

# Common 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

VANDERBILT  HEALTH

*2024 Vanderbilt Transplant APP Symposium*




# Disclosures

- Paid Consultant
  - Bethanamist (Trial Design, Drug , development), ongoing
  - Ellodi (Trial Design), Completed
  - Renexxion (Trial Design, Therapeutics), Completed
  
- Grant Funding
  - R01 (NIH) - Achalasia

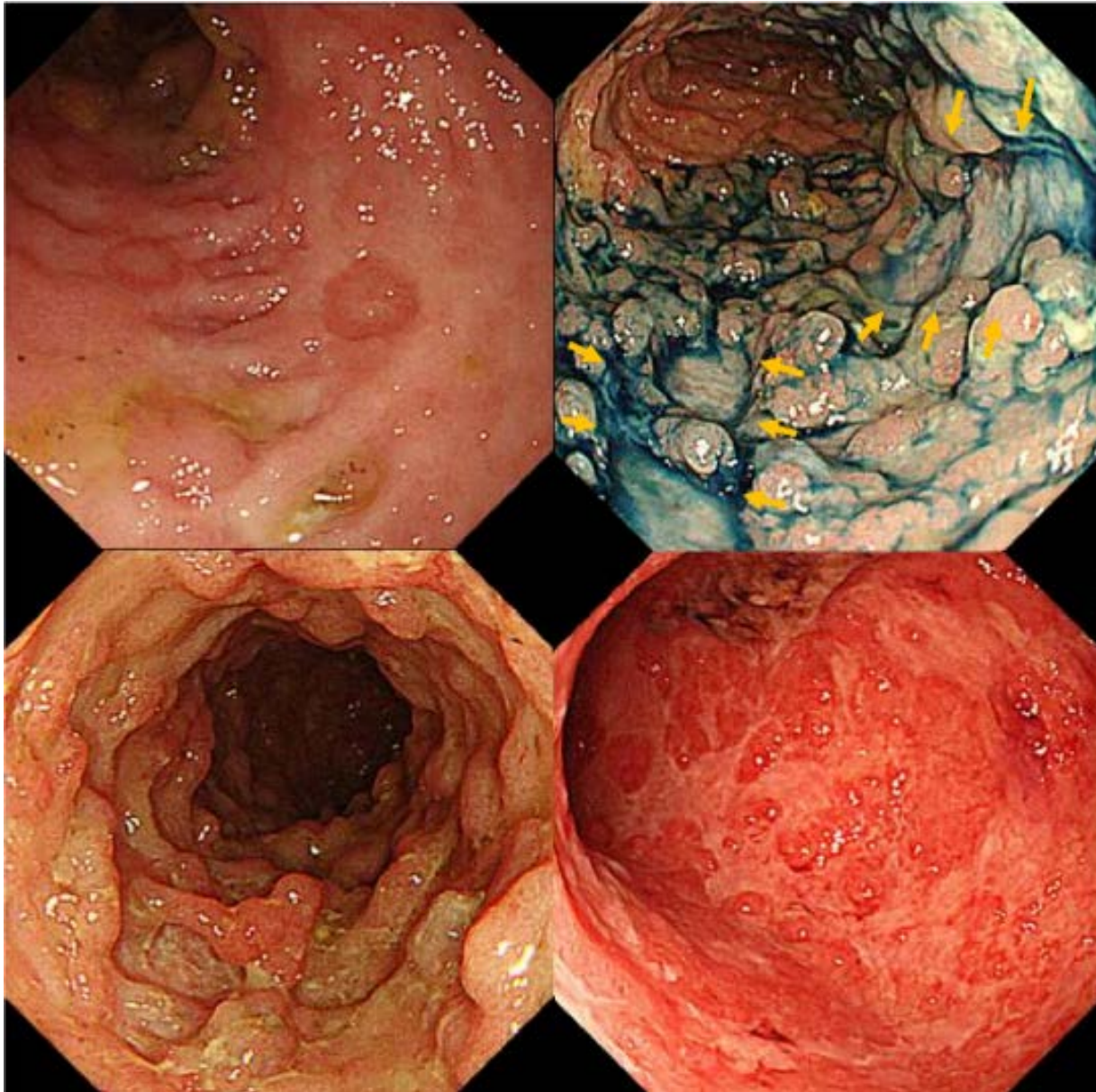
# Outline

- Disease complications
  - Infections
  - Mucosal Injury
  - Diverticular Disease
  - Biliary Tract Disease
  - Gastrointestinal Malignancy
  - Esophageal dysfunction
- Disease Diagnostics
  - Reflux
  - Gastric Emptying
  - Endoscopy



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

- Heart Transplant 4 years ago
- CT abdomen shows colonic thickening
- Colonoscopy performed showing the following:



# WHAT IS YOUR NEXT STEP IN THERAPY?

- A) START PO VANCOMYCIN FOR C. DIFFICILE
- B) STOP CELLCEPT FOR DRUG INDUCED COLITIS
- C) START GANCICLOVIR FOR CMV COLITIS
- D) REFER TO COLECTOMY FOR ISCHEMIC COLITIS
- E) START IBGUARD FOR IRRITABLE BOWEL SYNDROME

# Infections after Transplant

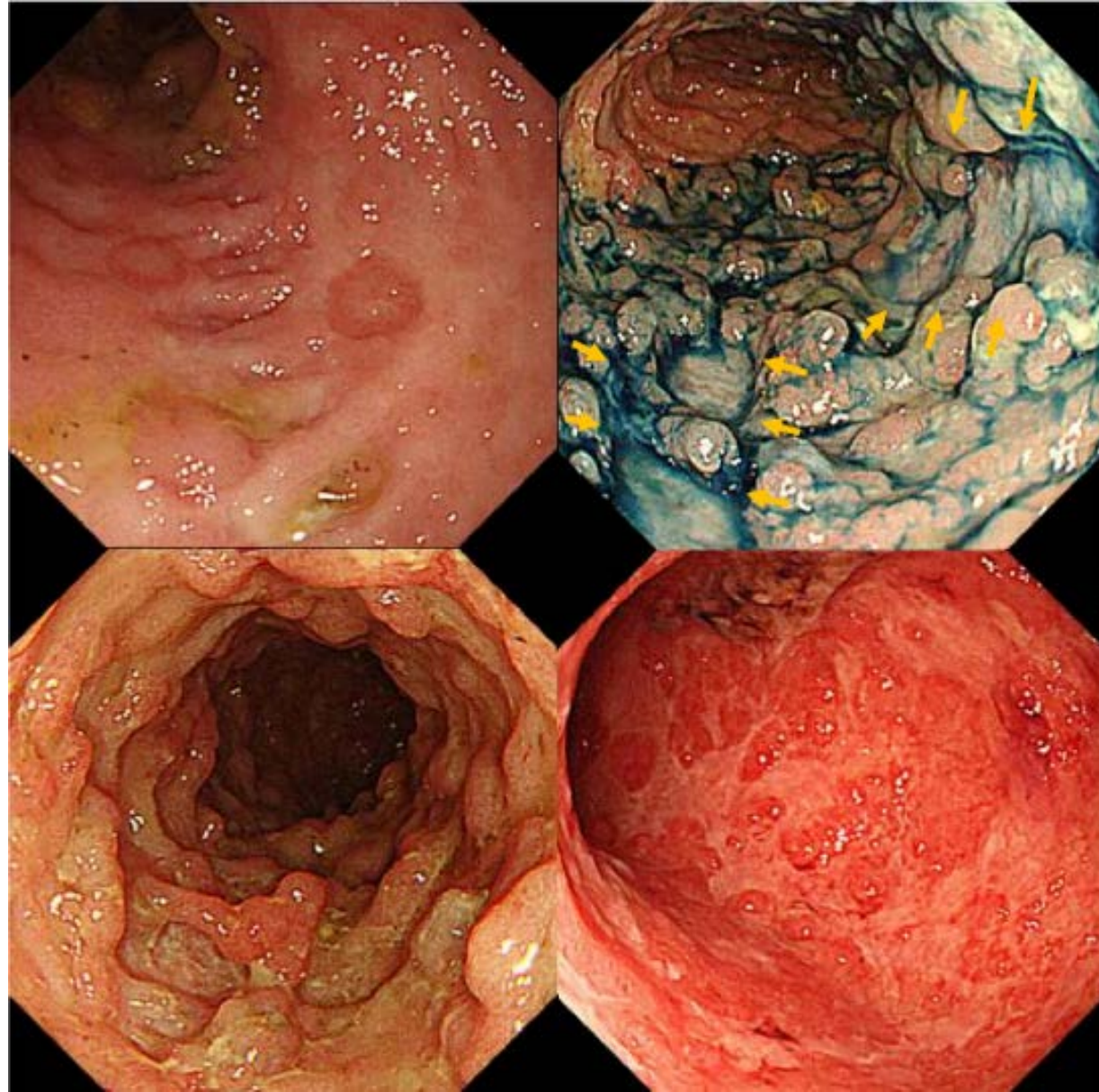
- Viral Infections
  - Cytomegalovirus (CMV)
  - Herpes Virus
- Fungal Infections
  - Candida

# Infections after Transplant

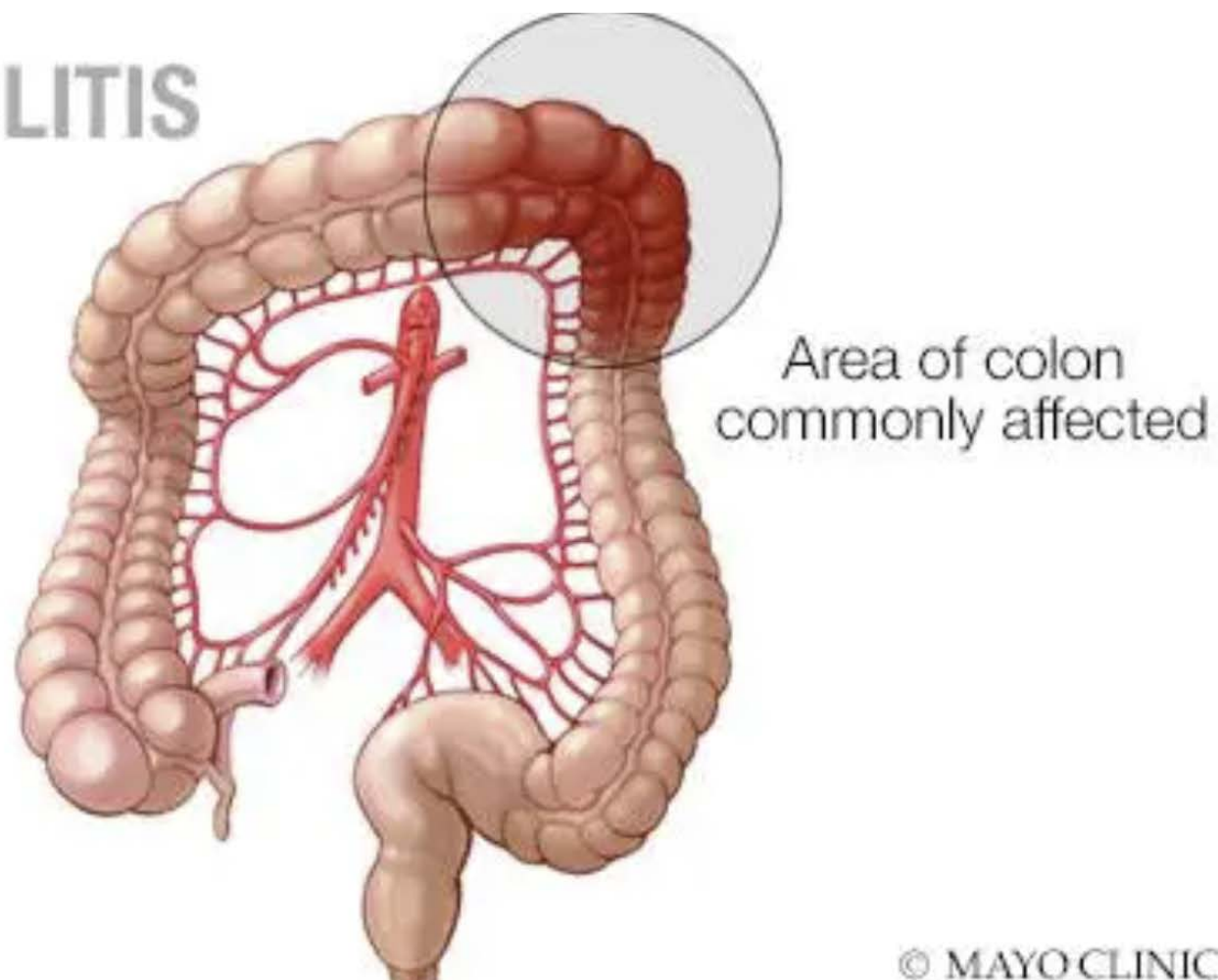
- Bacterial Infections
  - C. Difficile (recurrent antibiotics)
  - Helicobacter Pylori
- Parasitic Infections
  - *Strongyloides stercoralis*



## CMV Colitis



# ISCHEMIC COLITIS



## C. Difficile: Check Toxin and PCR

In Immunocompetent: need both for positive

In immunocompromised: toxin may be negative

Fecal Transplant: Open Biome on hold, other therapies are available



**IRRITABLE BOWEL SYNDROME**  
(IBS) is a Common Disorder that Affects the LARGE INTESTINE

# IRRITABLE BOWEL SYNDROME

## SYMPTOMS



Abdominal Pain, Cramping or Bloating



Excess Gas

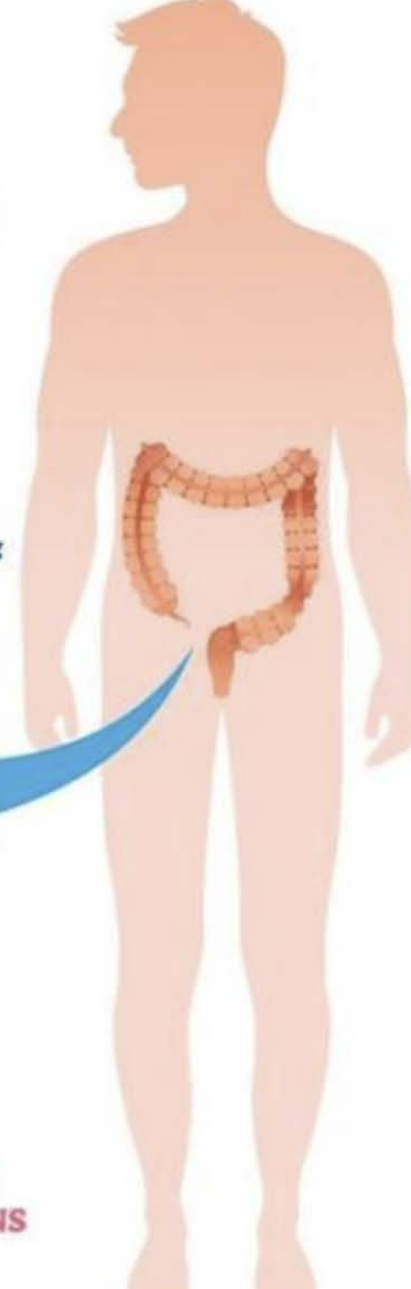
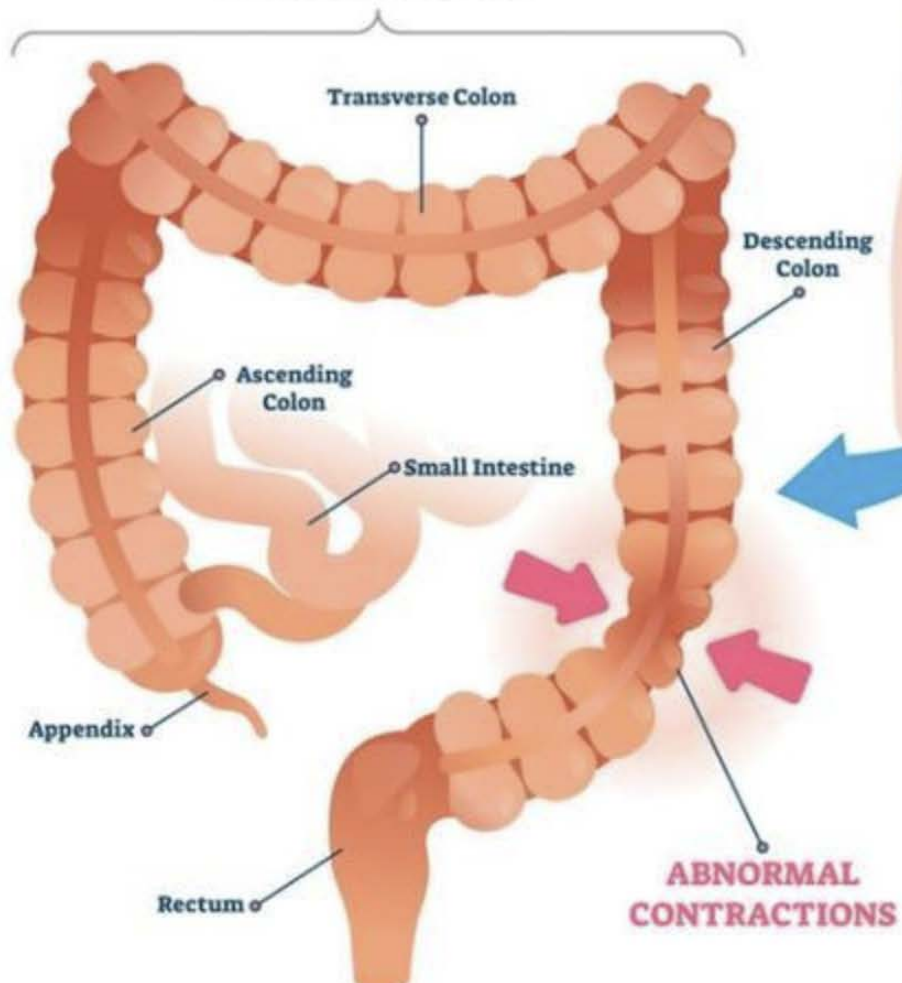


Diarrhea or Constipation



Mucus in the Stool

## LARGE INTESTINE



# WHAT IS YOUR NEXT STEP IN THERAPY?

- A) START PO VANCOMYCIN FOR C. DIFFICILE
- B) STOP CELLCEPT FOR DRUG INDUCED COLITIS
- C) START GANCICLOVIR FOR CMV COLITIS
- D) REFER TO COLECTOMY FOR ISCHEMIC COLITIS
- E) START IBGUARD FOR IRRITABLE BOWEL SYNDROME

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
- EGD and Colonoscopy show no infections, there is mild inflammation and erythema in the stomach and colon
- 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

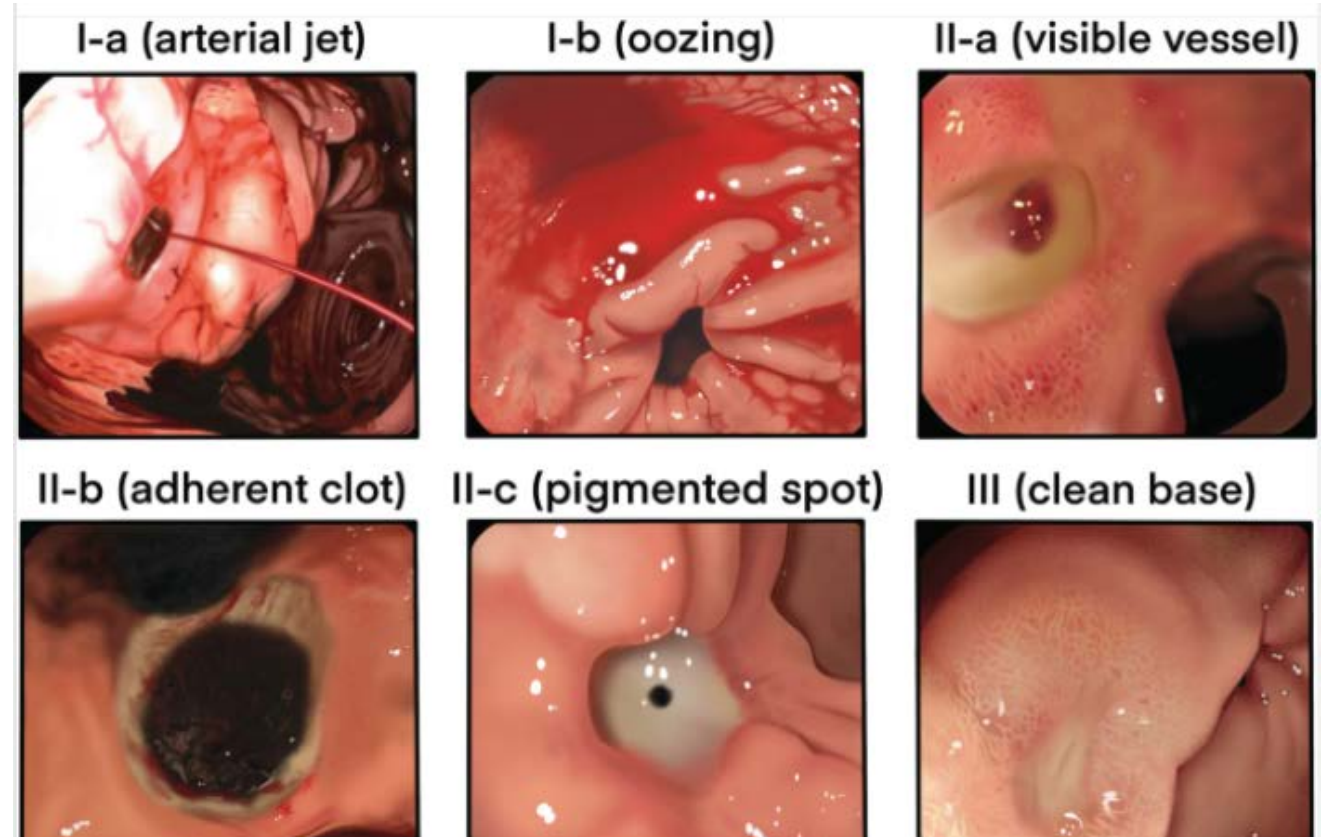
- Ulcerations

- 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)

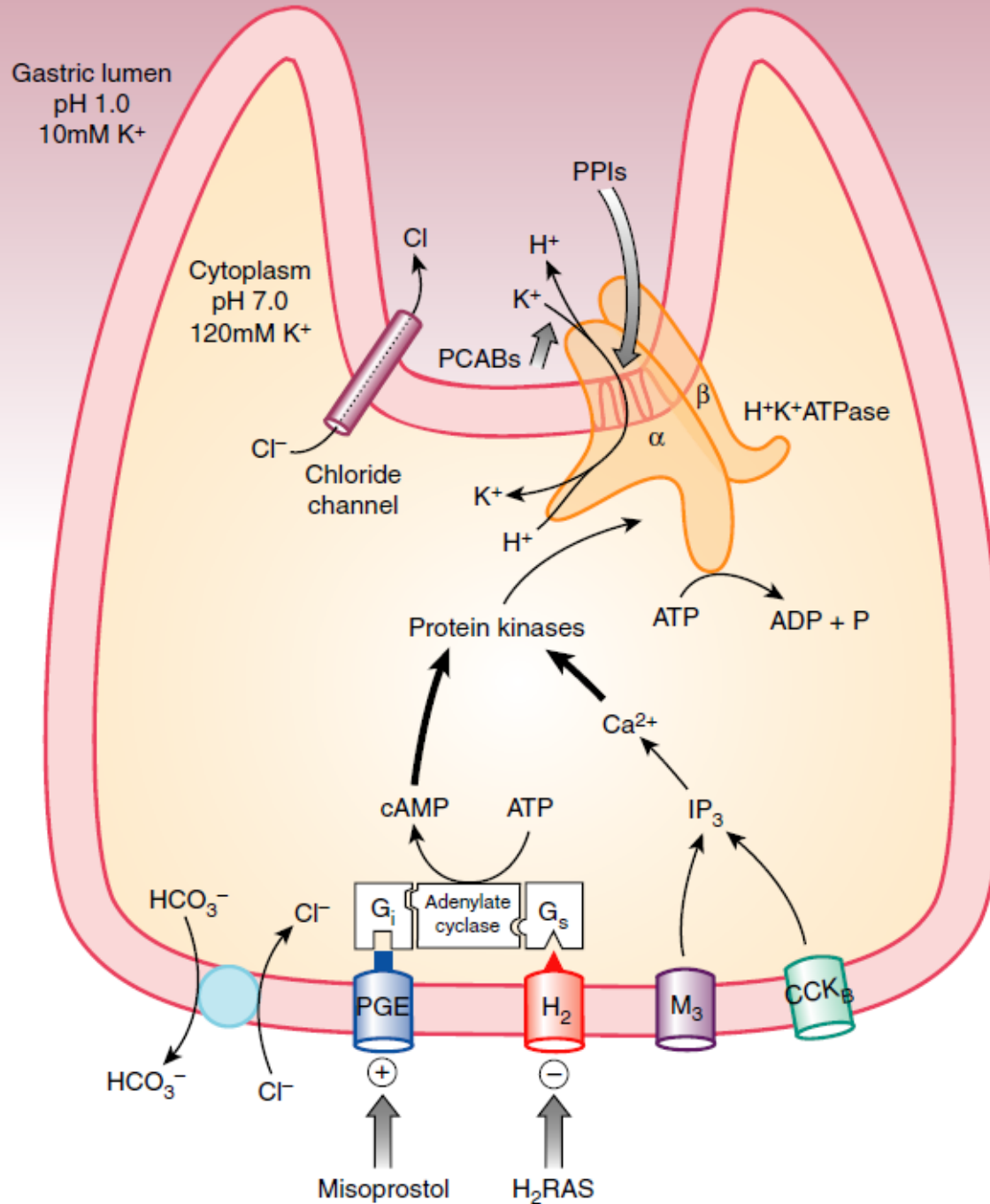
- Be Careful with Hepatitis C Organ donor – prefer to avoid PPIs as able while on therapy for Hepatitis C treatment absorption

- Side effects: 1.3 Hazard Ratio for enteric infections

- If recurrent *C. difficile*, *E. Coli* – I will try to stop, de-escalate
    - Dementia, Heart Disease, CKD not seen


- Anti-histamines (H2RA – famotidine)

# 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



49-year-old s/p kidney transplant  
(2019) presents 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?

# WHAT IS YOUR NEXT STEP IN THERAPY?

- A) START IV VANCOMYCIN
- B) URGENT COLECTOMY
- C) START PO VANCOMYCIN
- D) REFER FOR COLONOSCOPY IN 2 MONTHS
- E) START ACID SUPPRESSION TO IMPROVE MICROBIOME SUPPORT

# Diverticular Disease

- Diverticulosis vs. Diverticulitis (infection) vs. Diverticular bleed
  - Common, especially after 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 antibiotics

# Gastrointestinal complications in kidney transplantation



Mechanical injury during surgery

Metabolic/organic toxicity anti-rejection therapy correlated

## POSSIBLE COMPLICATIONS

**Bacteria, virus and fungal infection**

## EFFECTS ON PATIENTS

Compromise quality of life or pose a significant risk of mortality


## PREVENTION AND TREATMENT OF COMPLICATIONS

To prevent and treat without stop the immunosuppression drugs admitted as anti-rejection therapy.



# WHAT IS YOUR NEXT STEP IN THERAPY?

- A) START IV VANCOMYCIN
- B) URGENT COLECTOMY
- C) START PO VANCOMYCIN
- **D) REFER FOR COLONOSCOPY IN 2 MONTHS**
- E) START ACID SUPPRESSION TO IMPROVE MICROBIOME SUPPORT



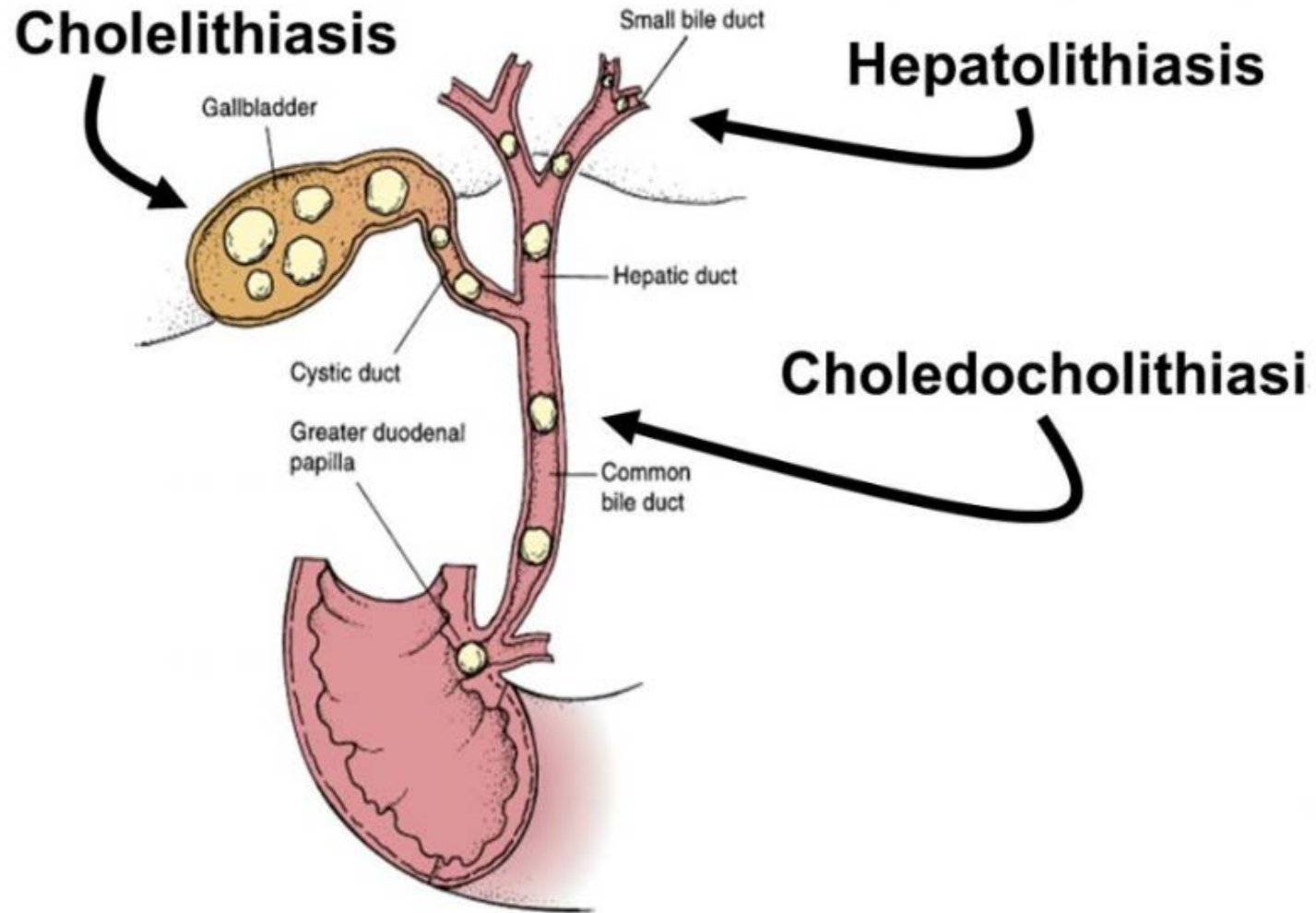
64-year-old presents with pain in the right upper quadrant. They are s/p kidney transplant 5 years ago.

- WBC is 17k
- RUQ U/S shows thickened gallbladder with a common bile duct of 1.8cm
- Patient is altered
- You notice patient is jaundiced
- Next steps?

# WHAT IS YOUR NEXT STEP IN THERAPY?

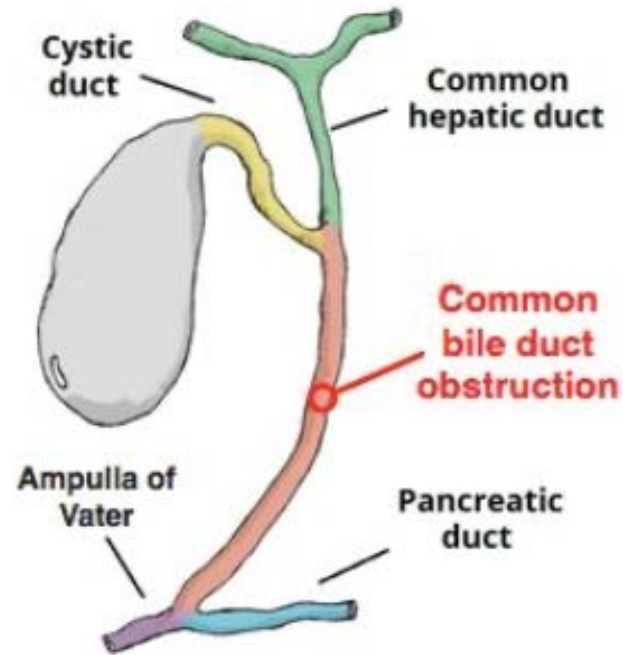
- A) CHOLECYSTECTOMY
- B) ERCP
- C) MRCP
- D) LIST FOR URGENT LIVER TRANSPLANT
- E) LIVER ULTRASOUND WITH DOPPLERS

# Biliary Tract Diseases



# Biliary Tract Diseases

## Bacterial infection in a patient with biliary obstruction



### ▲ Charcot's Triad

Fever  
Abdominal pain  
Jaundice

### ◆ Reynolds pentad

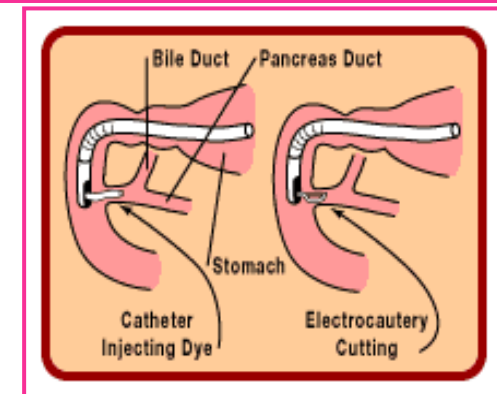
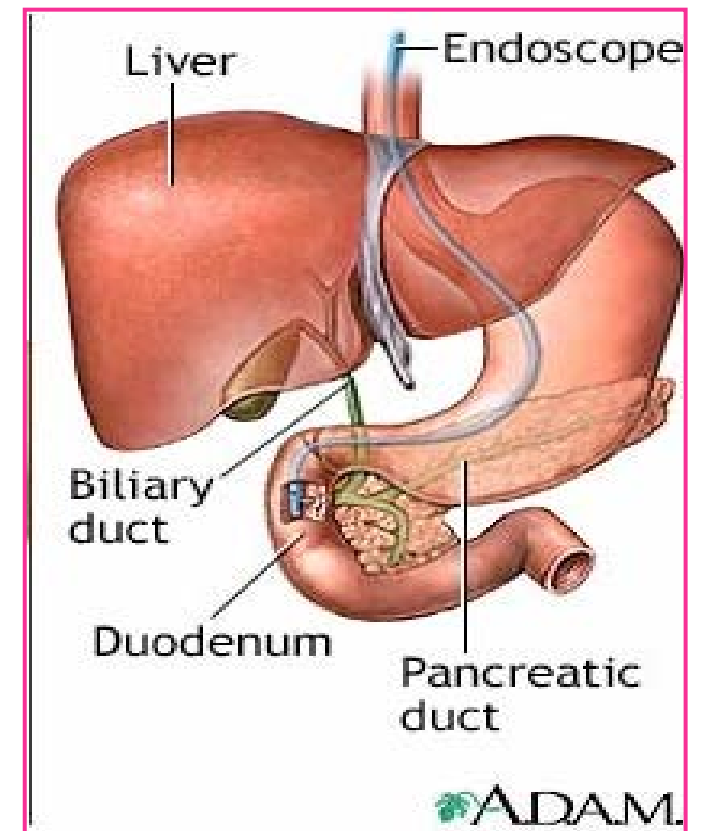
Fever  
Abdominal pain  
Jaundice  
+  
Confusion  
Hypotension

### Management

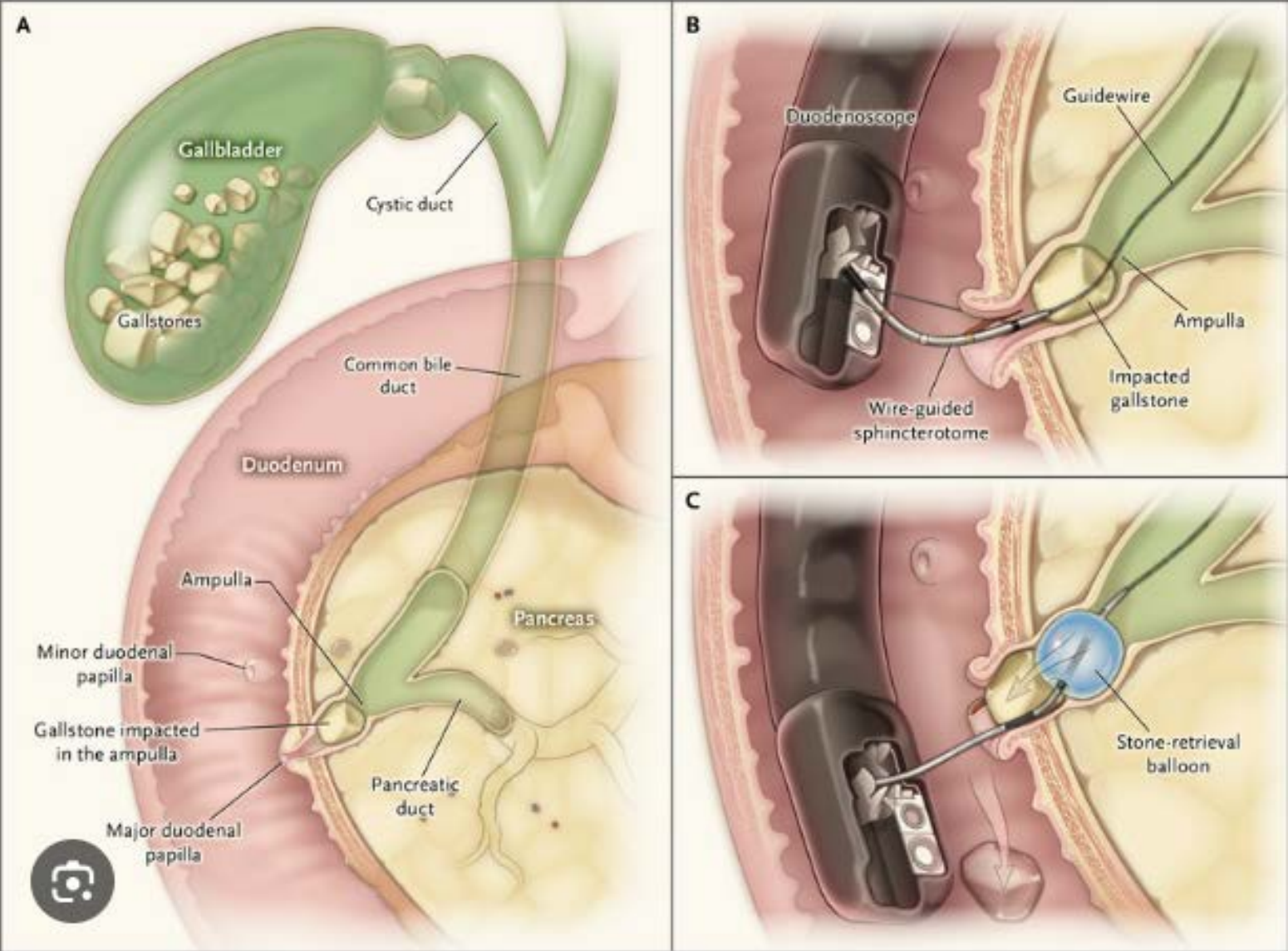
- Broad-spectrum antibiotics (e.g. Ampicillin-sulbactam)
- Biliary drainage (e.g. ERCP)

# Biliary Tract Diseases

- **E**ndoscopic **R**etrograde **C**holangi**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



# WHAT IS YOUR NEXT STEP IN THERAPY?

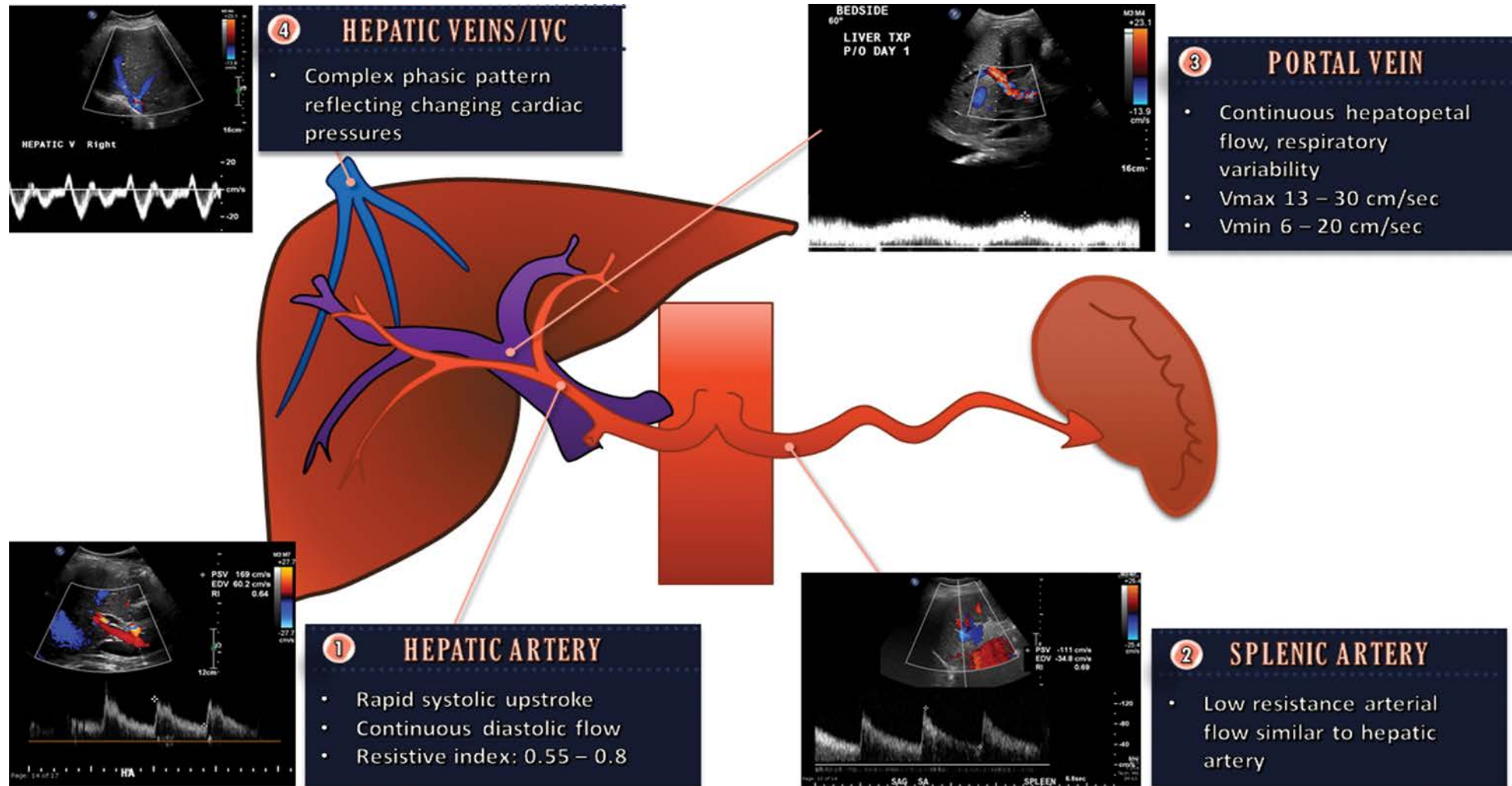
- A) CHOLECYSTECTOMY
- B) ERCP
- C) MRCP
- D) LIST FOR URGENT LIVER TRANSPLANT
- E) LIVER ULTRASOUND WITH DOPPLERS



# Hepatic Artery Thrombosis

- HAT – serious vascular complication after liver transplantations
  - Obtain STAT RUQ U/S with dopplers
  - If identified, recommend consultation with IR and if unable to clear clot, then transplantation to prevent biliary sepsis

# Hepatic Artery Thrombosis



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
- EBV Levels have been rising

# WHICH OF THE FOLLOWING IS THE PATIENT AT RISK FOR?

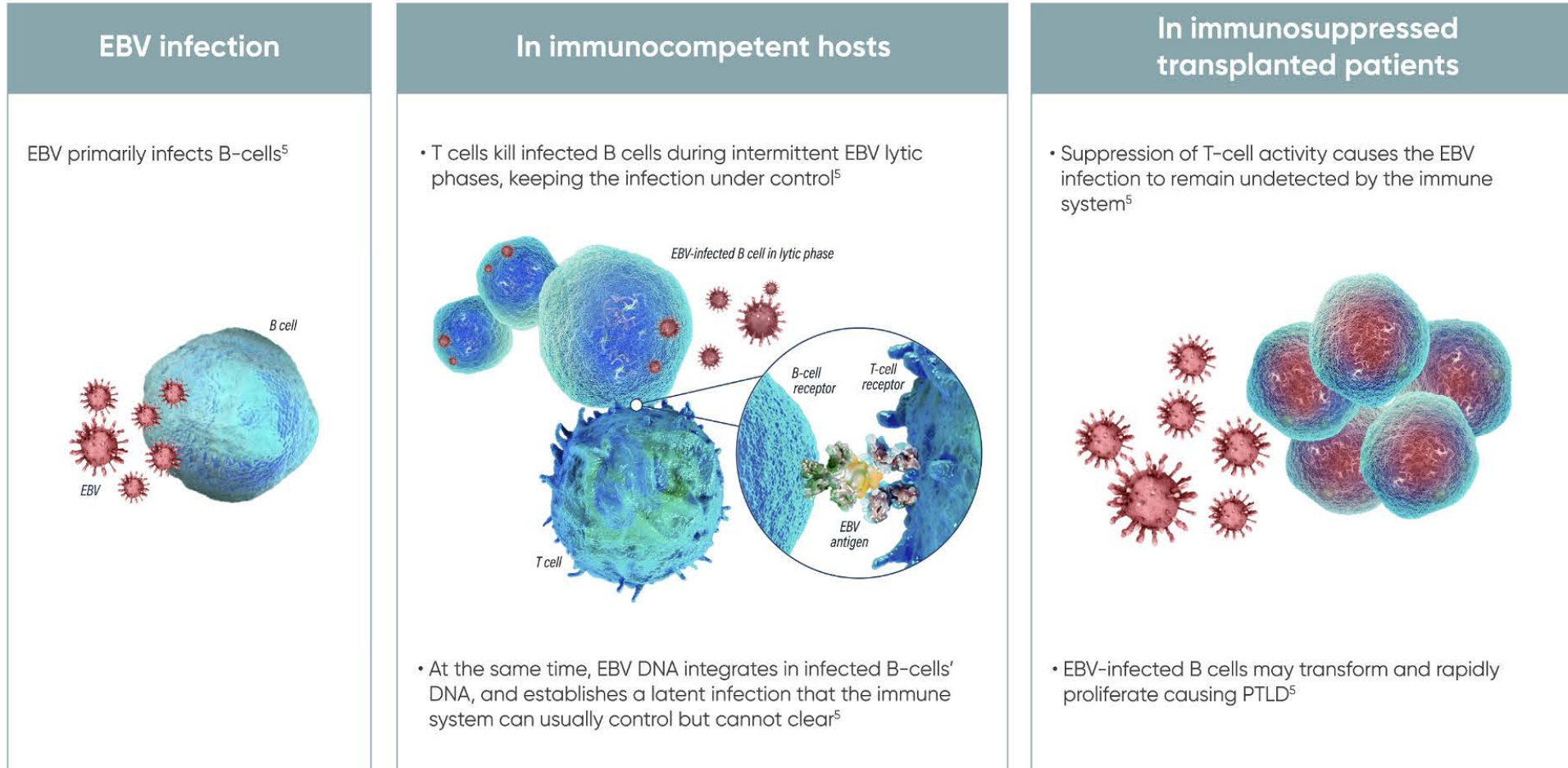
- A) HEPATIC ARTERY THROMBOSIS
- B) POST TRANSPLANT LYMPHOPROLIFERATIVE DISEASE
- C) CHOLANGITIS
- D) COLON CANCER
- E) PANCREATITIS

# Malignancies

- Post-transplant lymphoproliferative disorder (PTLD)
  - Can involve GI tract in 10% of transplant recipients
  - Early detection of rising EBV can prevent malignancy
  - 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


# Post-transplant lymphoproliferative disorder (PTLD)

Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) is a rare, acute and potentially life-threatening group of lymphoid disorders that arise after transplantation<sup>3,4</sup>.



# WHICH OF THE FOLLOWING IS THE PATIENT AT RISK FOR?

- A) HEPATIC ARTERY THROMBOSIS
- **B) POST TRANSPLANT LYMPHOPROLIFERATIVE DISEASE**
- C) CHOLANGITIS
- D) BK VIRUS
- E) PANCREATITIS



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

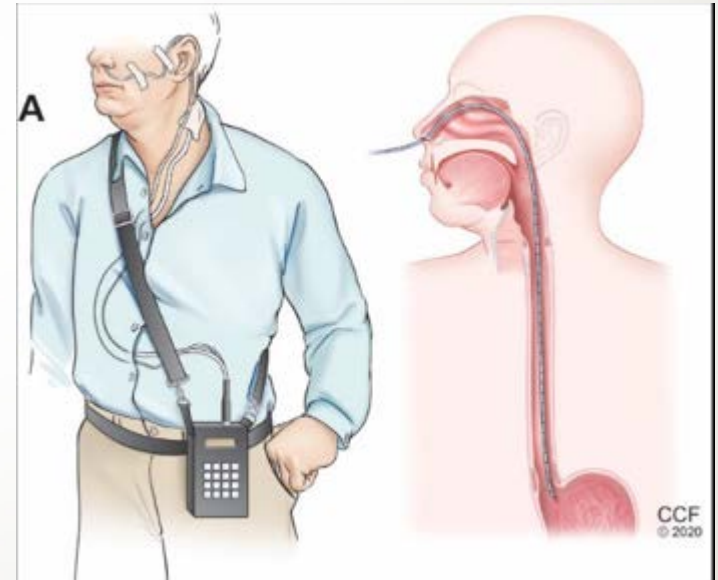
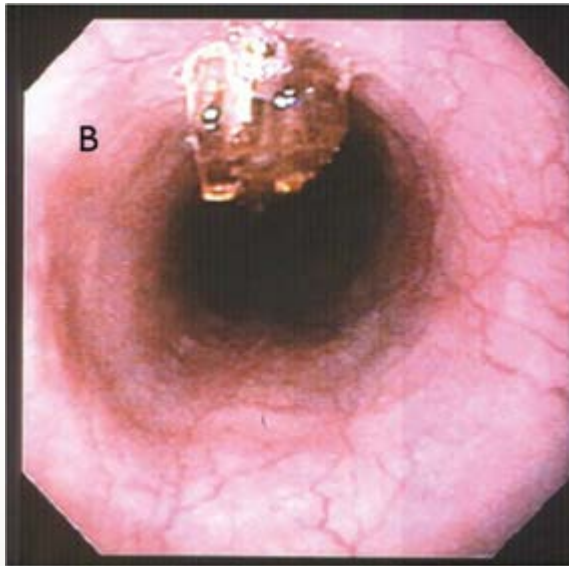
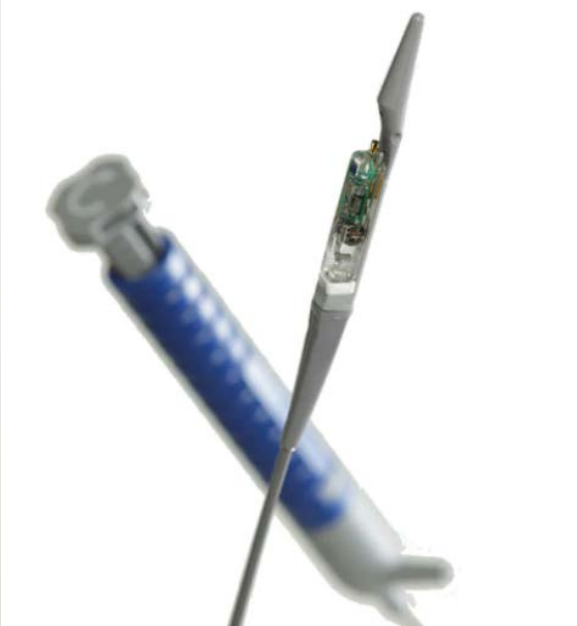
- Reflux testing
  - Ambulatory pH, Wireless pH capsule, pH with Impedance (MII-pH)
- Esophageal function testing:
  - High resolution manometry
- Limitation:
  - **Does not establish causality between esophageal disease and pulmonary microaspiration**

# Esophageal Function Testing

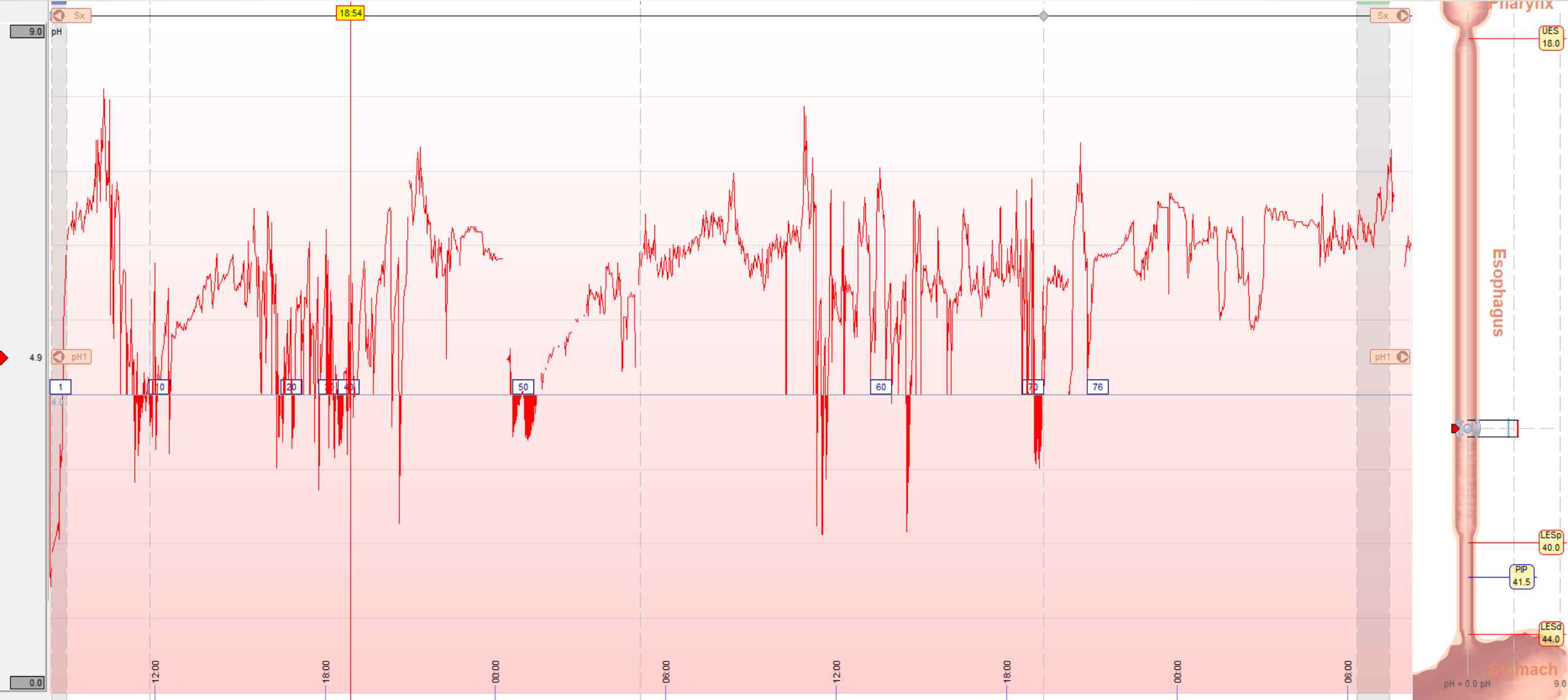
- Weak swallows associated with early rehospitalization
- Increased risk of CLAD (rejection) with decreased esophageal clearance

# Reflux Monitoring

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

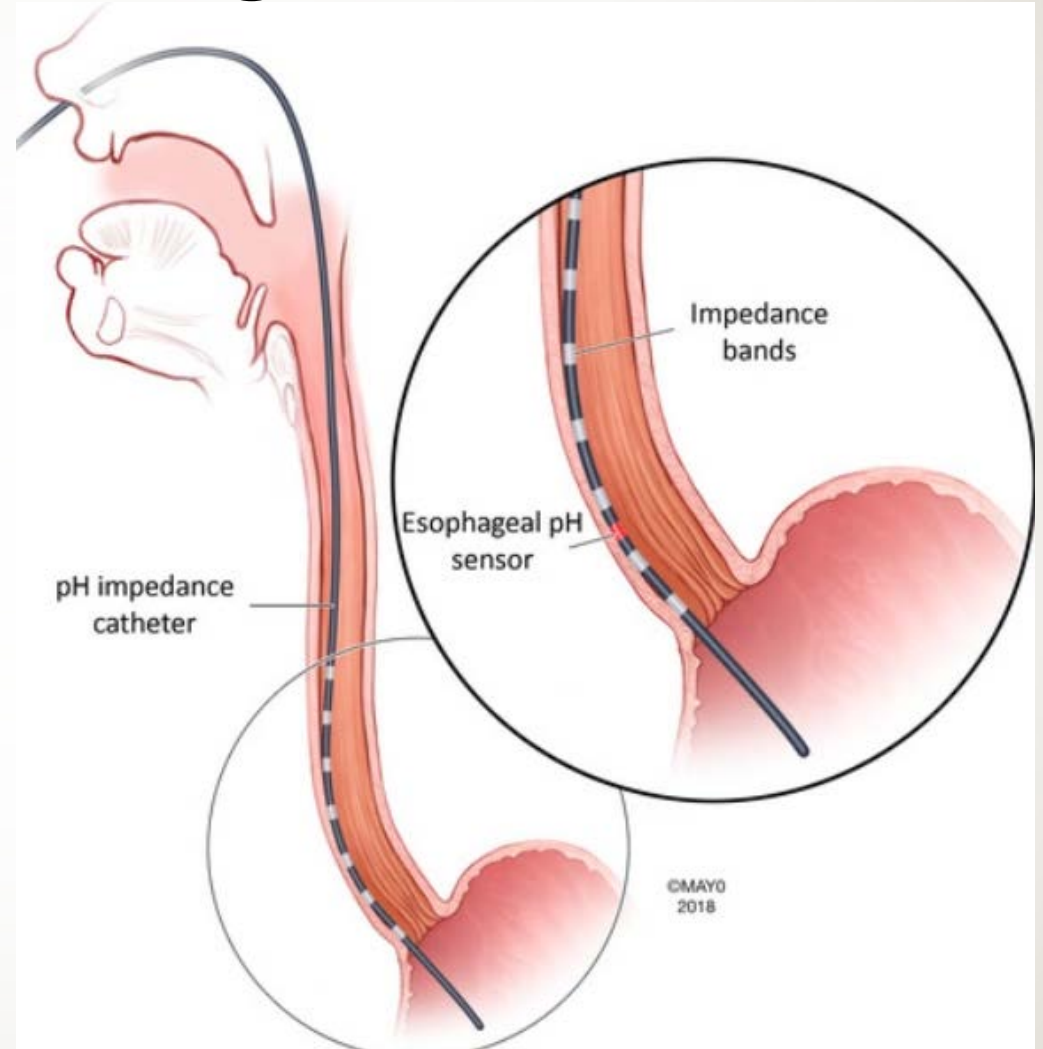


# Ambulatory Reflux Monitoring



# Impedance Monitoring

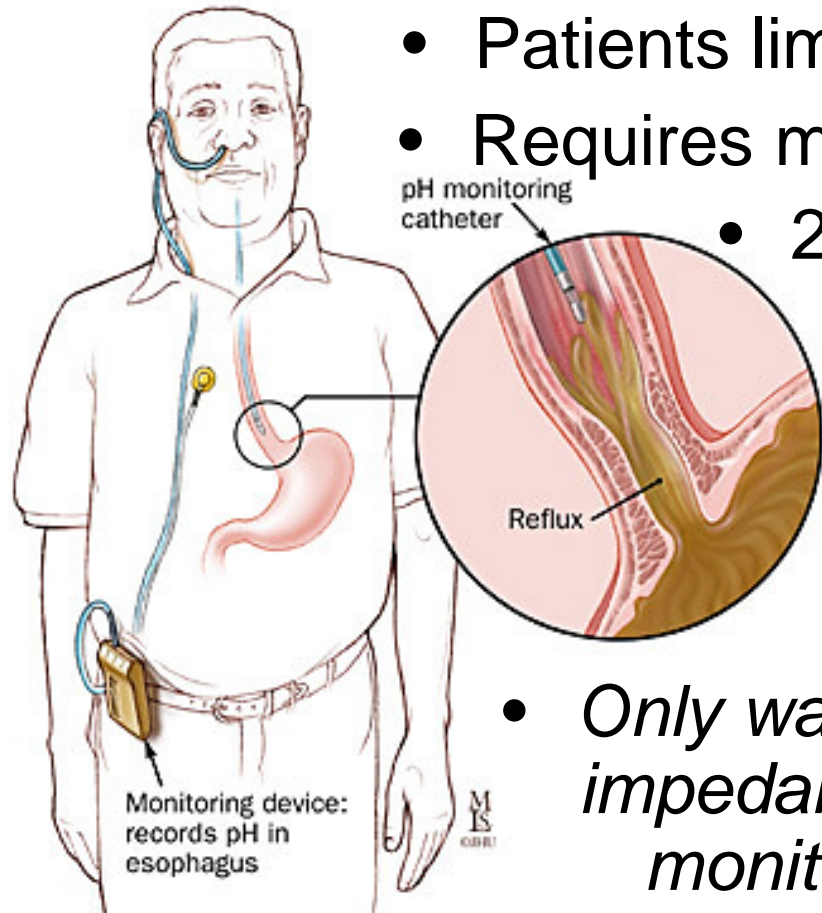
- Acid and non-acid testing
  - Impedance testing
  - Typically, on therapy;  
breakthrough symptoms
    - Despite adequate response to PPI, is there breakthrough symptoms of reflux leading to worsening lung dysfunction?



# Esophageal Reflux Monitoring

## Catheter-Based

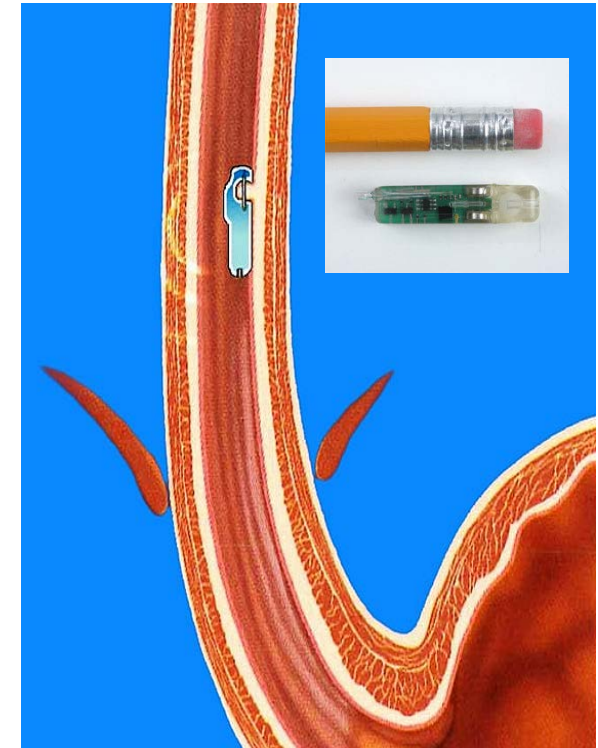
- Uncomfortable
- Embarrassing
- Patients limit activities
- Requires manometry
- 24-hour limit



- *Only way to do impedance-pH monitoring*

## Wireless (Bravo)

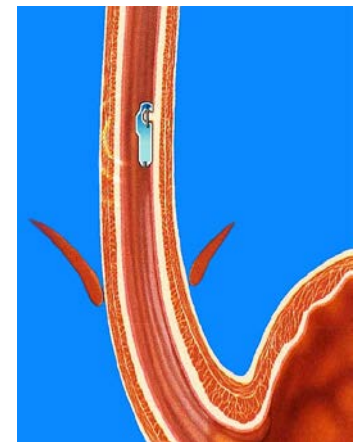
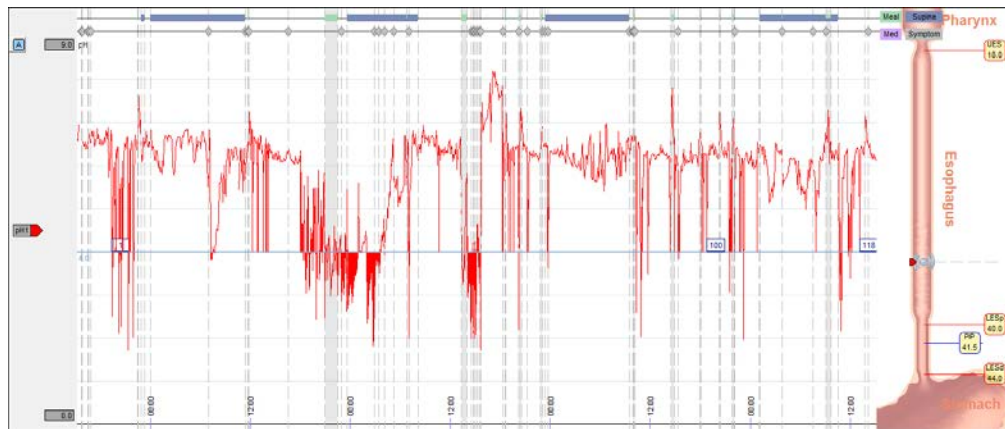
- More comfortable
- Less embarrassing
- Patients resume normal activities
- Does not require manometry
- 48-96 hours
- *Only for pH monitoring*



# Reflux Monitoring

## Catheter-Based or Wireless? On or Off PPIs?

- In patients for whom the diagnosis of GERD is suspected but not clear, and endoscopy shows no objective evidence of GERD, we recommend reflux monitoring be performed ***off therapy*** to establish the diagnosis.
  - If your question is “Does this patient have GERD?”, then perform pH monitoring ***off therapy***.



# Reflux Monitoring

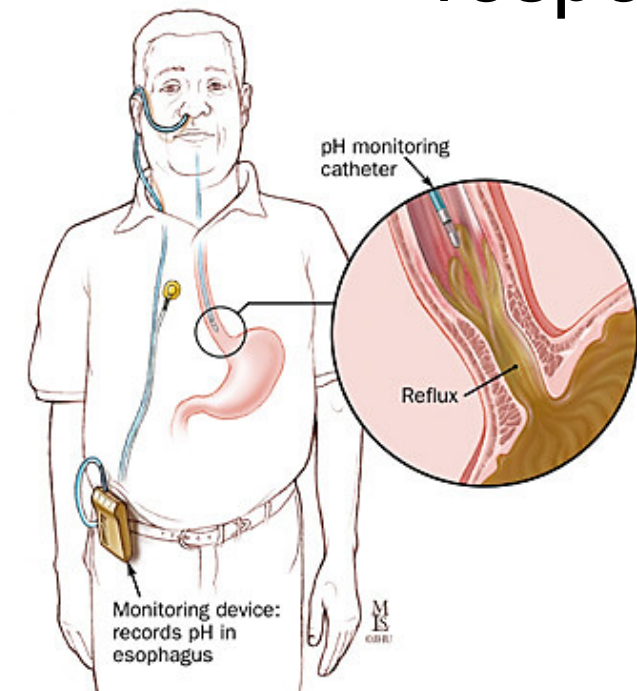
## Catheter-Based or Wireless? On or Off PPIs?

- We suggest esophageal **impedance-pH monitoring** performed **on PPIs** for patients with an established diagnosis of GERD whose symptoms have not responded adequately to twice-daily PPI therapy.

–If your question is “Why is this patient (who we know has GERD) still having symptoms on PPIs?”, then perform **impedance-pH monitoring** (catheter-based) **on therapy** to determine...

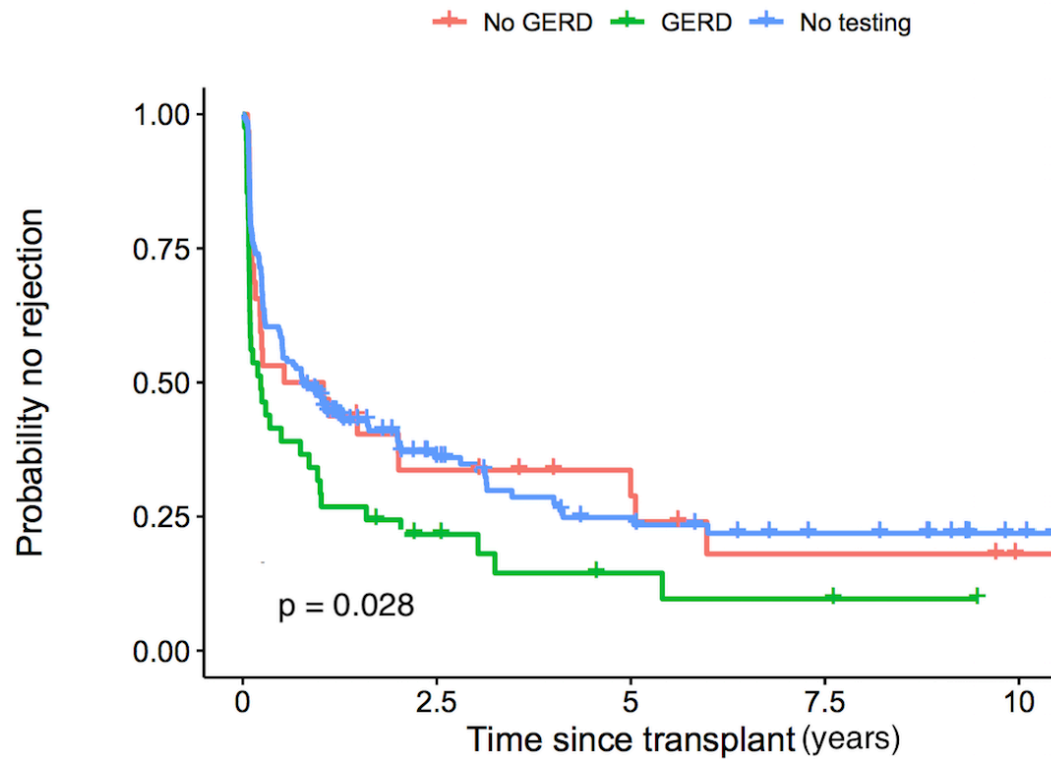
» Does abnormal acid reflux persist?

» Are symptoms associated with reflux episodes (acidic or non-acidic)?





# Pre-Transplant GERD Predicts Acute Rejection in Lung Transplant



Matt Meyers  
Vanderbilt Housestaff  
UoC GI Fellow  
Transplant Hepatology



Claudio Tombazzi  
Vanderbilt Housestaff '19  
VUMC GI Fellow  
Transplant Hepatology

DDW 2021

# Reflux Testing in Lung Transplant

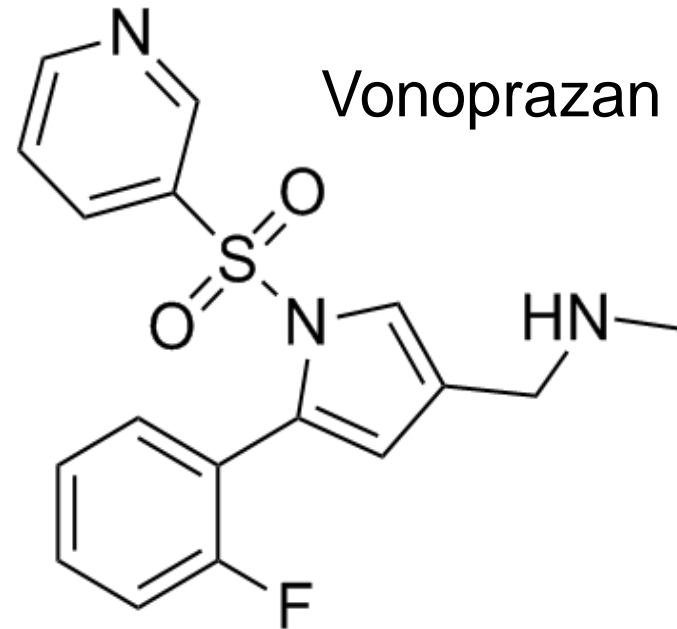
- pH parameters (AET) are associated with transplant outcomes
  - Acute Rejection
  - Chronic Rejection
  - 3-year survival

	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.

# 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

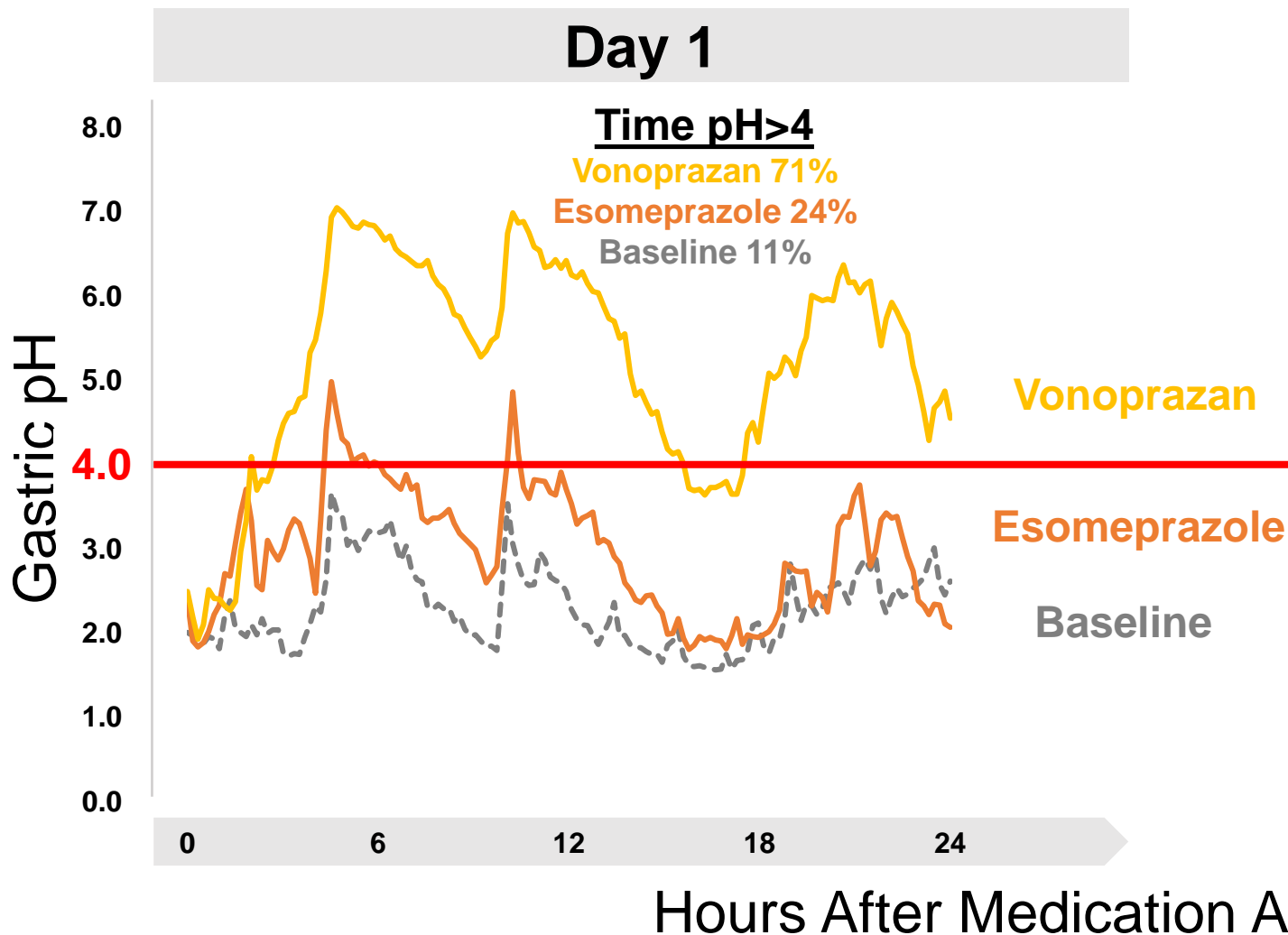


# P-CAB Pharmacologic Features

- P-CABs are acid stable
  - Do not require enteric coating
- P-CABs are active drugs, not prodrugs like PPIs
- P-CABs inhibit H<sup>+</sup>,K<sup>+</sup>-ATPase
  - Bind ionically (not covalently) to H<sup>+</sup>,K<sup>+</sup>-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

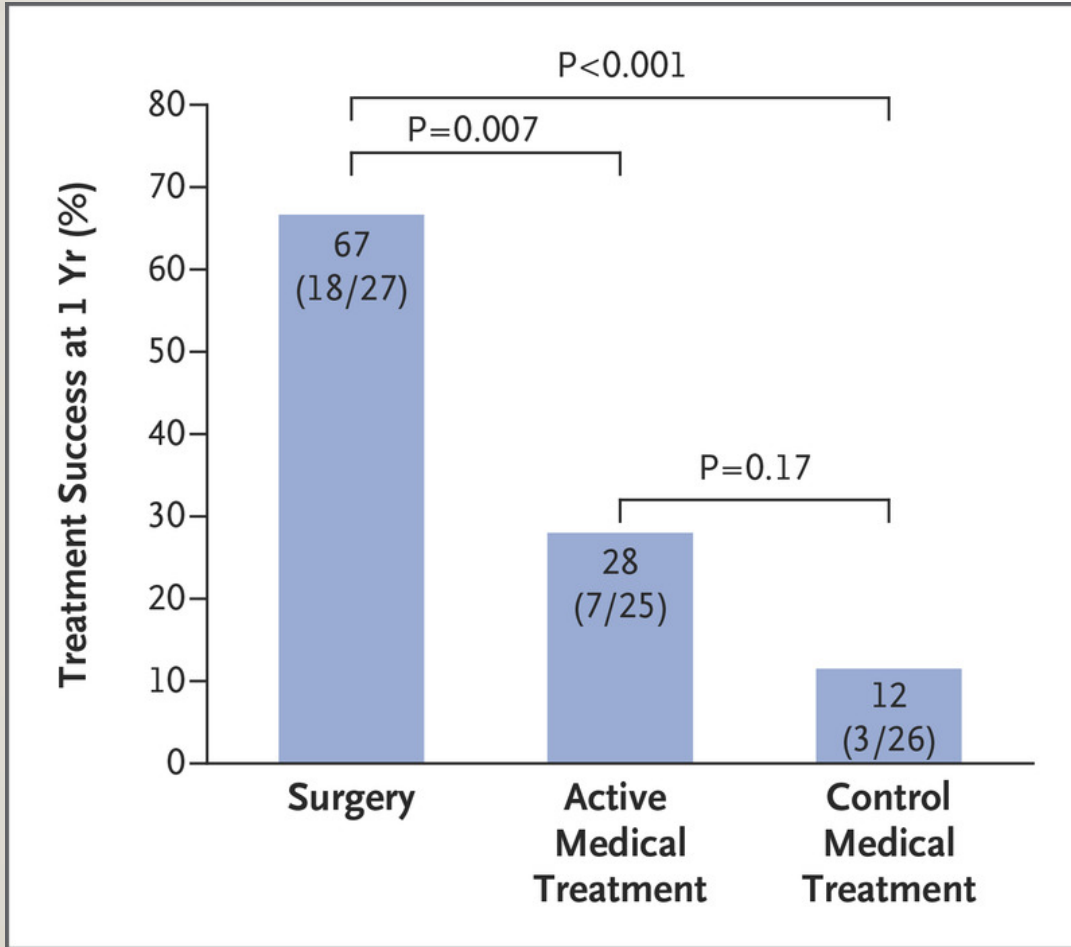
# Vonoprazan 20 mg vs. Esomeprazole 20 mg Effects on Gastric pH

Meds given once daily to 20 healthy Japanese men



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

# Laparoscopic Fundoplication



The NEW ENGLAND JOURNAL of MEDICINE

## Medical vs. Surgical Treatment for Refractory Heartburn

RANDOMIZED, CONTROLLED TRIAL

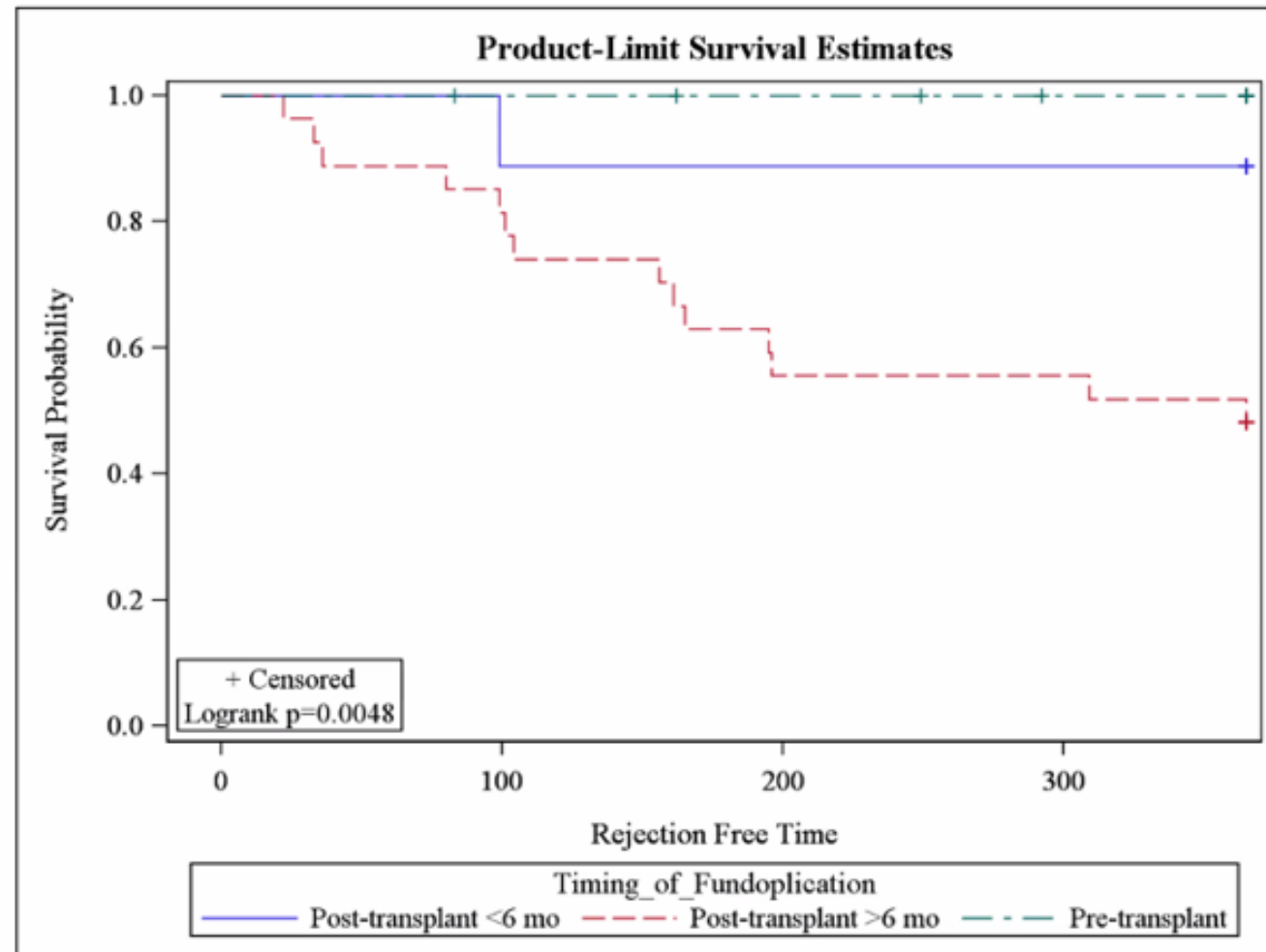
78 Patients with reflux-related, PPI-refractory heartburn	Antireflux Surgery (fundoplication) (N = 27)	Active Medical Treatment (N = 25) Omeprazole + Baclofen	Control Medical Treatment (N = 26) Omeprazole + Placebo
≥50% improvement in GERD-HRQL score at 1 yr	67%	28% P=0.007	12% P<0.001
Serious adverse events	Similar across all groups		
<b>Antireflux surgery superior to medical therapy for refractory heartburn</b>			

S.J. Spechler et al. 10.1056/NEJMoa1811424 Copyright © 2019 Massachusetts Medical Society

Side effects: dysphagia, gas-bloat syndrome, diarrhea

Spechler SJ et al. NEJM 2019;381:1513

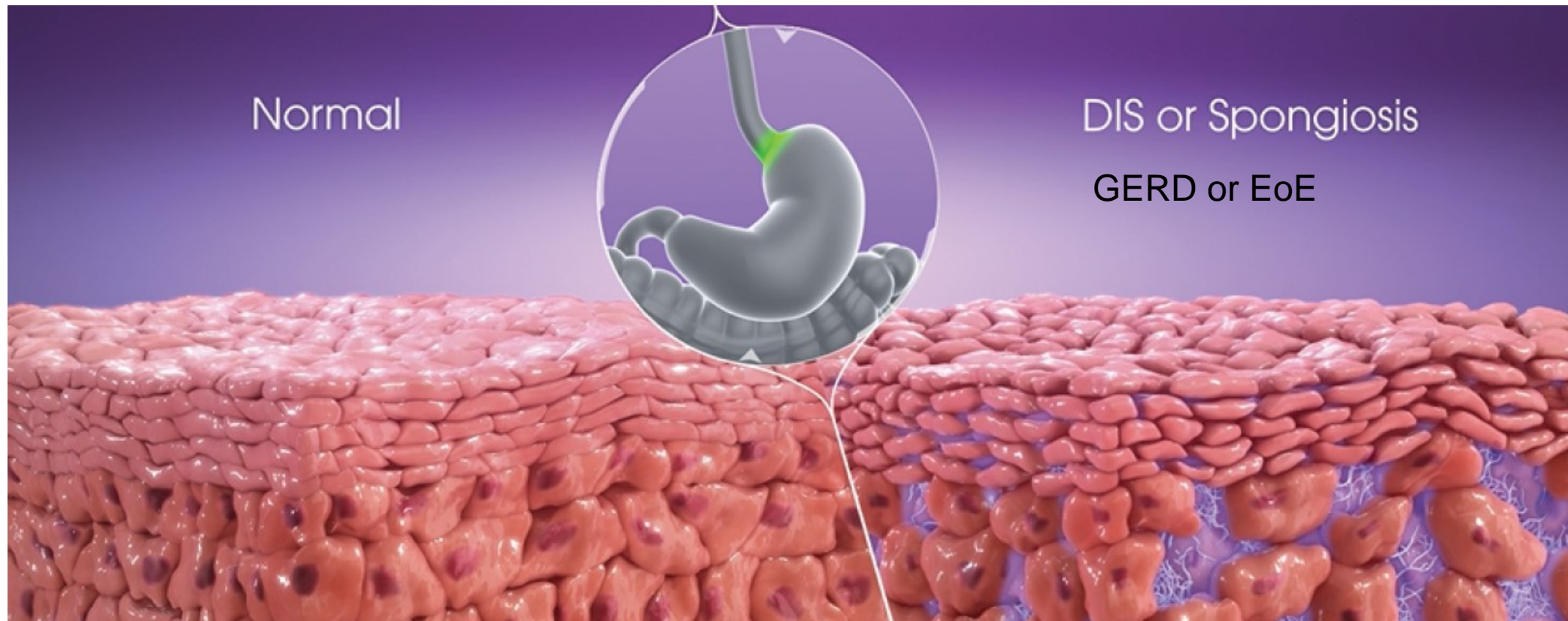
# Early fundoplication (<6 months) associated with greatest reduction in early allograft injury



# Mucosal integrity testing

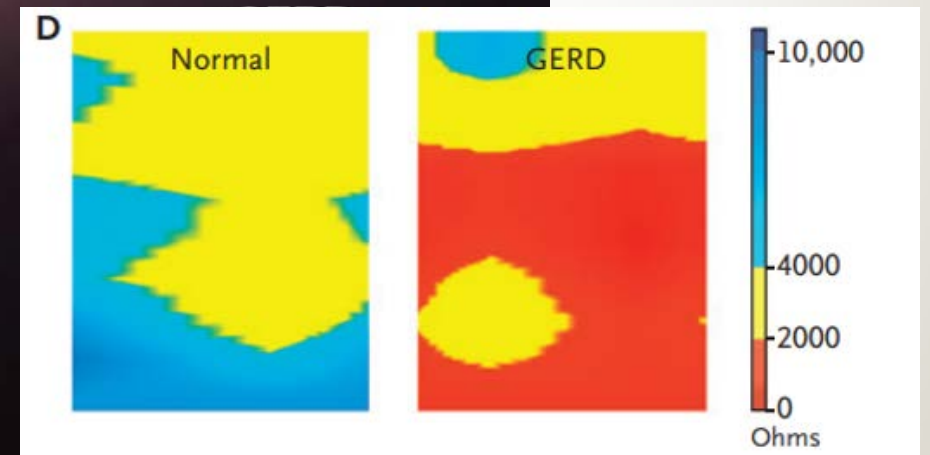
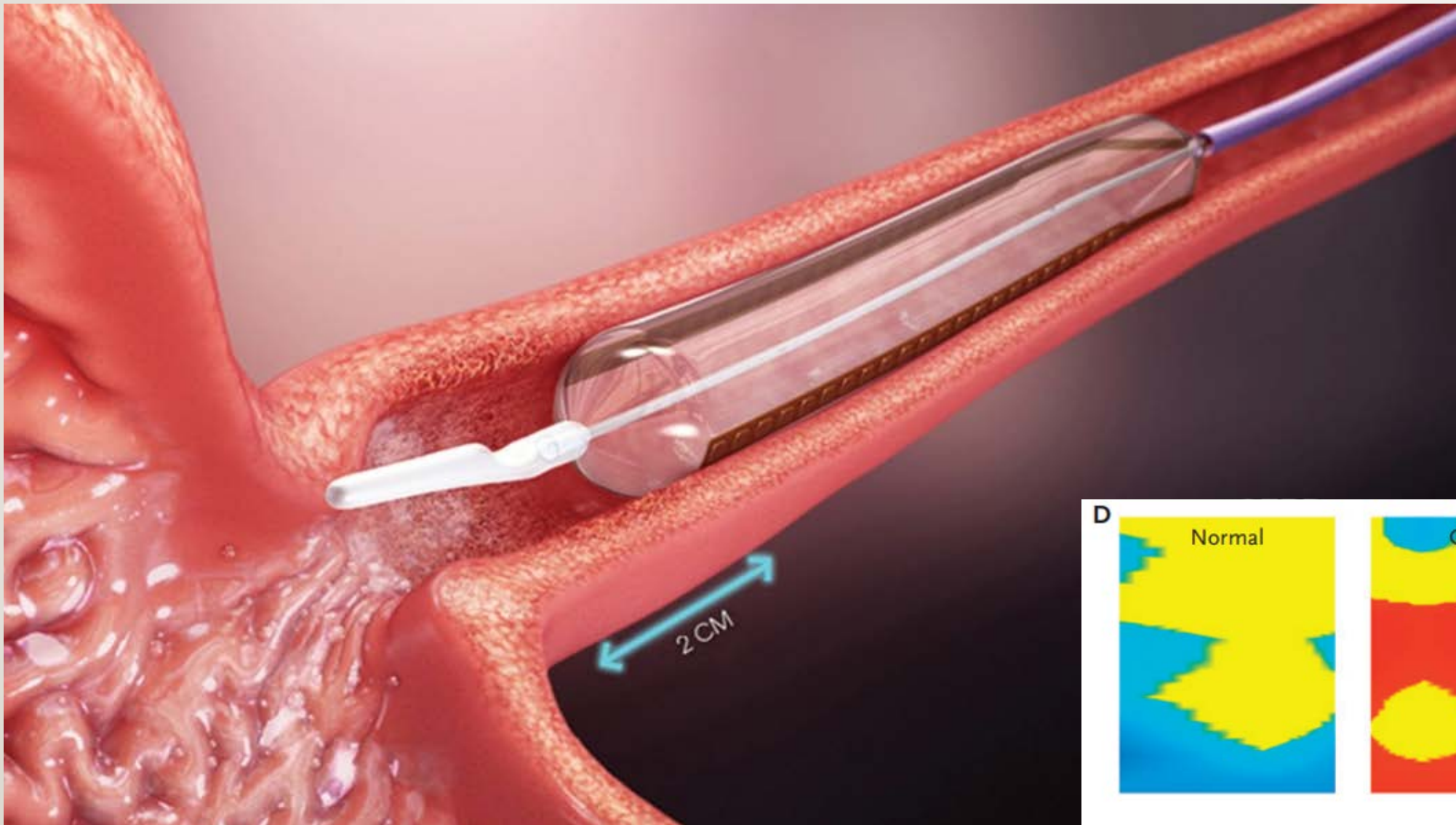


- Mucosal Integrity is affected by the presence of dilated intercellular spaces (DIS) which affects paracellular permeability.

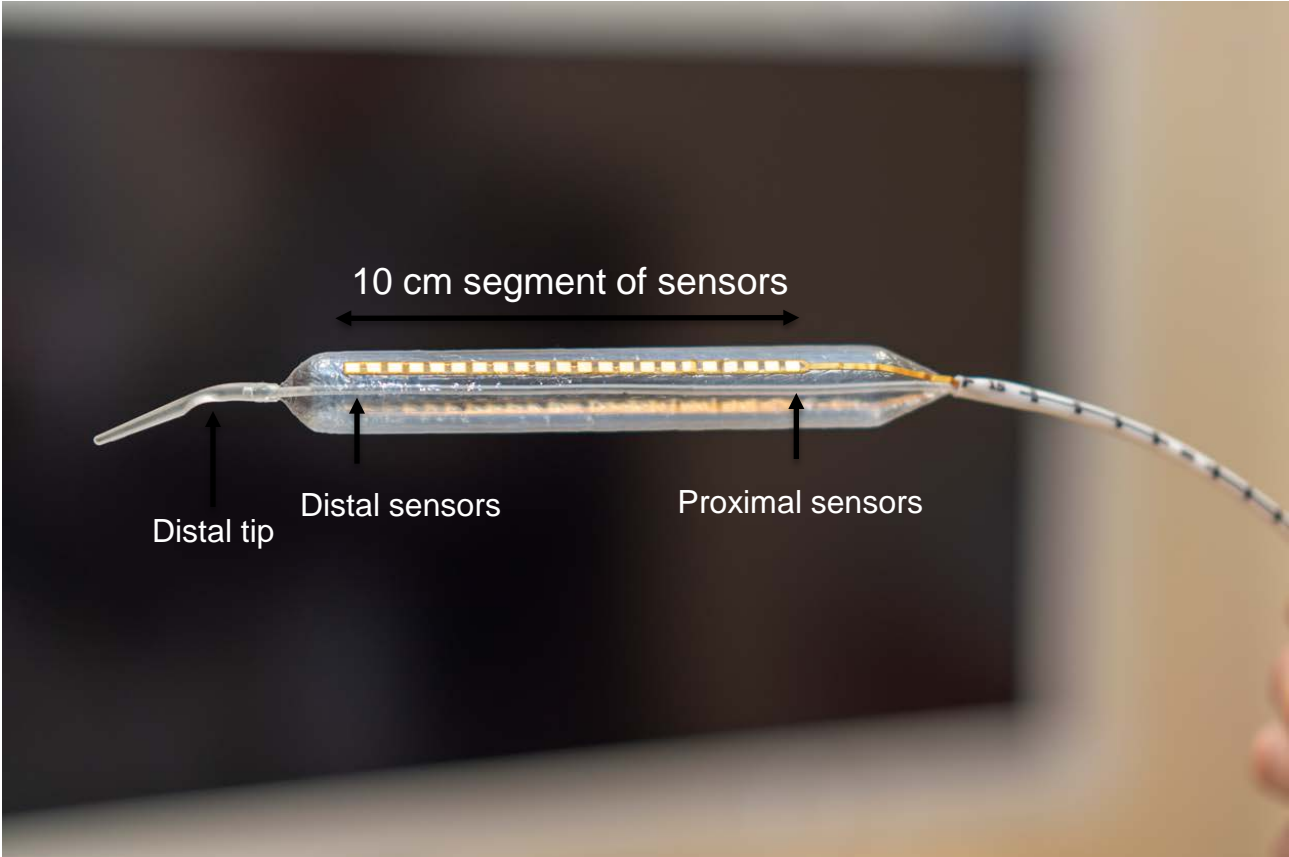




# Mucosal Integrity testing



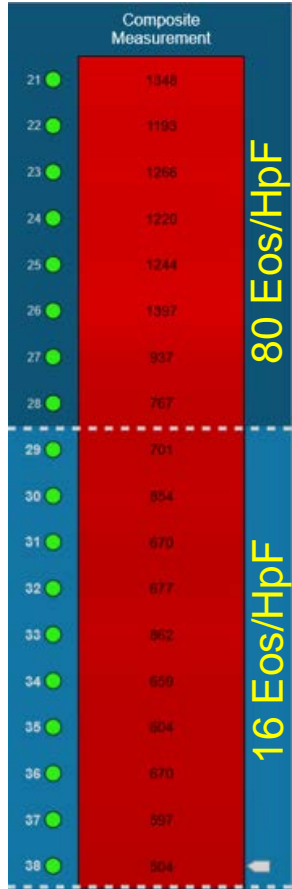
# Mucosal integrity testing (GERD/EoE)



# Mucosal integrity patterns in EoE

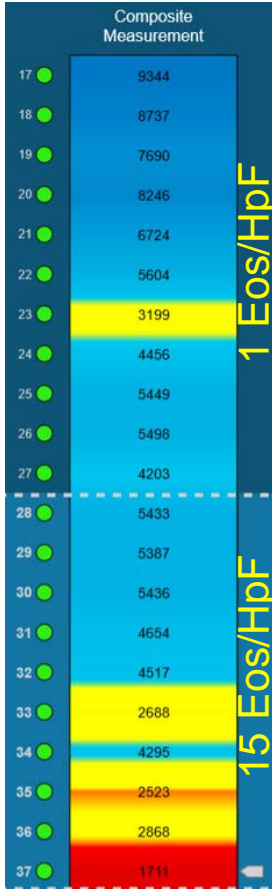


Untreated



DSQ = 4  
E1R2E0F1

4FED



DSQ = 0  
E1R2E0F2

6FED



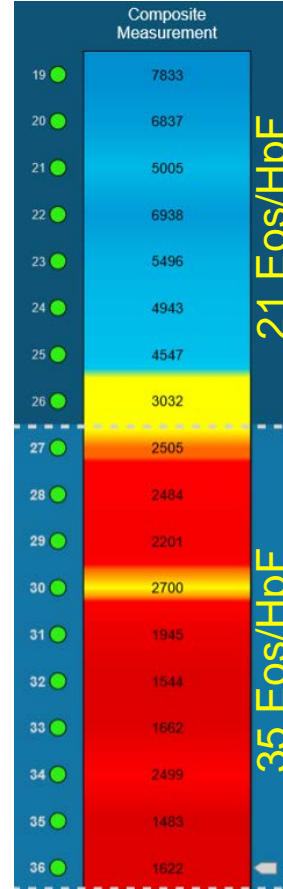
DSQ = 5  
E1R2E0F1

BID PPI



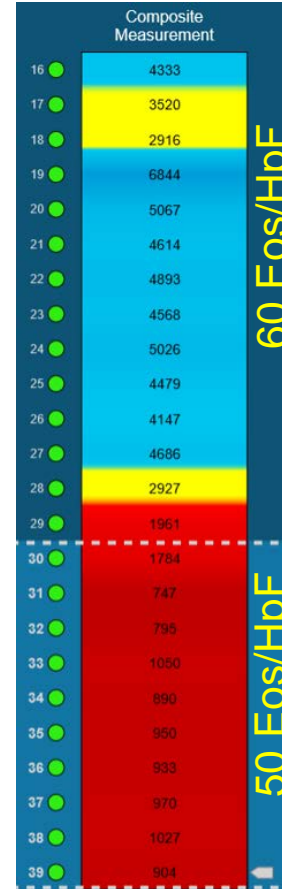
DSQ = 0  
E1R0E1F1

BID PPI



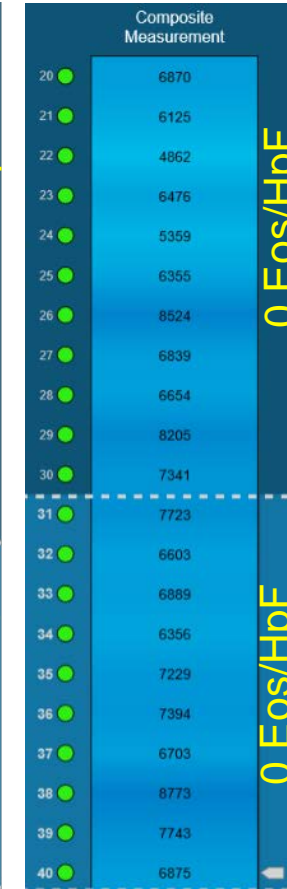
DSQ = 5  
E1R1E0F1

TCS

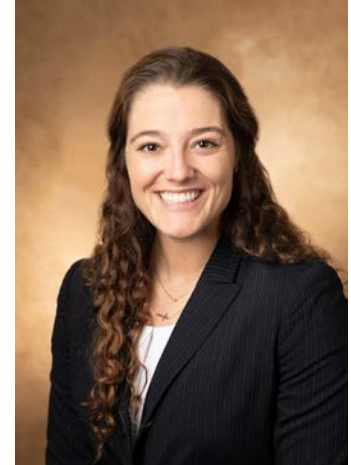


DSQ = 0  
E1R2E2F1

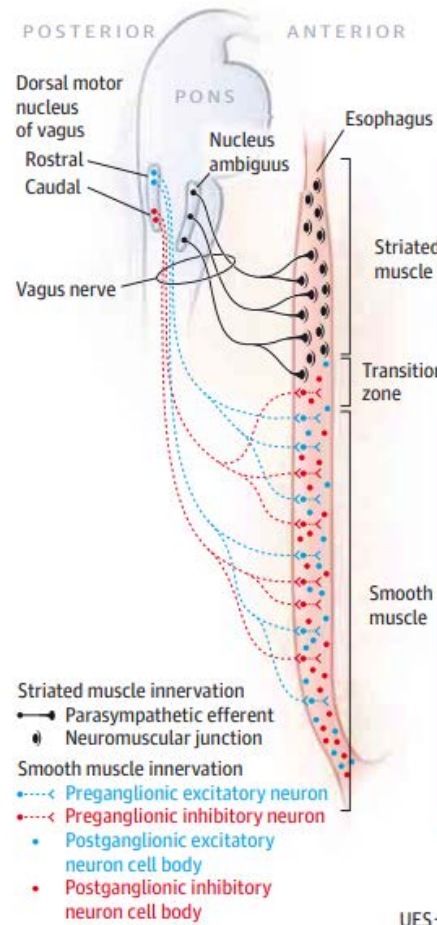
Dupilumab



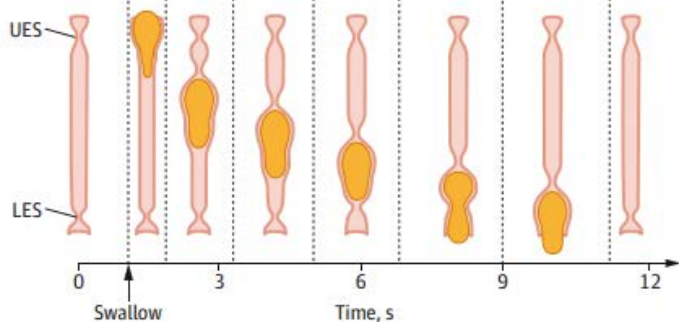
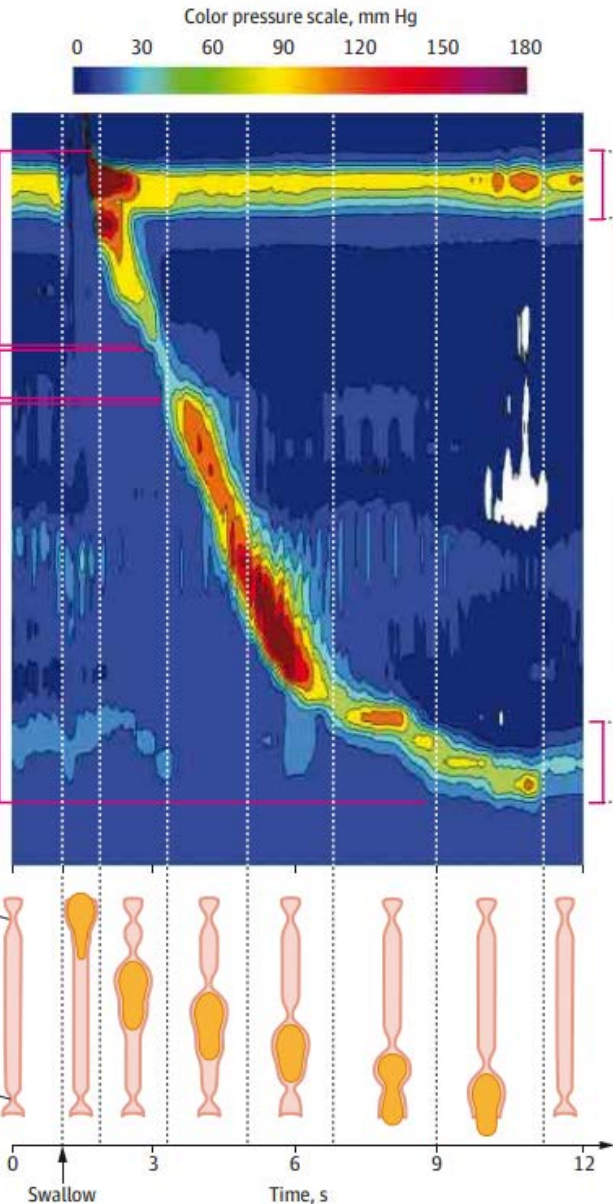
DSQ = 0  
E0R0E0F0



**A** Parasympathetic esophageal innervation

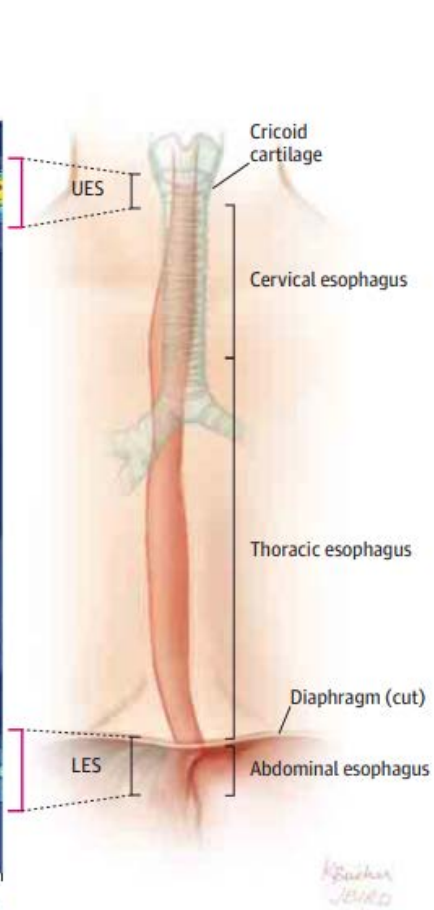


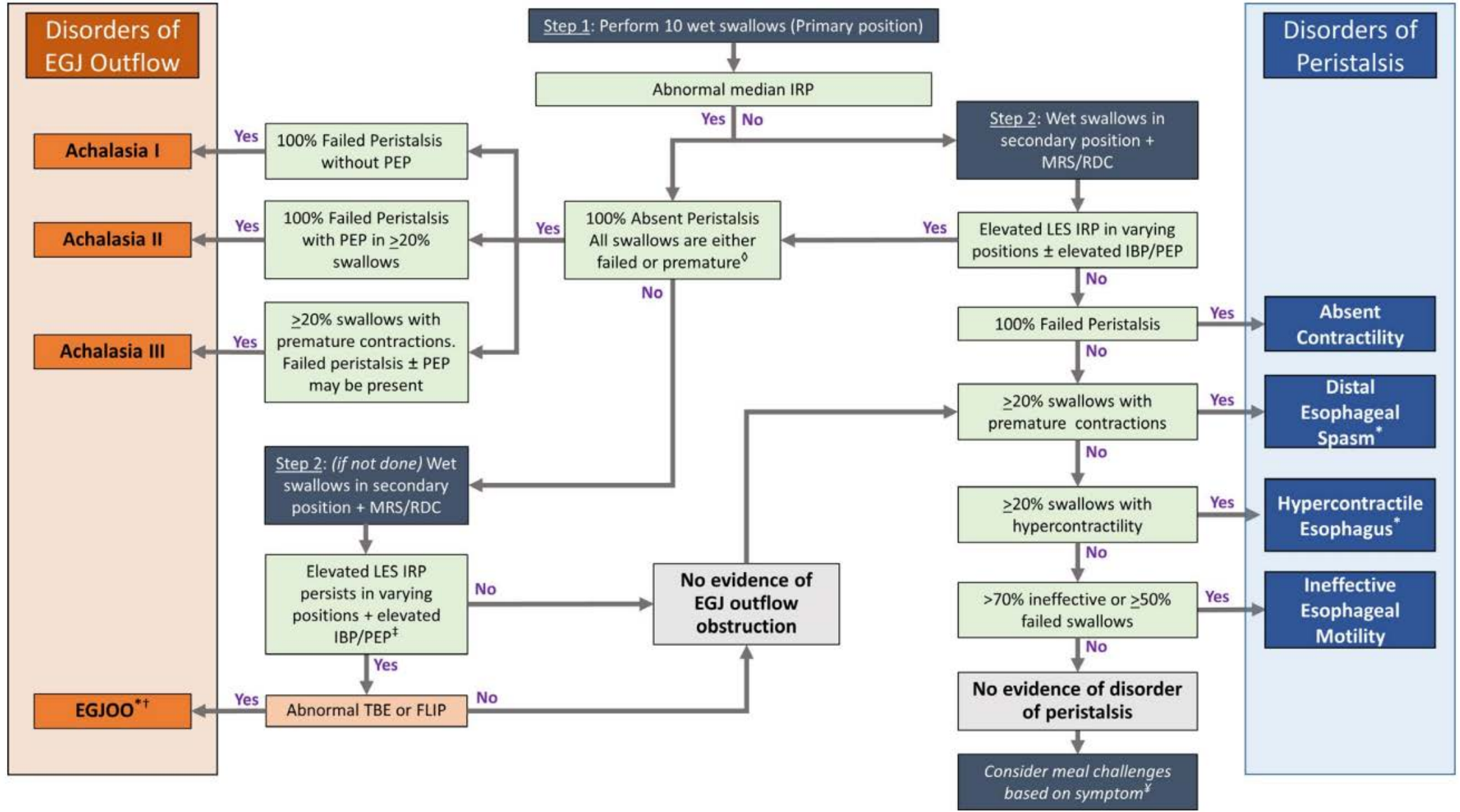
**B** Esophageal pressure topography (EPT) plot from high resolution manometry (normal study)

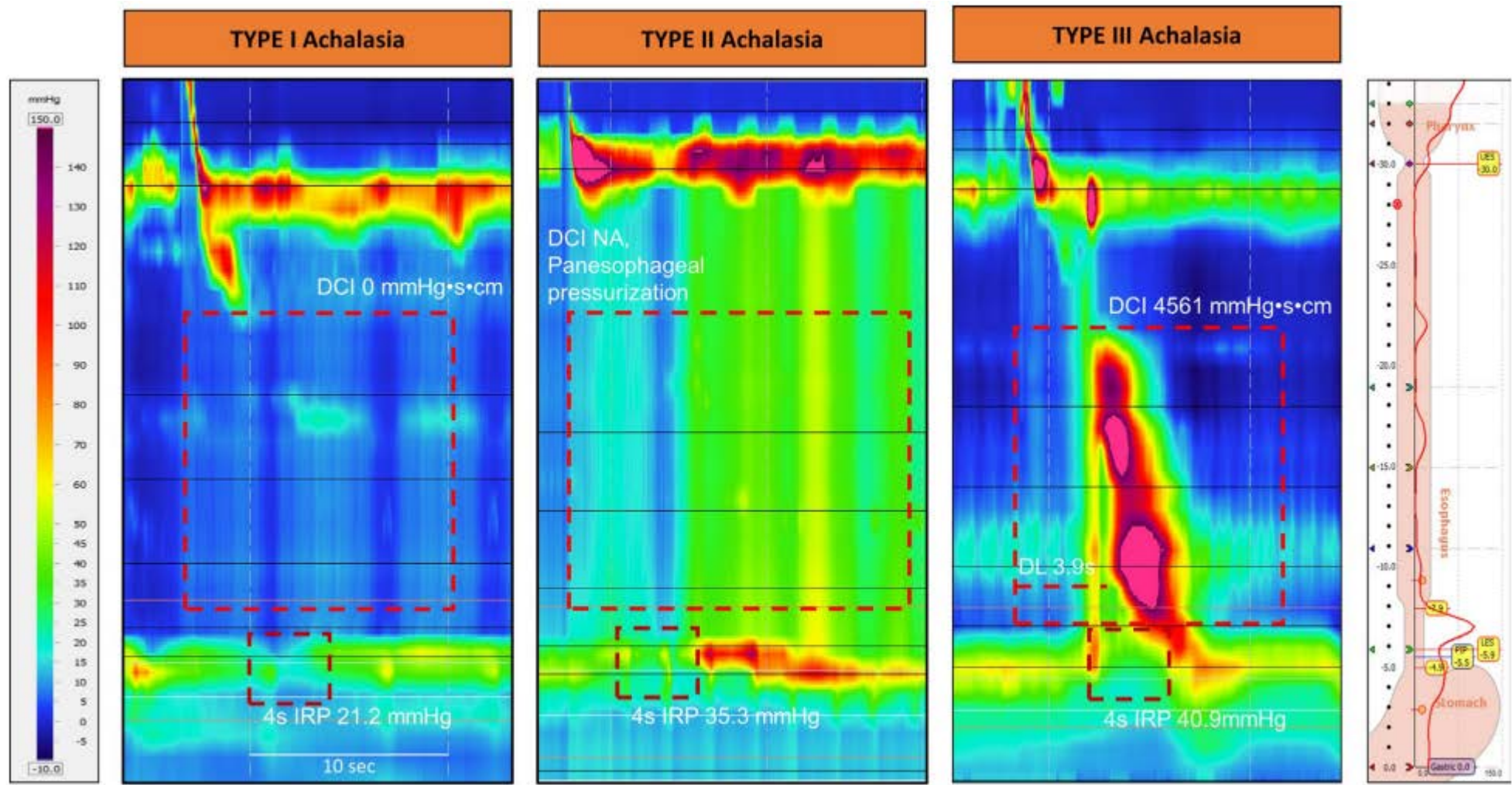


Schematic representation of esophageal motor activity during a swallow

**C** Anatomical correlation with EPT plot







100% Failed Peristalsis

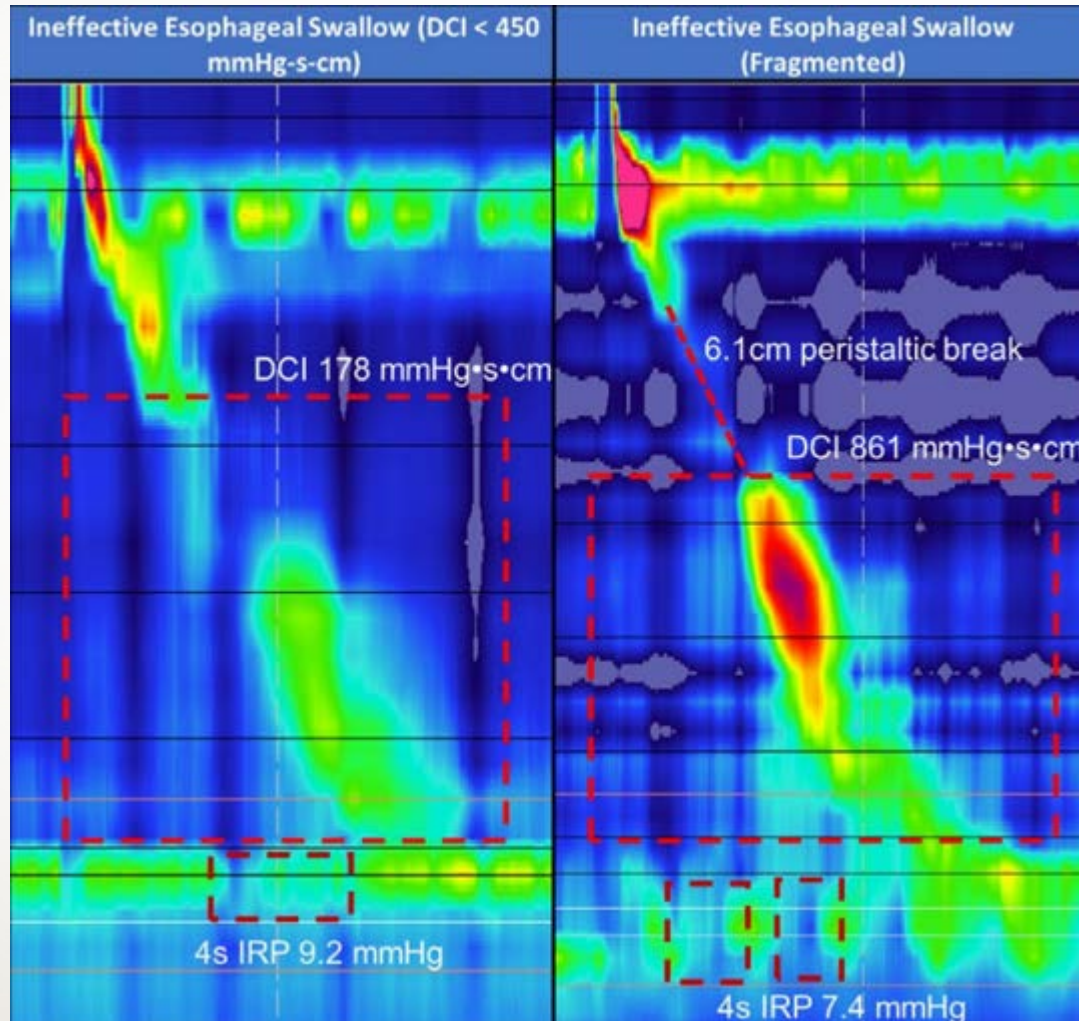
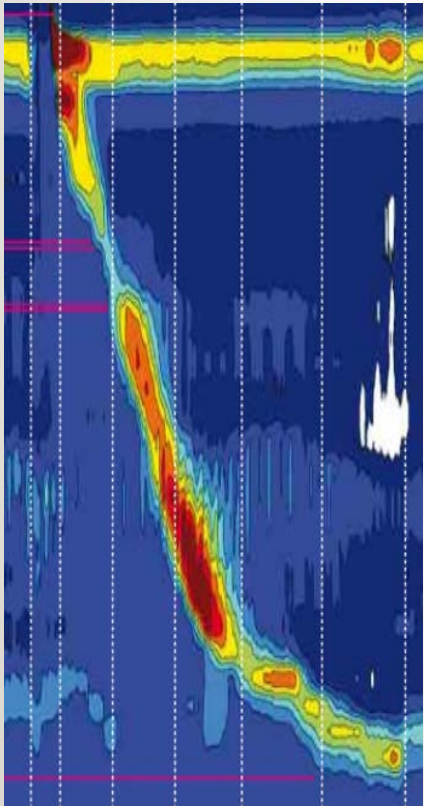
≥20% Pan-esophageal  
pressurization

≥20% premature/spastic  
contractions

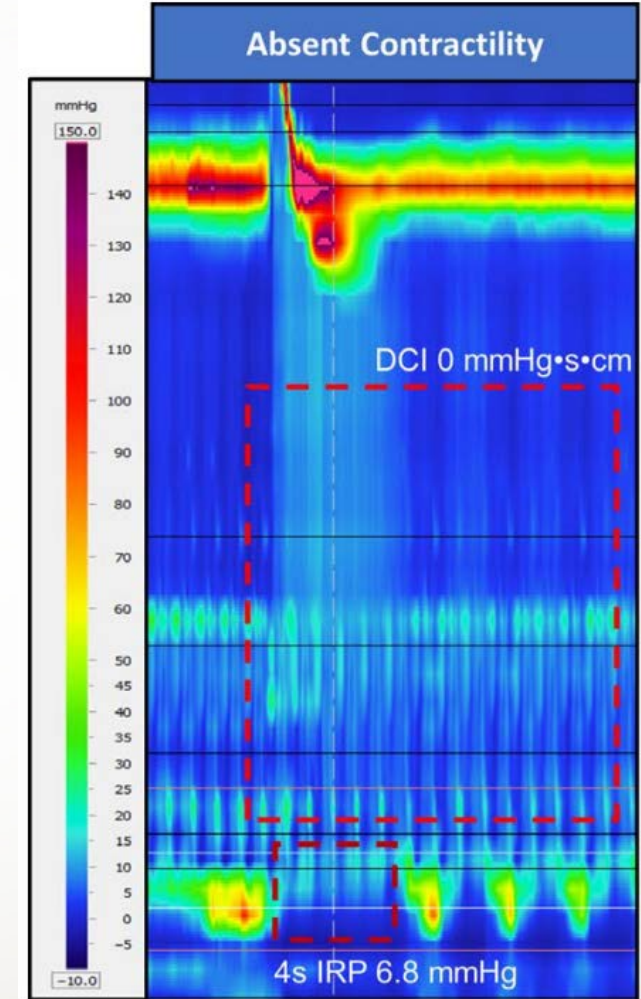
# Manometric patterns

## 1) Ineffective Motility

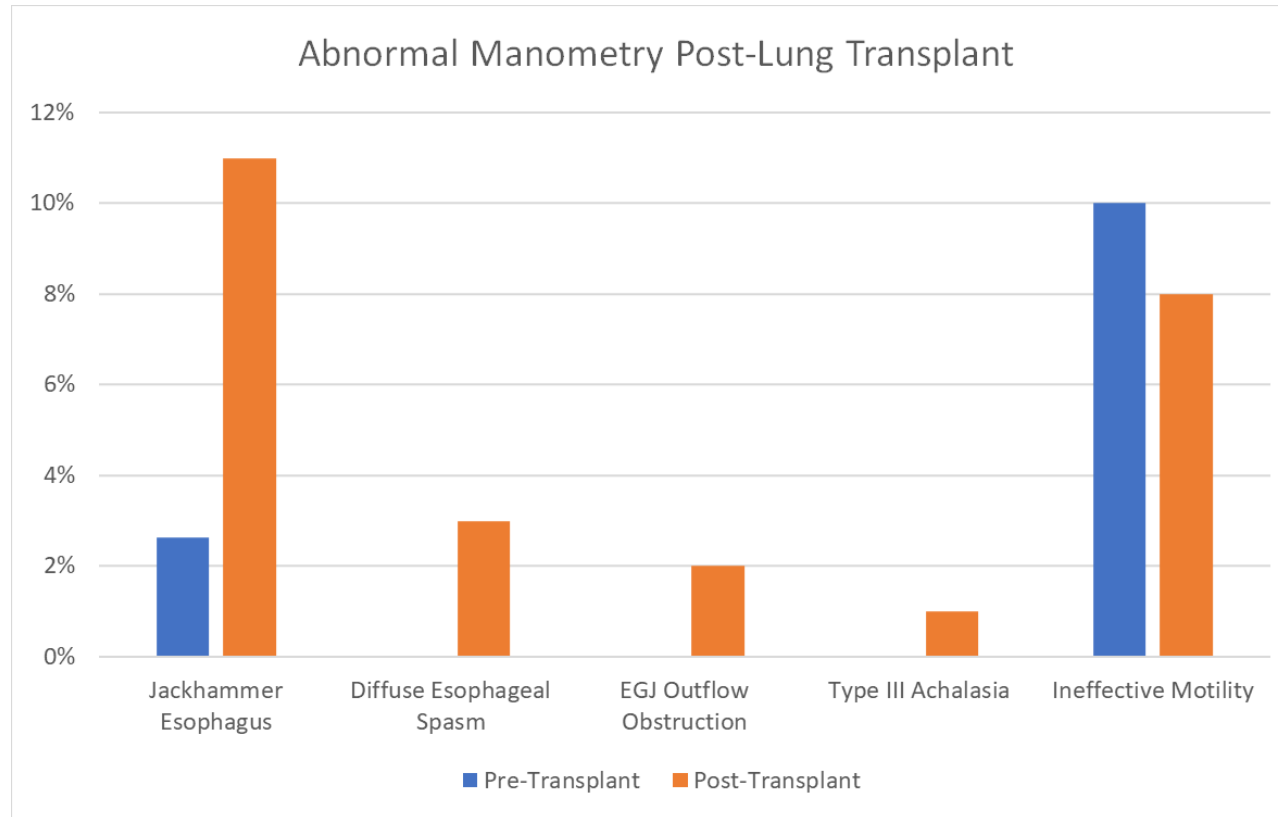
### Normal



## 2) Absent contractility



# Increased risk of hypercontractile esophagus post lung transplant



**Hashim Hayat**  
**MBBS**

**Housestaff**

Medicine Administration

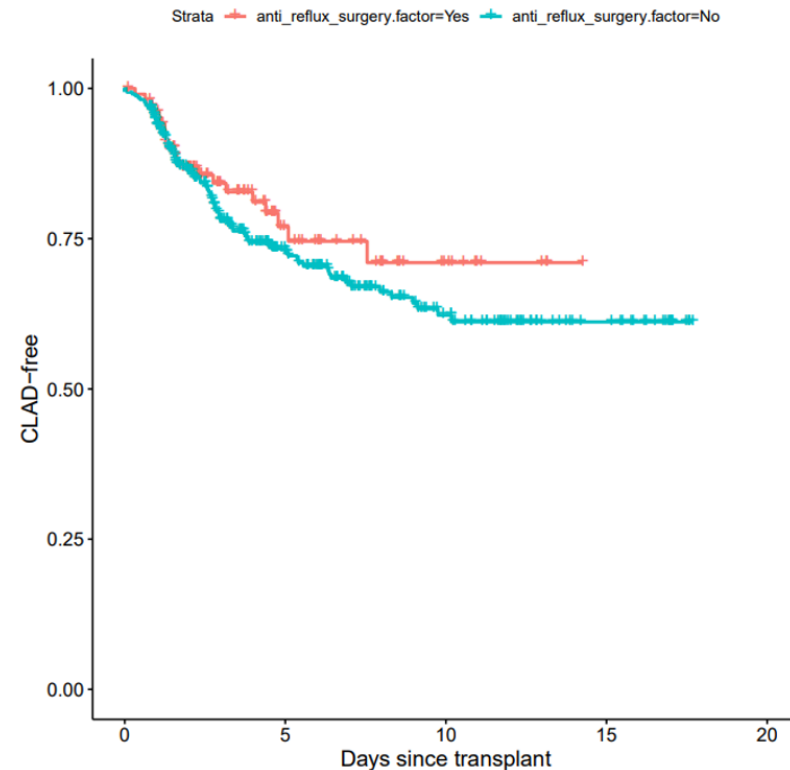
DDW 2022



# Personalized Interventions for esophageal dysmotility improves surgical outcomes

- Early diagnosis and management of non-acid and acid reflux in lung transplant recipients can reduce risk of CLAD

	Manometry (Pre), n=91	Manometry Post, n=127
Normal	75% (68/91)	75% (95/127)
Type II Achalasia	1% (1/91)	0% (0/127)
Type III	0% (0/91)	1% (1/127)
EGJ Outflow Obstruction	4% (4/91)	2% (2/127)
Diffuse Esophageal Spasm	3% (3/91)	3% (4/127)
Hypercontractile esophagus	3% (3/91)	11% (14/127)
Ineffective Motility	13% (12/91)	9% (11/127)
Absent Contractility	0% (0/91)	0% (0/127)
Type I Achalasia	0% (0/91)	0% (0/127)



**Krissie Lobon**  
MD

Housestaff

DDW 2024

# Patient:

66

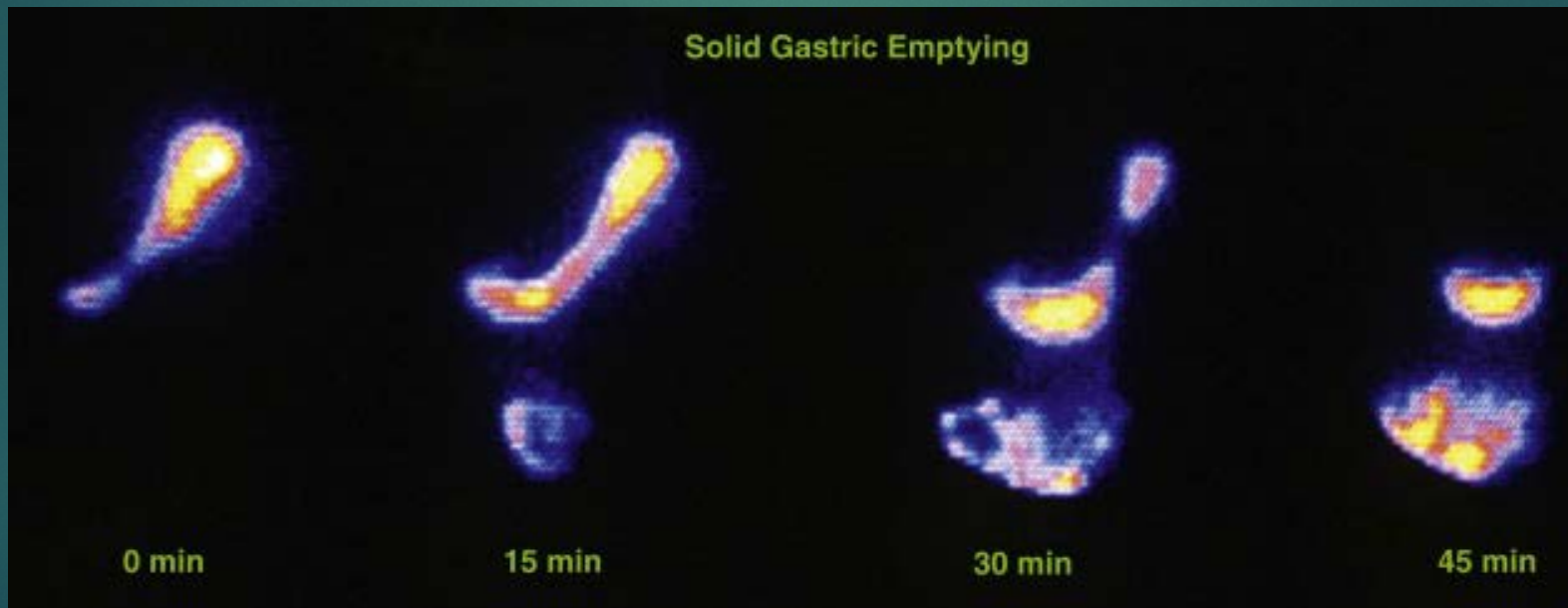
56-year-old presents for consideration for heart-transplantation. Prior poorly controlled diabetes with nausea/vomiting.

They are on opiates for chronic back pain.

They are on Ozempic for diabetes.

Patient reports he cannot eat solid food – ok to list for cardiac transplant?

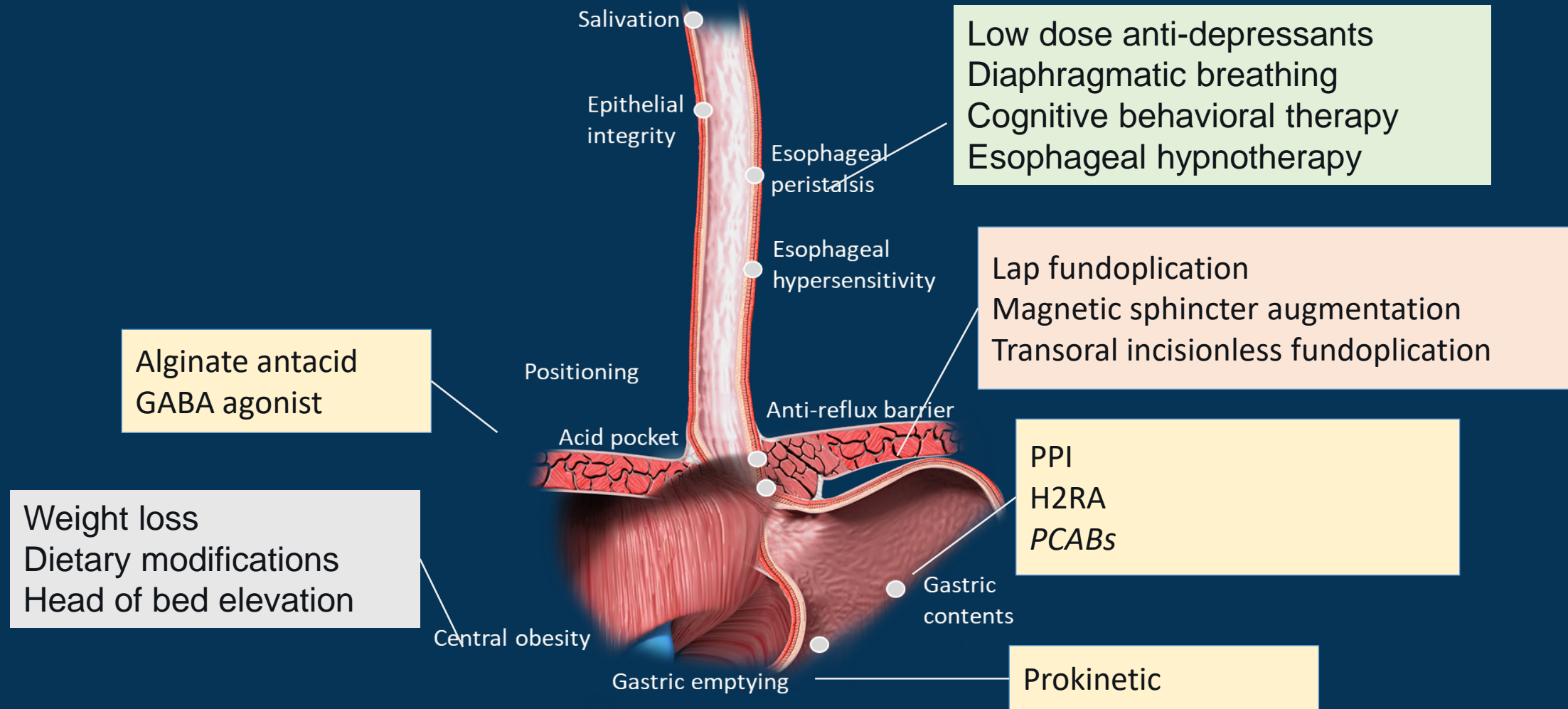
- ▶ EGD Normal – except retained food in the stomach
- ▶ Gastric emptying performed shows delayed motility – next steps?



# Gastroparesis

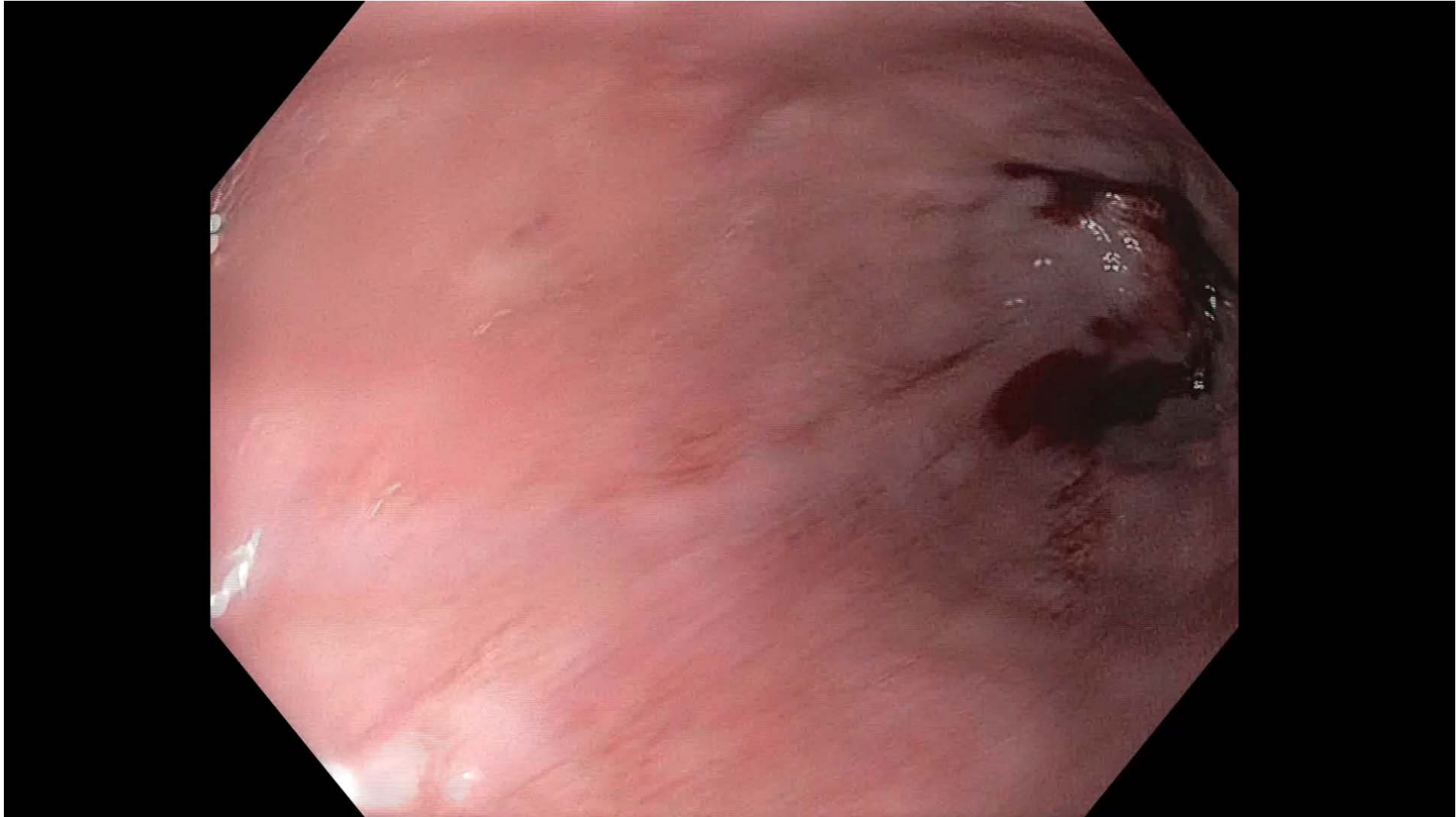
- Presentation: nausea, vomiting, fullness, “refractory reflux”
- Best test: gastric emptying test (off opiates)
- Treatment:
  - Dietary modification, Hydration and nutrition, Optimize glycemic control
  - Stopping GLP1-RA when able
  - Prokinetics
    - Metoclopramide – risk of tardive dyskinesia (only AGA approved therapy)
    - 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)

# Critical to Understand Mechanism of Symptom & Target Accordingly



# Post Transplant Survivorship

- Screening for Barrett's Esophagus (order EGD)
- *Best Practice Advice 1: Screening with standard upper endoscopy may be considered in individuals with at least 3 established risk factors for BE and EAC, including individuals who are*
- **Male**
- **non-Hispanic white**
- **age >50 years**
- **history of smoking**
- **chronic gastroesophageal reflux disease (GERD)**
- **Obesity**
- **Family history of BE or EAC.**



# Post Transplant Survivorship: Colon cancer

- Guidelines have changed to 45 for Screening for Average Risk
- High risk: 1 first degree relative with colon cancer / two 2<sup>nd</sup> degree relatives or advanced adenoma (tubulovillous)
- Screening for Colon Cancer
  - Colonoscopy (screening and prevention)
  - Cologuard (2.0) vs. FIT
  - Blood testing (not colon specific, excellent for advanced cancers)
- For patients with cystic fibrosis: 2018 Guidelines
  - We recommend colonoscopy as the preferred screening method, initiation of screening at age 40 years, 5-year re-screening and 3-year surveillance intervals (unless shorter interval is indicated by individual findings), and a CF-specific intensive bowel preparation.
  - Organ transplant recipients with CF should initiate CRC screening at age 30 years within 2 years of the transplantation because of the additional risk for colon cancer associated with immunosuppression.
  - How will gene editing changes this risk?



# Conclusions

- Pre-transplant work-up may help define post-transplant outcomes
  - Colon cancer
  - Barrett's / esophageal cancer
  - Motility
- Infectious risks remain high
- Vascular problems (low flow, VAD, ischemia status)
- Post-transplant survivorship is important
  - Cancer risk rises with immunosuppression
  - Optimism for improved non-invasive testing (Cancer detection, not prevention)

# Acknowledgements

- Vanderbilt Esophageal Group
  - Michael Vaezi and Dan Patel
  - Chris Slaughter
  - Michael Holzman and Chetan Aher (Foregut surgery)
  - Eric Lambright and Caitlin DeMarest (Thoracic surgery)
- Pulmonary
  - Ciara Shaver, Ivan Robbins, Anil Trindade, David Erasmus, Stephanie Norfolk, Justin Hewlett, James Tolle, Haley Hoy
- Rheumatology
  - Tracy Frech / Erin Wilfong
- Columbia University
  - Michael Gershon, MD and Anne Gershon, MD (Virology)

Rishi.D.Naik@vumc.org  
@RishiNaikMD

VANDERBILT  HEALTH