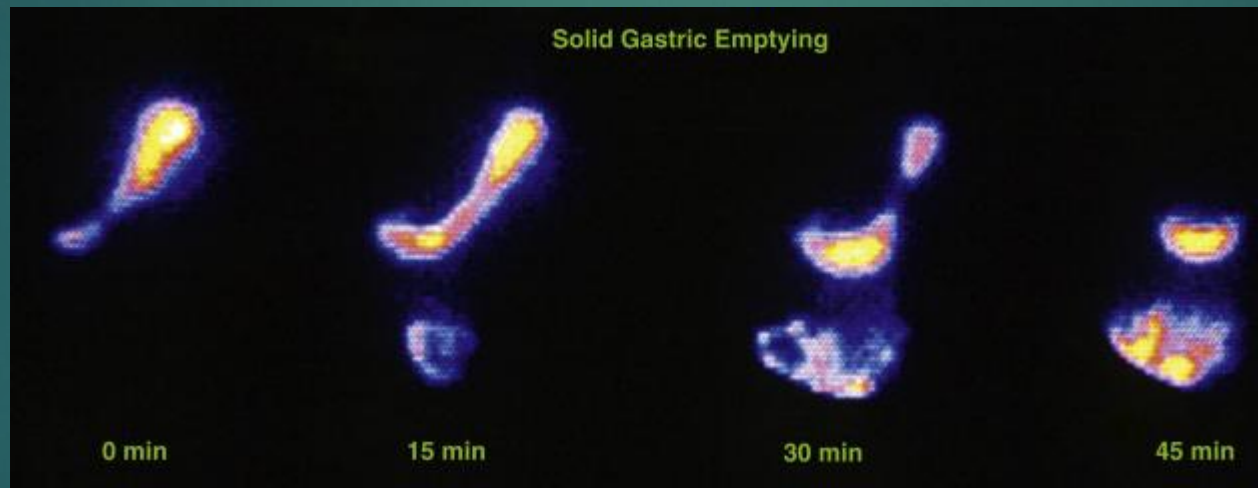
- Post-transplant lymphoproliferative disorder (PTLD)
 - Can involve GI tract in 10% of transplant recipients
 - Often, there are abnormal enlarged lymph nodes that are hard to biopsy
 - Driver is typically EBV
 - Biopsies are key
 - Therapy: lowering immunosuppression (or cessation) plus transplant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

Patient:

30

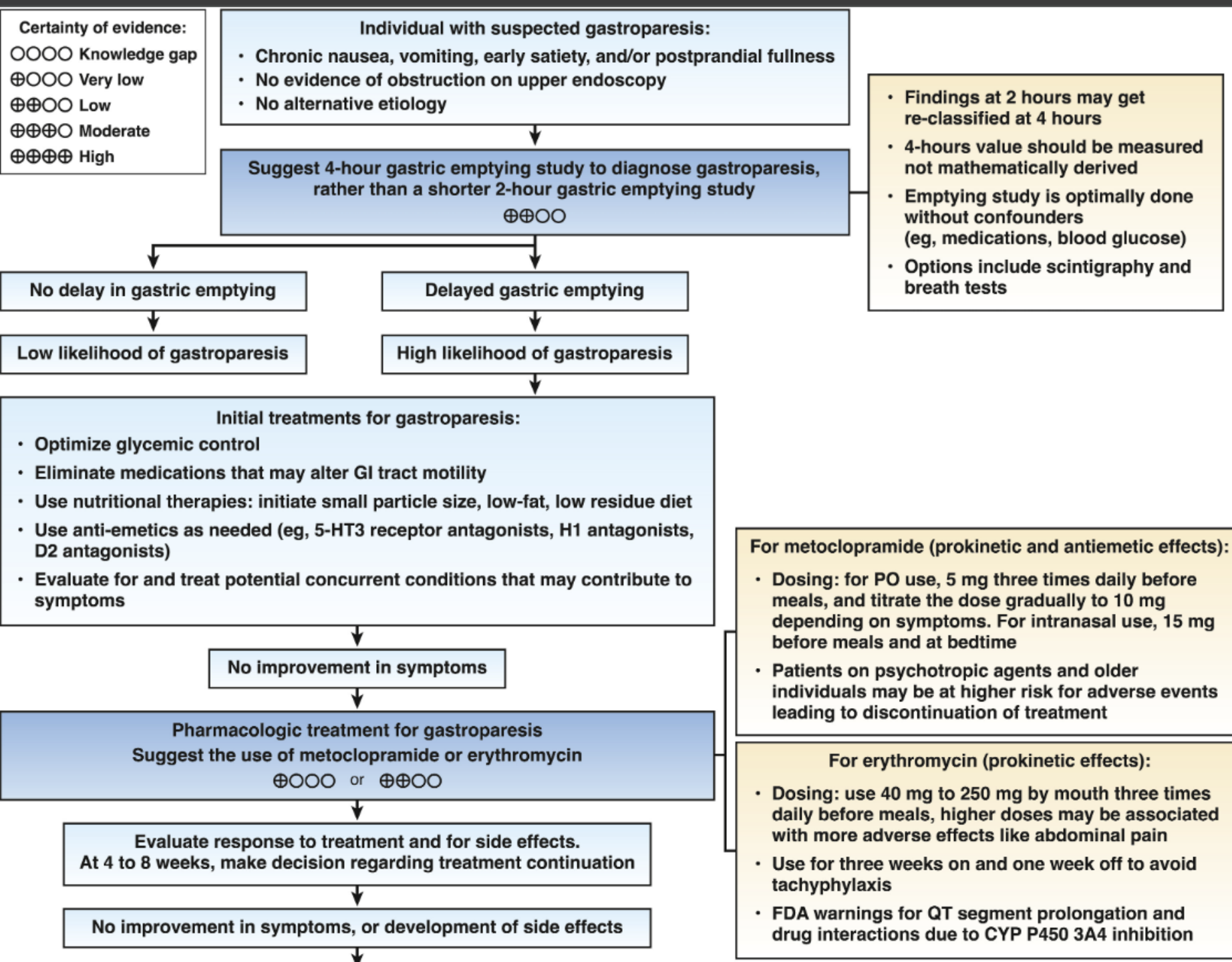
56-year-old presents for consideration for heart-transplantation. Prior poorly controlled diabetes with nausea/vomiting. Patient reports he cannot eat solid food – ok to list for cardiac transplant?

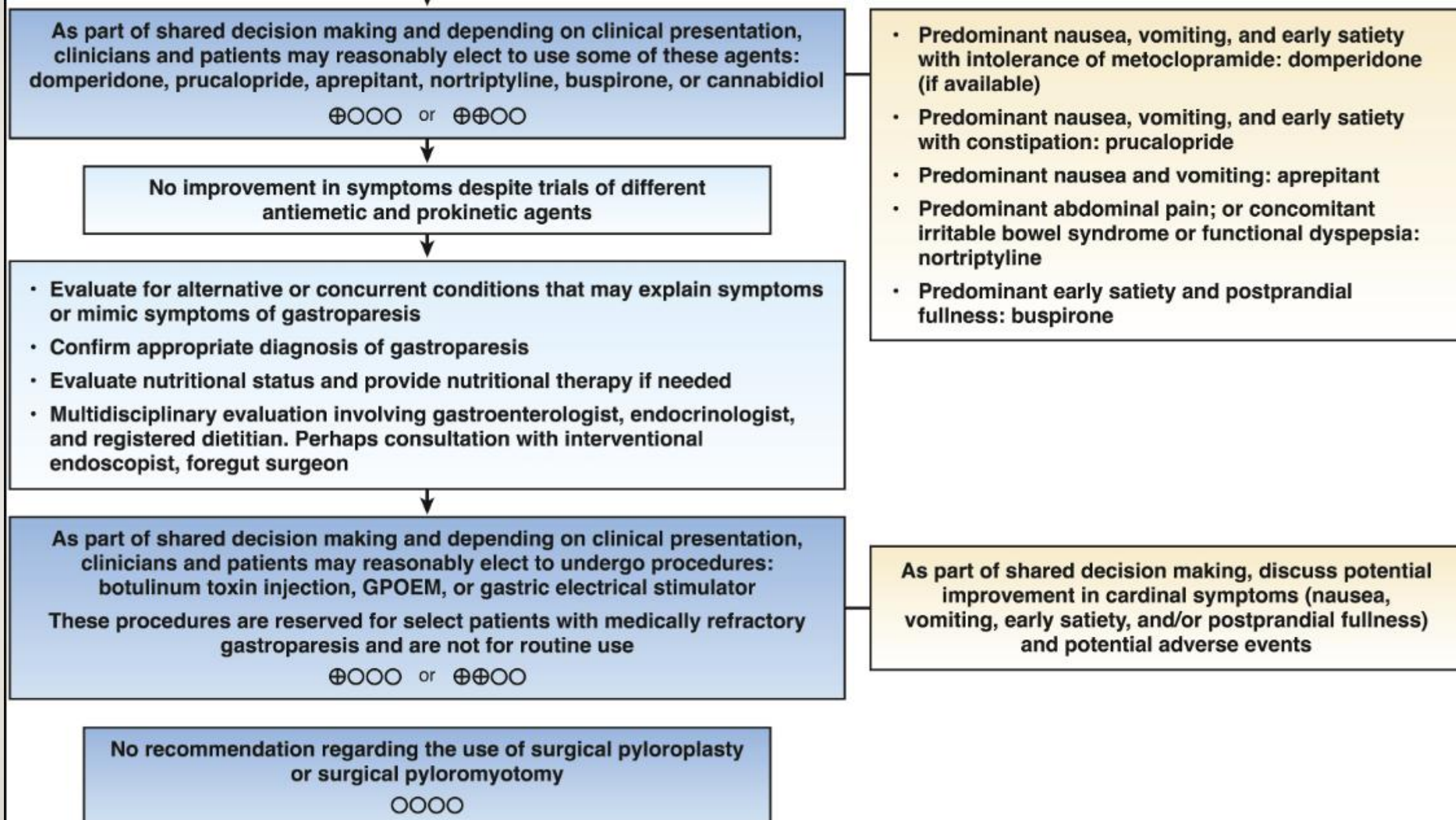
- ▶ EGD Normal – except retained food in the stomach
- ▶ Gastric emptying performed shows delayed motility – next steps?



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 arrhythmias
 - Macrolide antibiotics
 - Erythromycin – inpatient, tachyphylaxis
 - 5HT4 agonist: Prucalopride (off-label) - (Cisapride – led to cardiac arrhythmias and death)
 - Surgery
 - G-POEM
 - Surgical J tube (or G-J tube)







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

- Esophagram performed showing retention and concern for Achalasia

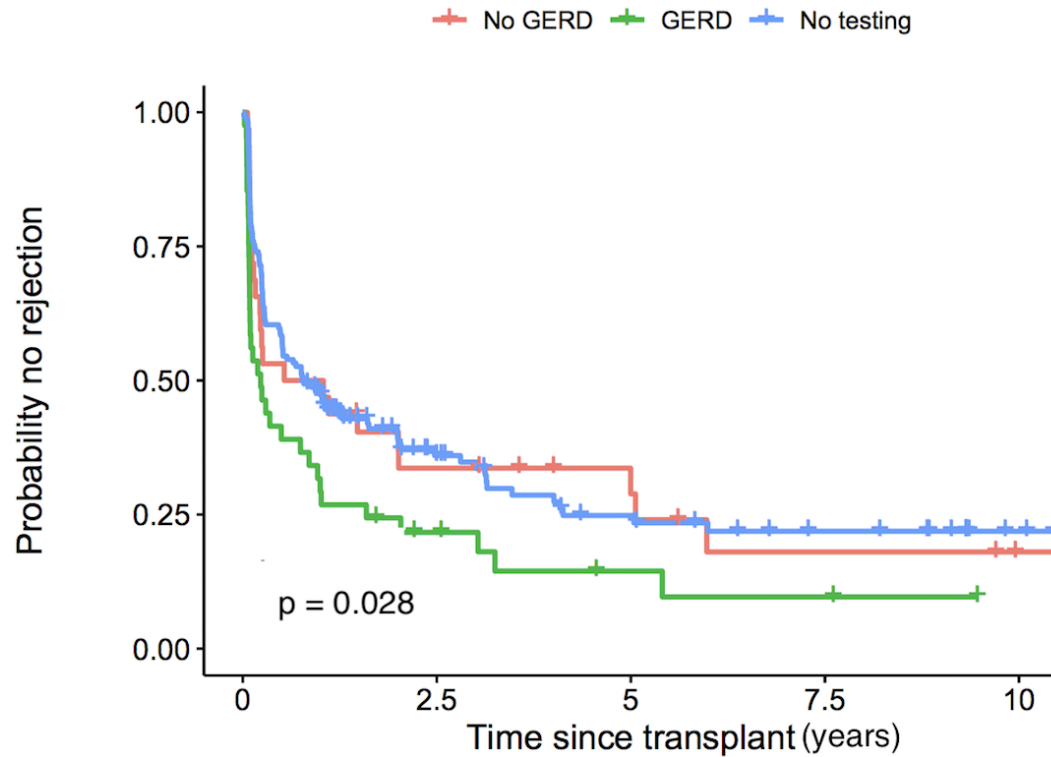
GERD testing

- 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

Pre-Transplant GERD Predicts Acute Rejection in Lung Transplant



p = 0.028

DDW 2021



Matt Meyers
Vanderbilt Housestaff
UoC GI Fellow
Transplant Hepatology



Claudio Tombazzi
Vanderbilt Housestaff '19
VUMC GI Fellow
Transplant Hepatology

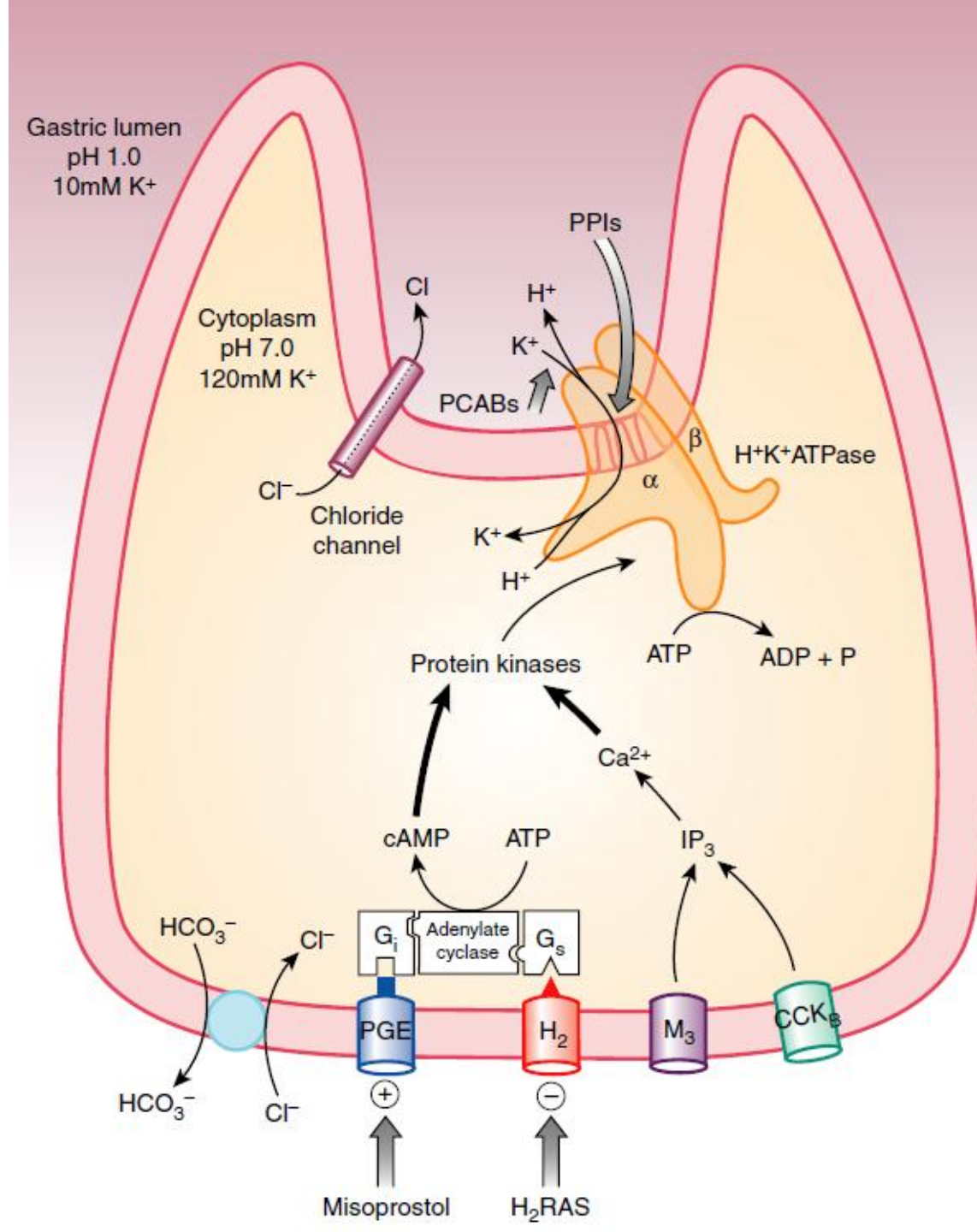
Reflux Testing in Lung Transplant

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

	Hazard Ratio for BOS	<i>P</i>
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

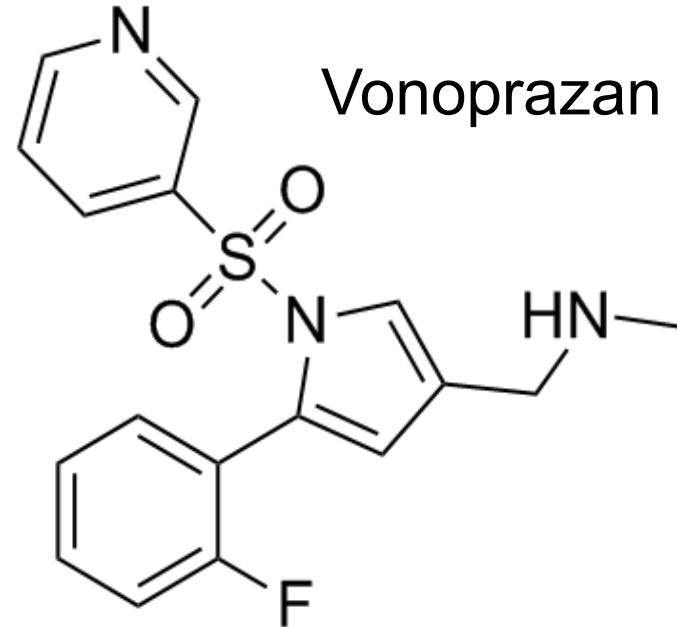
- Only actively secreting parietal cells are affected by PPIs
 - *Fasting* - only ~5% of proton pumps actively secreting
 - *With meals* - 60-70% of proton pumps actively secreting
 - Food can affect bioavailability of some PPIs
 - Give PPIs 30-60 minutes before a meal
- PPIs have short half-life (~90 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

PPI Pharmacokinetics

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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

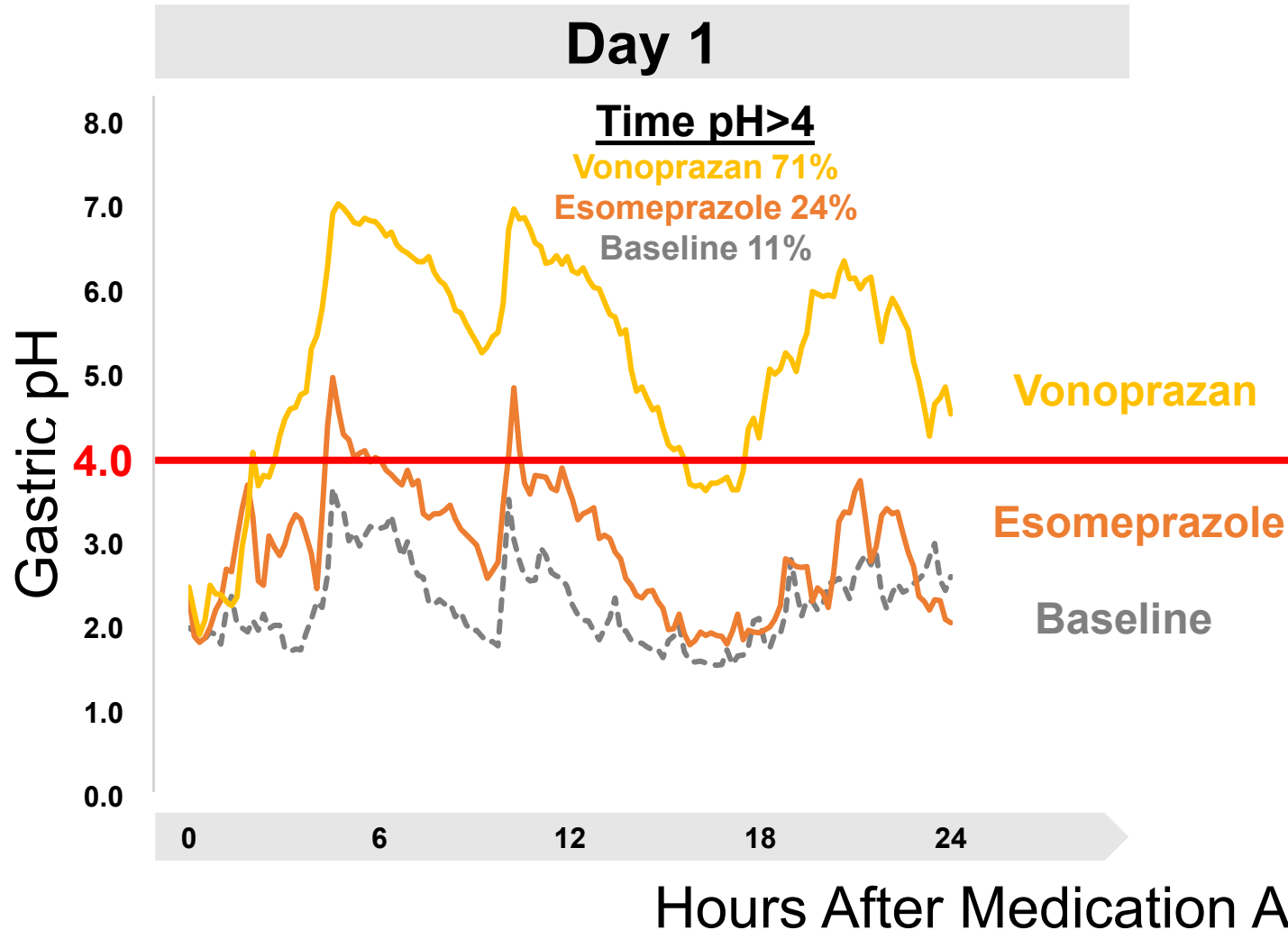


P-CAB Pharmacologic Features

- 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

Vonoprazan 20 mg vs. Esomeprazole 20 mg Effects on Gastric pH

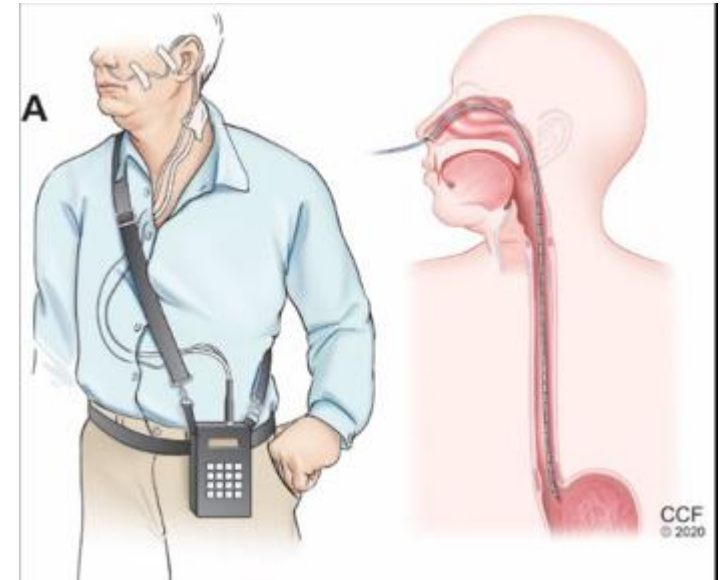
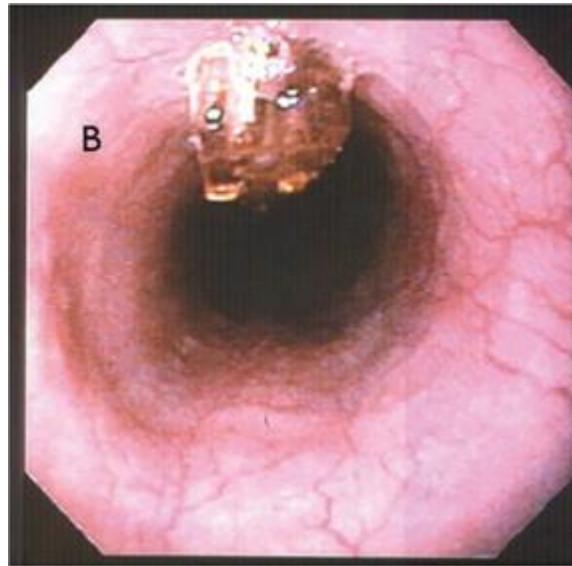
Meds given once daily to 20 healthy Japanese men



Data from Sakurai Y et al. Aliment Pharmacol Ther 2015;42:719-30.

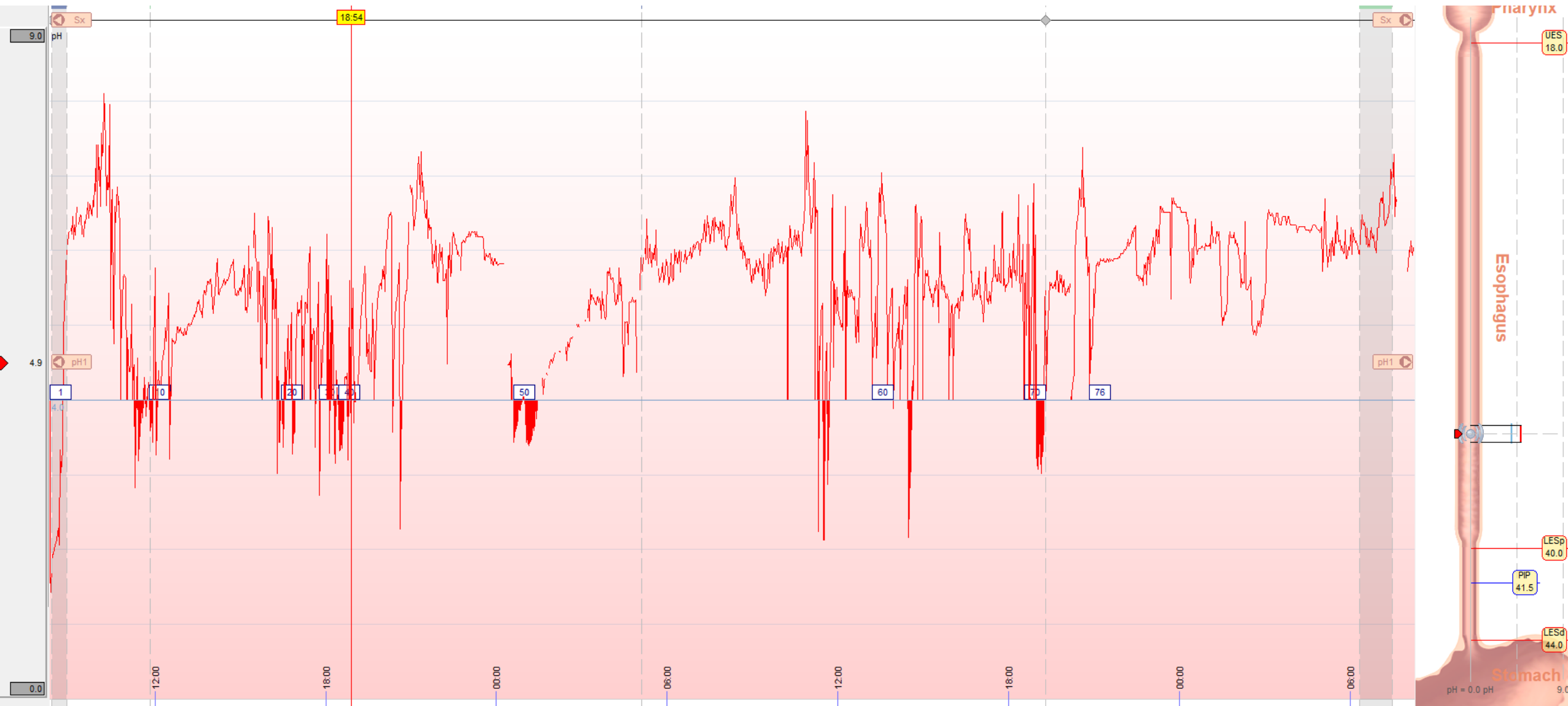
Reflux Monitoring

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



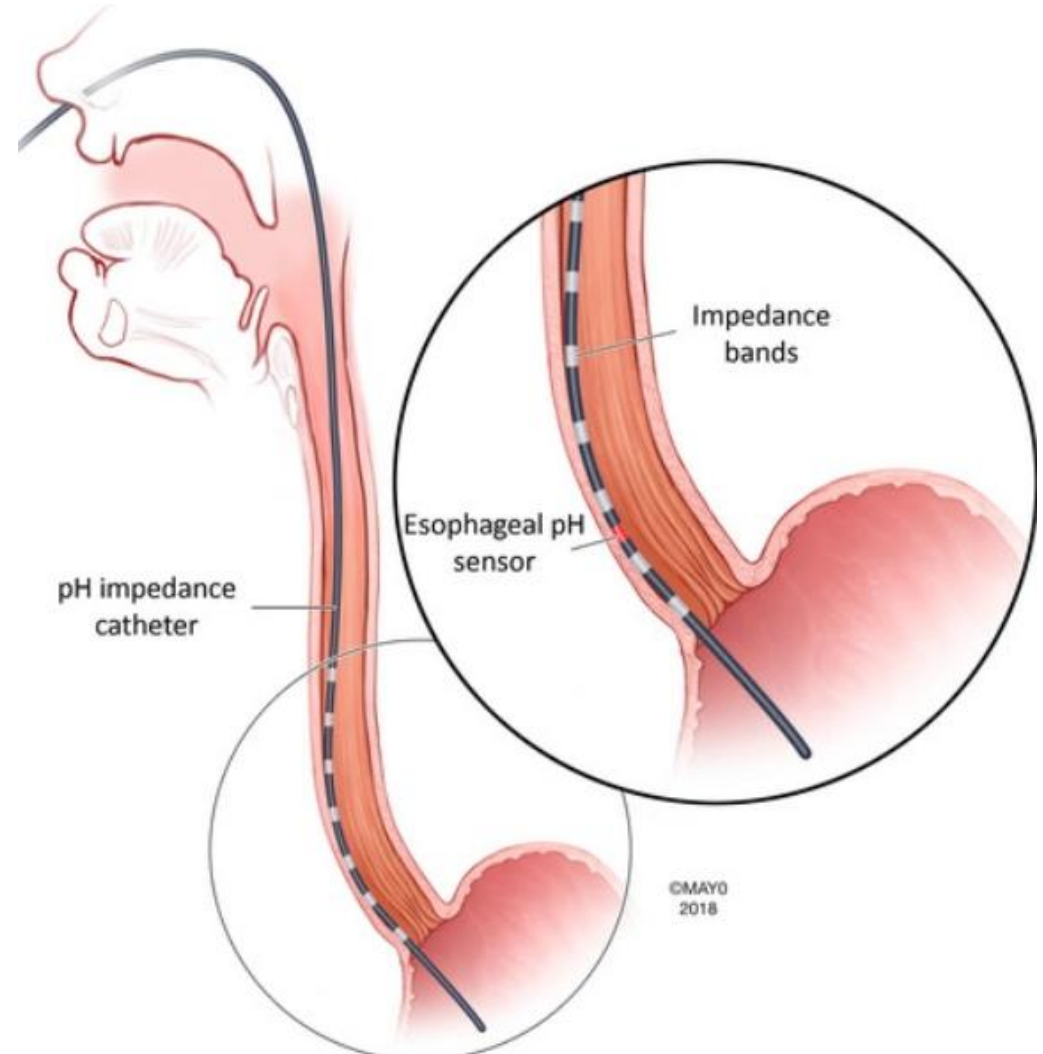
Young A, et al. Cleveland Clinic Journal of Medicine Apr 2020, 87 (4) 223-230
www.Medtronic.com

Ambulatory Reflux Monitoring



Impedance Monitoring

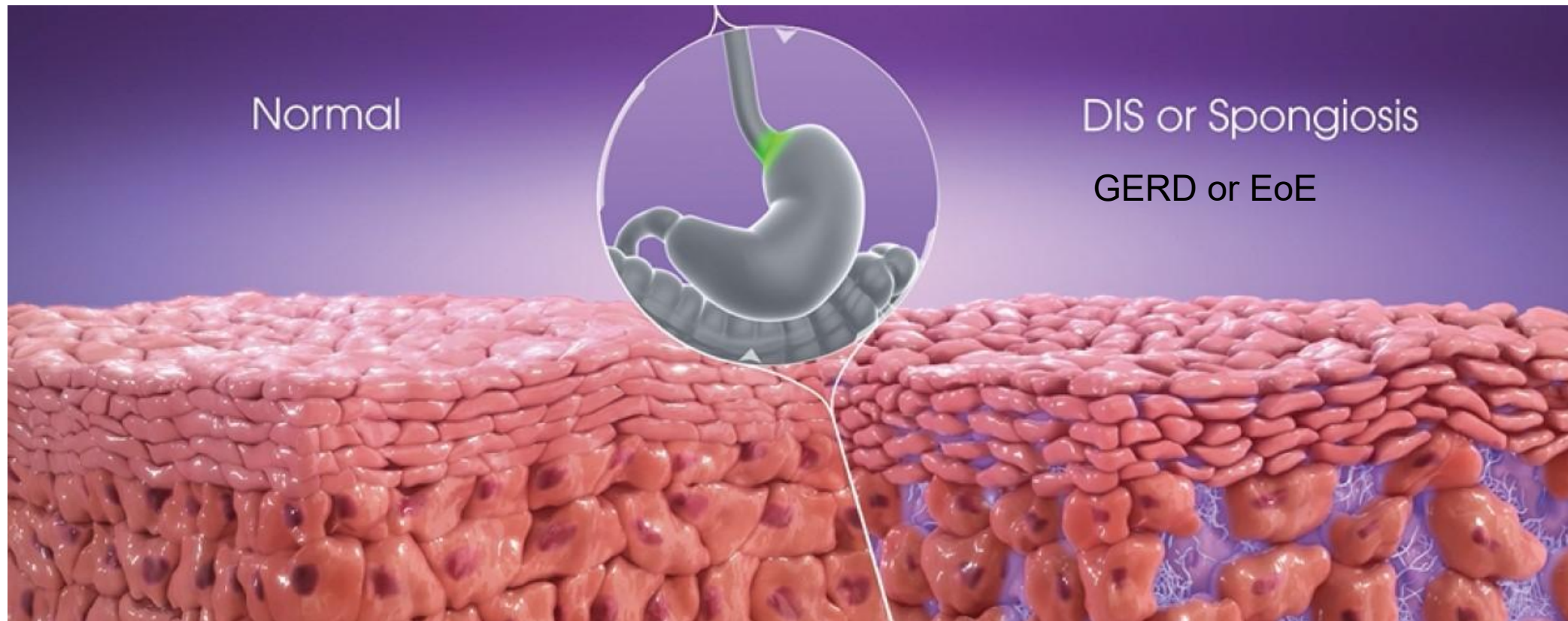
- Acid and non-acid testing
 - Impedance testing
 - Typically, on therapy; breakthrough symptoms
 - Despite adequate response to PPI, is there breakthrough symptoms of reflux leading to worsening lung dysfunction?



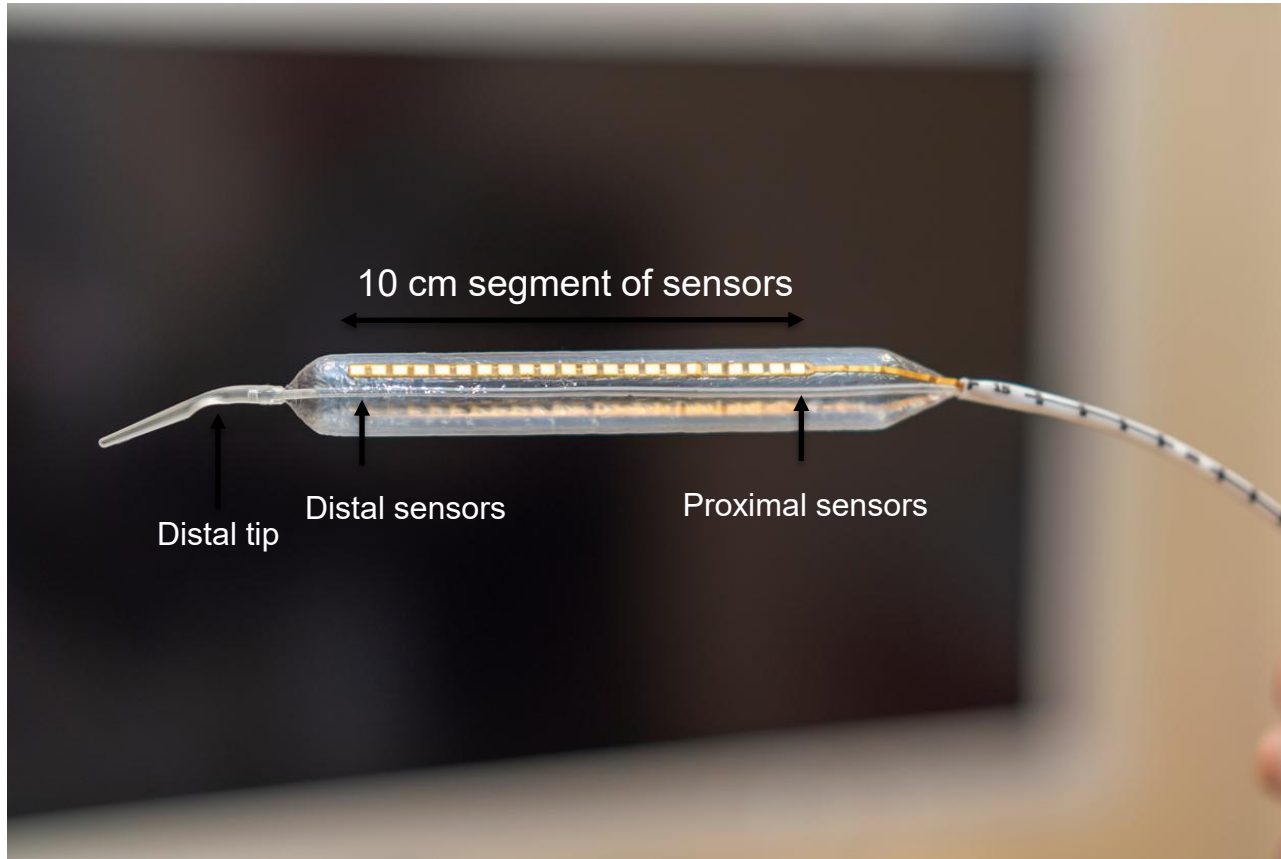
Mucosal integrity testing



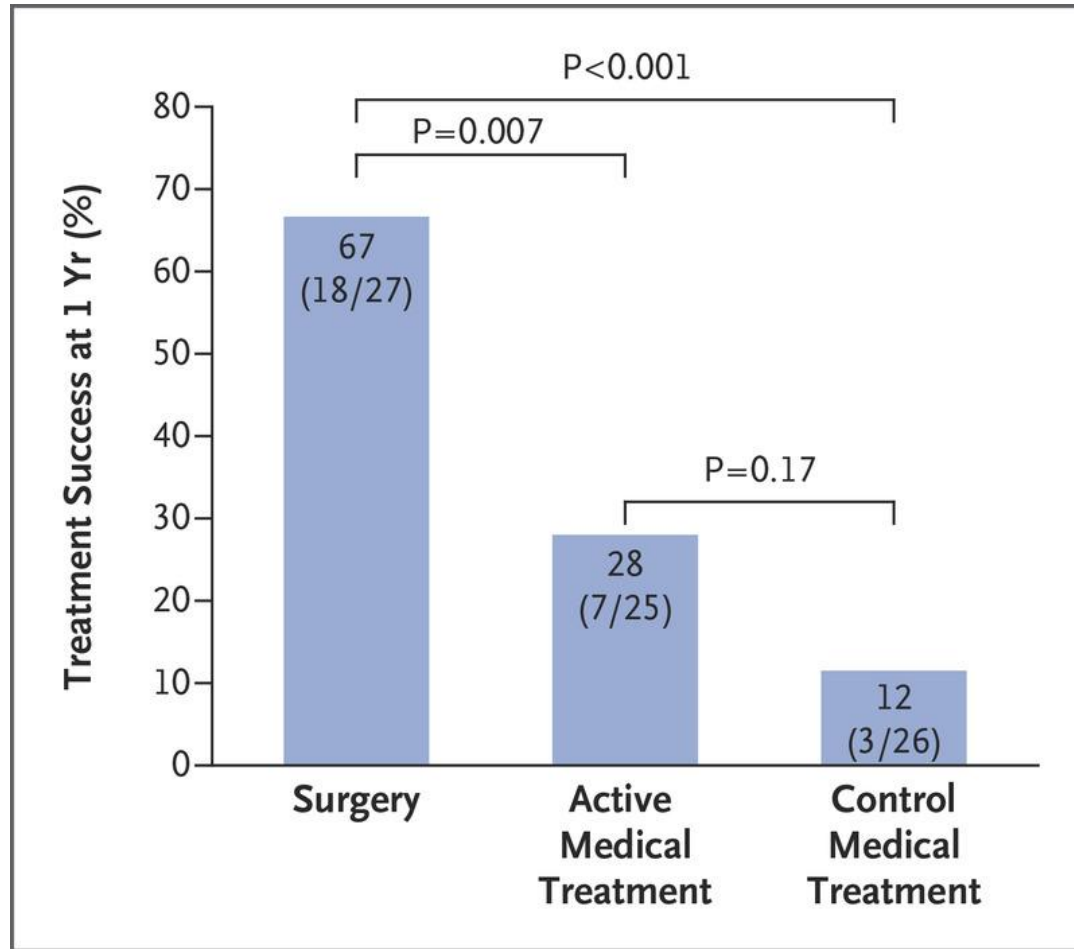
- Mucosal Integrity is affected by the presence of dilated intercellular spaces (DIS) which affects paracellular permeability.



Mucosal integrity testing (GERD/EoE)



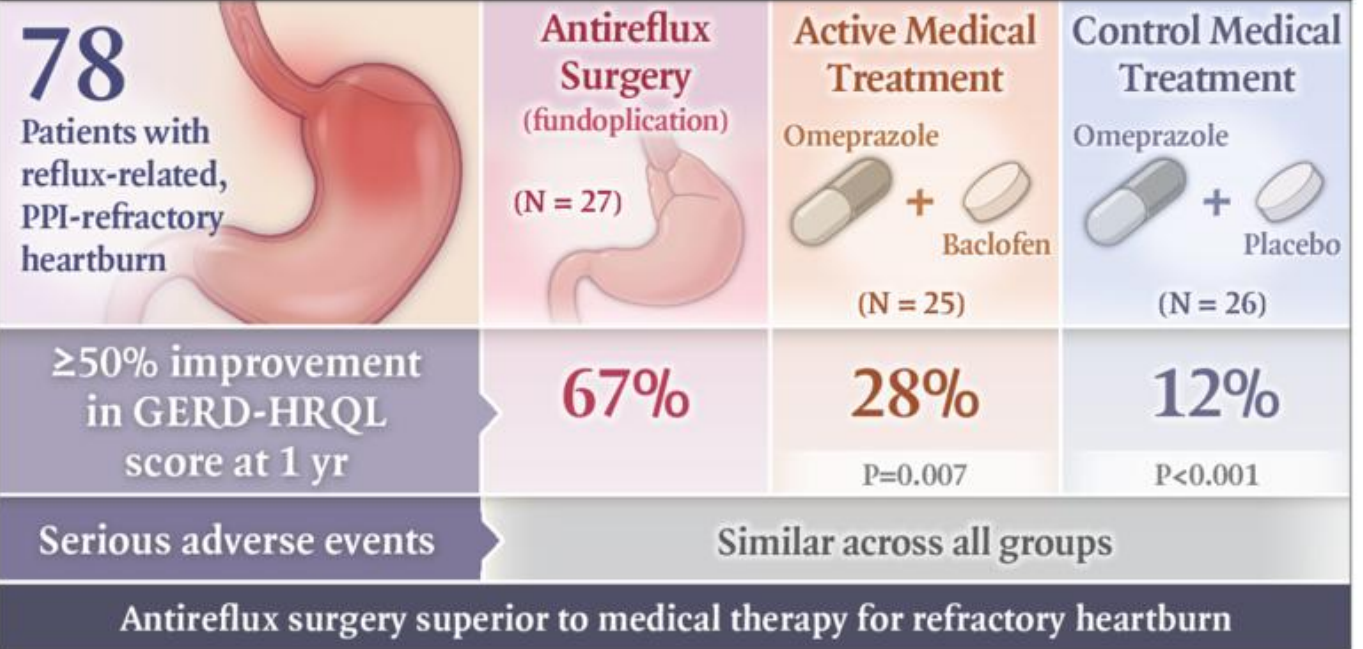
Laparoscopic Fundoplication



The NEW ENGLAND JOURNAL of MEDICINE

Medical vs. Surgical Treatment for Refractory Heartburn

RANDOMIZED, CONTROLLED TRIAL



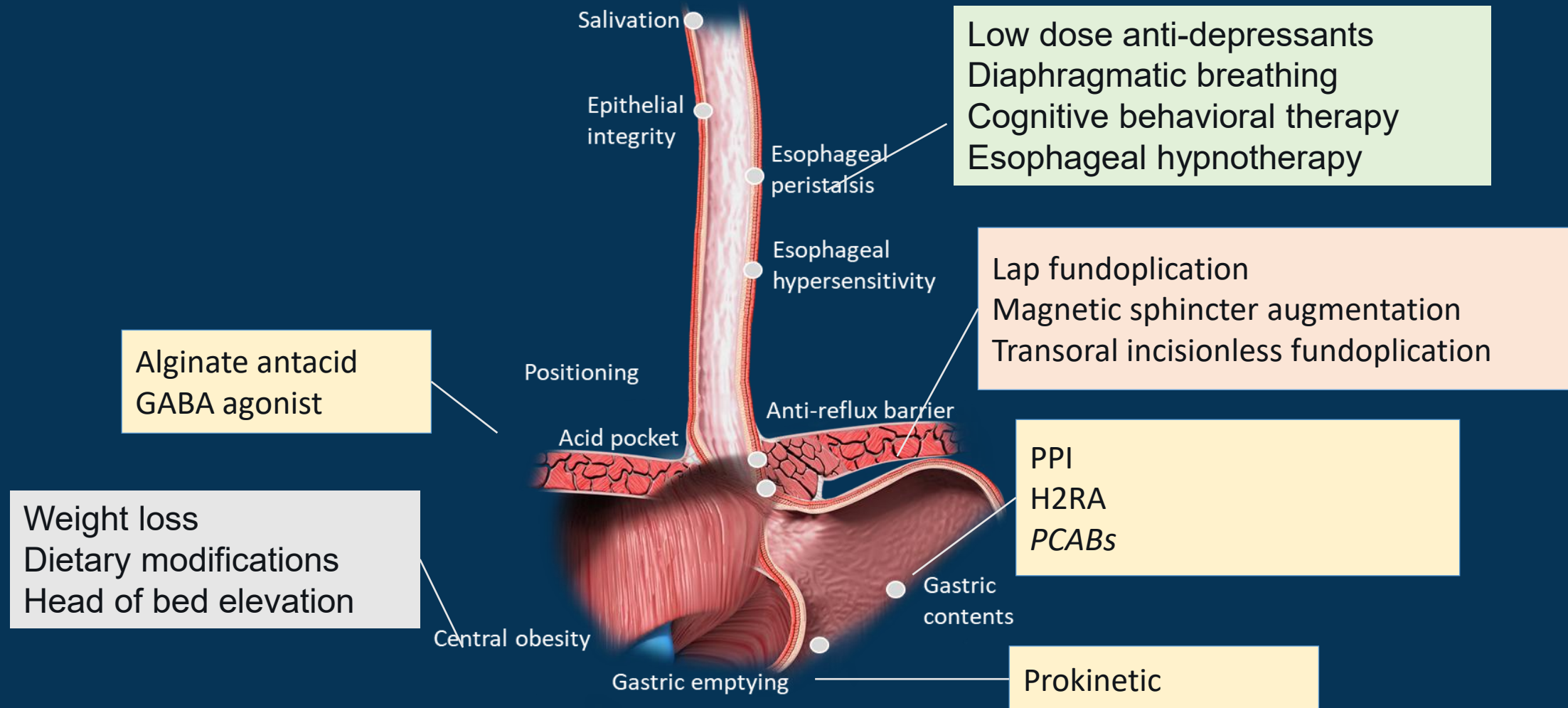
S.J. Spechler et al. 10.1056/NEJMoa1811424

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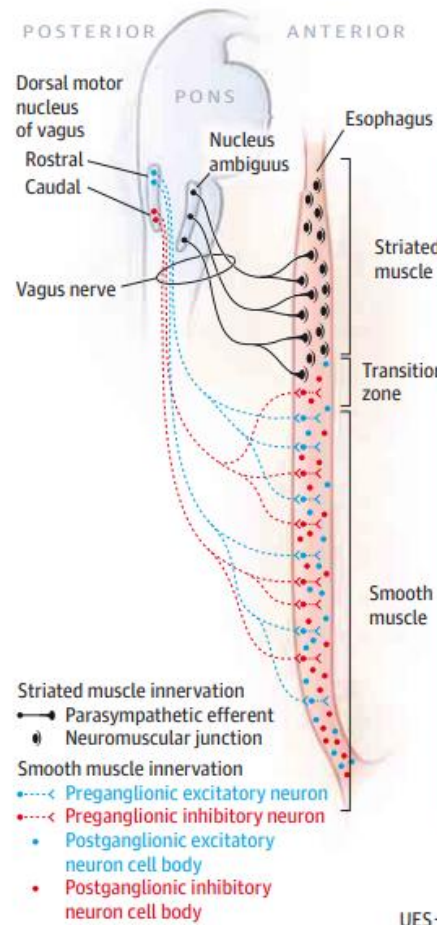
Side effects: dysphagia, gas-bloat syndrome, diarrhea

Spechler SJ et al. NEJM 2019;381:1513

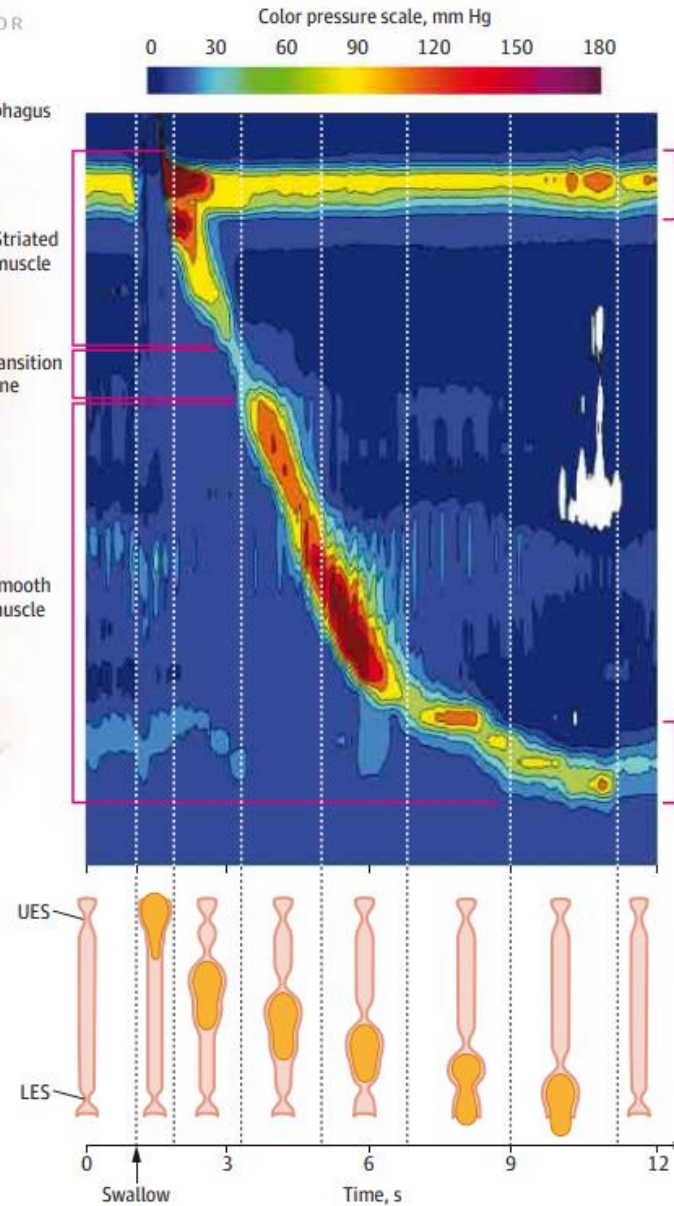
Critical to Understand Mechanism of Symptom & Target Accordingly



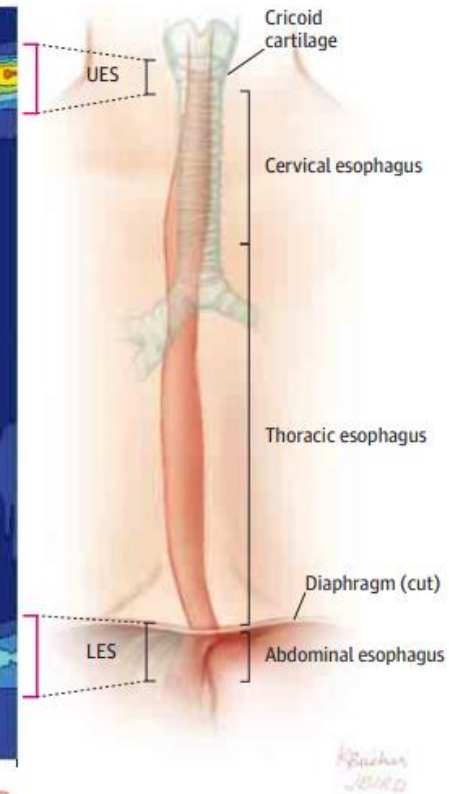
A Parasympathetic esophageal innervation

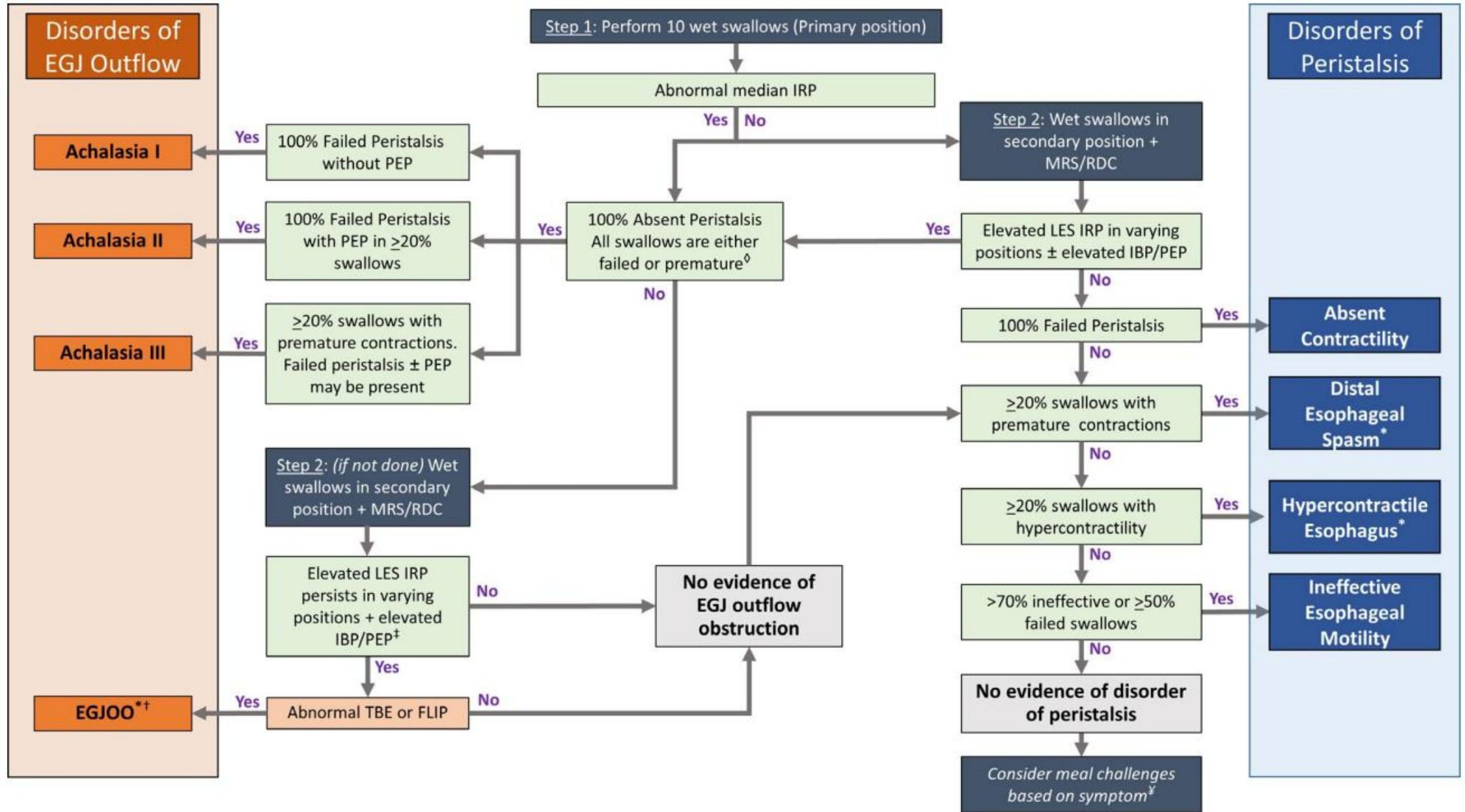


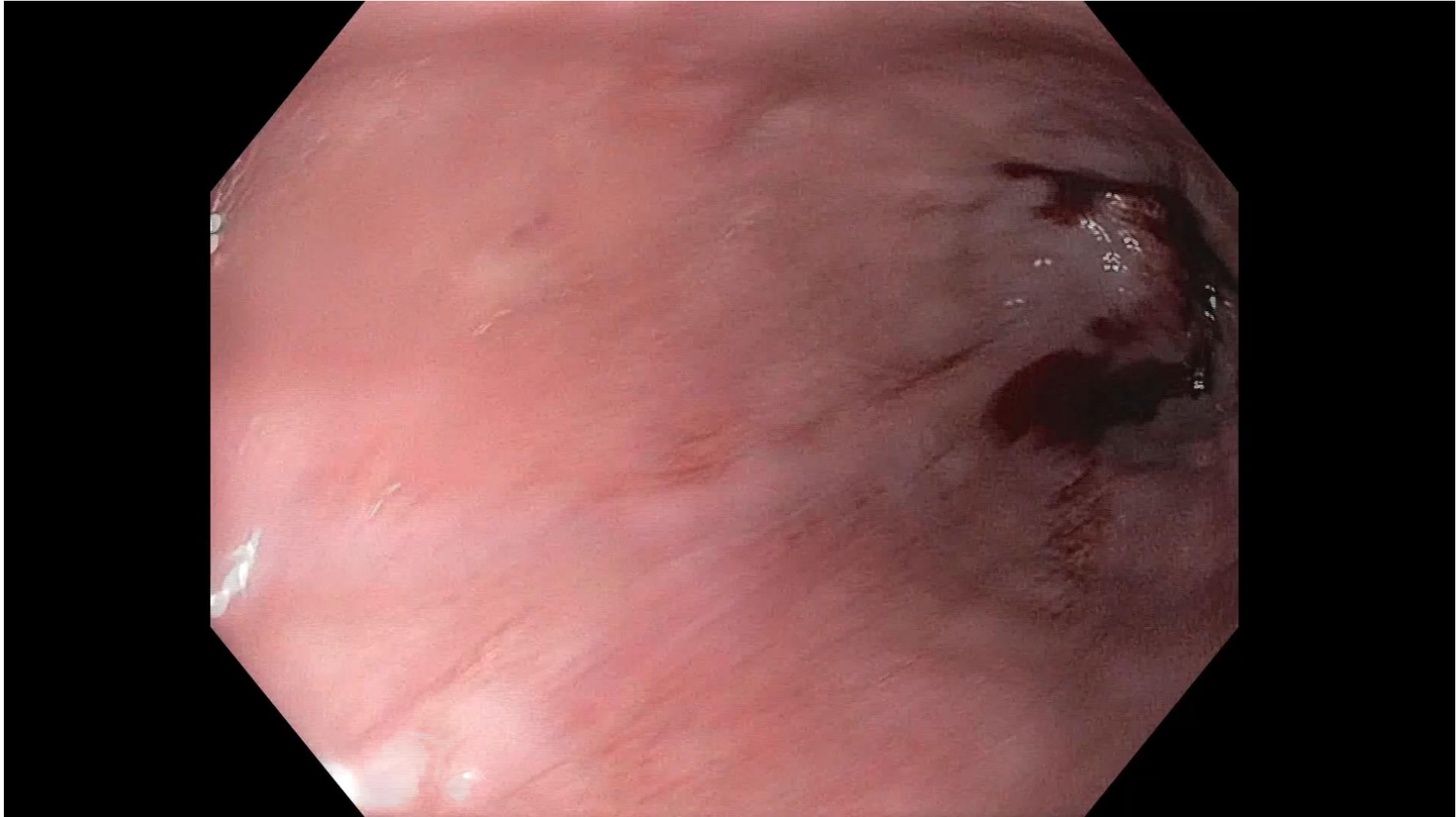
B Esophageal pressure topography (EPT) plot from high resolution manometry (normal study)



C Anatomical correlation with EPT plot







Acknowledgements

- Vanderbilt Esophageal Group
 - Michael Vaezi and Dan Patel
 - Chris Slaughter
 - Michael Holzman and Chetan Aher (Foregut surgery)
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Rishi.D.Naik@vumc.org
@RishiNaikMD

