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Understanding the Impact of Esophageal Physiology in Transplantation

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Disclosure

I have the following relevant financial relationship to disclose:

Research Support:

Esophageal Neurodegeneration: supported by R01DK093094-09A1

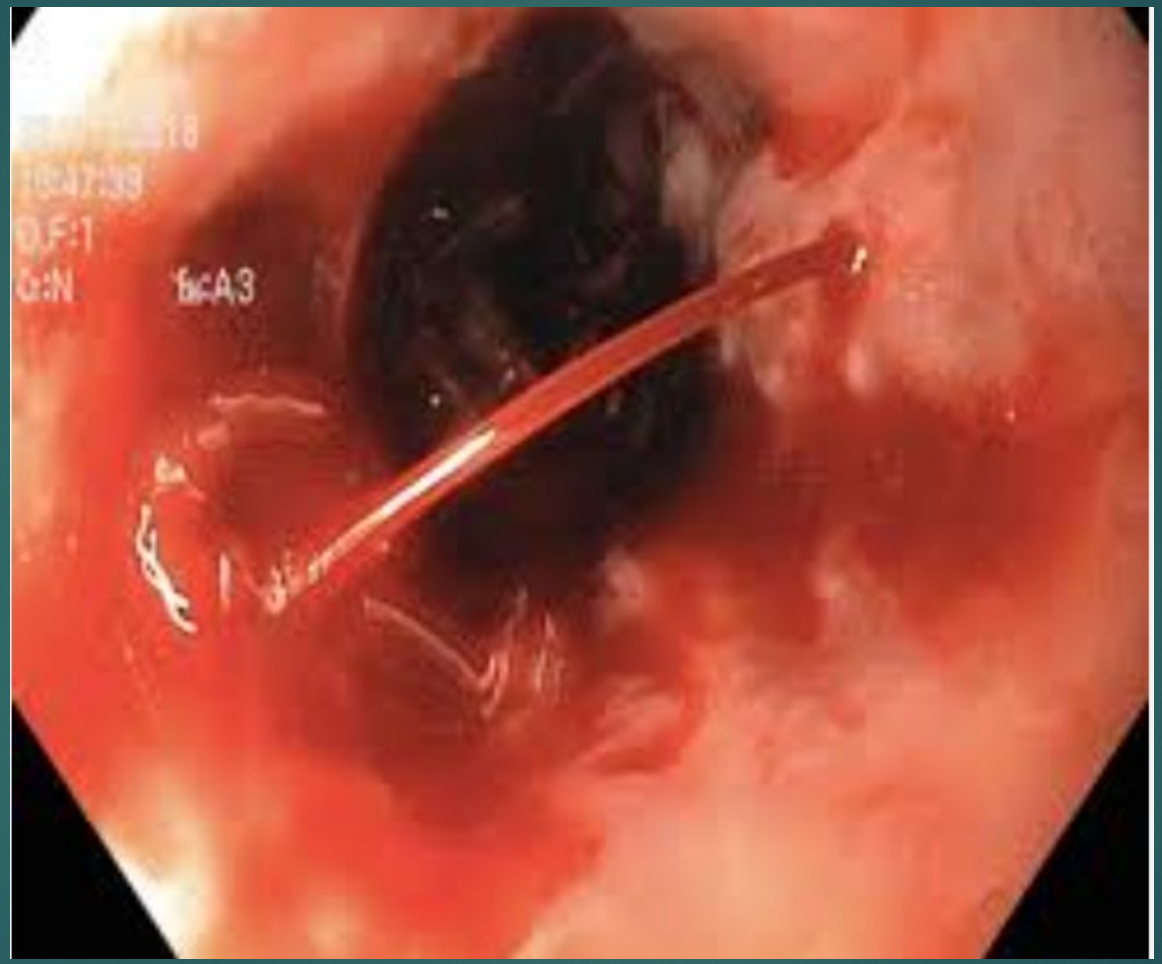
Vanderbilt University Medical Center co-owns the patent with Diversatek for MiVu™

I will be discussing off-label use of medications

Outline

1) Esophageal Manifestations and Management
2) Treatment Options

Patient with hematemesis shows the following on EGD



Bleeding Esophageal Varices should prompt discussion on liver transplant candidacy

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Esophageal Work-up

1) Diagnostic evaluation of mucosal disorders
   - Upper endoscopy
   - Ambulatory Reflux Testing
   - Mucosal Integrity
2) Diagnostic evaluation of motor disorders
   - Manometry
   - Functional Luminal Imaging Probe (FLIP)

Endoscopy

- Esophagogastroduodenoscopy (EGD)
  - Initial diagnostic test for dysphagia
    - Rules out esophageal cancer, Barrett's esophagus, or infectious process
    - Diagnostic and therapeutic (dilation)
  - Evaluation for GERD (heartburn, regurgitation)
    - Esophagitis, Hiatal hernia
- Increased risk of esophageal cancer given chronic reflux
  - SSc can be considered a risk factor for Barrett's esophagus screening

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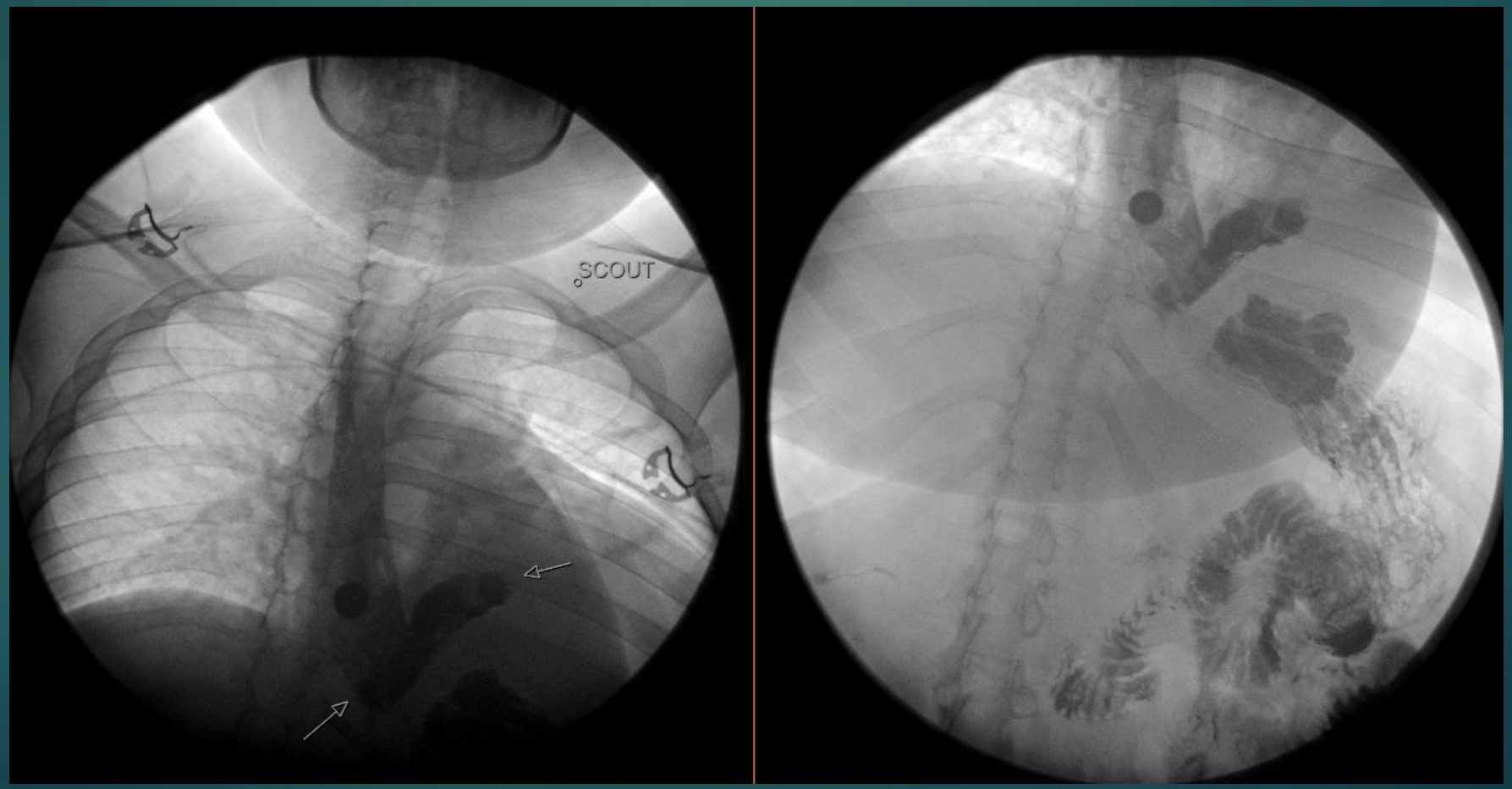
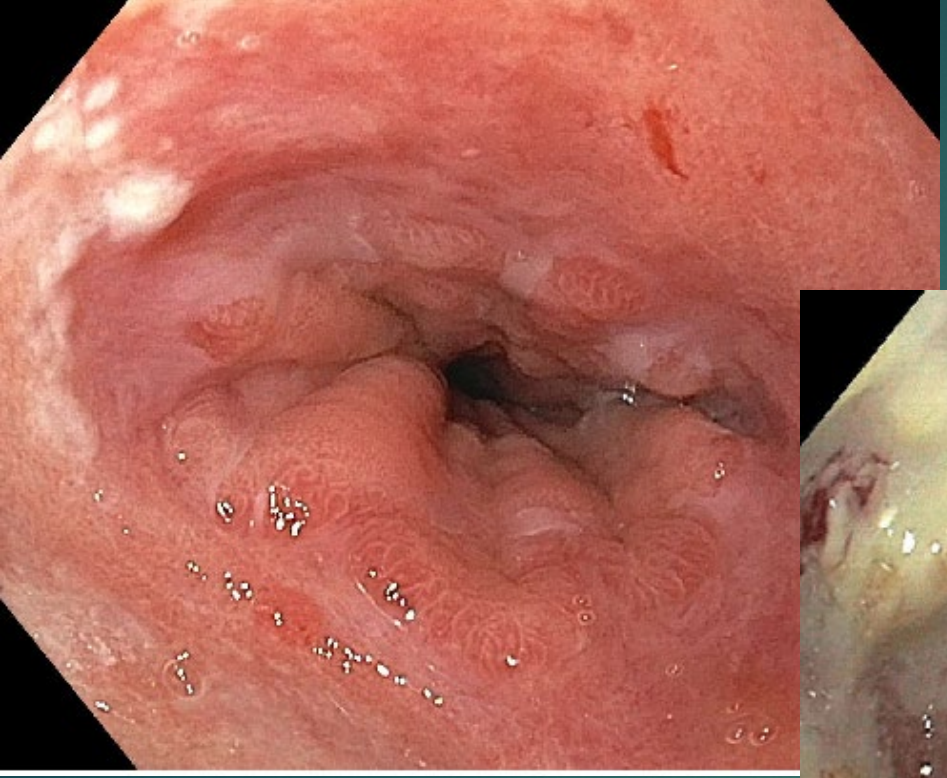
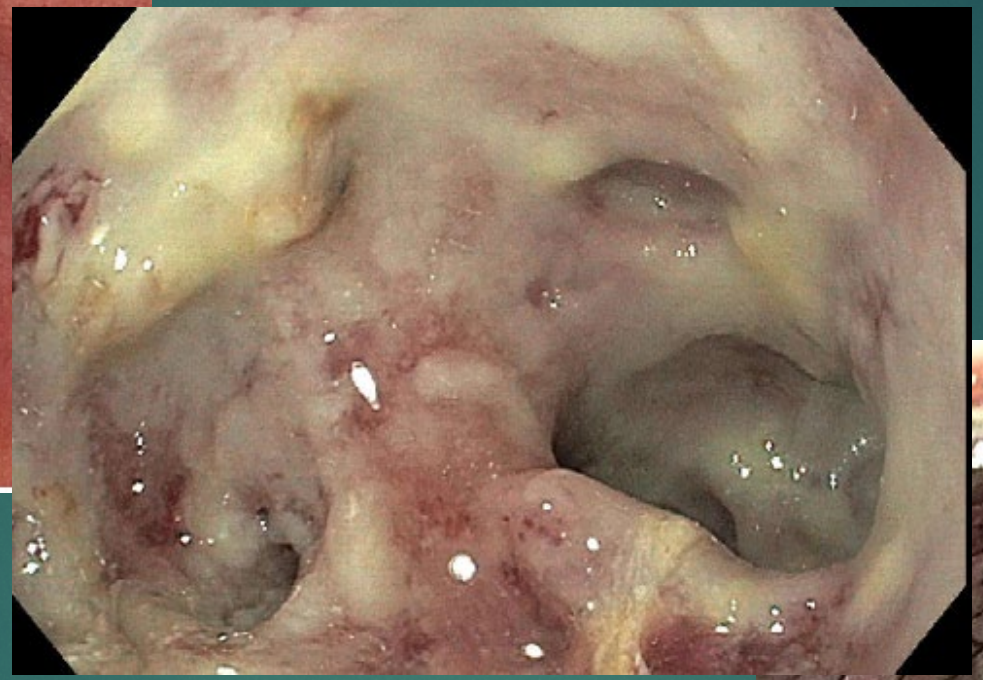
EGD

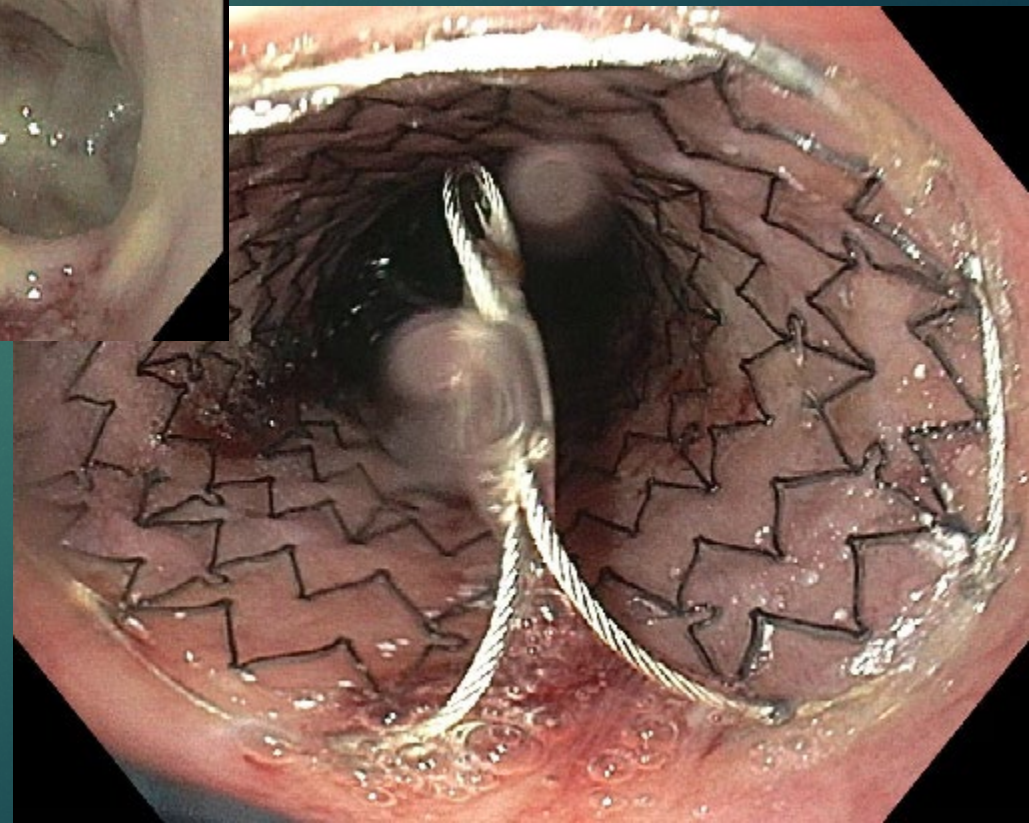
Patient:

24 YO BF with lupus/dermatomyositis overlap complicated by pericarditis, panniculitis, calcinosis cutis developed diffuse leg rashes and worsening shortness of breath being considered for expedited lung transplant evaluation: Esophagram performed:









Patient 1:

-Esophageal-pleural fistula extending into lung parenchyma & bronchi with left lower lobe abscess

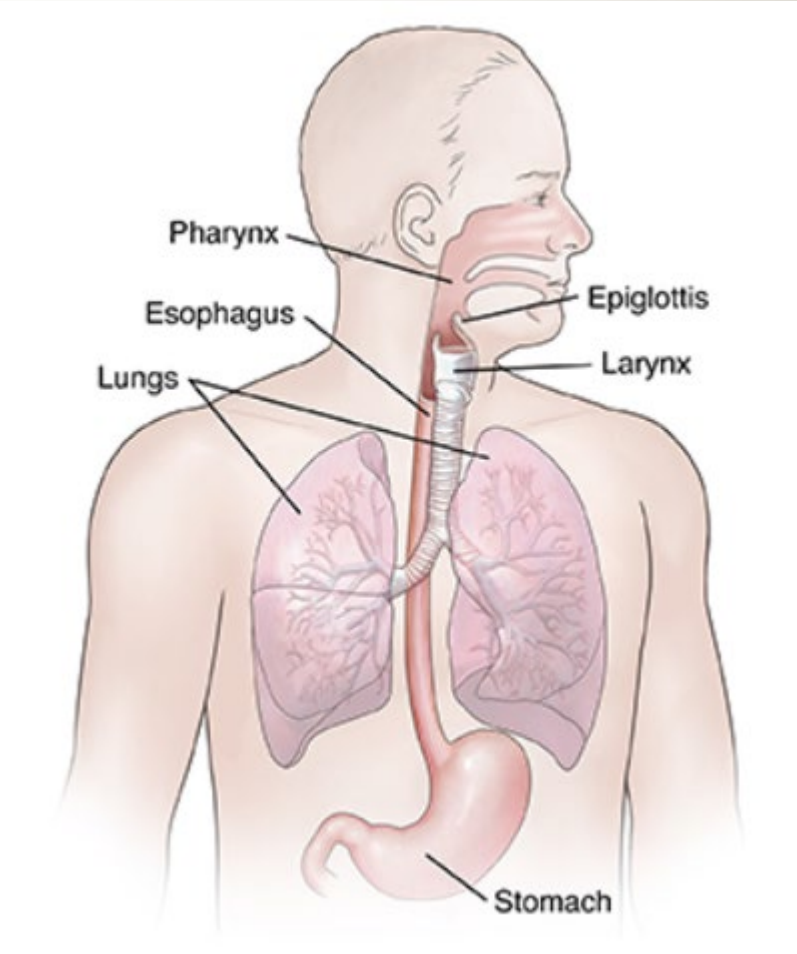
- Not candidate for endoscopic suturing
- Fully covered stent placed
- Nasojejunal tube placed through stent

- Medications: IVIG, prednisone 9mg, Dapsone

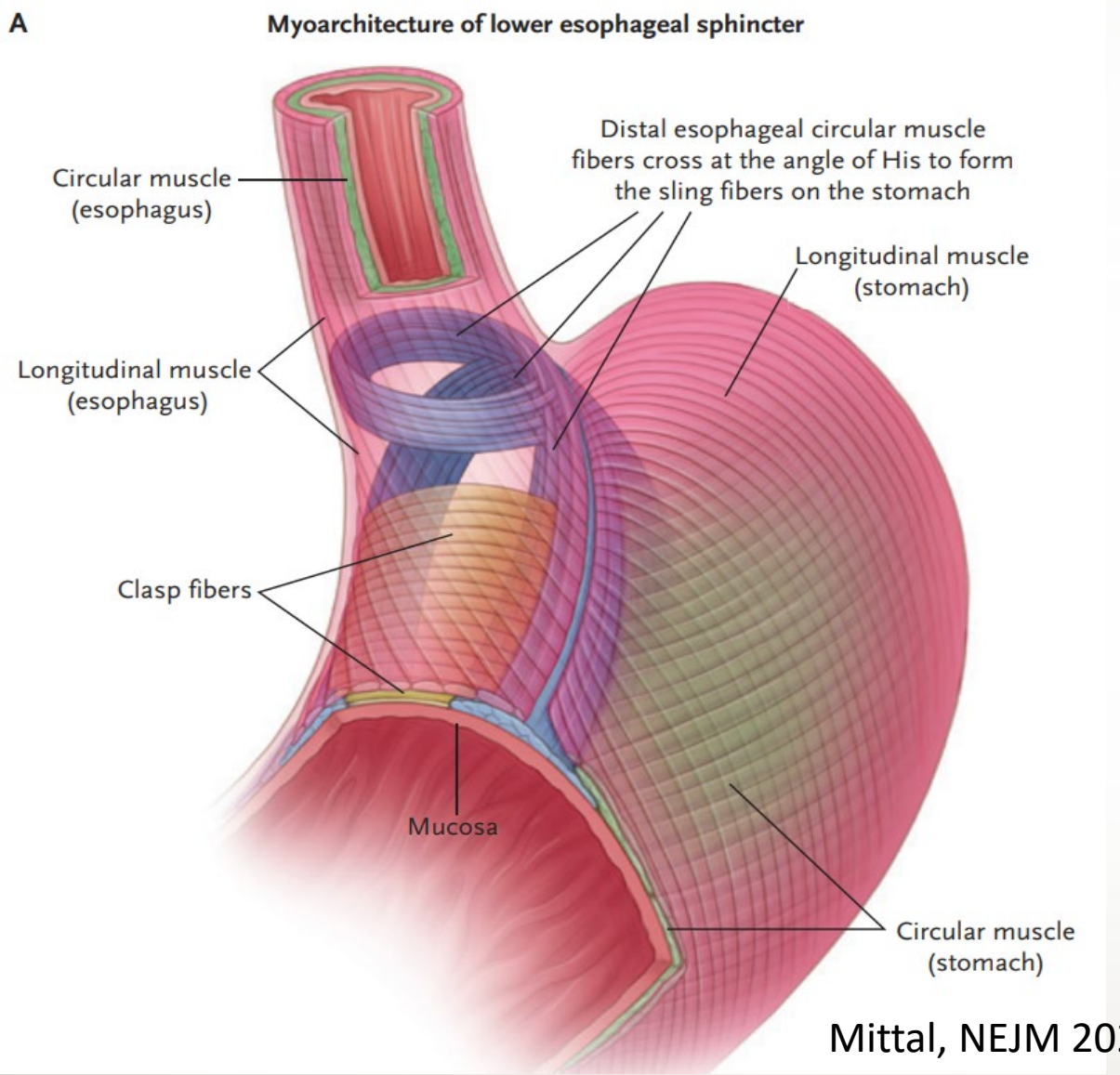
- Persistent leak – continued comorbidities, multiple MDRs, sepsis – unable to list for lung transplantation

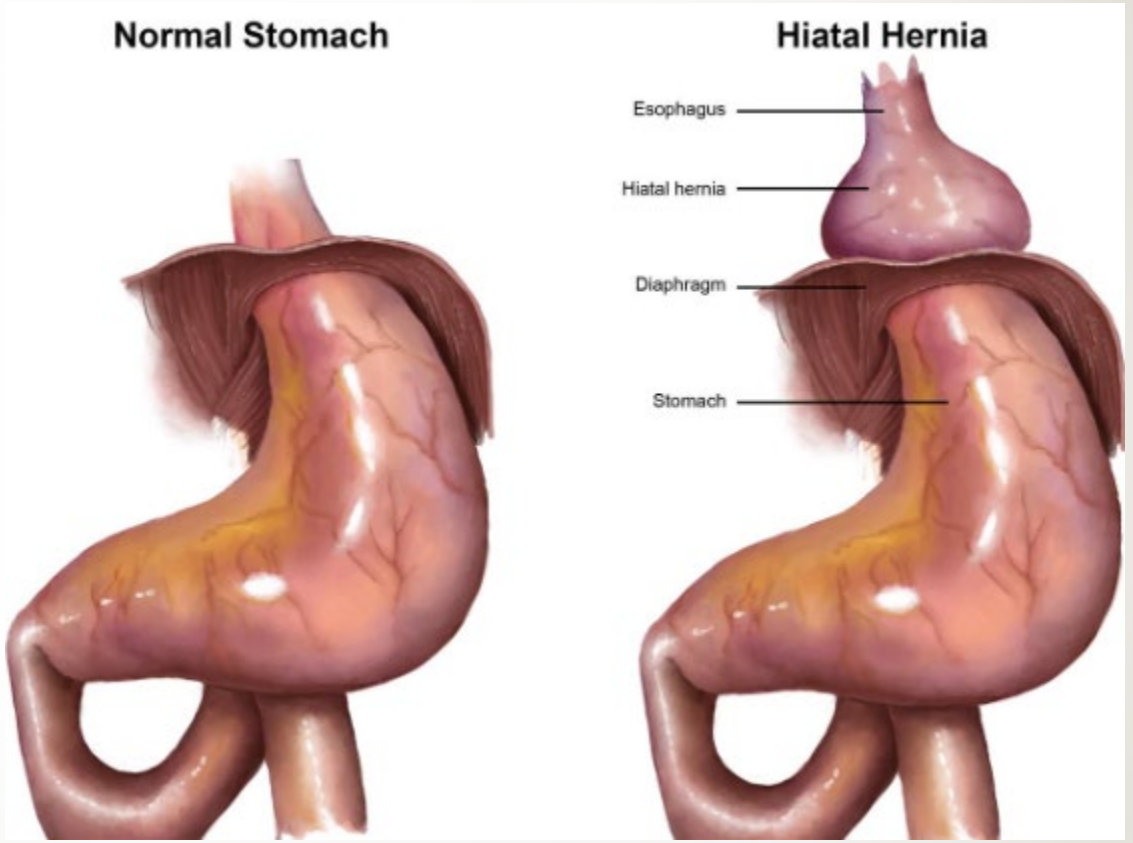
GERD and Lung Transplant

- GERD is a prevalent and modifiable risk factor for rejection after transplantation
- GERD is associated with worse pulmonary function after transplantation
- GERD symptoms do no predict or reliably correlate with airway disease



Why do we reflux?





Mittal, NEJM 2020

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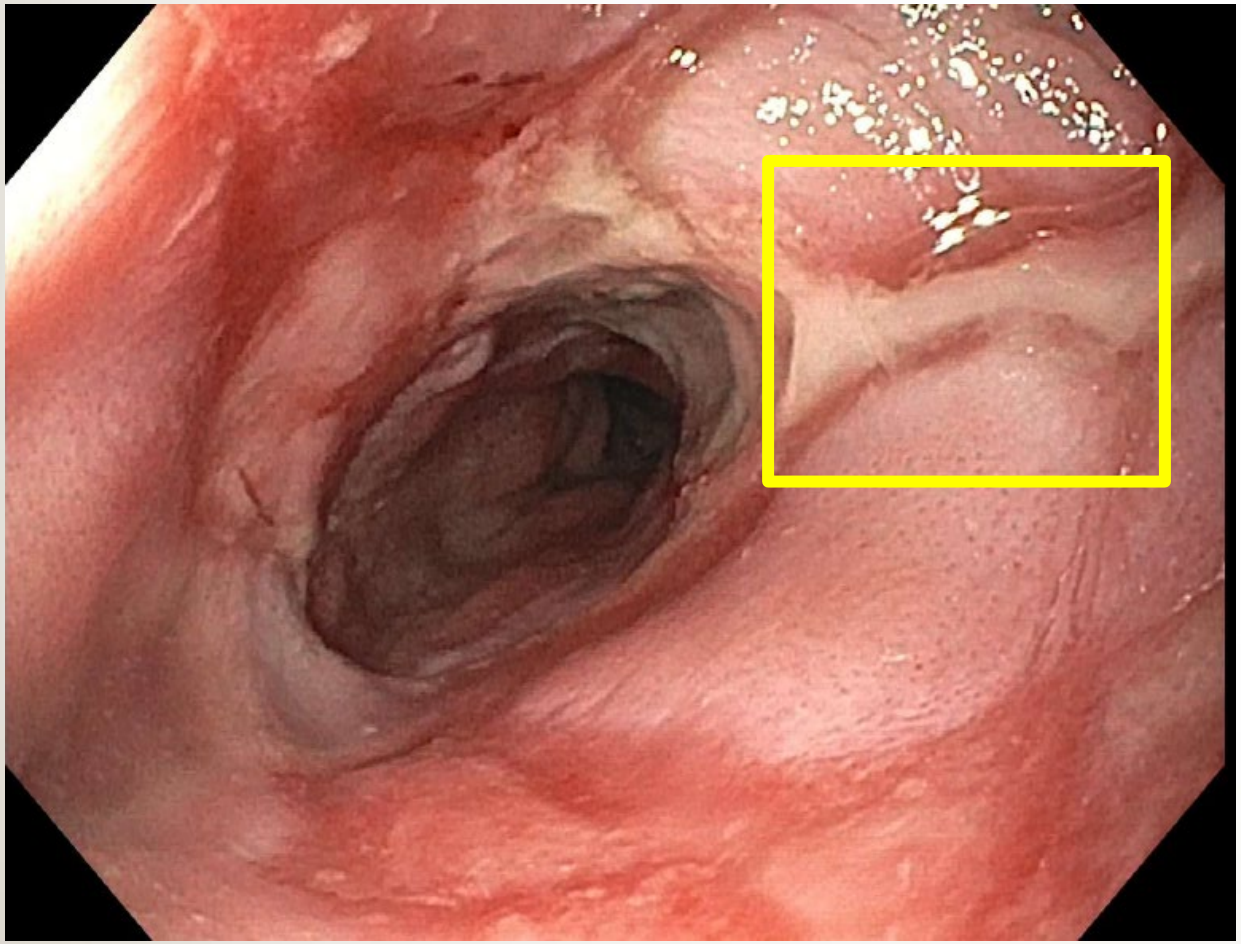
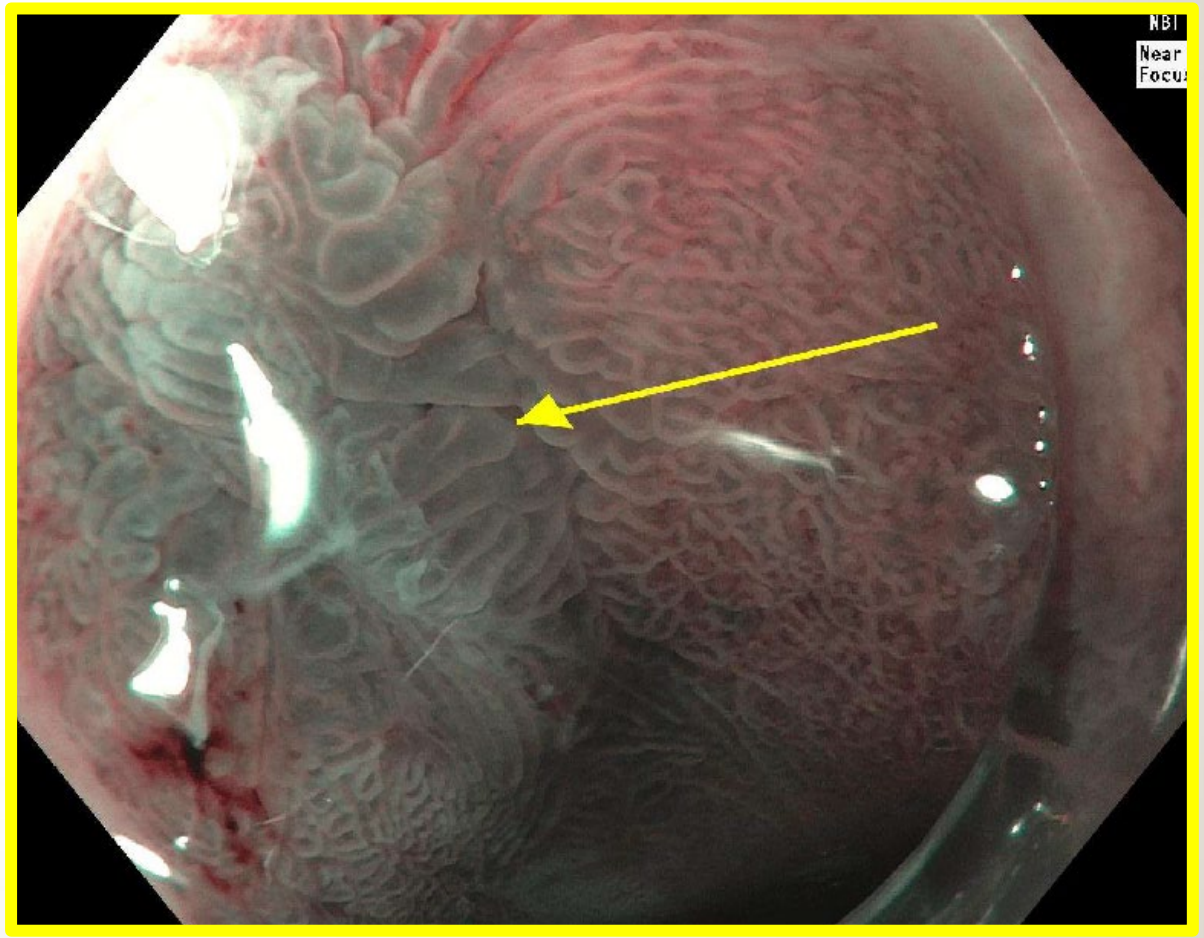
Endoscopy and Reflux





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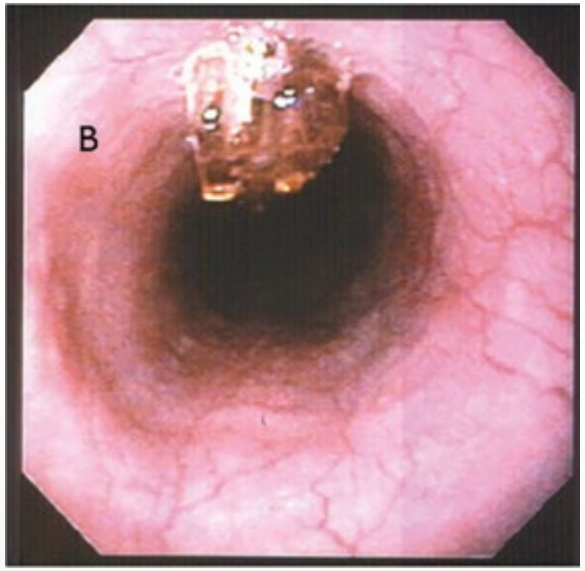
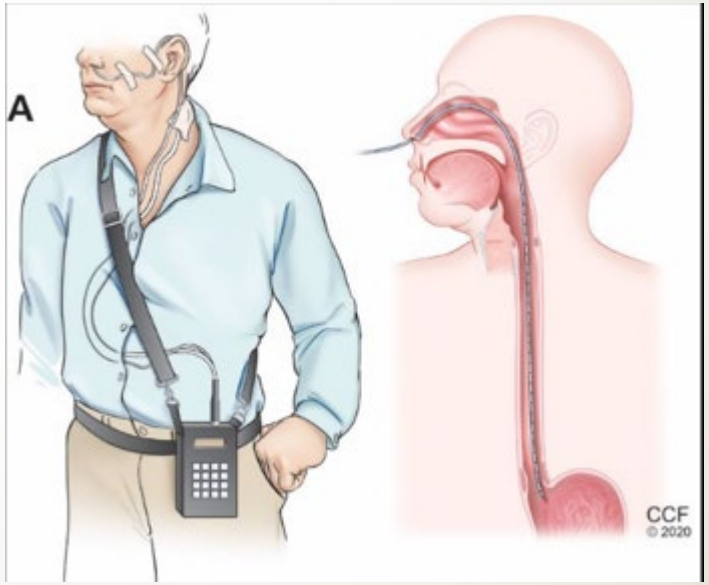
Reflux Monitoring

- Acid reflux testing
  - Wireless pH - Placed endoscopically during EGD
  - Transnasal pH monitoring
  - Off acid-suppression; post-lung transplant can determine need for fundoplication





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

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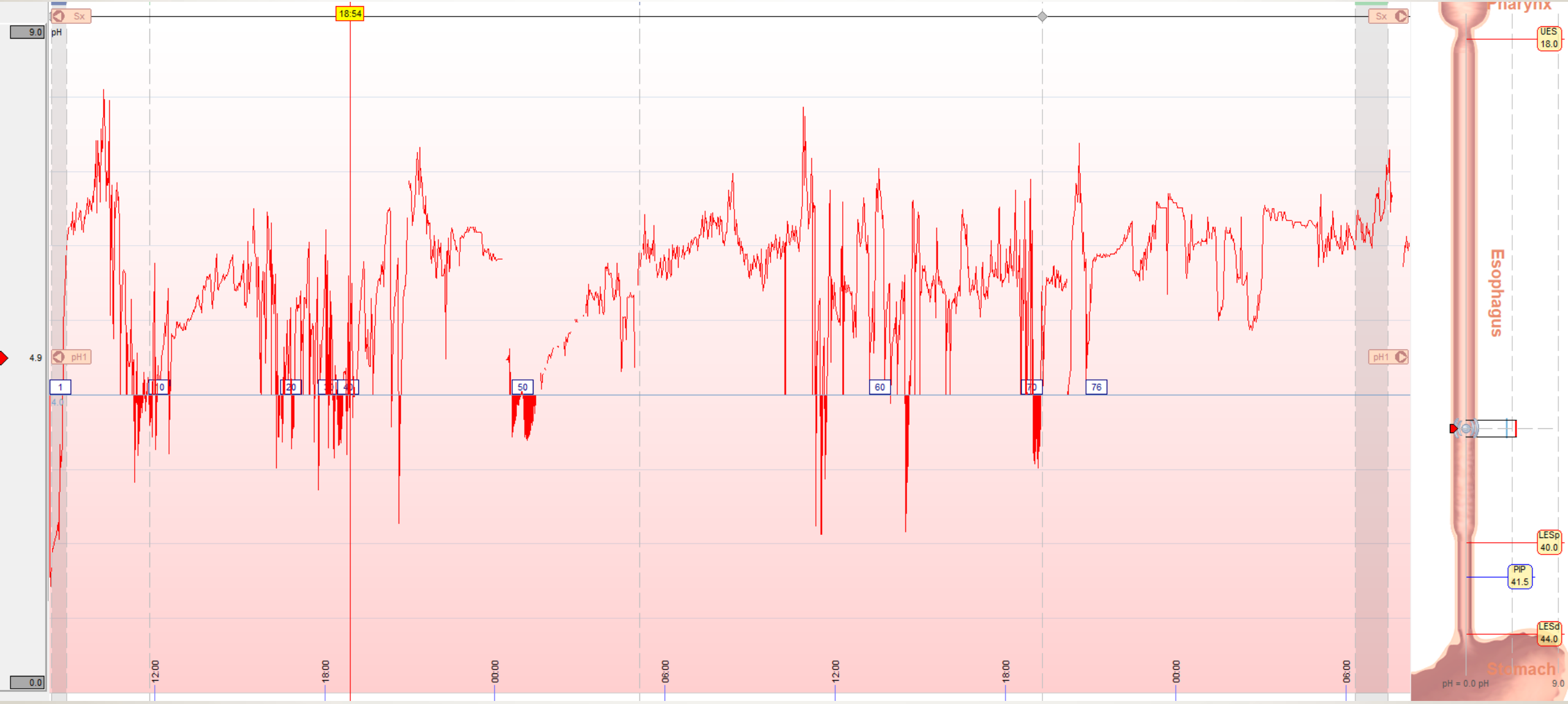
Ambulatory Reflux Monitoring



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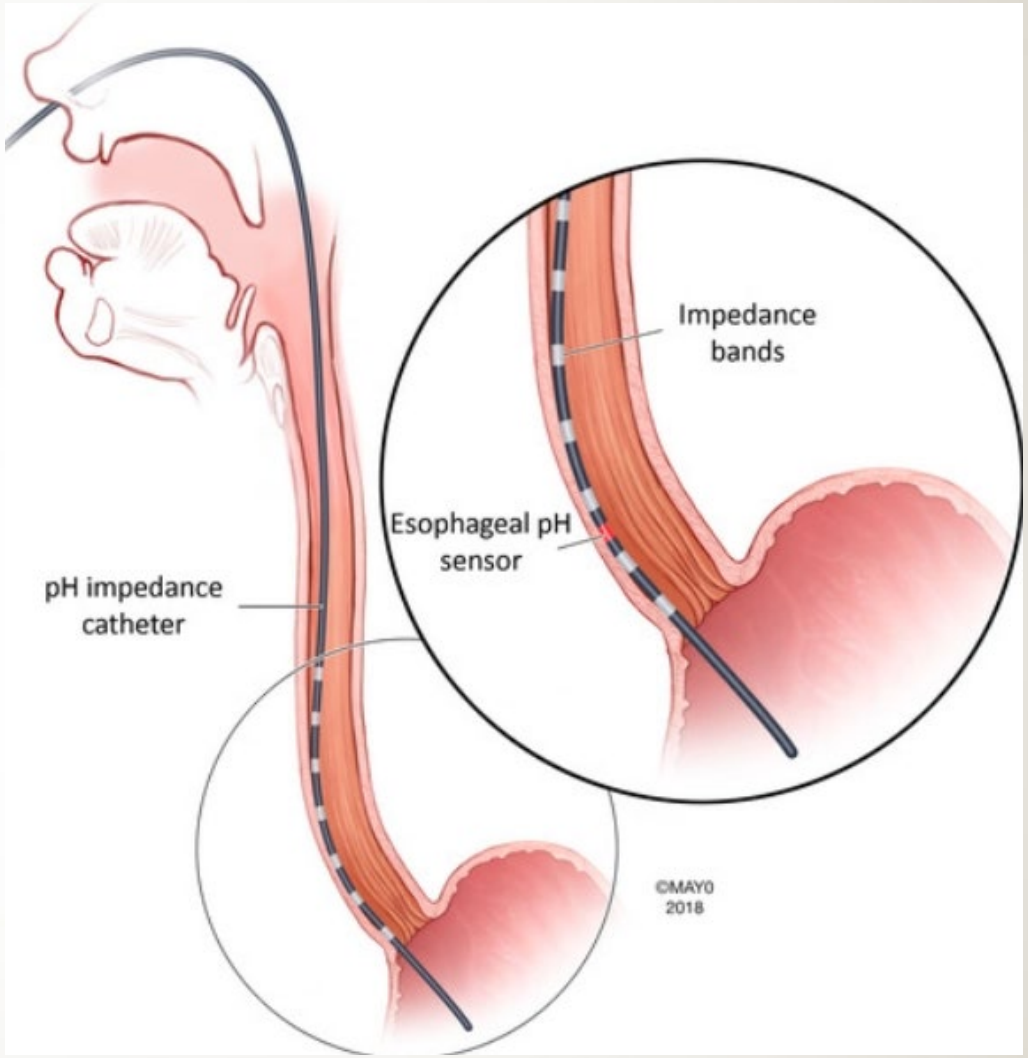
Impedance Monitoring

- Acid and non-acid testing
  - Impedance testing
  - No sedation needed
  - For pre-lung transplantation, perform off therapy
  - For routine use, we typically perform on therapy
    - 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)

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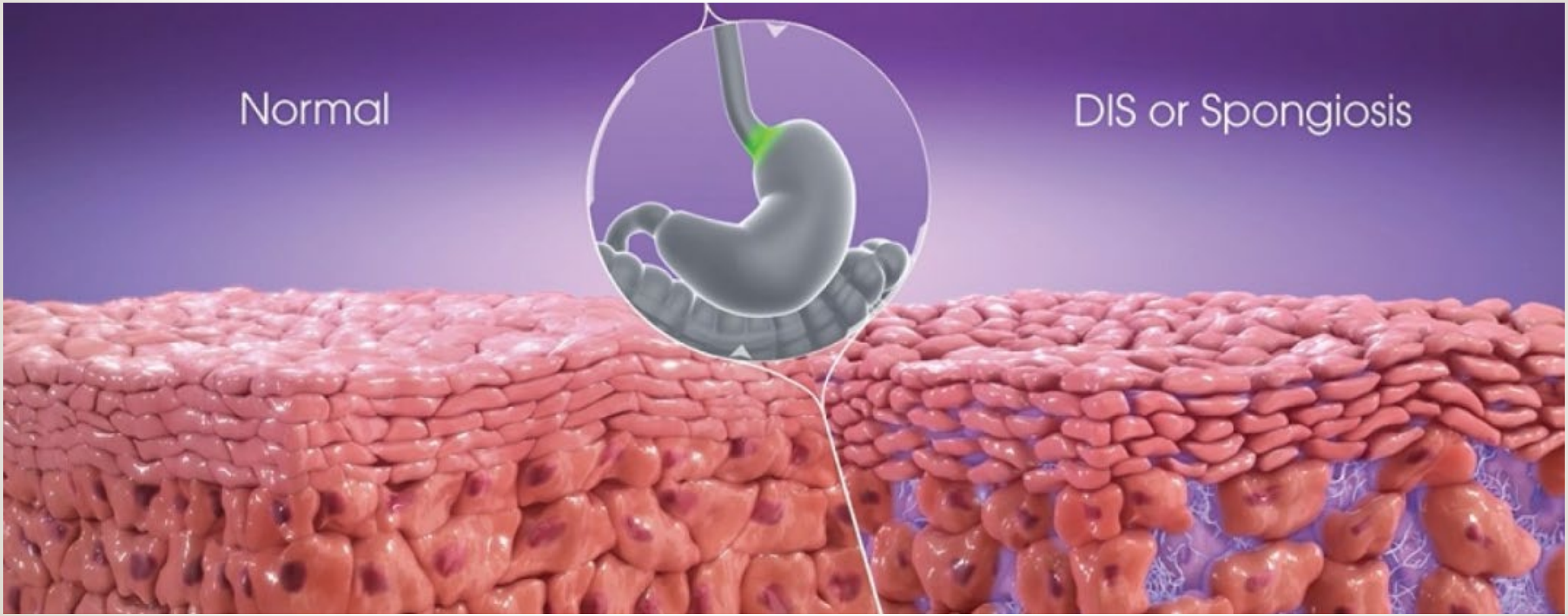
Reflux Changes to the Esophagus



https://diversatekhealthcare.com/mucosal-integrity-mivu-2/

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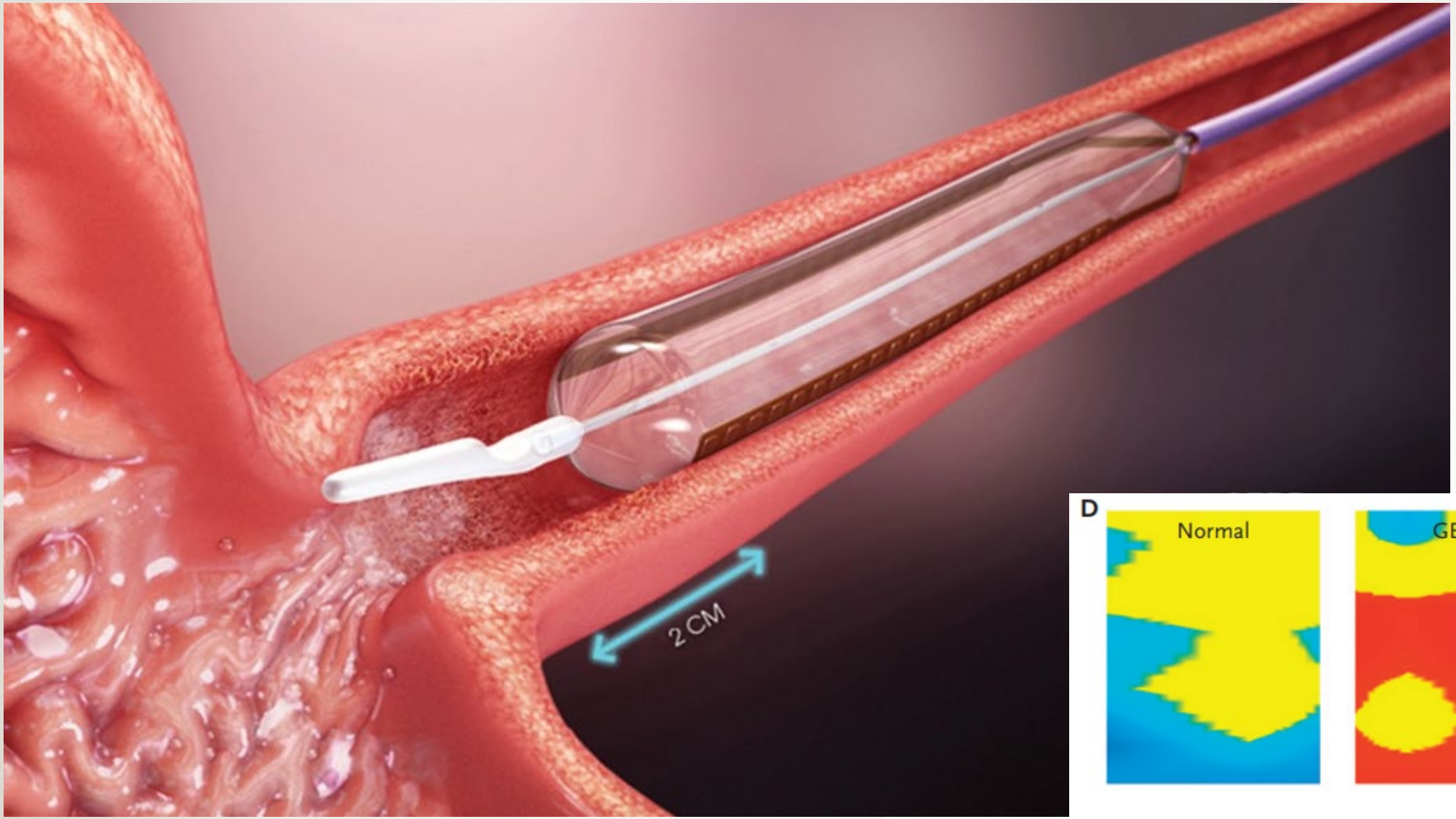
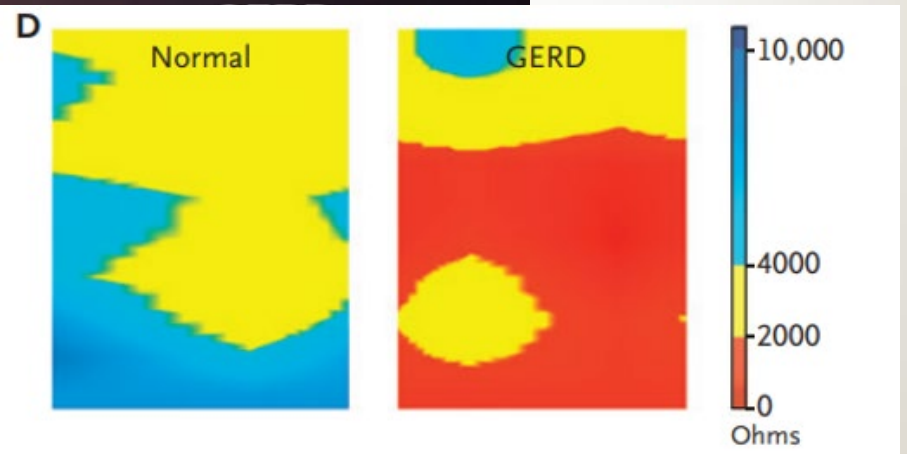
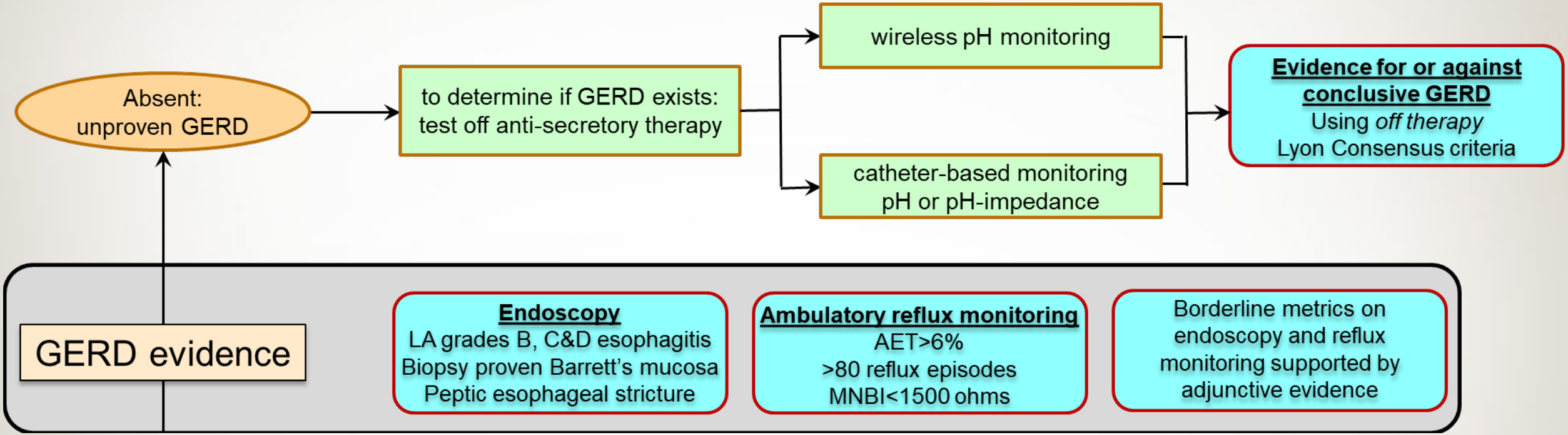
Mucosal Integrity testing





https://diversatekhealthcare.com/mucosal-integrity-mivu-2/

Modern Definition of Actionable GERD



Exclude mimickers of GERD:

- Achalasia
- Rumination
- Esophageal mucosal/immunologic conditions: EoE, lichen planus
- Disorder of brain gut interaction

Gyawali CP, et al. Modern Diagnosis of GERD: Lyon Consensus 2.0. *Gut*. 2023

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Esophageal Work-up

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   - Mucosal Integrity

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   - Manometry
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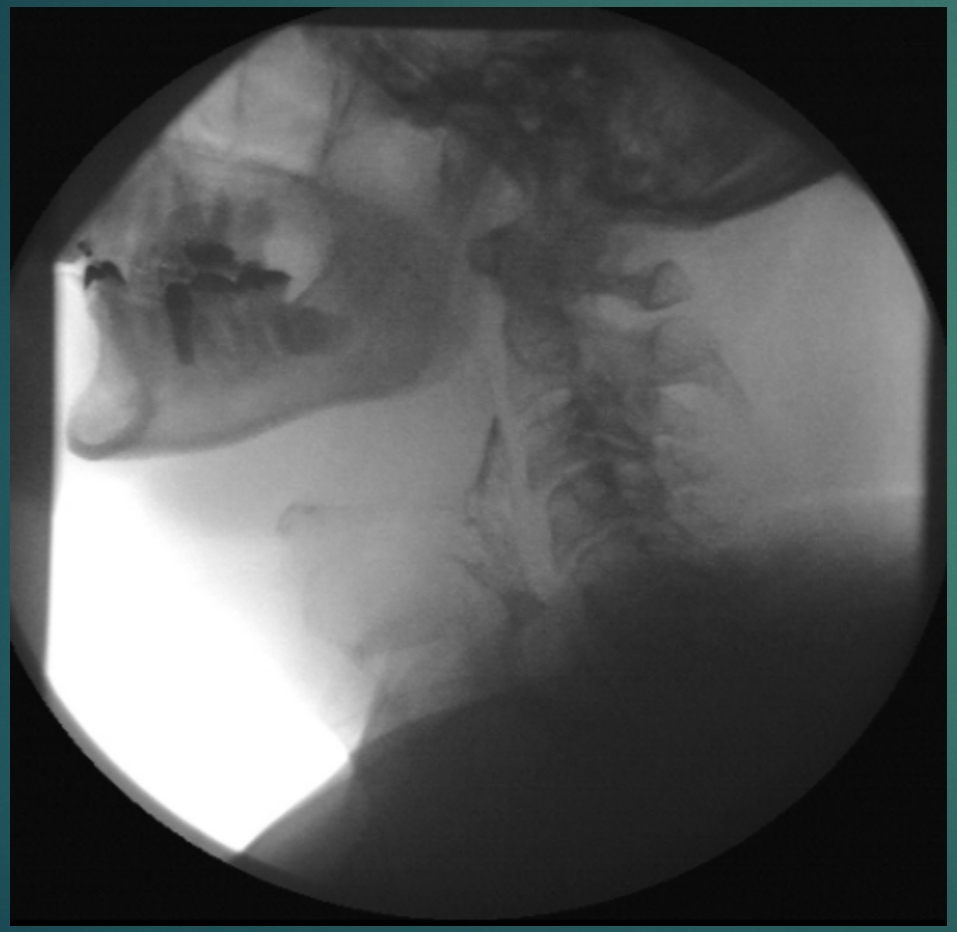
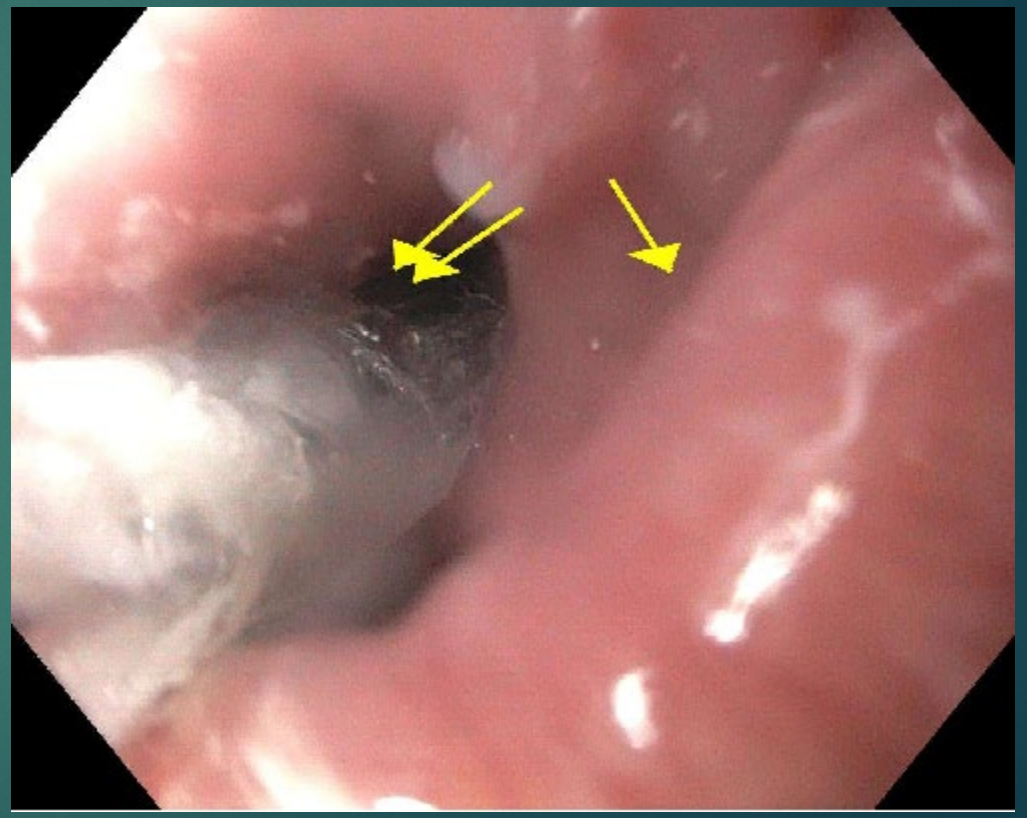
Patient 2:

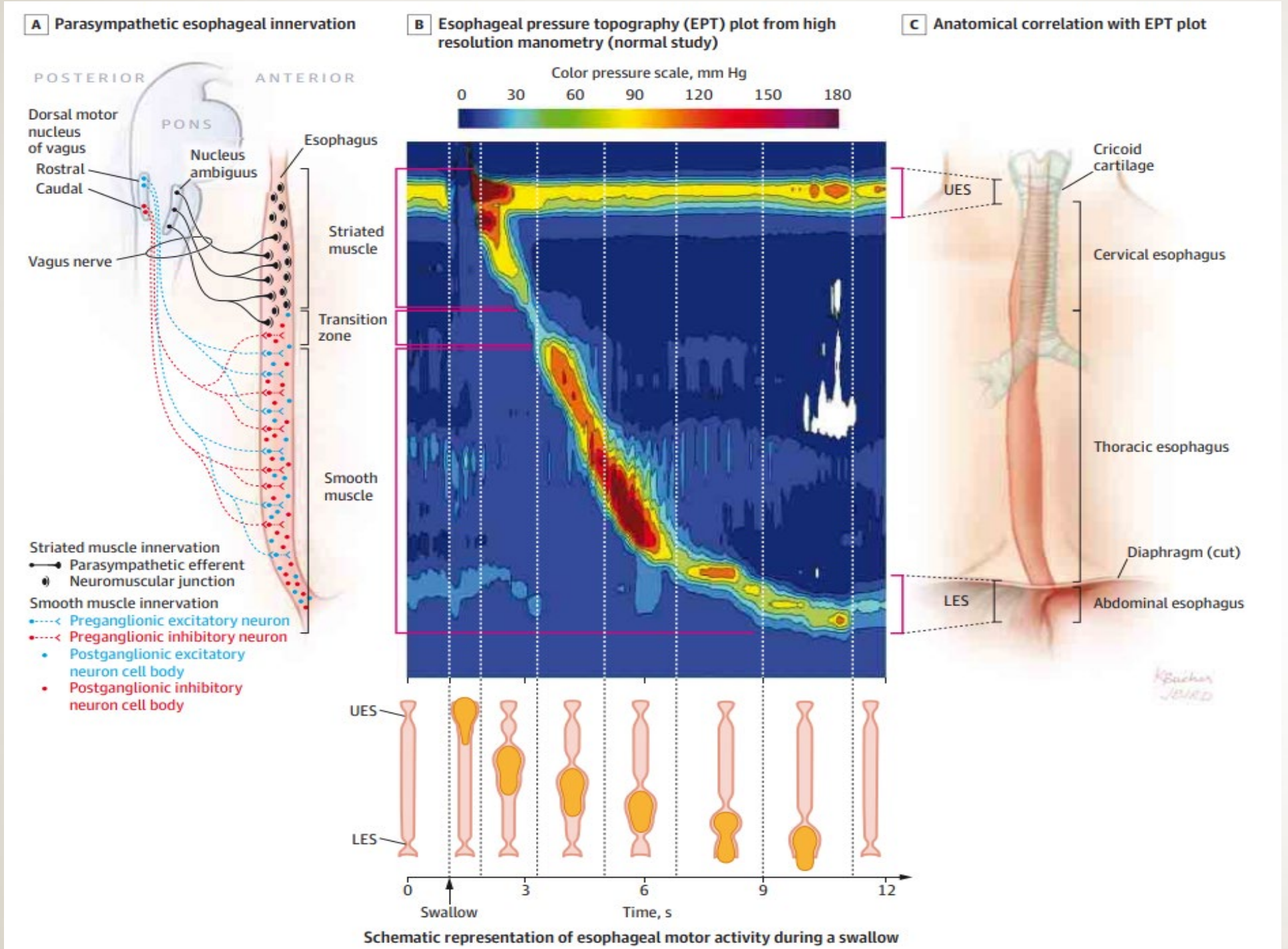
- 69-year-old with subcutaneous lupus (OSH) with proximal muscle weakness, rash, and dysphagia (+Mi2) on Rituximab with dysphagia.

- What are your next steps?

Patient 2: VFSS and EGD: Zenker's







Schematic representation of esophageal motor activity during a swallow

Pandolfino, JAMA 2015

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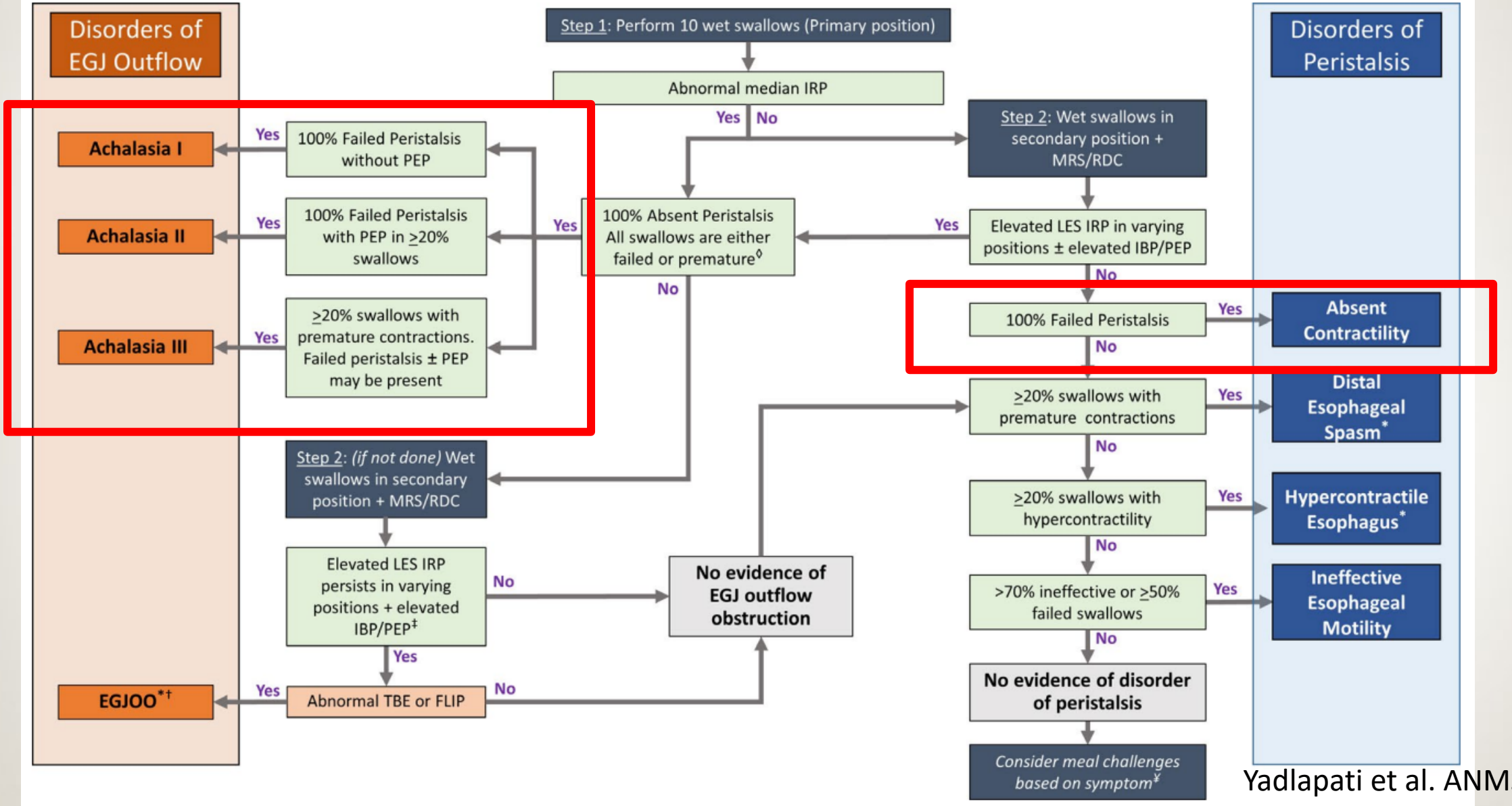
2021 Chicago Classification 4.0



Yadlapati et al. ANMS 2021

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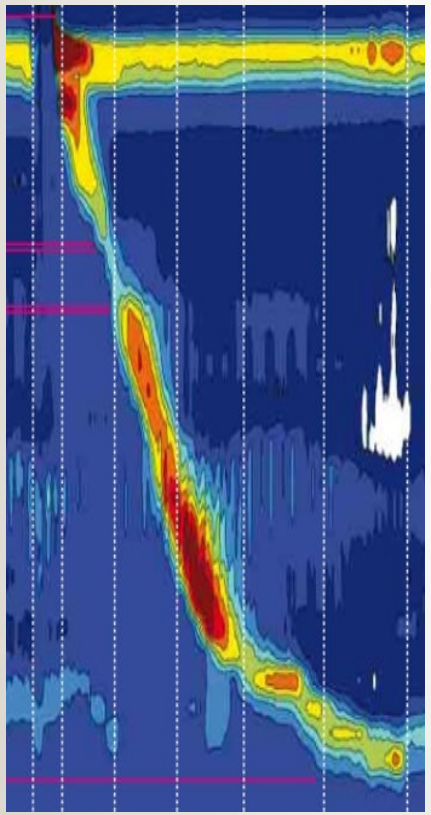
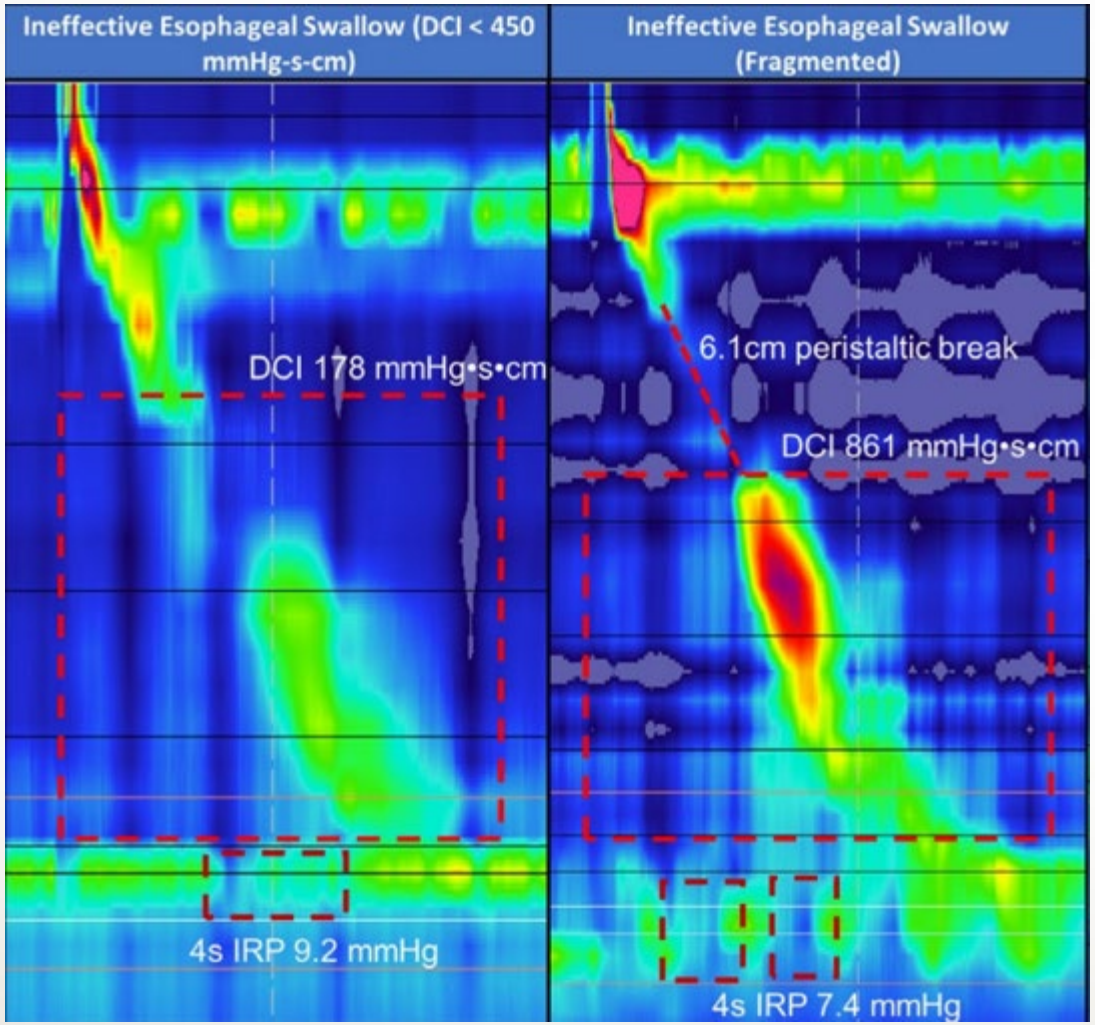
Manometric patterns in scleroderma

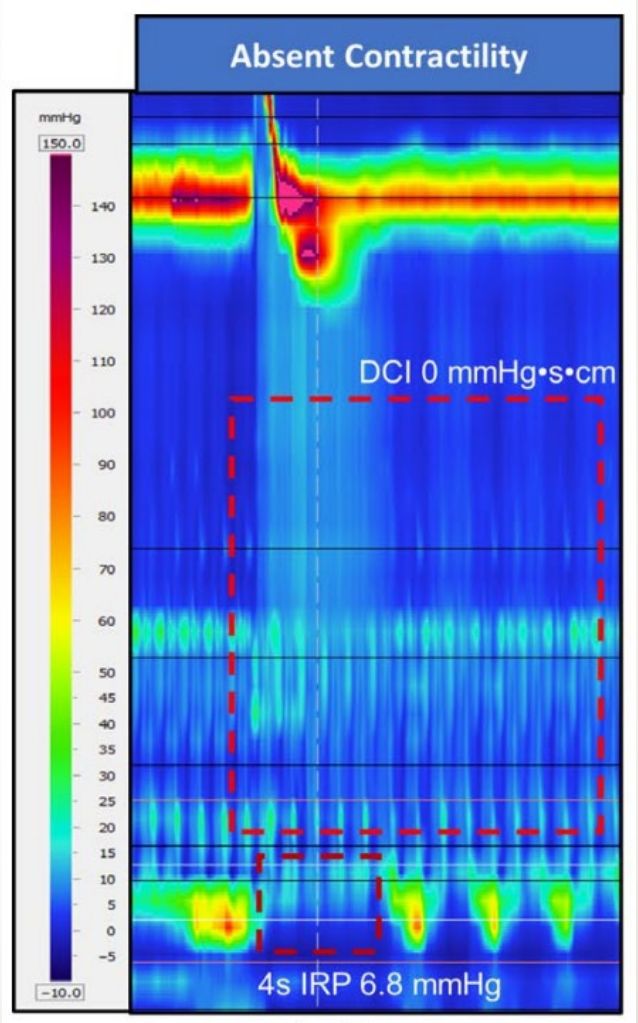
Normal



1) Ineffective Motility



2) Absent contractility



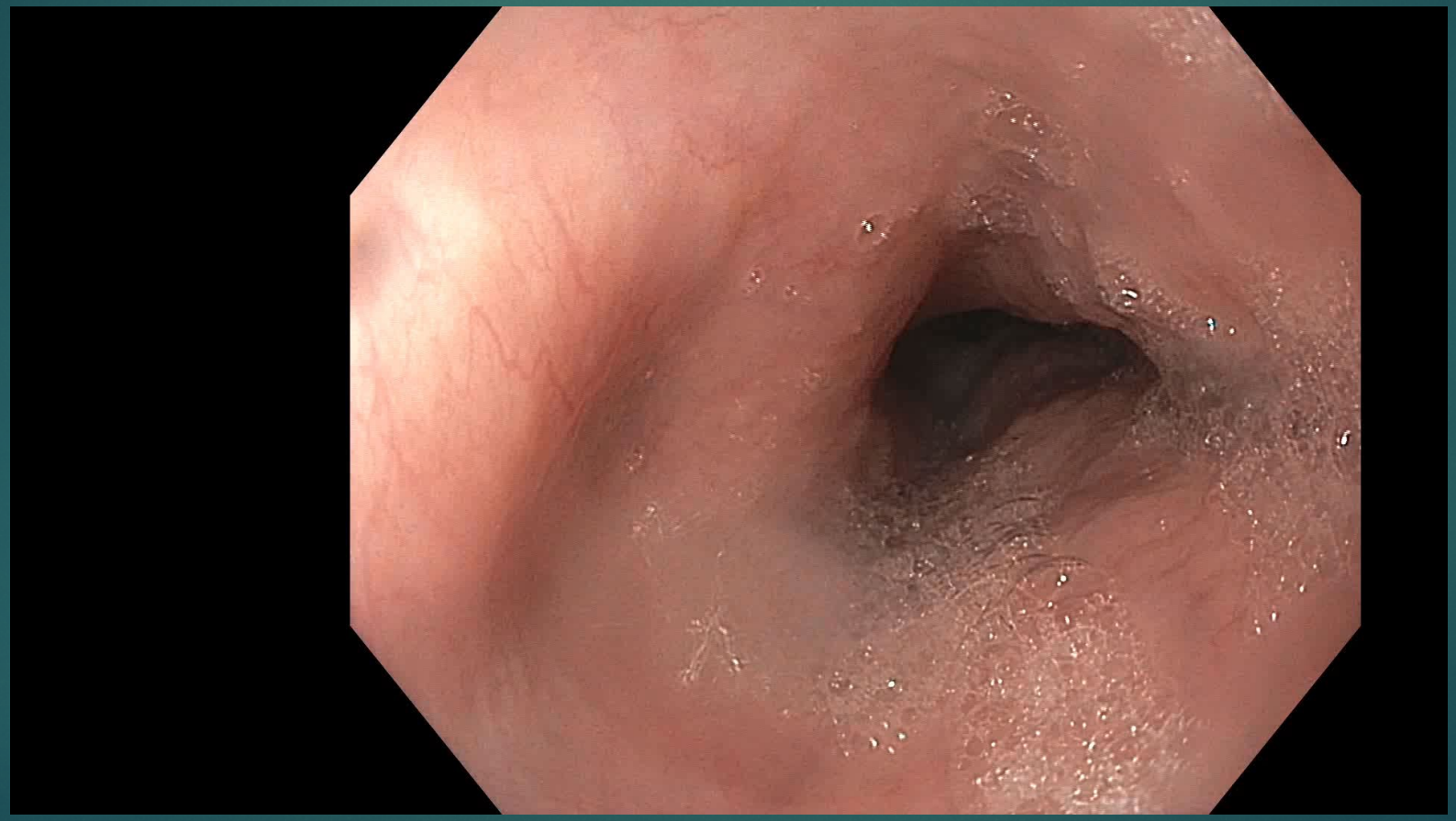
Yadlapati et al. ANMS 2021

Patient:

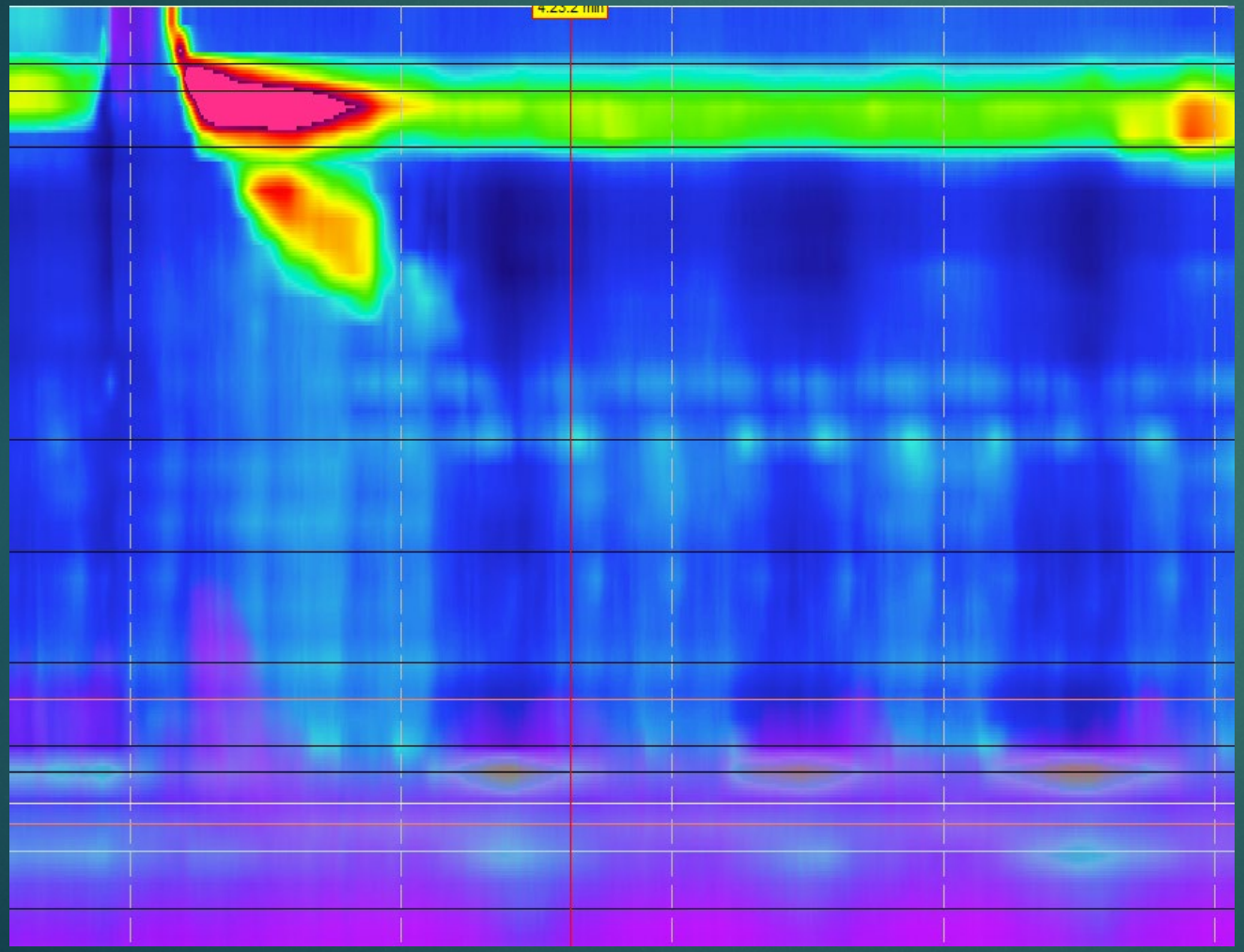
47-year-old presents with scleroderma presents in cardiogenic shock. CT shows significant ILD. Discussion for dual-listing heart/lung transplant.

How does endoscopy / esophageal testing impact transplant?

Endoscopic Video



Manometry: Absent contractility



- Many centers for lung transplantation, this is a contraindication for lung transplant
- Some centers – placement of distal feeding (J tube) and strict NPO
- Check your local transplant committee

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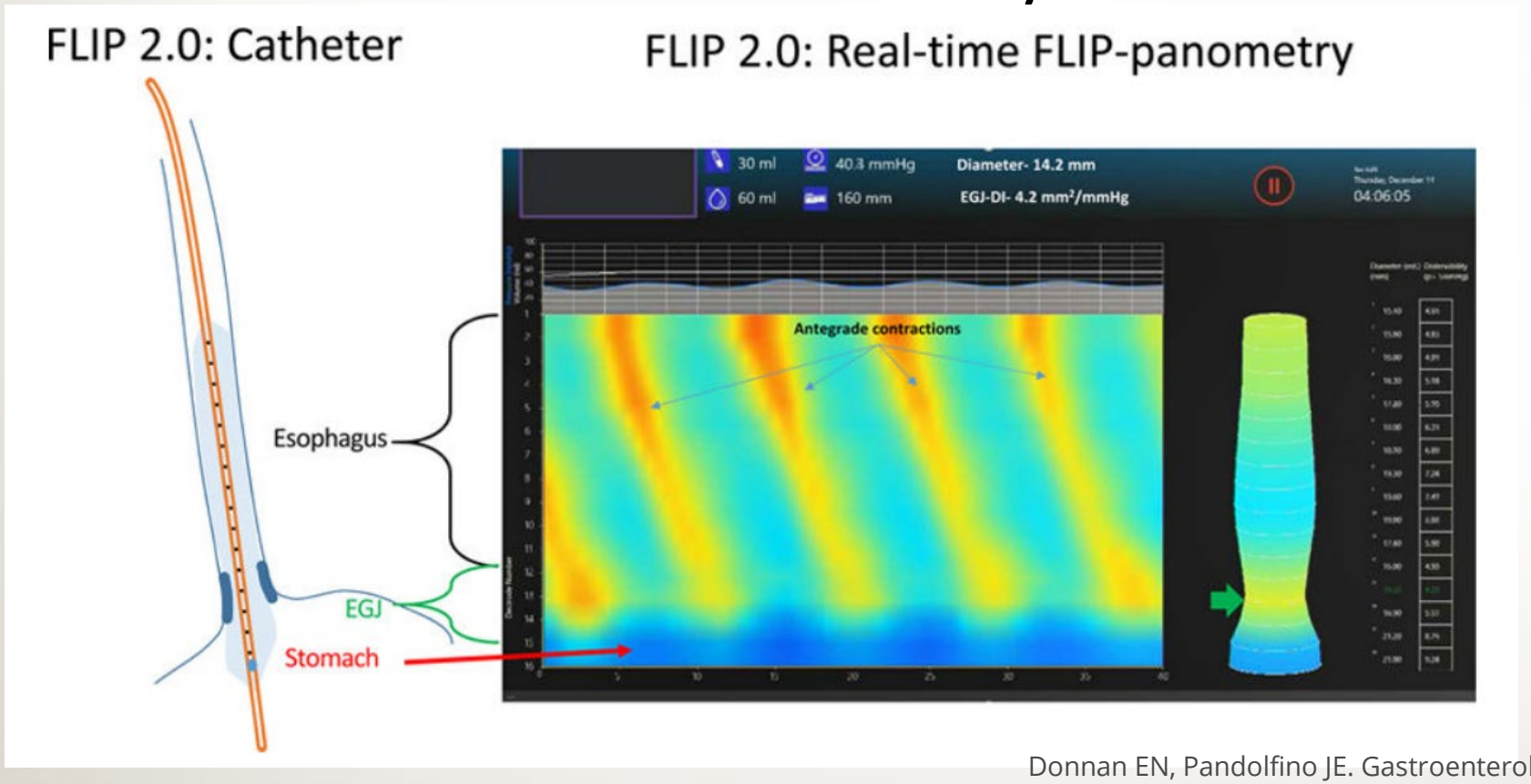
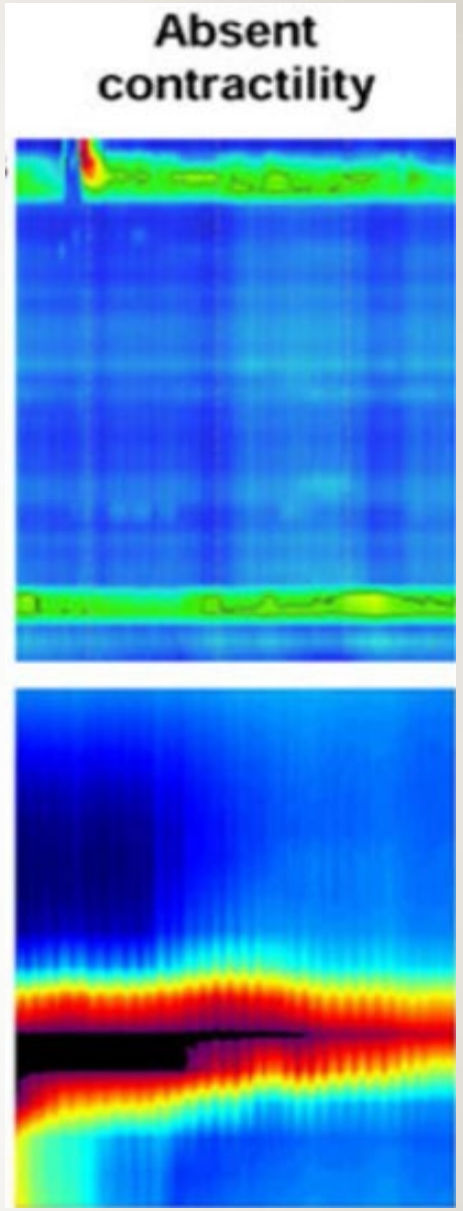
Functional luminal imaging probe (FLIP)

- 3-D image of the esophageal lumen
- Measures wall stiffness and dynamics of the





Donnan EN, Pandolfino JE. Gastroenterology Clinics of North America. 2020 Sep;49(3):427-435.

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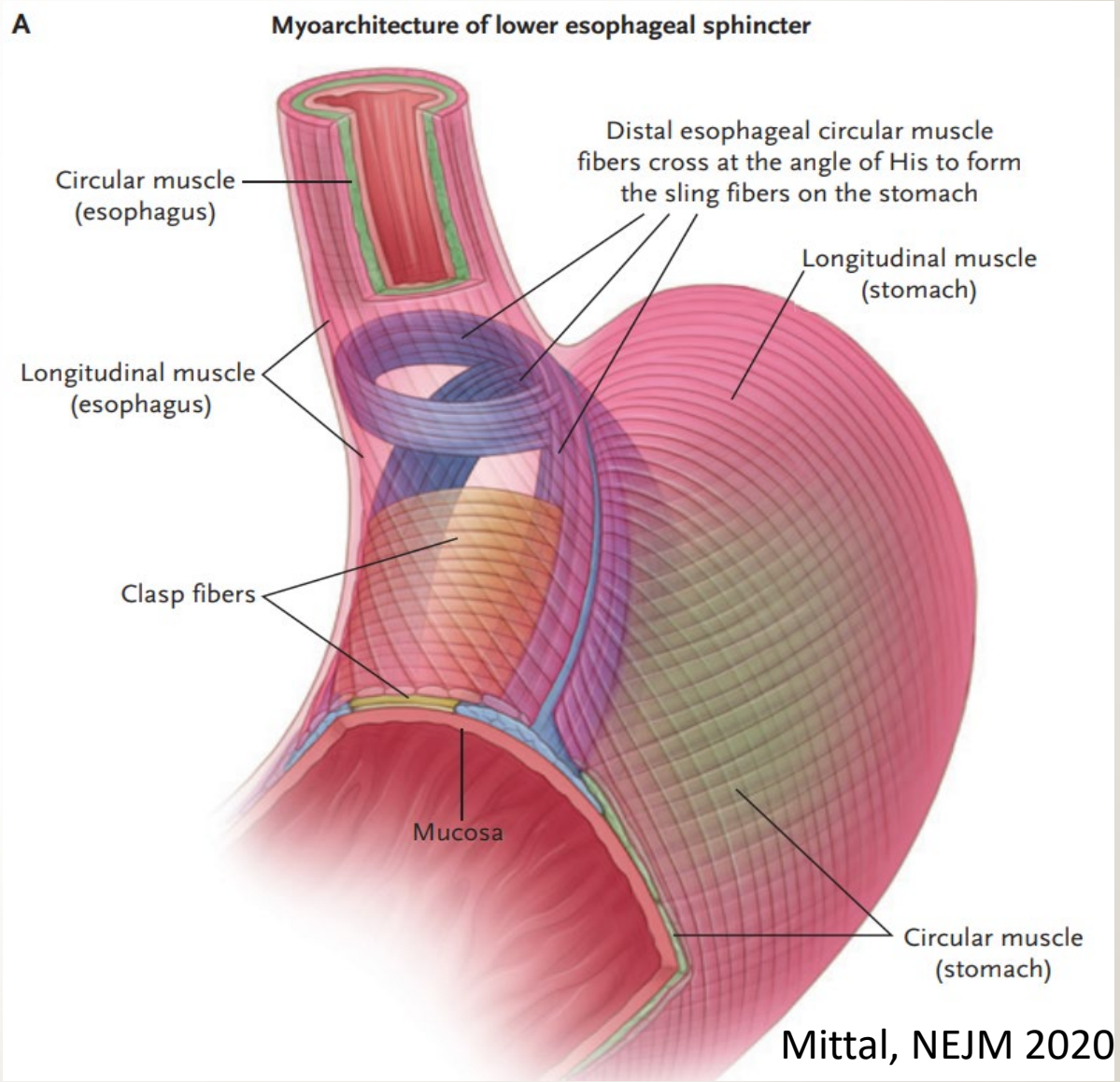
Scleroderma and the GI tract

- Esophagus
  - Esophageal reflux
  - Esophageal dysmotility
- Stomach
  - Gastroparesis
  - Gastric antral vascular ectasia (GAVE)
- Small Intestine
  - Small intestinal bacterial overgrowth
  - Small intestinal pseudo-obstruction
- Colon
  - Constipation
  - Colonic pseudo-obstruction
  - Anorectal dysfunction



Mittal, NEJM 2020

Pharmacological Treatment Options

Medication	Primary indication(s)	Main effects in the GI tract	Considerations
Metoclopramide	Esophageal dysmotility, refractory GERD gastroparesis [211]	Increased frequency of esophageal contraction, increased LES pressures, improved gastric emptying*	Serious neurological adverse effects may occur (e.g., tardive dyskinesia, dystonia, depression, and neuroleptic malignant syndrome)
Erythromycin	Esophageal dysmotility [212], gastroparesis [213]	Increases esophageal and gastric motility [214]	Tachyphylaxis; caution with long QT/cardiac arrhythmia; avoid in patients with myasthenia gravis and skeletal muscle disorders
Buspirone	Refractory GERD, esophageal dysmotility [20,215], early satiety [216]	Increased esophageal peristalsis and lower esophageal sphincter (LES) pressure; increased gastric accommodation [217]	Caution with serotonin syndrome; restlessness may appear early in treatment

McMahan, Nature Reviews, 2022

Pharmacological Treatment Options

Medication	Primary indication(s)	Main effects in the GI tract	Considerations
Mirtazapine	Gastroparesis [218,219], weight loss [220]	Increased gastric emptying; may reduce diarrhea	May cause weight gain, increased appetite, increased sleep, bad dreams; caution in patients with constipation; avoid in patients with hyperlipidemia, mania, seizures, glaucoma, QT prolongation, muscle disease
Baclofen	GERD [221], gastroparesis	Inhibition of transient lower esophageal sphincter relaxation, improved GER [221], stimulation of gastric motility [221,222]	May aggravate constipation; avoid in patients with psychosis, seizures, chronic kidney disease, functional bladder disorders
Pyridostigmine	Esophageal dysmotility [223,224], gastroparesis [225], chronic intestinal-pseudo-obstruction	Increase GI transit, especially in the colon [136,228]	Contraindicated in mechanical intestinal or urinary obstruction, and particular caution should be used in its administration to

McMahan, Nature Reviews, 2022

Pharmacological Treatment Options

Medication	Primary indication(s)	Main effects in the GI tract	Considerations
Domperidone	Esophageal dysmotility, GERD [211], gastroparesis [229], chronic constipation [230]	Increased overall GI transit; Improves nausea and vomiting	May cause cardiac arrhythmia, increase QT interval; avoid in patients with electrolyte disturbances, cardiac, hepatic or renal problems, GI bleeding and pregnancy
Prucalopride	Chronic constipation [231], ileus [232], intestinal pseudo-obstruction[233], gastroparesis [234]	Increased gastric, small bowel and colonic transit	Avoid in patients with significant depression, intestinal perforation or obstruction; severe inflammatory conditions of the intestinal tract (e.g. IBD, megacolon/megarectum)
Octreotide	Intestinal pseudo-obstruction [142]	Stimulates intestinal motility	Requires subcutaneous injections qd-tid; may exacerbate diarrhea, constipation, and gas

McMahan, Nature Reviews, 2022

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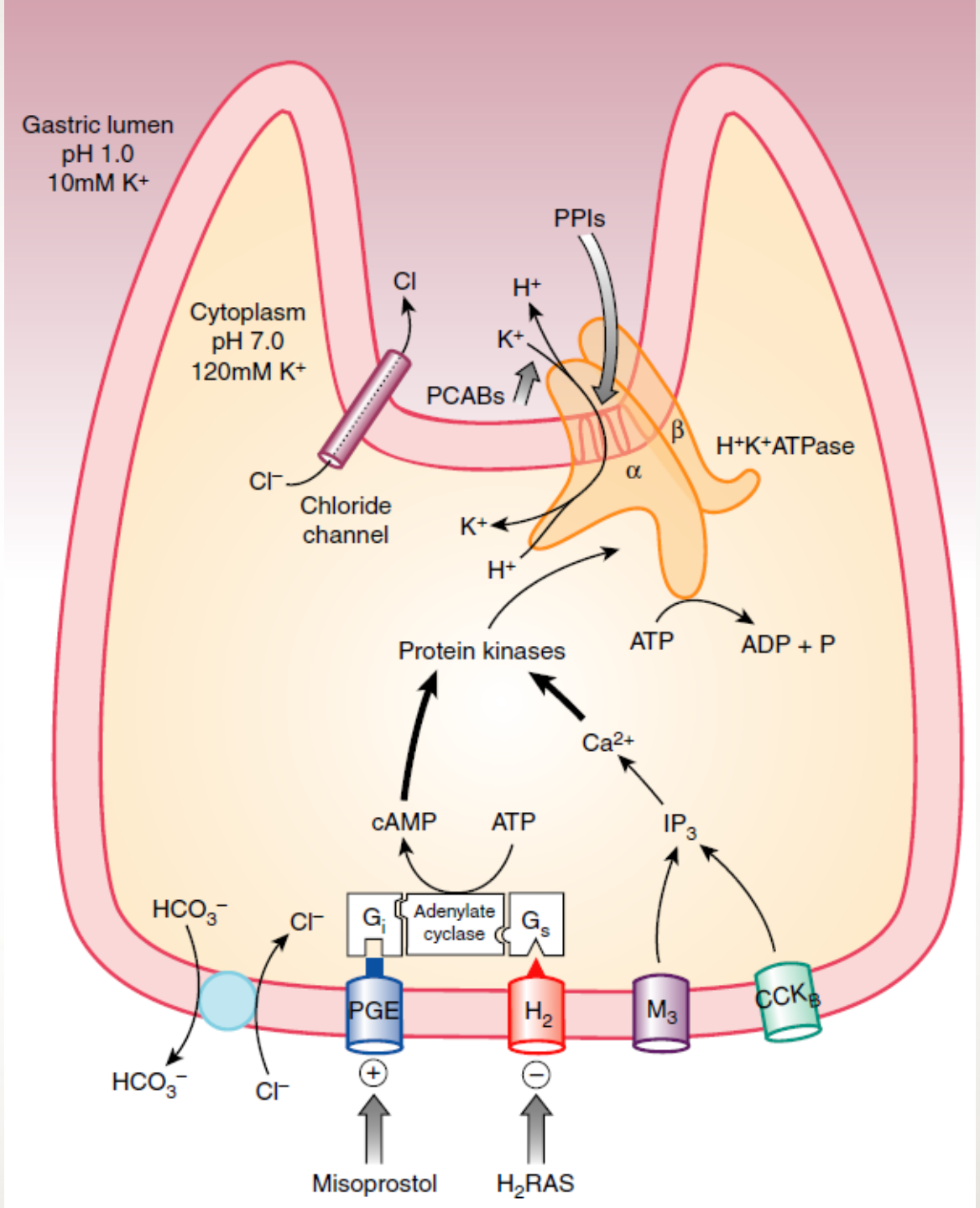
Acid-suppression



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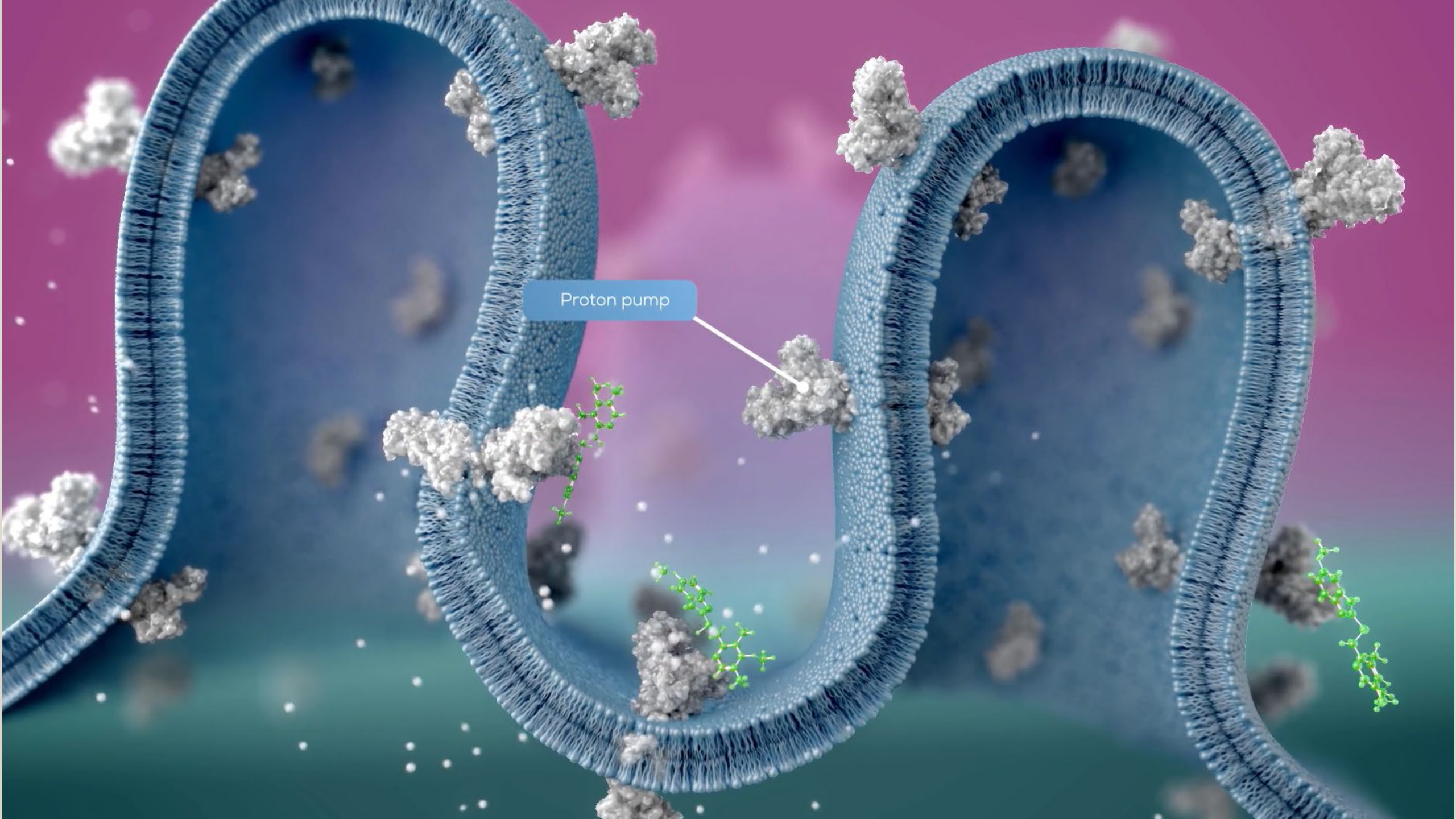
PPI Pharmacokinetics

- 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


Proton pump

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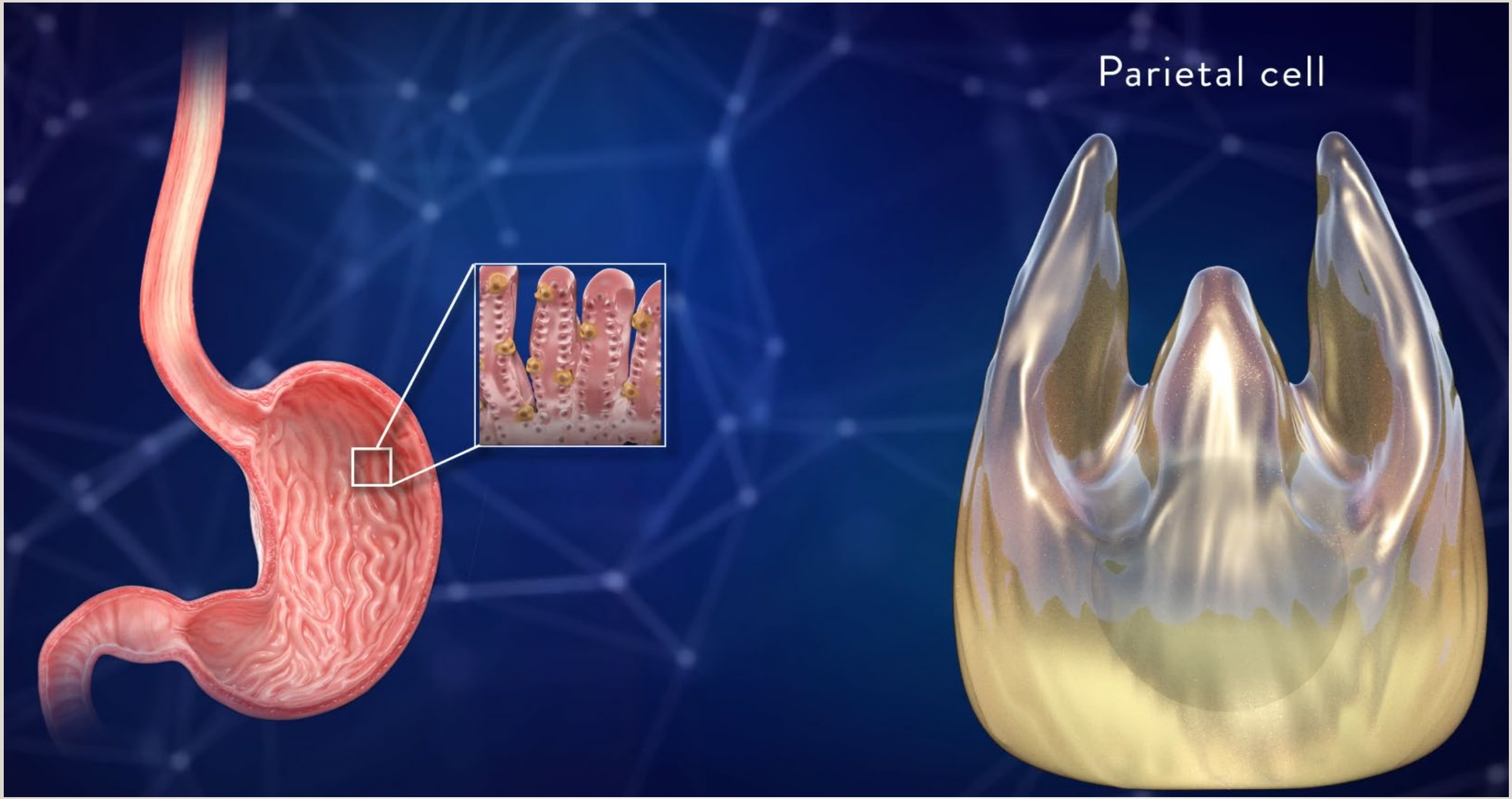

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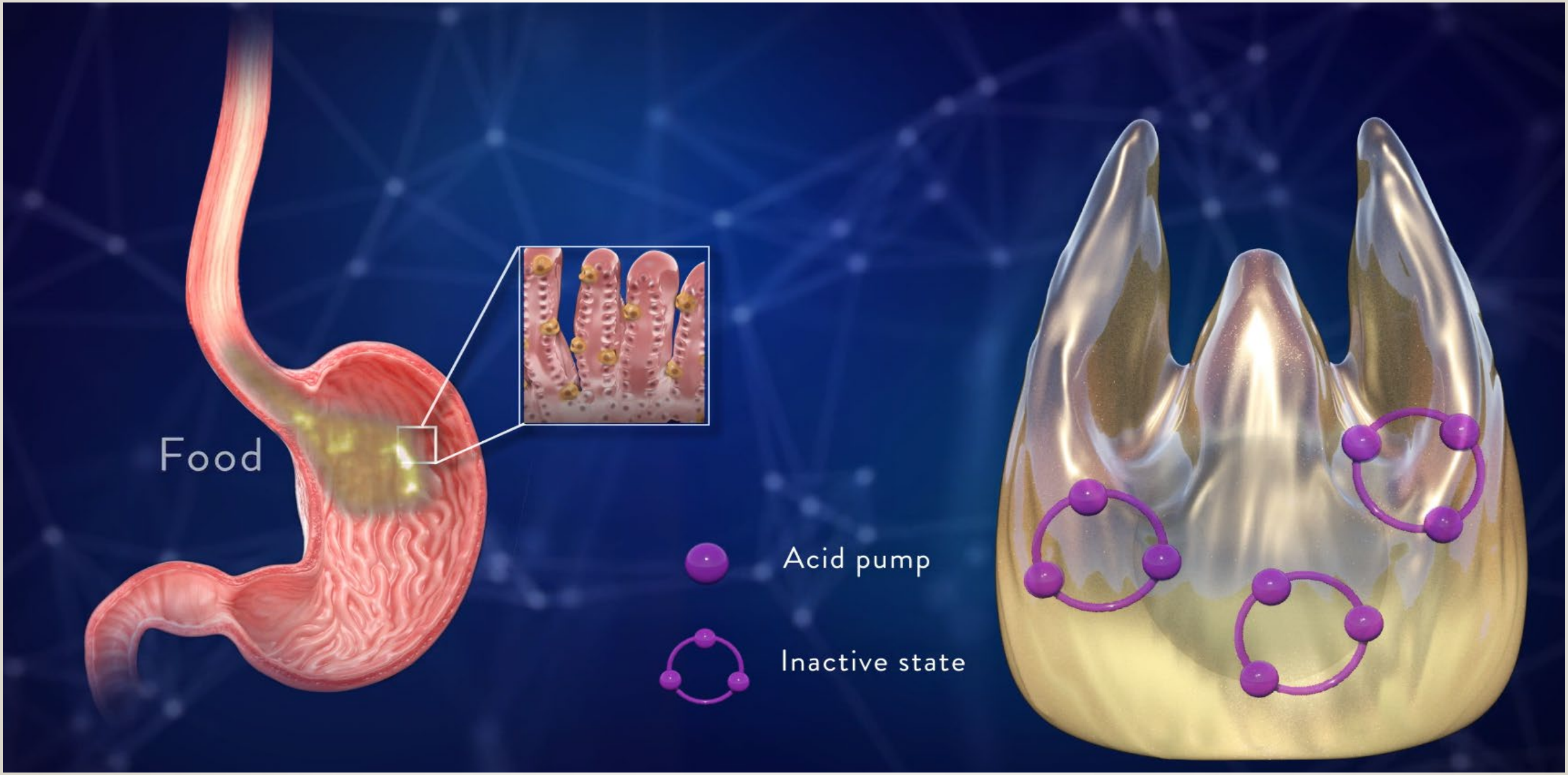
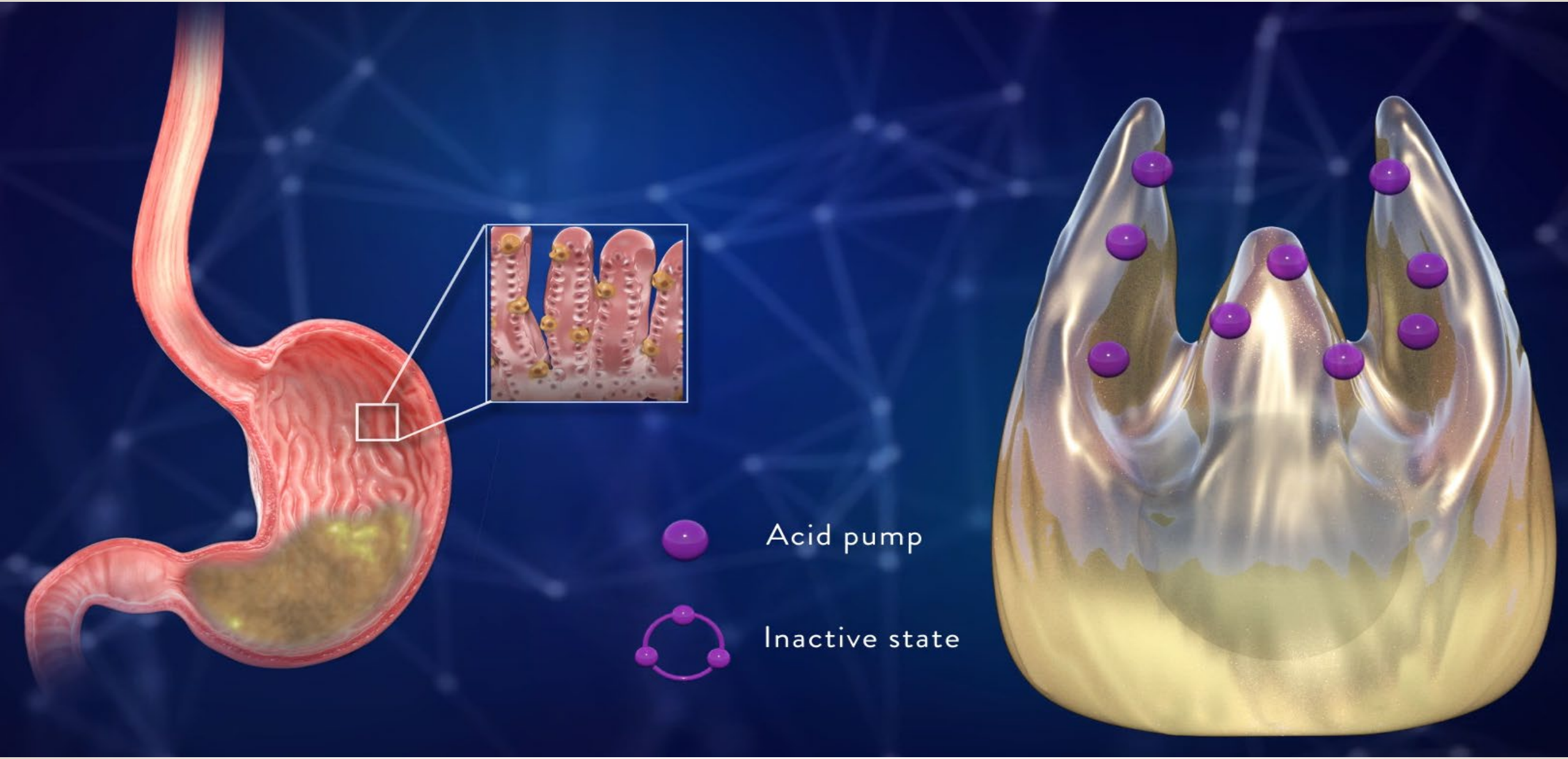


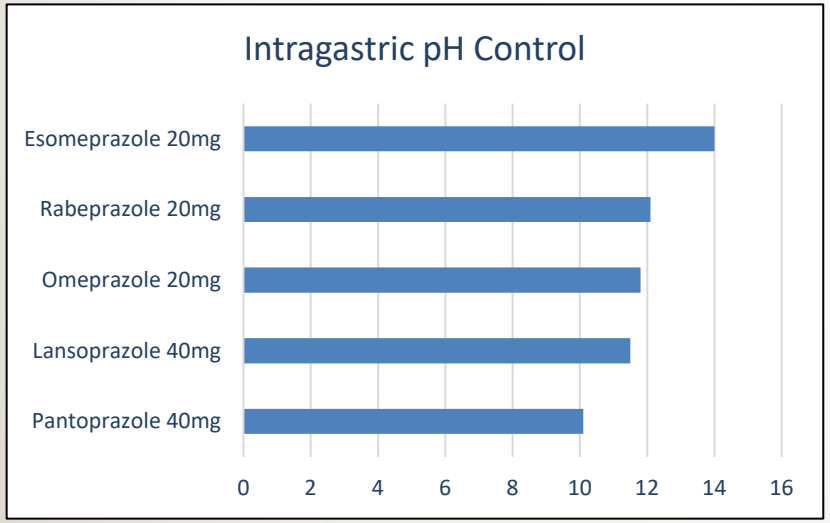

Acid pump
Inactive state

Position Yourself for Success with PPIs

- PPIs are acid labile molecules
- PPIs are not constructed the same
  - Varying levels of intra-gastric pH control
  - Varying levels of metabolism through CYP2C19

Before meal dosing (before breakfast/dinner)

If switching PPI consider one with:
- Greater intra-gastric pH suppression
- Less metabolism via CYP2C19
- Less potential for drug-drug interaction



Proton pump inhibitor (PPI)	Cytochrome P450 metabolism	Interaction potential*
Omeprazole	Major: CYP2C19 Minor: CYP3A4	High
Esomeprazole	Major: CYP2C19 Minor: CYP3A4	Moderate
Pantoprazole	Major: CYP2C19 Minor: CYP3A4	Low
Lansoprazole	CYP2C19 CYP3A4	Moderate
Rabeprazole	Major: Non-enzymatic Minor: CYP2C19 Minor: CYP3A4	Low

Scott SA, et al. Expert Opinion on Drug Metabolism & Toxicology. 2013

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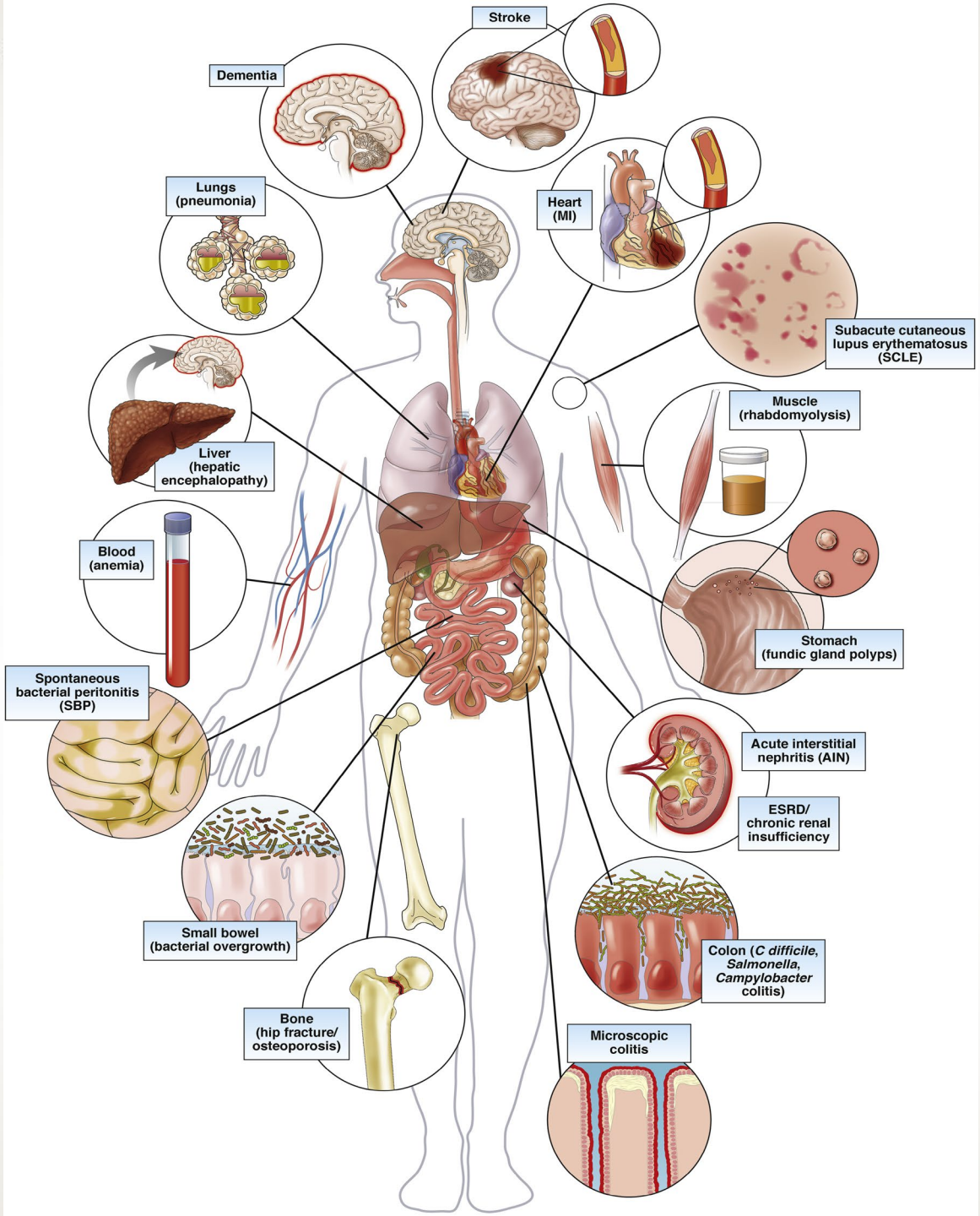


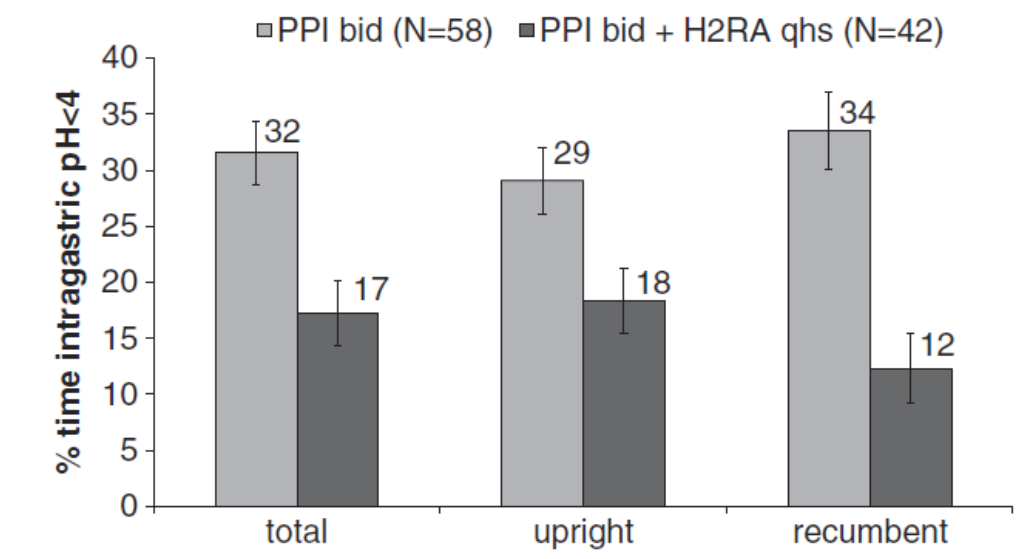
Vaezi, Gastro, 2017

PPI's can increase enteric infections (OR 1.33)

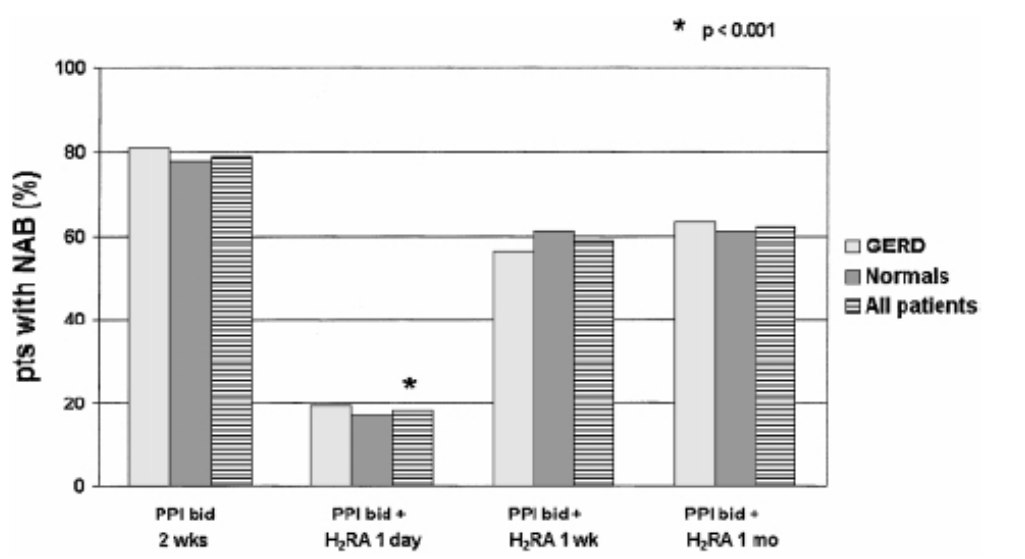
Outcome	Incident events, n (%)		Pantoprazole, 40 mg od, vs placebo	
	Pantoprazole, 40 mg od (n = 8791)	Placebo (n = 8807)	OR (95% CI)	*P* value
Gastric atrophy	19 (0.2)	26 (0.3)	0.73 (0.40–1.32)	.30
Clostridium difficile	9 (0.1)	4 (<0.1)	2.26 (0.70–7.34)	.18
Other enteric infection	119 (1.4)	90 (1.0)	1.33 (1.01–1.75)	.04
Chronic kidney disease	184 (2.1)	158 (1.8)	1.17 (0.94–1.45)	.15
Dementia	55 (0.6)	46 (0.5)	1.20 (0.81–1.78)	.36
Pneumonia	318 (3.6)	313 (3.6)	1.02 (0.87–1.19)	.82
Fracture	203 (2.3)	211 (2.4)	0.96 (0.79–1.17)	.71
COPD	146 (1.7)	124 (1.4)	1.18 (0.93–1.51)	.17

Moayyedi 2019

Adjunctive H2RA

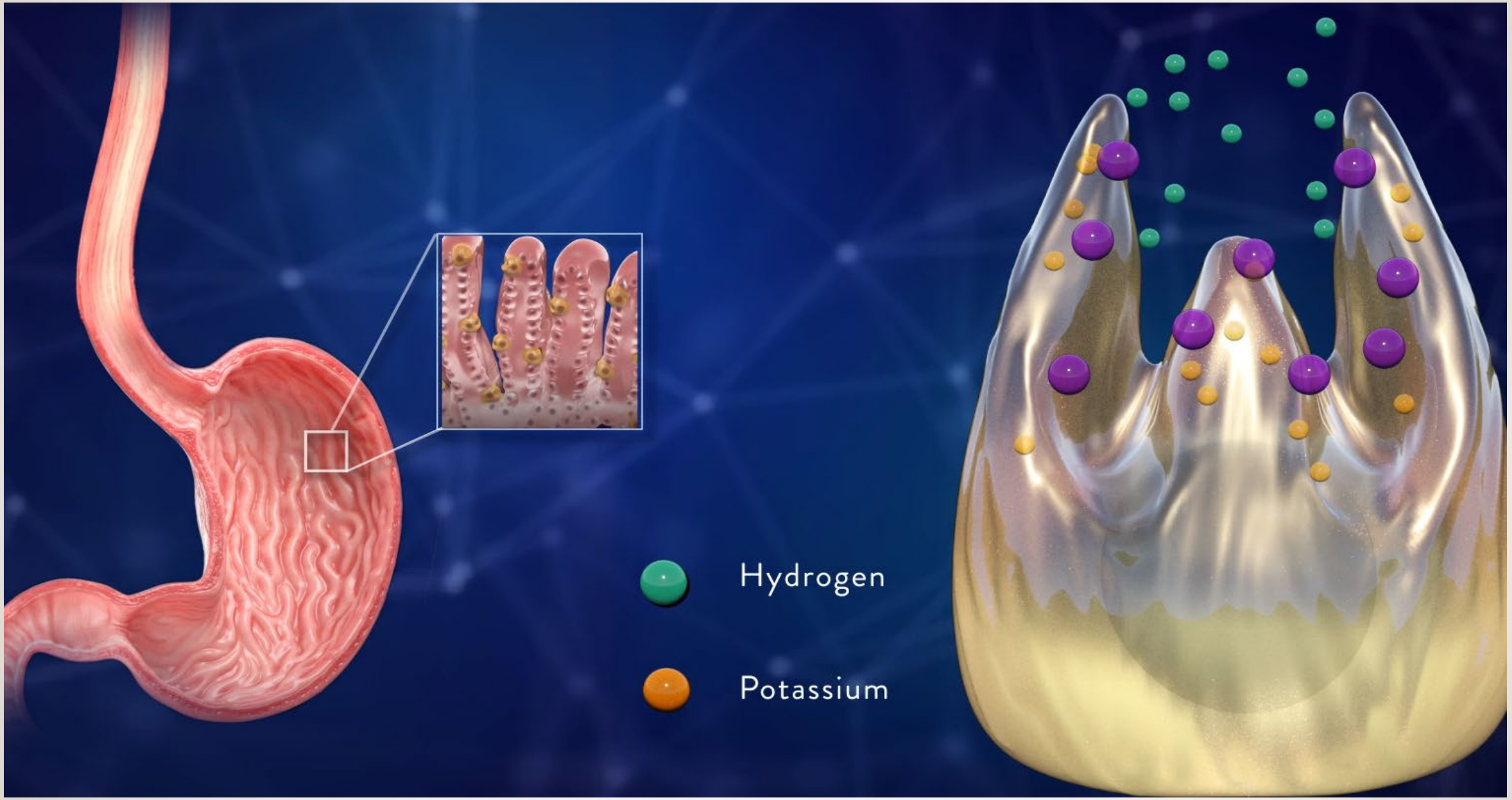


Nocturnal H2RA can augment BID PPI in controlling nocturnal acid breakthrough & nighttime symptoms



Up to 50% of patients may experience tachyphylaxis

Mainie I, et al. J Clin Gastroenterol 2008
Xue S, Katz P, et al. APT 2001
Fackler W, et al. Gastroenterology 2002


Hydrogen
Potassium

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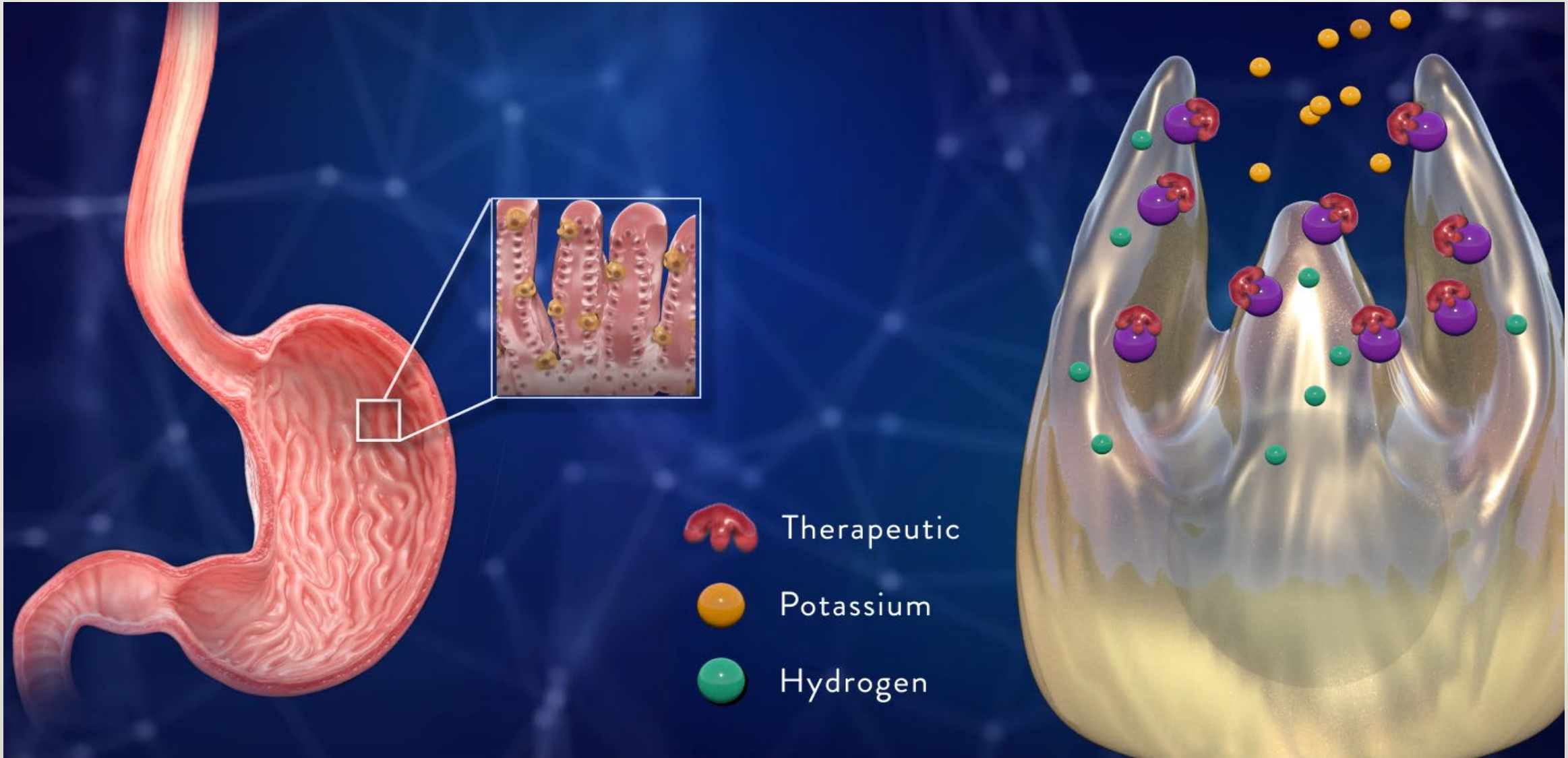
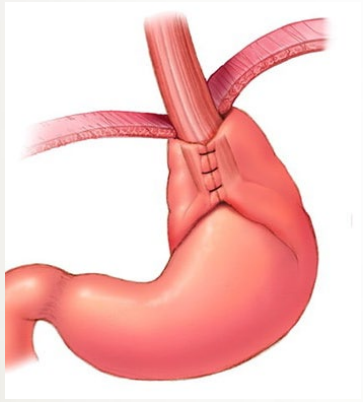
Potassium Competitive Acid Blockers (PCAB) (vonoprazan)

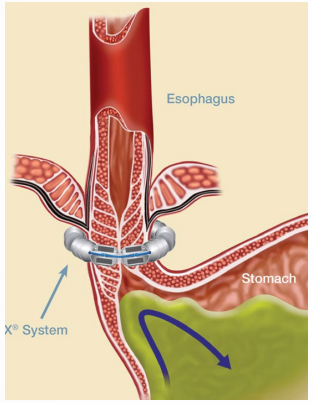


Mechanical Restoration of Anti-Reflux Barrier

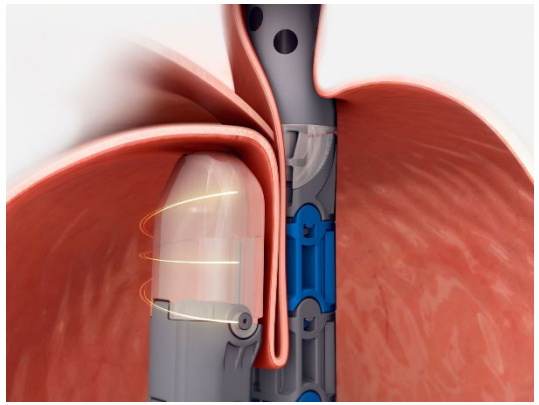
Laparoscopic fundoplication



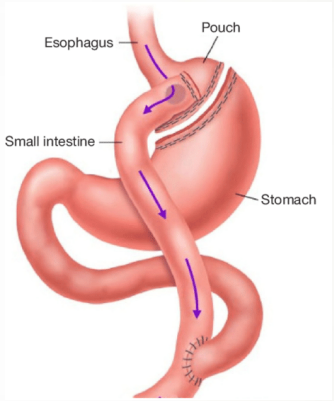
Magnetic Sphincter Augmentation



Transoral Incisionless Fundoplication



Roux-en-Y-gastric bypass



Appropriate patient selection, pre-operative evaluation, & expertise is essential

Schuitenmaker JM, et al. *CGH 2022*

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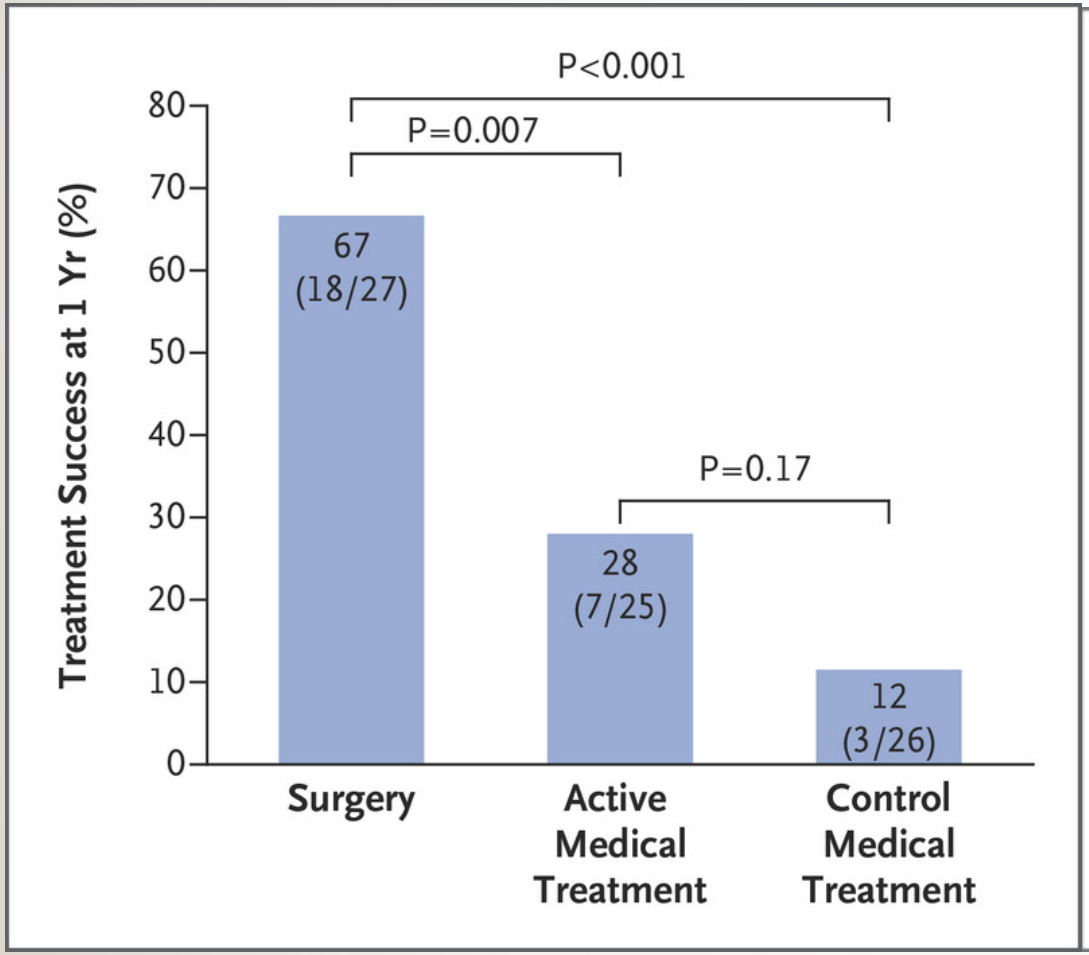
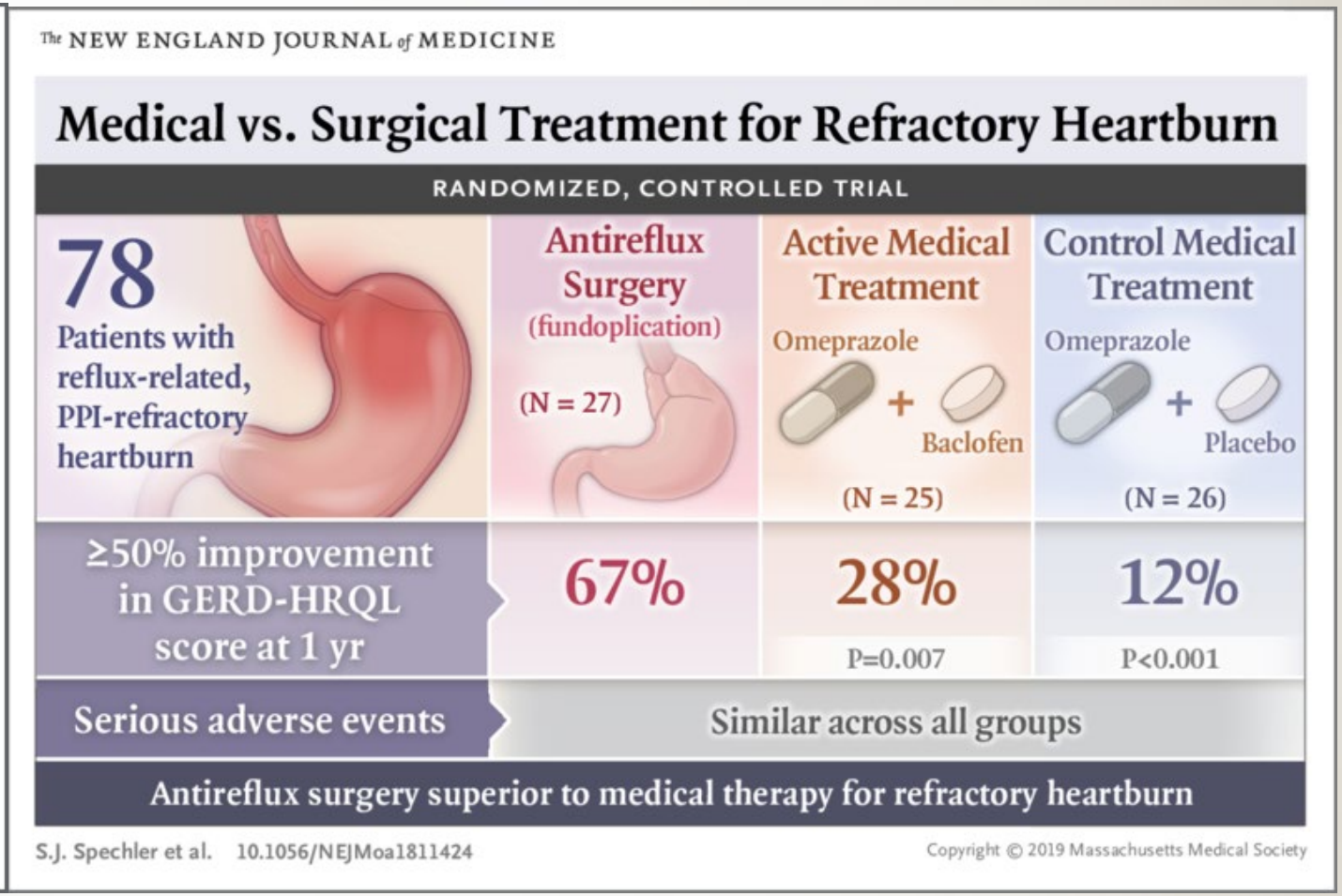
Laparoscopic Fundoplication

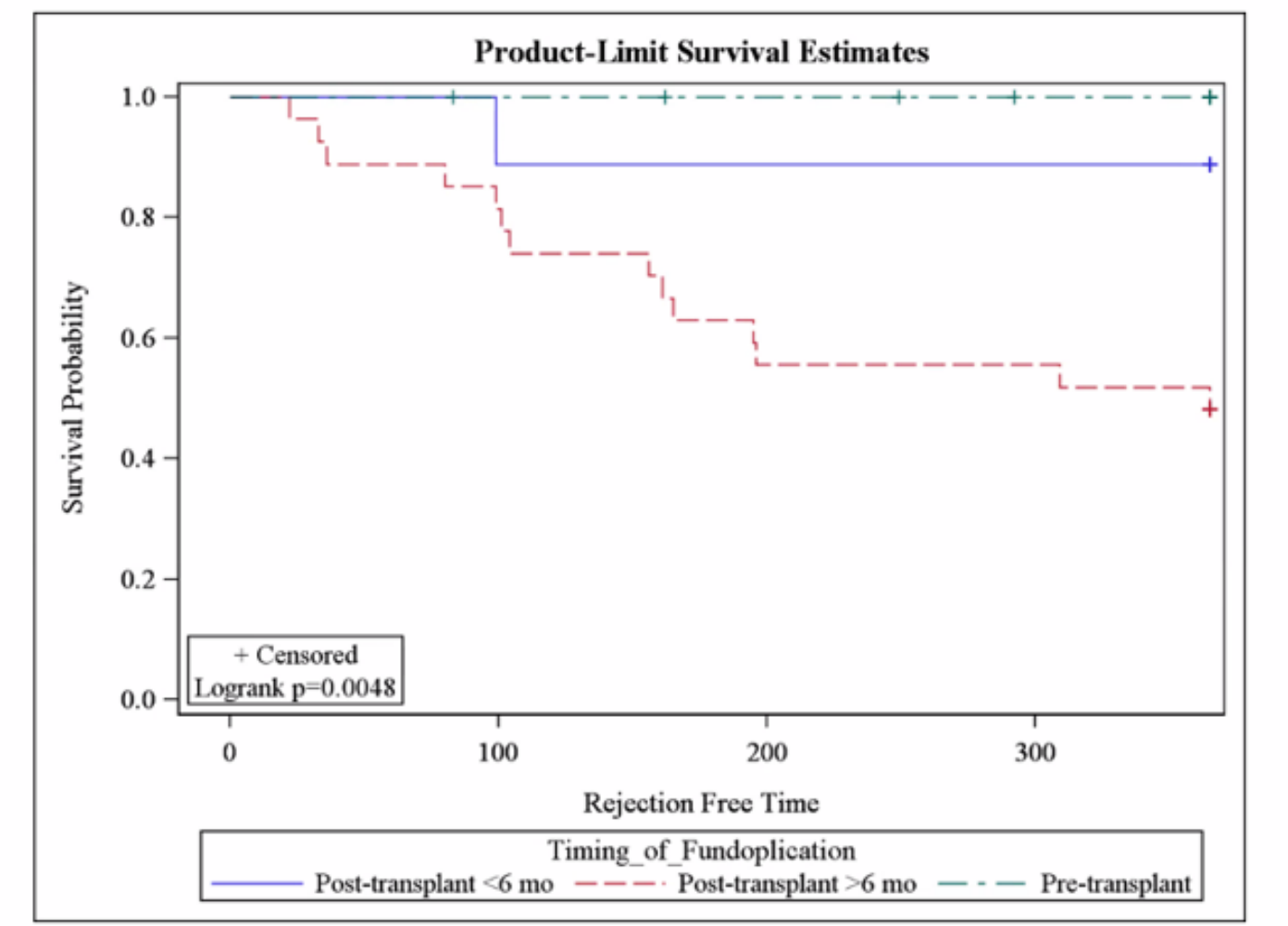




Side effects: dysphagia, gas-bloat syndrome, diarrhea

Spechler SJ et al. NEJM 2019;381:1513

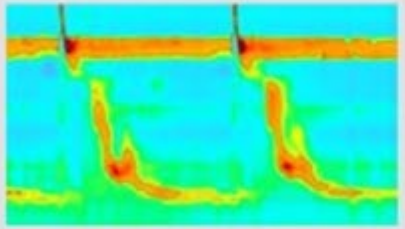
Early fundoplication (<6 months) associated with greatest reduction in early allograft injury



Lo 2016

Routine Reflux Testing Guides Timely Anti-Reflux Treatment to Reduce Lung Transplant Rejection

175 Lung Transplant Patients

Pre-Transplant	Post-Transplant	
 Reflux Monitoring	**Timely Reflux Treatment** 	Time to **Acute Rejection** 
 Esophageal Manometry	**Delayed Reflux Treatment** 	Time to **Chronic Lung Allograft Dysfunction** 
	No Reflux 	

Lo et al. *Clin Trans Gastroenterol.* 2022. [doi]

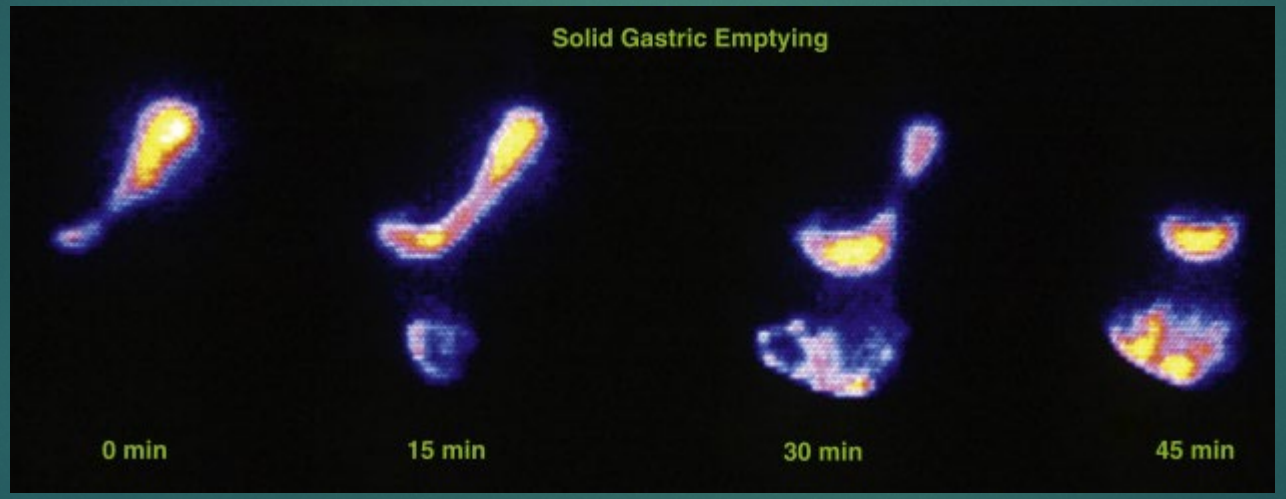
Clinical and Translational GASTROENTEROLOGY

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?

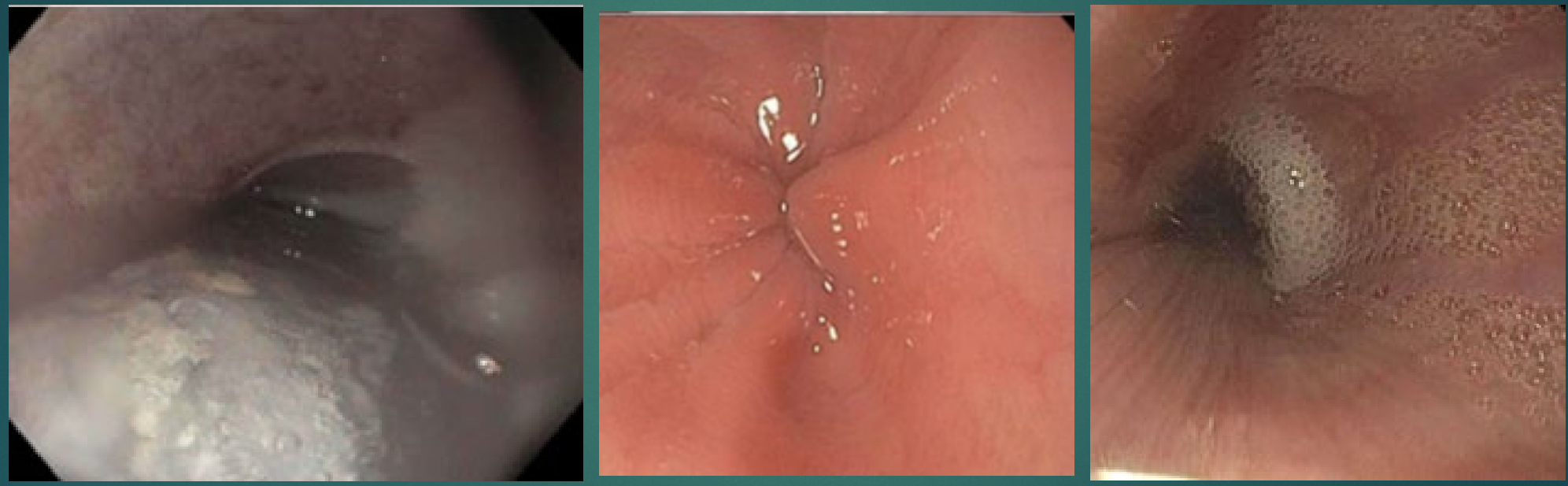
- EGD Normal – except retained food in the stomach
- Gastric emptying performed shows delayed motility – next steps?



Gastroparesis

- Presentation: nausea, vomiting, fullness, “refractory reflux”
- Best test: gastric emptying test (aware of opiates and GLP1-agonist)
- Treatment:
  - Dietary modification, Hydration and nutrition, Optimize glycemic control
  - Prokinetics
    - Metoclopramide – risk of tardive dyskinesia
    - 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)

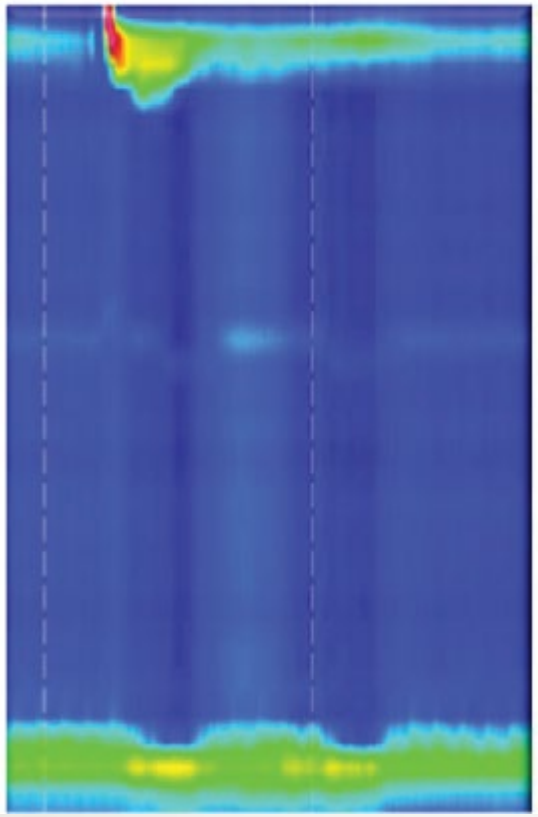
Patient with renal failure presents with nausea/vomiting and dysphagia

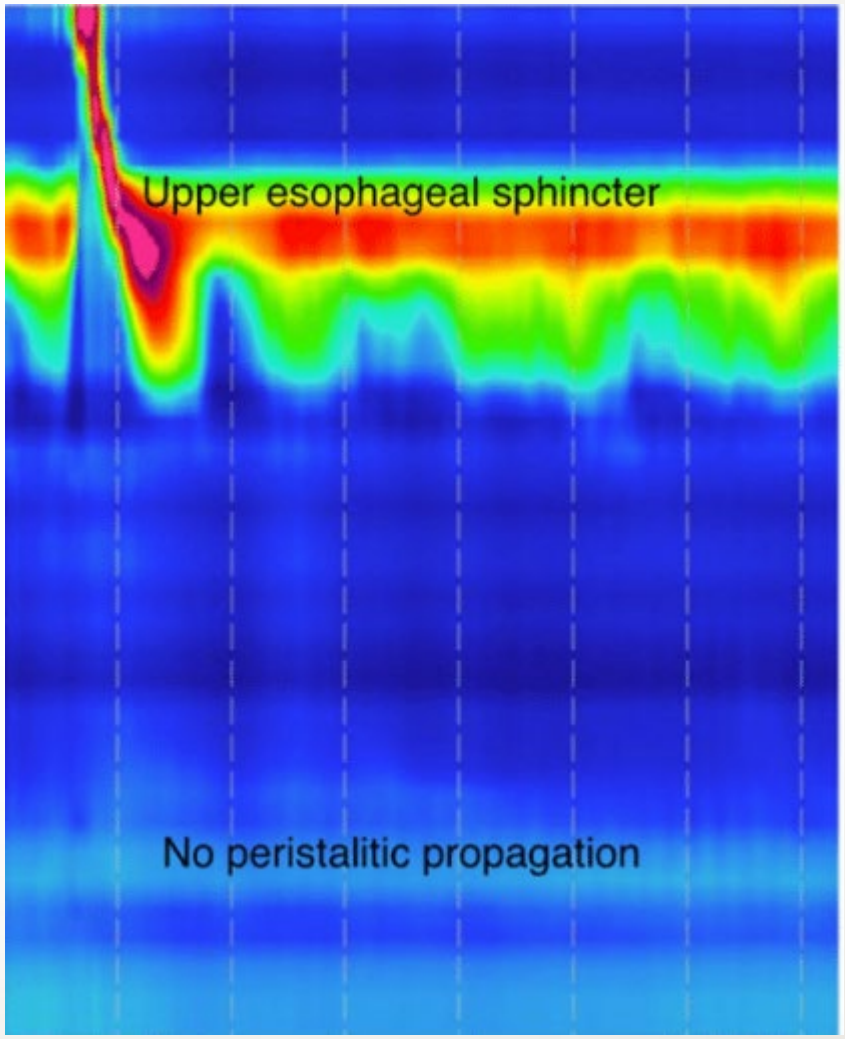


Krill, Naik, Vaezi, CEG 2016

Achalasia vs. Scleroderma-like esophagus

Type I
Classic achalasia with failed peristalsis





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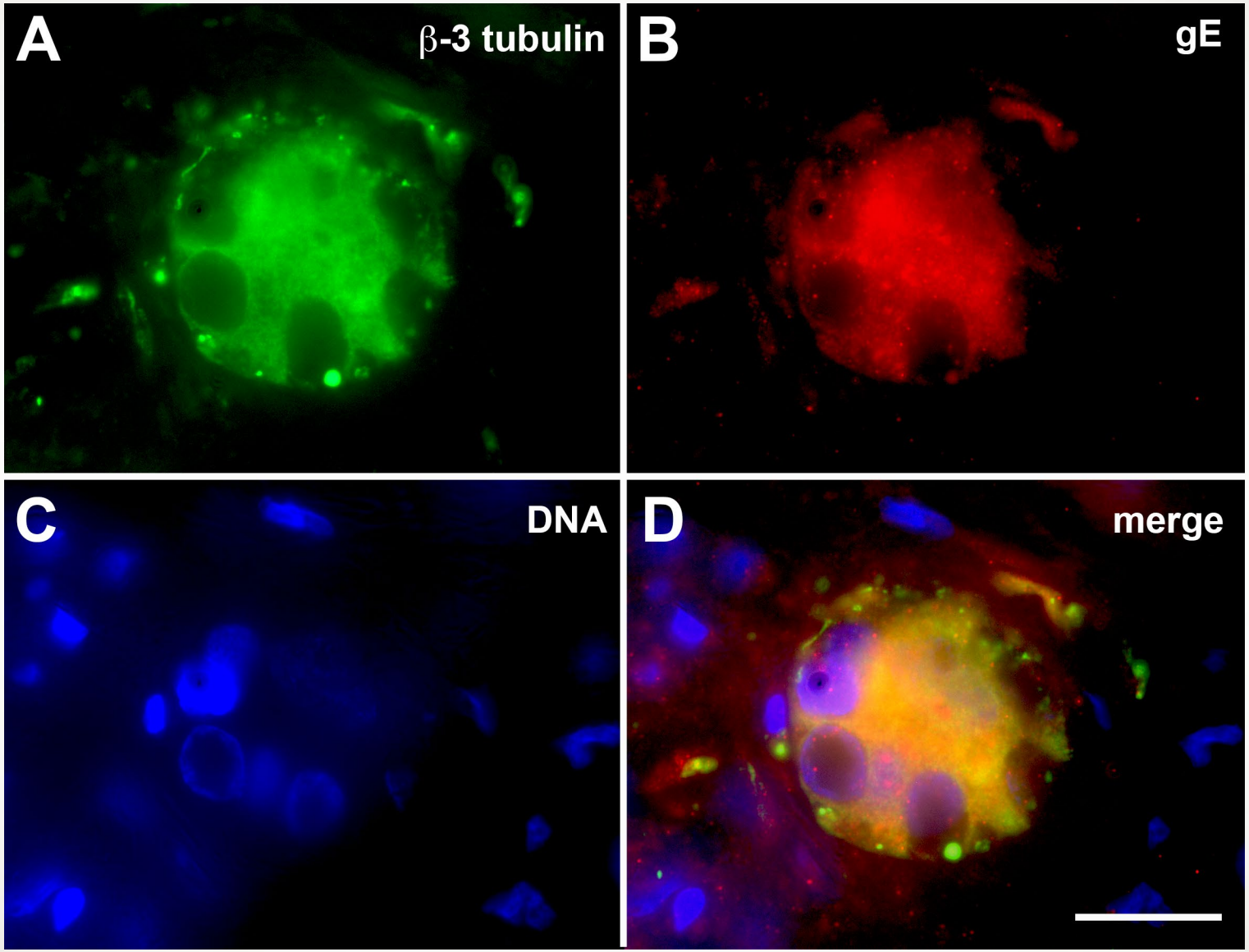
RESULTS



Naik, Patel, Vaezi Gastroenterology 2021

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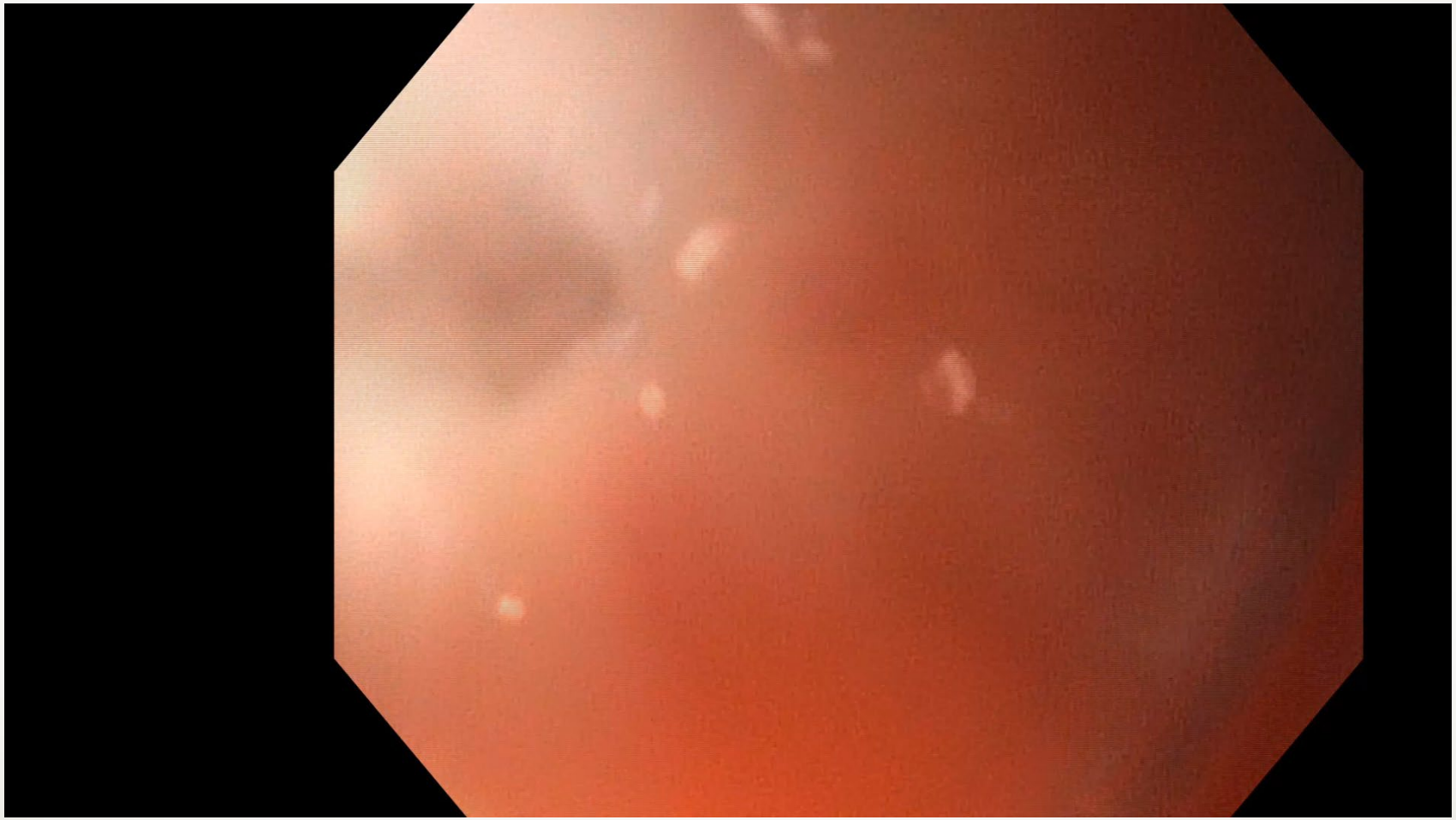
Achalasia and VZV

- **Active** VZV infection of the esophagus is present in achalasia

- VZV DNA was detected prospectively in their **saliva,** resected esophagus contained **VZV transcripts** and **VZV-immunoreactive proteins** in nerve cell bodies and neurites.

- VZV is an enteric pathogen that reactivates from latency in esophageal neurons in achalasia

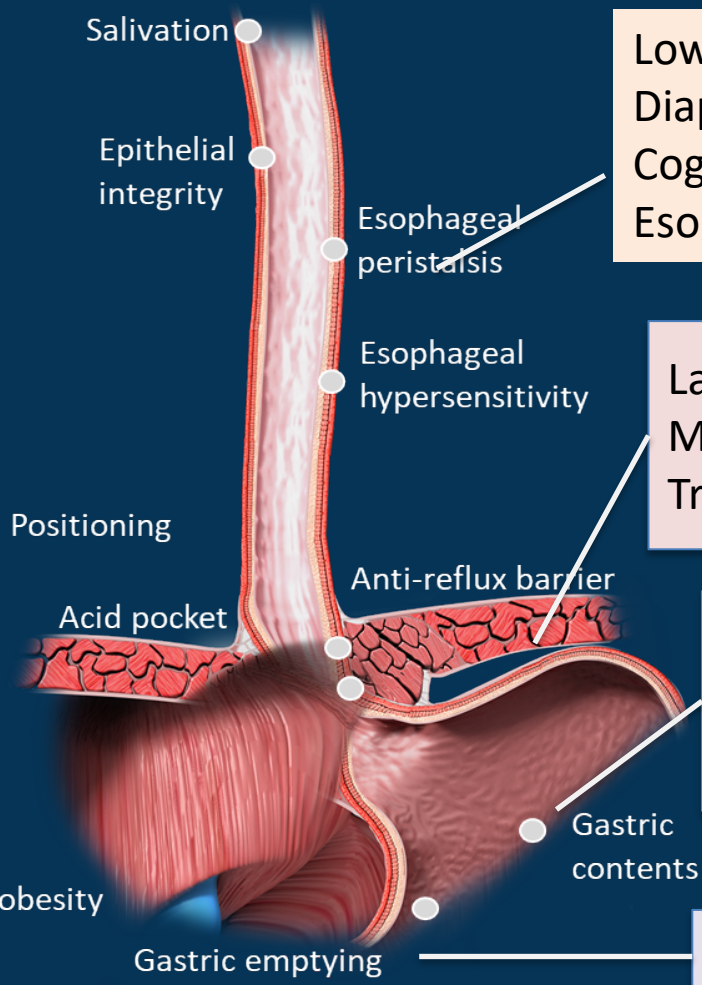
Complications of Achalasia beyond aspiration



Achalasia

- Treatment is not curative – but placement of enteral nutrition can allow a patient to then go for definitive procedure
  - Heller Myotomy
  - POEM
  - Pneumatic Dilation
- Post liver transplantation, portal HTN is improved, allowing myotomy of the esophagus (even if history of esophageal varices)

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
Left lateral night-time position

Prokinetic

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Conclusions

- EGD should be the first test for dysphagia
- Liquid dysphagia should prompt evaluation for motility disorders
- Pulmonary – GI – Rheumatology Axis: Limitations on Lung Transplant
- Can lessons from Achalasia help restore LES function in scleroderma?

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Acknowledgements

- Vanderbilt
  - Rheumatology

  - Pulmonary/Lung Transplant
  - Esophageal Center

THANKS!

Any questions?