

New concepts in common esophageal disorders: GERD and EoE

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Disclosures

- Medical advisory board for EvoEndo

Case

40 yo man with h/o asthma and eczema presents with complaints of nocturnal fevers, drenching night sweats and 25 lb weight loss. Physical exam is significant for bulky axillary lymphadenopathy

What should we do next?

- A. Start ABVD chemotherapy for 2 weeks and assess symptom response
- B. Biopsy lymph node
- C. Refer to oncologist

What should we do next?

Start ABVD chemotherapy for 2 weeks
and assess symptom response

Biopsy lymph node

Refer to oncologist

Objectives

- Understand scenarios that merit ambulatory reflux testing
- Be able to describe options available for ambulatory reflux testing
- Understand when to perform ambulatory reflux studies off and on PPI therapy (hint, almost always OFF)
- Describe conditions other than GERD associated with GERD symptoms
- Identify patient features that merit an evaluation for EoE
- Compare available EoE treatments

Case 1

40 yo white man with h/o asthma, eczema, tobacco use, obesity presents to discuss management of heartburn.

- Describes burning pain in epigastric/retrosternal area
- Notes occasional regurgitation
- Has tried OTC antacids with intermittent benefit
- Symptoms recur if he stops taking medications

What should we do next?

- A. Start Omeprazole 40 mg taken before breakfast
- B. Refer for ambulatory reflux testing
- C. Refer to GI for cognitive consultation
- D. Refer to GI for upper endoscopy
- E. Start a TCA

What should we do next?

Start Omeprazole 40 mg
taken before breakfast

Refer for ambulatory
reflux testing

Refer to GI for cognitive
consultation

Refer to GI for upper
endoscopy

Start a TCA

AGA Clinical Practice Update on the Personalized Approach to the Evaluation and Management of GERD: Expert Review

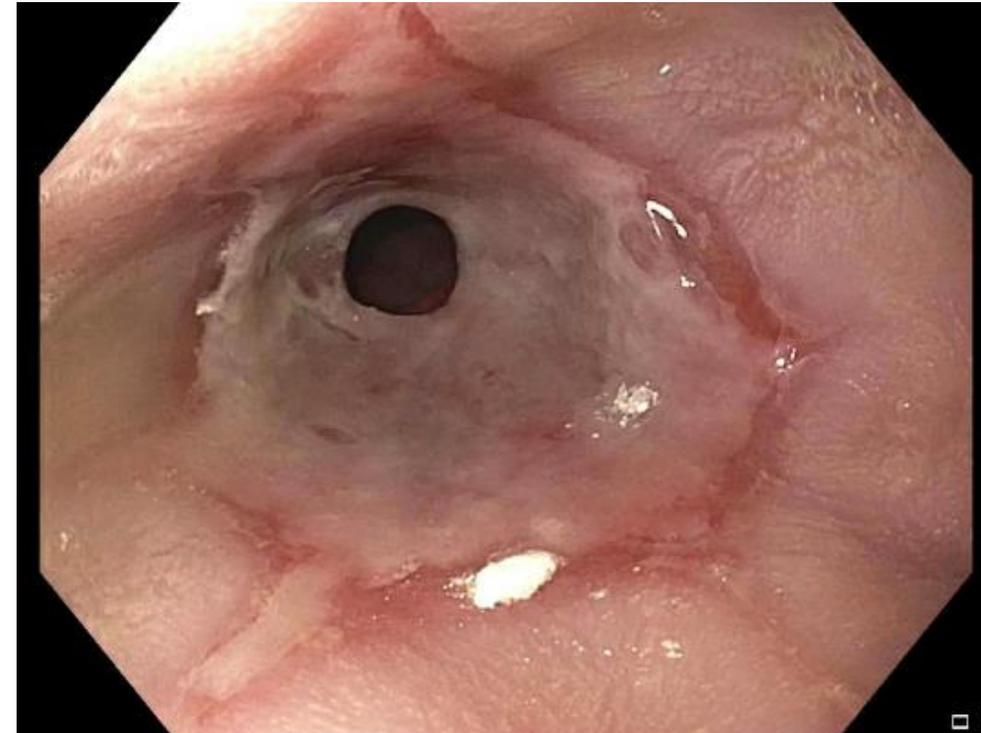
Best Practice Advice 1:

Clinicians should develop a care plan for investigation of symptoms suggestive of GERD, selection of therapy (with explanation of potential risks and benefits), and long-term management, including possible de-escalation, in a shared-decision making model with the patient.

ACG 2022 GERD Guidelines

- **GERD** is objectively defined by LA Grade B, C or D esophagitis, peptic stricture, Barrett's mucosa > 3cm, and esophageal acid exposure >6%.
- There is no gold standard for the diagnosis of GERD!

- Symptoms are not GERD



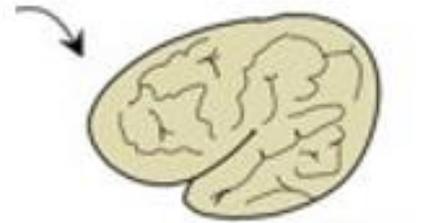
PPI Diagnostic Test

- A trial of therapy with a PPI as a diagnostic “test” in patients with the typical symptoms of heartburn and regurgitation, with the underlying assumption that a PPI response establishes the diagnosis of GERD. Sensitivity 78% and specificity 54%!
- Average cost saving of \$570 per patient

Risk Factor Modification

Stress Reduction

Belly Breathing



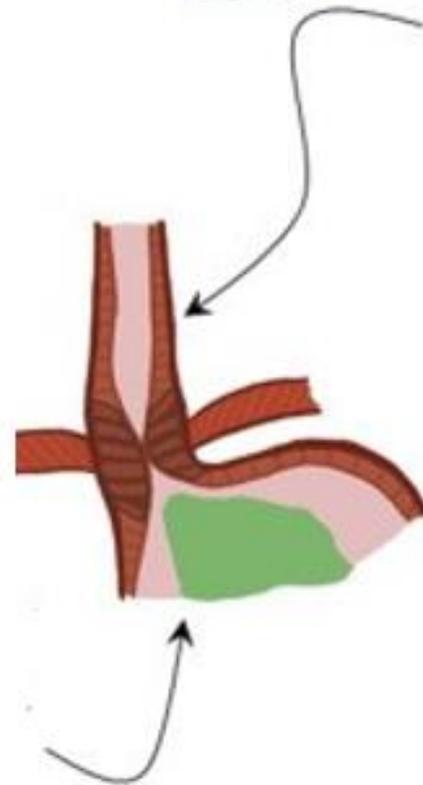
Quit Smoking

Avoid Trigger Foods

Chew gum or use oral lozenges

Weight management

Avoid tight fitting clothing

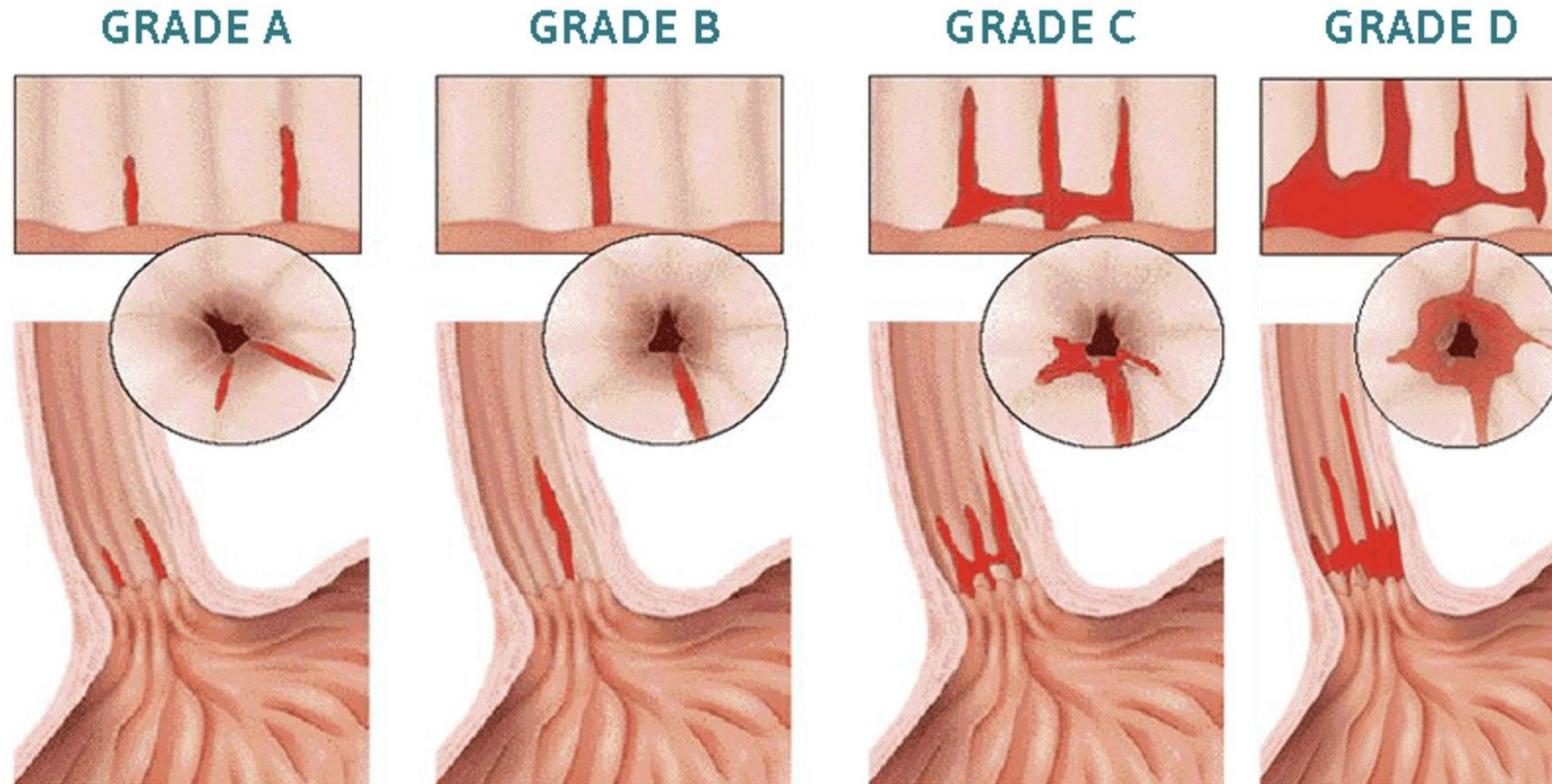


Avoid late meals

If you have nighttime symptoms,
raise the head of your bed

Endoscopy to Diagnose GERD

Los Angeles Classification of Reflux Esophagitis



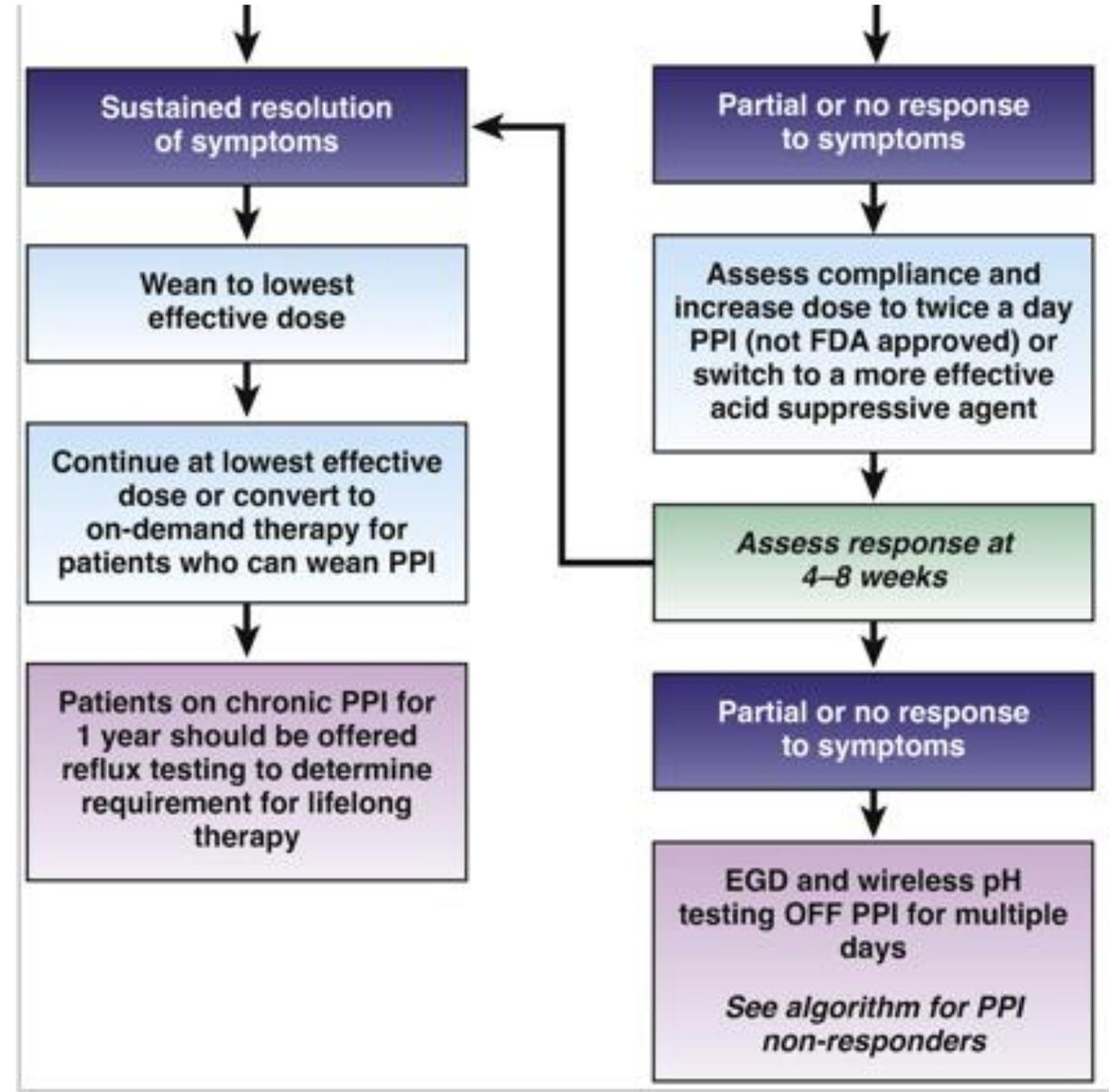
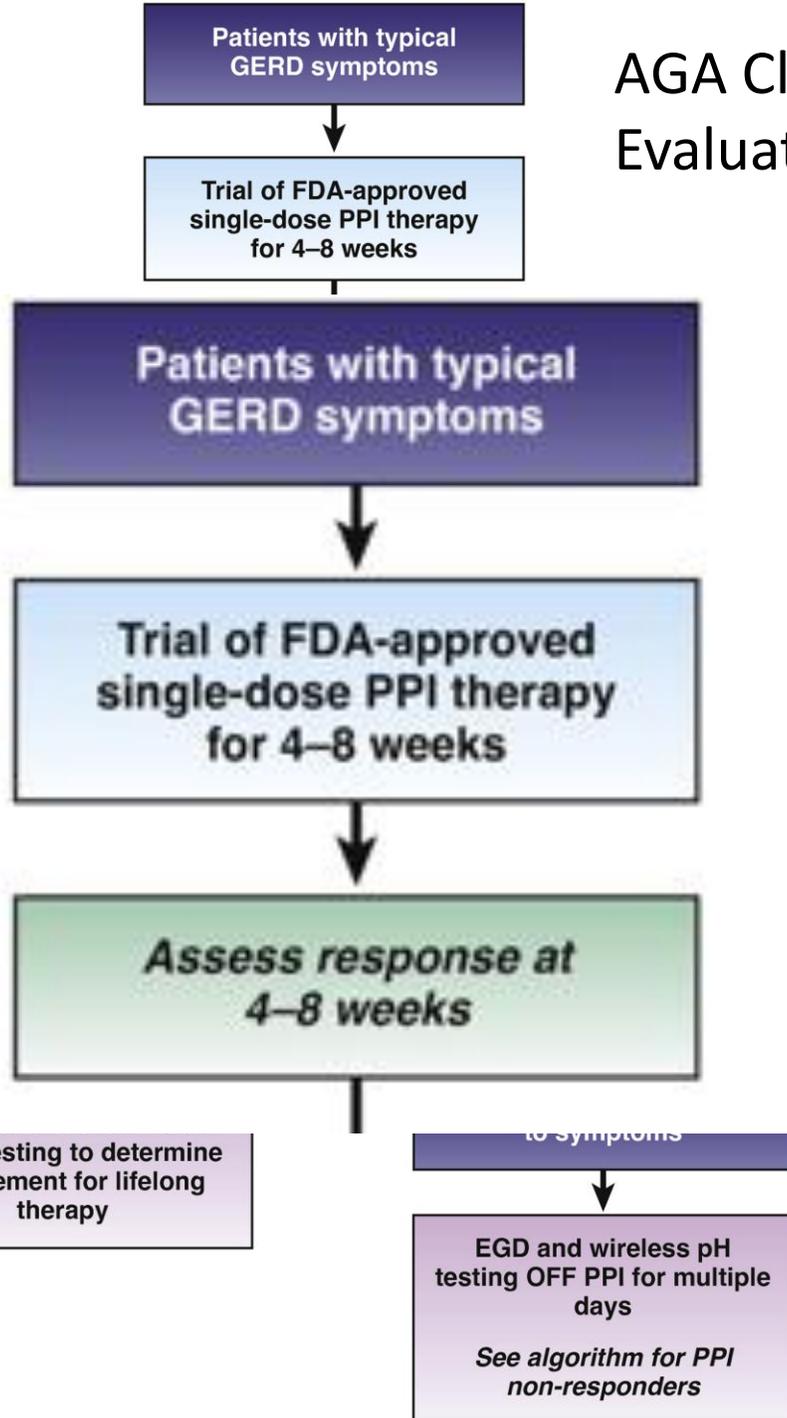
One or more mucosal break $<5\text{mm}$ that does not extend between the tops of two mucosal folds

One or more mucosal break $>5\text{mm}$ that does not extend between the tops of two mucosal folds

One or more mucosal break that is continuous between the tops of two or more mucosal folds but that involves $<75\%$ of the circumference

One or more mucosal break that involves $>75\%$ of the esophageal circumference

AGA Clinical Practice Update on the Personalized Approach to the Evaluation and Management of GERD: Expert Review



Case 2

40 yo with long standing heartburn is referred for management of GERD symptoms.

- Describes lifetime burning pain in epigastric/retrosternal area
- Has been on PPI daily or twice daily since high school (Nexium 40mg)
- Still has breakthrough symptoms several times per week

What might your next step entail?

- A. Referral for upper endoscopy
- B. Referral for upper endoscopy with wireless pH capsule placement OFF PPI
- C. Switch PPI
- D. Add nocturnal H2 receptor antagonist (eg Famotidine)

What might your next step entail?

Referral for upper endoscopy

Referral for upper endoscopy with
wireless pH capsule placement OFF PPI

Switch PPI

Add nocturnal H2 receptor antagonist
(eg Famotidine)

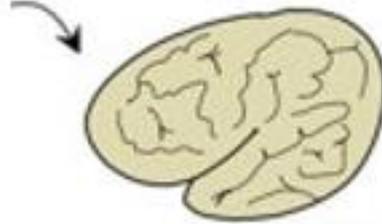
AGA Clinical Practice Update on the Personalized Approach to the Evaluation and Management of GERD

If troublesome heartburn, regurgitation, and/or non-cardiac chest pain do not respond adequately to a PPI trial or when alarm symptoms exist, clinicians should:

- investigate with endoscopy and
- in the absence of erosive reflux disease or Barrett's esophagus
- perform prolonged wireless pH monitoring off medication (96-hour preferred if available) to confirm and phenotype GERD or to rule out GERD

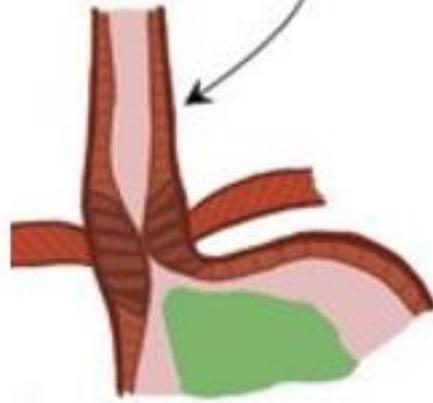
All that burns is not GERD

**Hypervigilance
Catastrophizing**

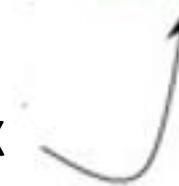


Reflux Hypersensitivity

Functional heartburn



Reflux

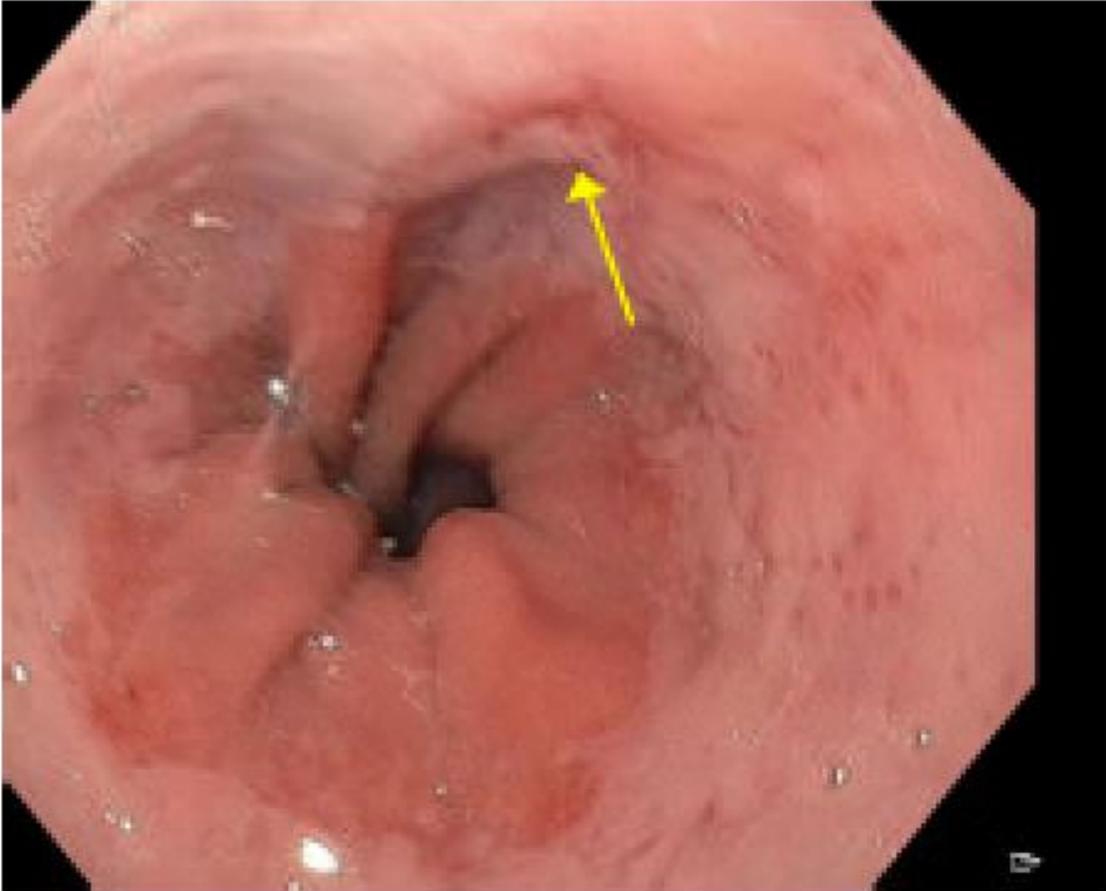


Endoscopy in GERD



- Vast majority normal
- Rates of healing erosive esophagitis with PPIs ~ 80-95%

Case 2



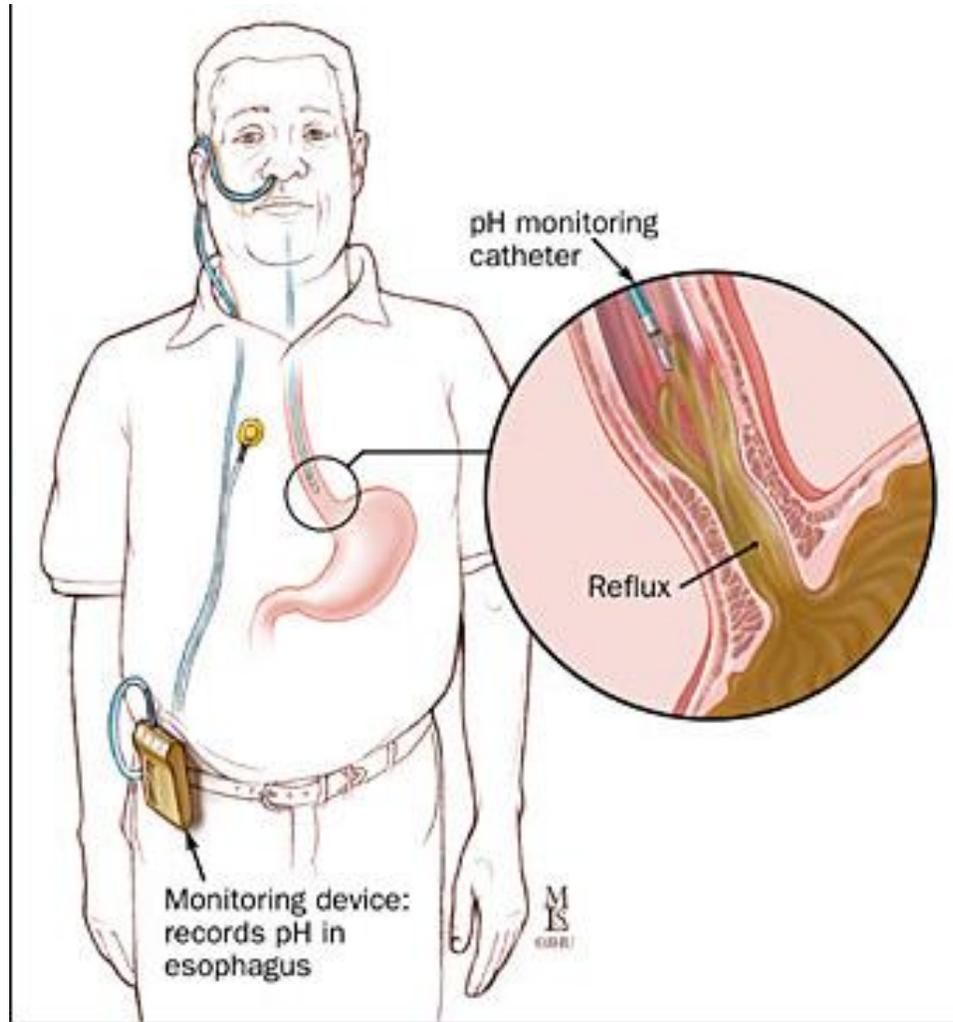
- LA Class A erosive Esophagitis

1 Lower Third of the
Esophagus : Esophagitis

When to Order Reflux Monitoring?

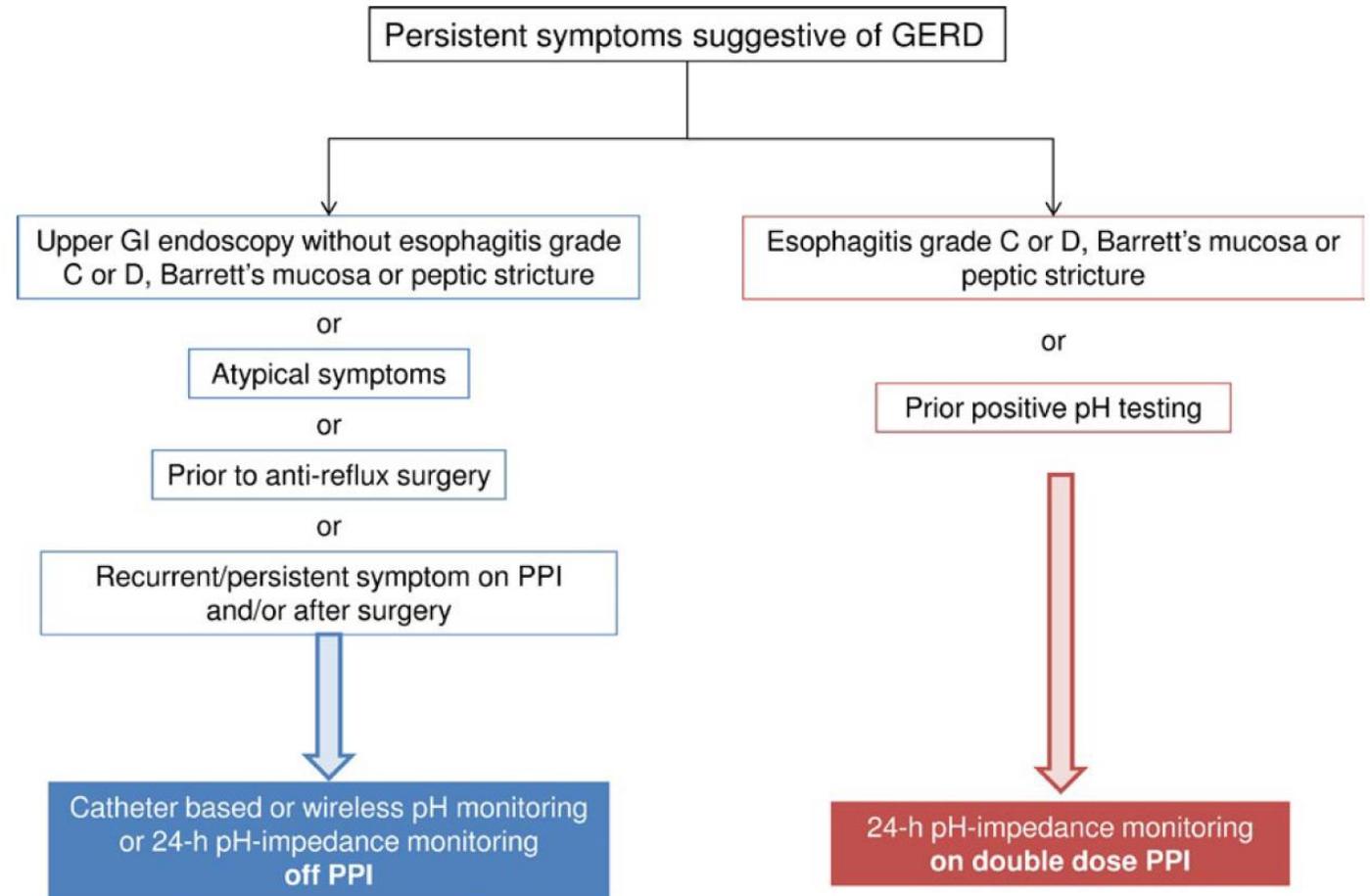
- In patients for whom the diagnosis of **GERD is suspected but not clear**, and endoscopy shows no objective evidence of GERD
- In patients with **extraesophageal manifestations of GERD without typical GERD symptoms**
 - Typical GERD symptoms: heartburn and regurgitation
 - Extraesophageal symptoms: cough, throat discomfort, voice change
- In patients with **chest pain** who have had adequate evaluation to exclude heart disease

A word about ambulatory pH testing



PPI or No?

- **OFF PPI** if the diagnosis of GERD has not been established
- **ON PPIs** for patients with an established diagnosis of GERD whose symptoms have not responded adequately to twice-daily PPI therapy.
 - In these patients, impedance/pH testing is recommended to document reflux hypersensitivity for weakly acidic or nonacidic reflux and for acid reflux.



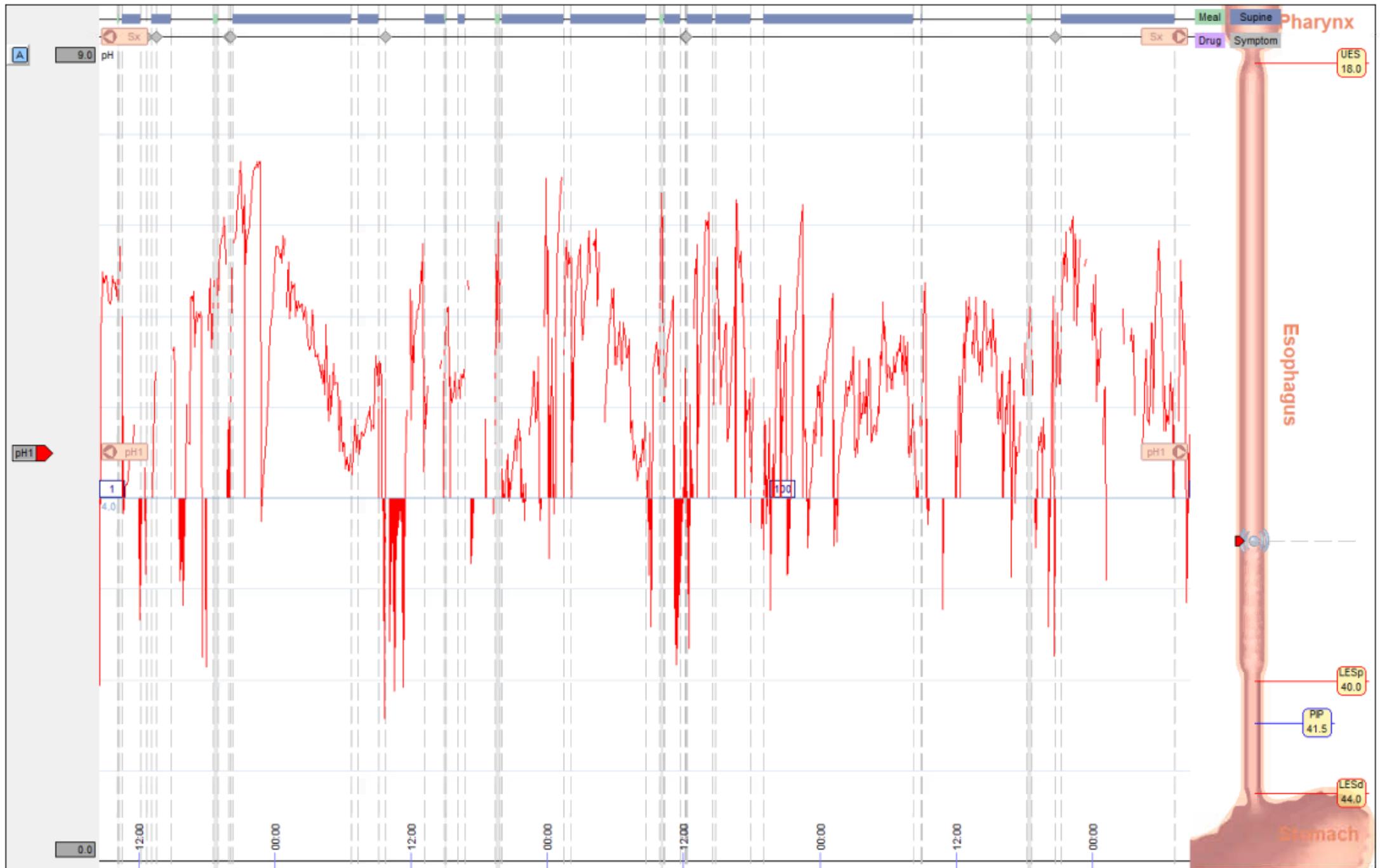
What is assessed on Reflux monitoring?

- Acid Exposure Time

- <4% is normal and >6% is pathologic

- Symptom Correlation

- **Symptom Index** = Total # of Reflux Episodes Associated with a Symptom/ The Total # of Symptom Episodes
 - **Symptom Index > 50%** is considered positive
- **Symptom Association Probability**: Fisher exact test of the probability that the reflux and symptom are associated.
 - **SAP >95%** is considered positive



Case 2 Wireless pH testing results

Symptom Correlation to Reflux (Impedance)

<u>Symptom</u>	<u>Occurrences</u>	<u>Acid Related</u>	<u>Nonacid Related</u>	<u>All Reflux Related</u>	<u>Unrelated</u>
Belch	12	12	0	12	0
Cough	16	9	6	14	2
Heartburn	13	11	1	12	1
Regurgitate	10	7	4	9	1
Nexium	2	0	0	0	2
2 Tums	1	1	0	1	0

Reflux Symptom Index (Impedance)

<u>Symptom</u>	<u>Acid</u>	<u>Nonacid</u>	<u>All Reflux</u>
Belch	100%	0%	100%
Cough	56%	38%	88%
Heartburn	85%	8%	92%
Regurgitate	70%	40%	90%
Nexium	0%	0%	0%
2 Tums	100%	0%	100%

Esophageal Acid Exposure: **15.9%**
 (<4% is normal and >6% is pathologic)

Symptom Indices for belch, cough, heartburn, Regurgitation were each **>50%**.

SAP >95% for heartburn and belch

What are next options?

- A. Antireflux Surgery
- B. Add on H2B
- C. Continue current therapy, a breakthrough a few times a week isn't bad!

What are next options?

Antireflux Surgery

Add on H2B

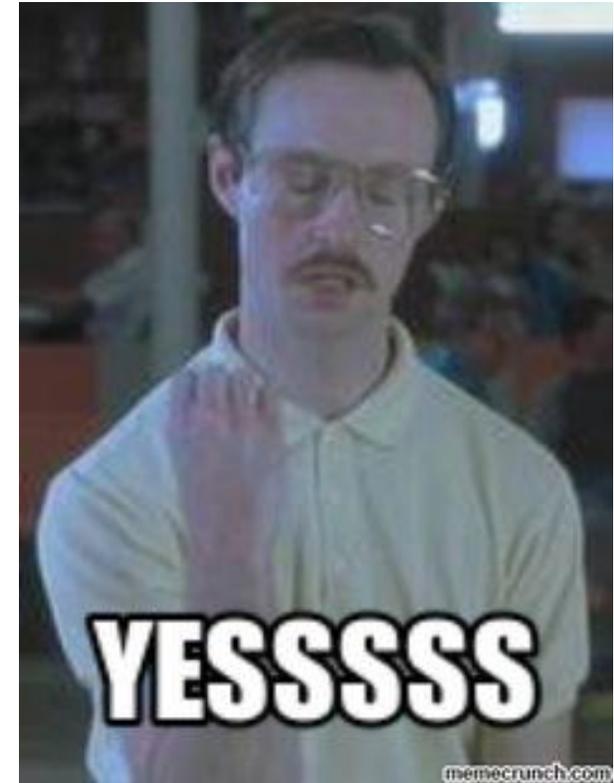
Continue current therapy,
a breakthrough a few
times a week isn't bad!

What to say About long term PPI?

“PPIs are the most effective medical treatment for GERD. Some medical studies have identified an association between the long-term use of PPIs and the development of numerous adverse conditions including intestinal infections, pneumonia, stomach cancer, osteoporosis-related bone fractures, chronic kidney disease, deficiencies of certain vitamins and minerals, heart attacks, strokes, dementia, and early death. Those studies have flaws, are not considered definitive, and do not establish a cause-and-effect relationship between PPIs and the adverse conditions. High-quality studies have found that PPIs do not significantly increase the risk of any of these conditions except intestinal infections. Nevertheless, we cannot exclude the possibility that PPIs might confer a small increase in the risk of developing these adverse conditions. For the treatment of GERD, gastroenterologists generally agree that the well-established benefits of PPIs far outweigh their theoretical risks.”

Case 2

- Patient goes for laparoscopic hiatal hernia repair + Nissen fundoplication.
- Notes significant improvement in his symptoms and is able to discontinue PPI completely.



What is the risk of need to return to PPI after anti-reflux surgery?

- Risk of PPI use after ARS was >50% of patients became long-term PPI users 10–15 years post surgery.

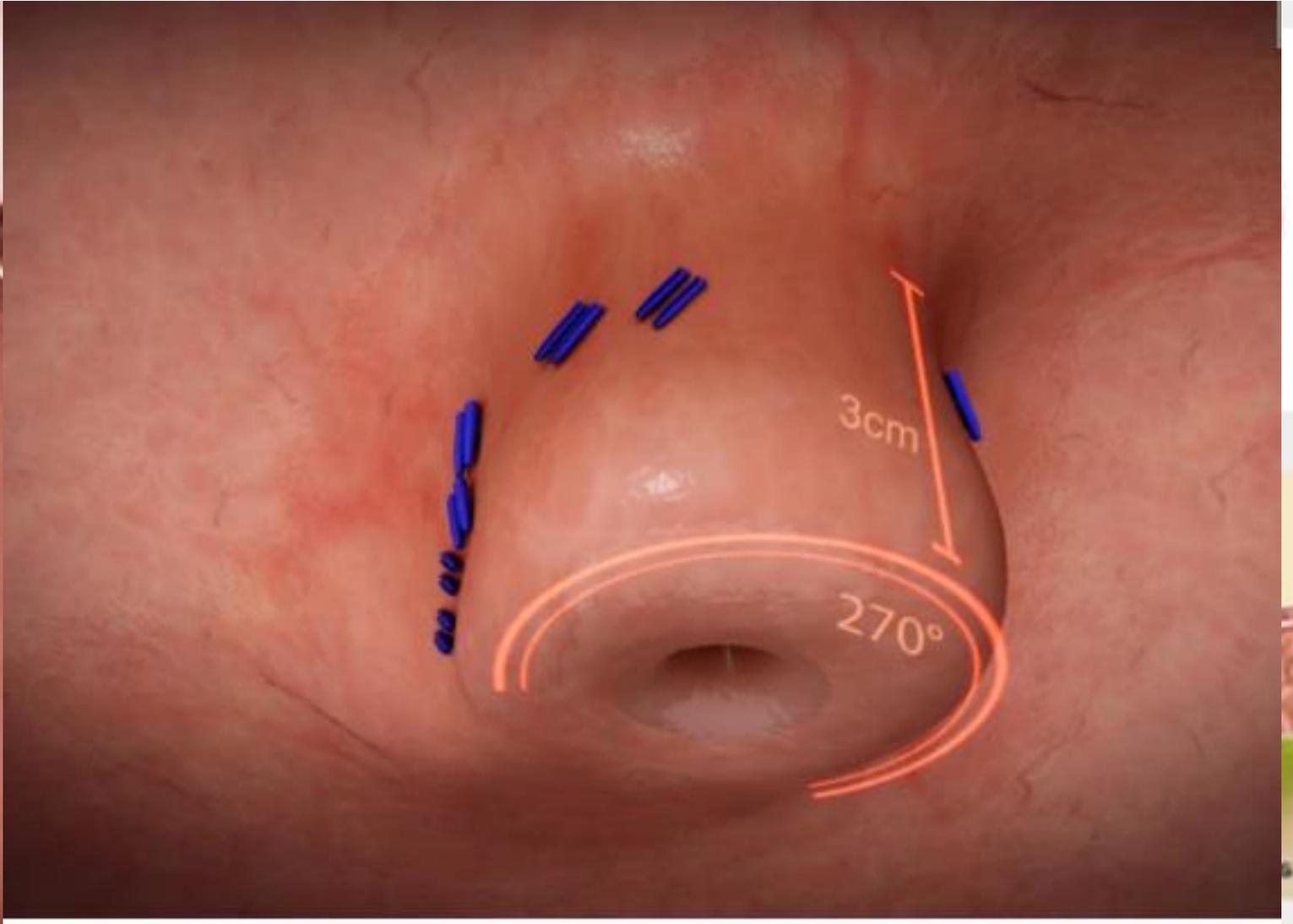
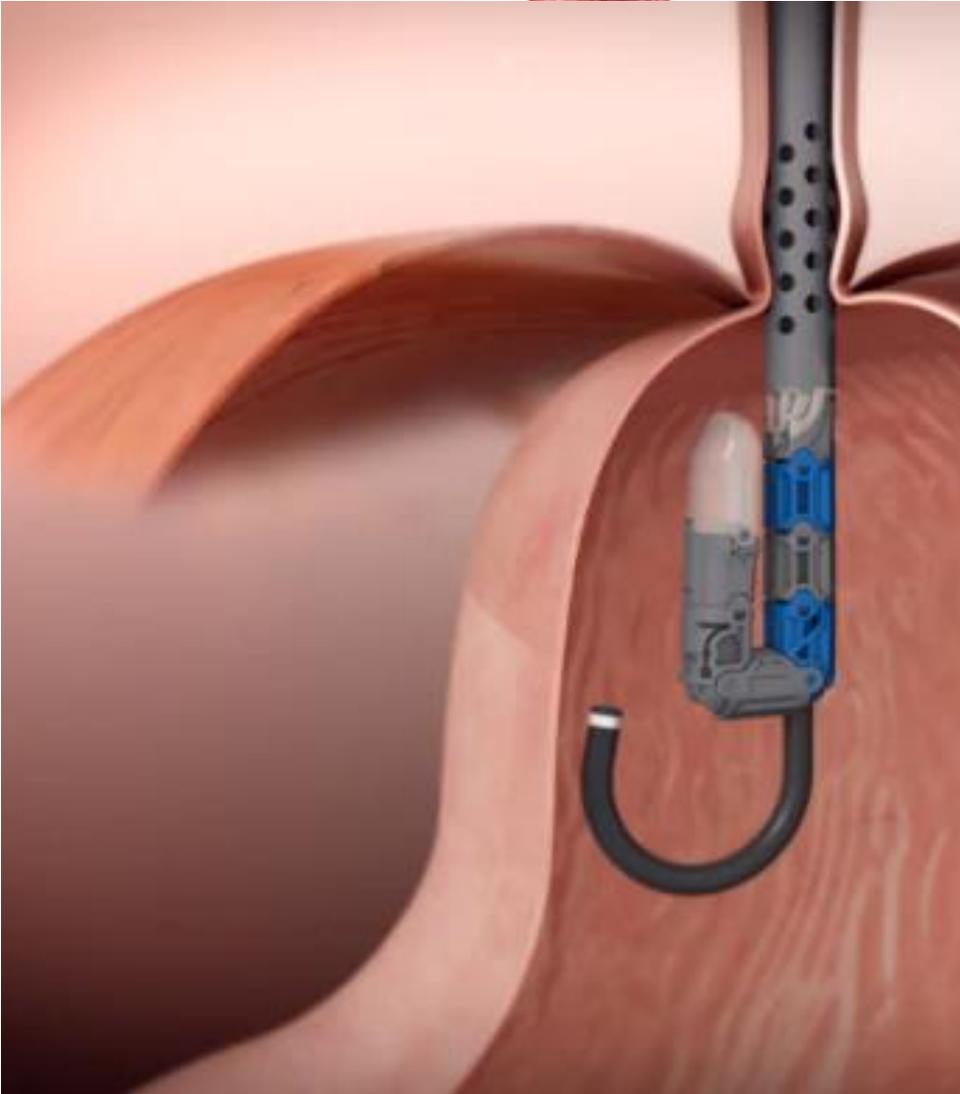
Antacid Medication Use and Monthly Costs to Patients Before and After Laparoscopic Nissen Fundoplication

	Preoperative	Early Follow-up	Late Follow-up
Patients taking antacid medications	97 (97%)	19 (19%)*	31 (37%)*†
PPI‡	59 (59%)	8 (8%)*	26 (31%)*†
H ₂ -antagonist‡	46 (46%)	4 (4%)*	1 (1%)*
OTC antacid‡	22 (22%)	7 (7%)*	1 (1%)*
Promotility agent	30 (30%)	8 (8%)*	3 (4%)*
Antacid medications/patient§	1.82 ± 0.9	0.3 ± 0.6*	0.4 ± 0.6*
Antacid medication costs§	\$168 ± \$91	\$30 ± \$54*	\$53 ± 87*†

Lødrup A, Pottegård A, Hallas J, *et al.* Use of proton pump inhibitors after antireflux surgery: a nationwide register-based follow-up study. *Gut* 2014;**63**:1544-1549.

Bloomston, Mark *et al.* "Symptoms and antireflux medication use following laparoscopic Nissen fundoplication: outcome at 1 and 4 years." *JSLS : Journal of the Society of Laparoendoscopic Surgeons* vol. 7,3 (2003): 211-8.

Esophagus



©2017
MAYO

A. Fundus wrapped around back side of esophagus

B. Wrap secured with sutures to anchor lower esophagus below diaphragm

Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial. JAMA 2011

GERD Diagnosis ACG Guidelines

	GRADE quality of evidence	GRADE strength of recommendation
Diagnosis of GERD		
For patients with classic GERD symptoms of heartburn and regurgitation who have no alarm symptoms, we recommend an 8-wk trial of empiric PPIs once daily before a meal.	Moderate	Strong
We recommend attempting to discontinue the PPIs in patients whose classic GERD symptoms respond to an 8-wk empiric trial of PPIs.	Low	Conditional
In patients with chest pain who have had adequate evaluation to exclude heart disease, objective testing for GERD (endoscopy and/or reflux monitoring) is recommended.	Low	Conditional
We do not recommend the use of a barium swallow solely as a diagnostic test for GERD.	Low	Conditional
We recommend endoscopy as the first test for evaluation of patients presenting with dysphagia or other alarm symptoms (weight loss and GI bleeding) and for patients with multiple risk factors for Barrett's esophagus.	Low	Strong
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.	Low	Strong
We suggest against performing reflux monitoring off therapy solely as a diagnostic test for GERD in patients known to have endoscopic evidence of LA grade C or D reflux esophagitis or in patients known to have long-segment Barrett's esophagus.	Low	Strong

Case 3:

65 yo reports longstanding heartburn for 10 years duration. Has been on famotidine BID though symptoms are refractory to this. Tried daily omeprazole for several weeks and noted no improvement. Is uninterested in repeat trial of PPI due to concern about possible osteoporosis

- Prior EGD 2 years ago did not show evidence of erosive esophagitis despite symptoms at that time

What would you do next?

- A. Cajole into PPI use
- B. Ambulatory reflux monitoring off acid suppressive therapy
- C. Refer for antireflux surgery evaluation
- D. Start Tricyclic Antidepressant

What would you do next?

Cajole into PPI use

Ambulatory reflux monitoring
off acid suppressive therapy

Refer for antireflux surgery
evaluation

Start Tricyclic Antidepressant

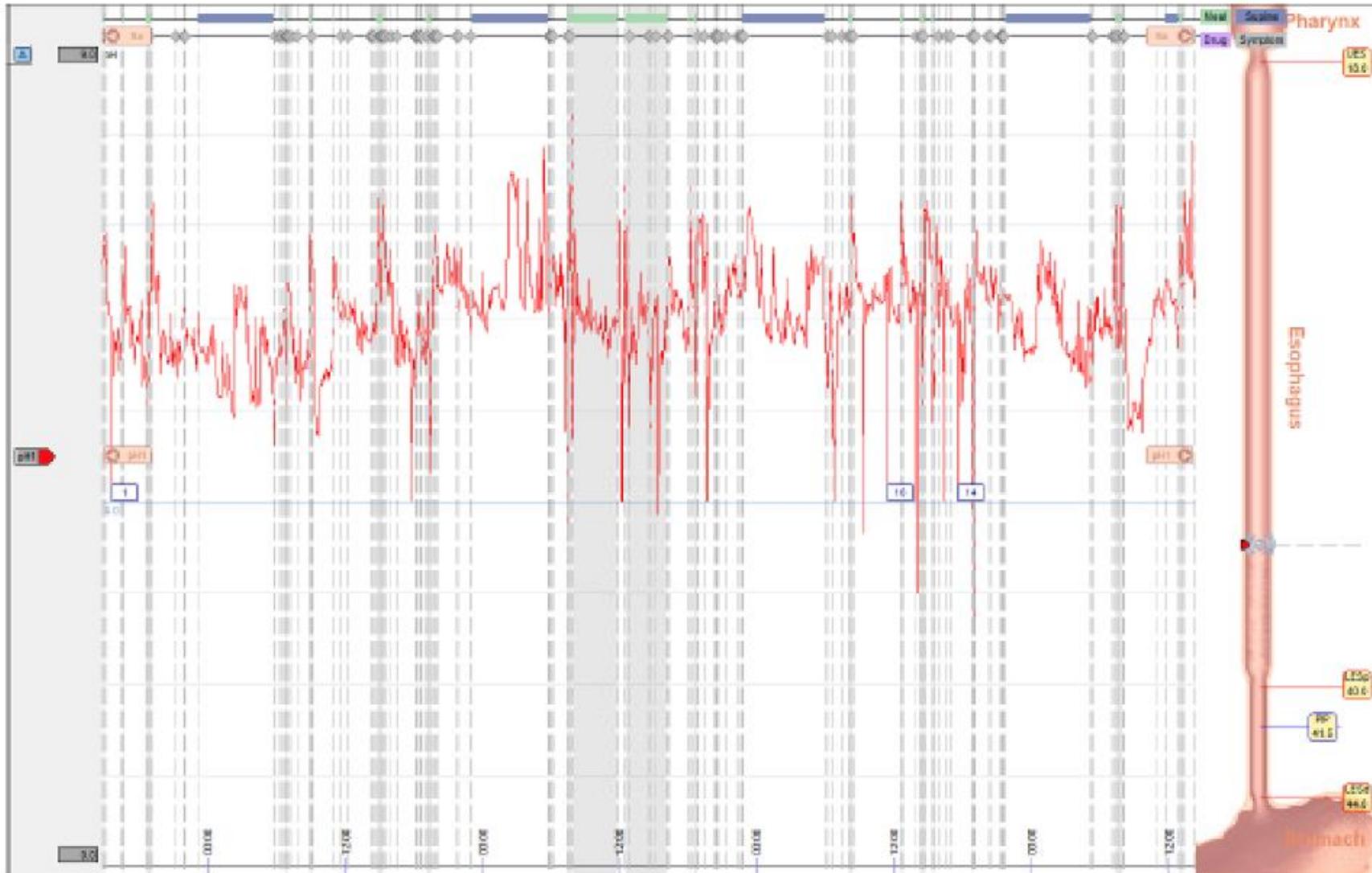
We need to confirm or refute GERD

EGD + wireless pH capsule if no evidence of erosive esophagitis.



Normal upper endoscopy

Case 3:



Wireless pH capsule results (bravo)

REFLUX MONITORING SUMMARY

Acid Exposure Summary	Total	Normal	Upright	Normal	Supine	Normal
Acid exposure time (%)	0.3	<4.9	0.5	<7.3	0.0	<1.4
Longest reflux (min)	3.9	<16.0	3.9		N/A	
DeMeester Score	1.5	<14.7				
Symptom Association Summary	Heartburn	Belch	Gas	dysphagia	Cough	
Number of occurrences	15	48	11	2	1	
Symptom index for reflux (SI)	0.0	0.0	0.0	0.0	0.0	
Symptom association prob. (SAP)*	79.9	96.2	98.7	0.0	0.0	

BRAVO

Total

Period Durations (HH:MM)	Total	Upright	Supine
Total Time	95:37	66:31	29:06
Analysis Time	81:15	52:20	28:55

Acid Reflux Analysis	Total	Upright	Supine
Acid exposure time (HH:MM)	00:15	00:15	00:00
Acid exposure time (%)	0.3	0.5	0.0
Number of refluxes	14	14	0
Number of long refluxes	0	0	0
Longest reflux (min)	3.9	3.9	N/A

DeMeester Score	Score	Normal*
Ch 1	1.5	<14.7

* 95th percentile

- No evidence of pathologic esophageal acid exposure
- Esophageal pH < 4 for 0.3% of study (normal < 4%, pathologic > 6%)
- No pathologic esophageal acid exposure on any day of study individually
- No obvious association between reflux events and symptom episodes
- Overall study is not consistent with pathologic reflux disease.

Case 3: 65 yo with chronic troublesome heartburn not responsive to PPI or H2RA with minimal reflux on wireless pH testing

- What would you do now?
 - A. Refer for antireflux surgery
 - B. Order esophageal manometry
 - C. Refer to a psychologist
 - D. Start a Tricyclic Antidepressant

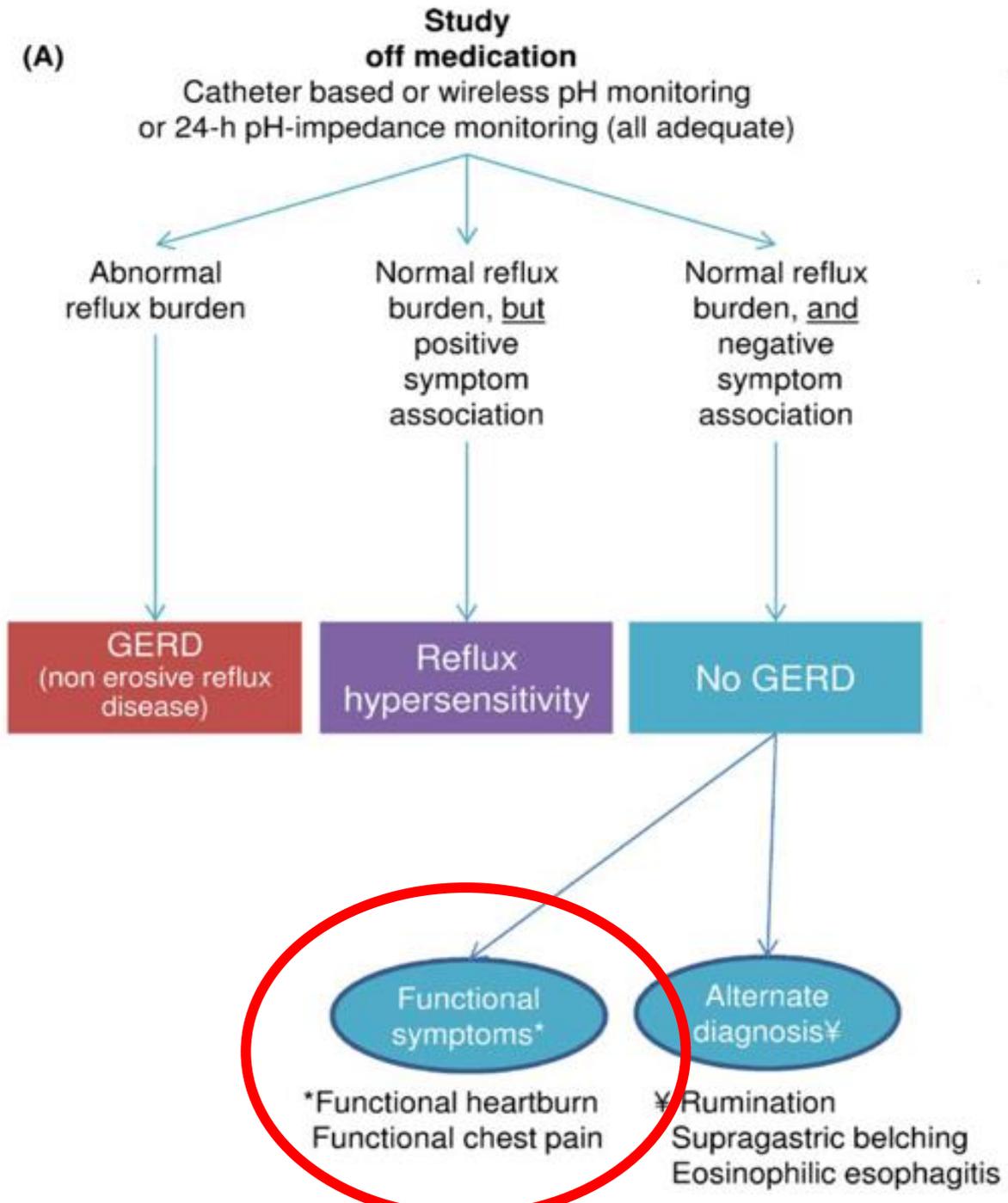
What would you do now?

Refer for antireflux
surgery

Order esophageal
manometry

Refer to a psychologist

Start a Tricyclic
Antidepressant



Functional Heartburn

- Typical heartburn symptoms
- Normal upper endoscopy
- Normal esophageal pH testing
- Negative correlation between symptoms and reflux events

Functional Heartburn Treatments

AGA also recommends CBT, diaphragmatic breathing, and relaxation strategies

Table 1. Therapeutic Options for Functional Heartburn

Therapeutic options
Lifestyle modifications
Improved sleep experience
Pharmacotherapy
Tricyclic antidepressants
Selective serotonin reuptake inhibitors
Tegaserod
Histamine 2 receptor antagonists
Melatonin
Alternative/complementary medicine
Acupuncture
Psychological intervention
Hypnotherapy

Case 4

- 25 year old medical student
- Long history of food (mostly meats and breads) getting stuck in their chest (“eats too quickly”)
- Also notes history of exercise-induced asthma

What would you do next?

- A. Start daily omeprazole, re-assess symptoms in 6-8 weeks
- B. Refer for upper endoscopy
- C. Order esophagram
- D. Check celiac serologies

What would you do next?

Start daily omeprazole, re-assess symptoms in 6-8 weeks

Refer for upper endoscopy

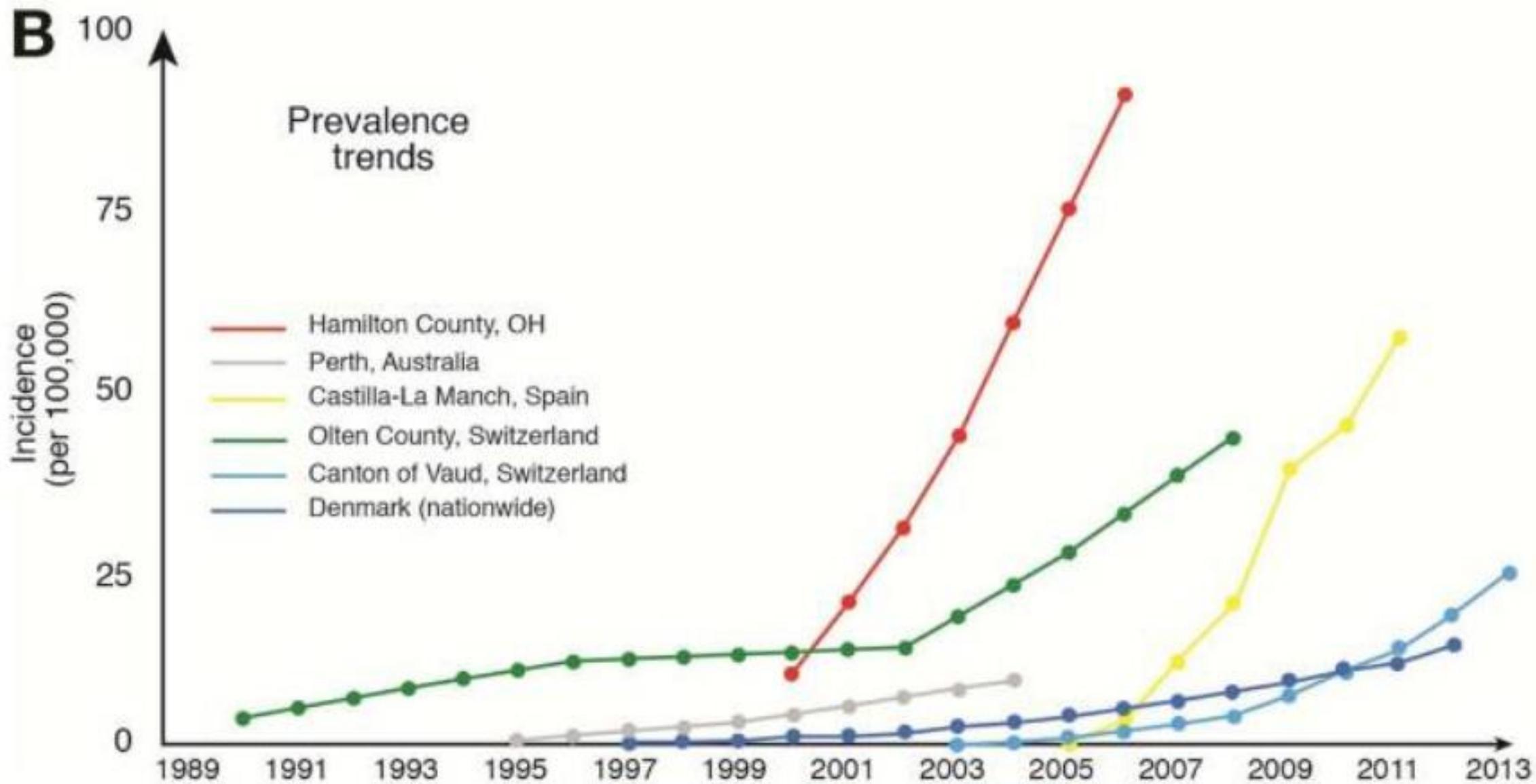
Order esophagram

Check celiac serologies

Eosinophilic Esophagitis (EoE)

EoE Basics

- Chronic immune/antigen-mediated esophageal disease
- Clinicopathologic diagnosis:
 - Symptoms of esophageal dysfunction
 - Eosinophilic infiltrate in the esophagus
 - Absence of other potential causes of esophageal eosinophilia

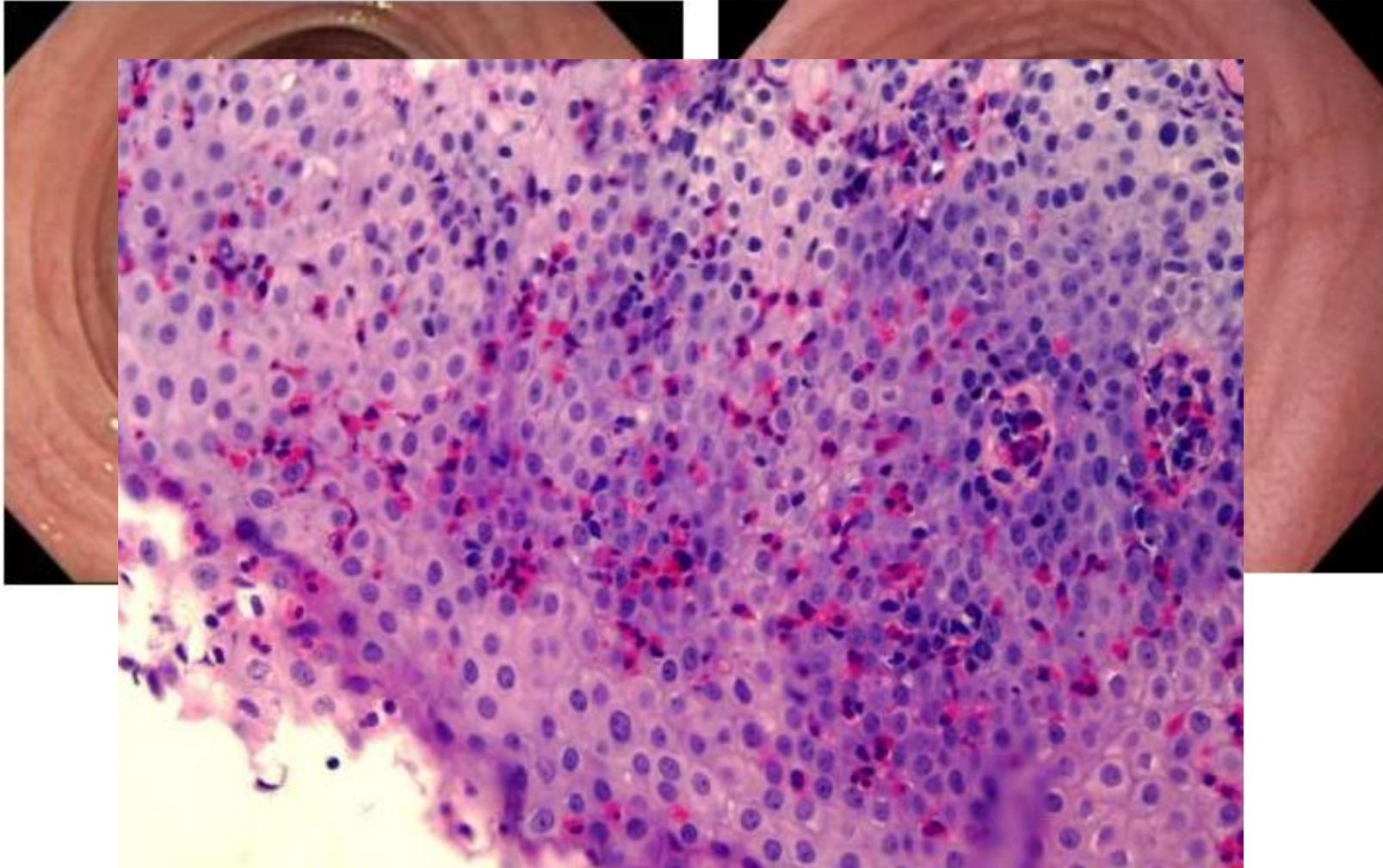


Clinical Features of EoE

- In adults & adolescents: dysphagia (25-100%)
- ~ 50% of cases of acute food impaction
- Food avoidance

- In children more non-specific (Feeding intolerance, failure to thrive, abdominal pain)
- Associated with other allergic diseases

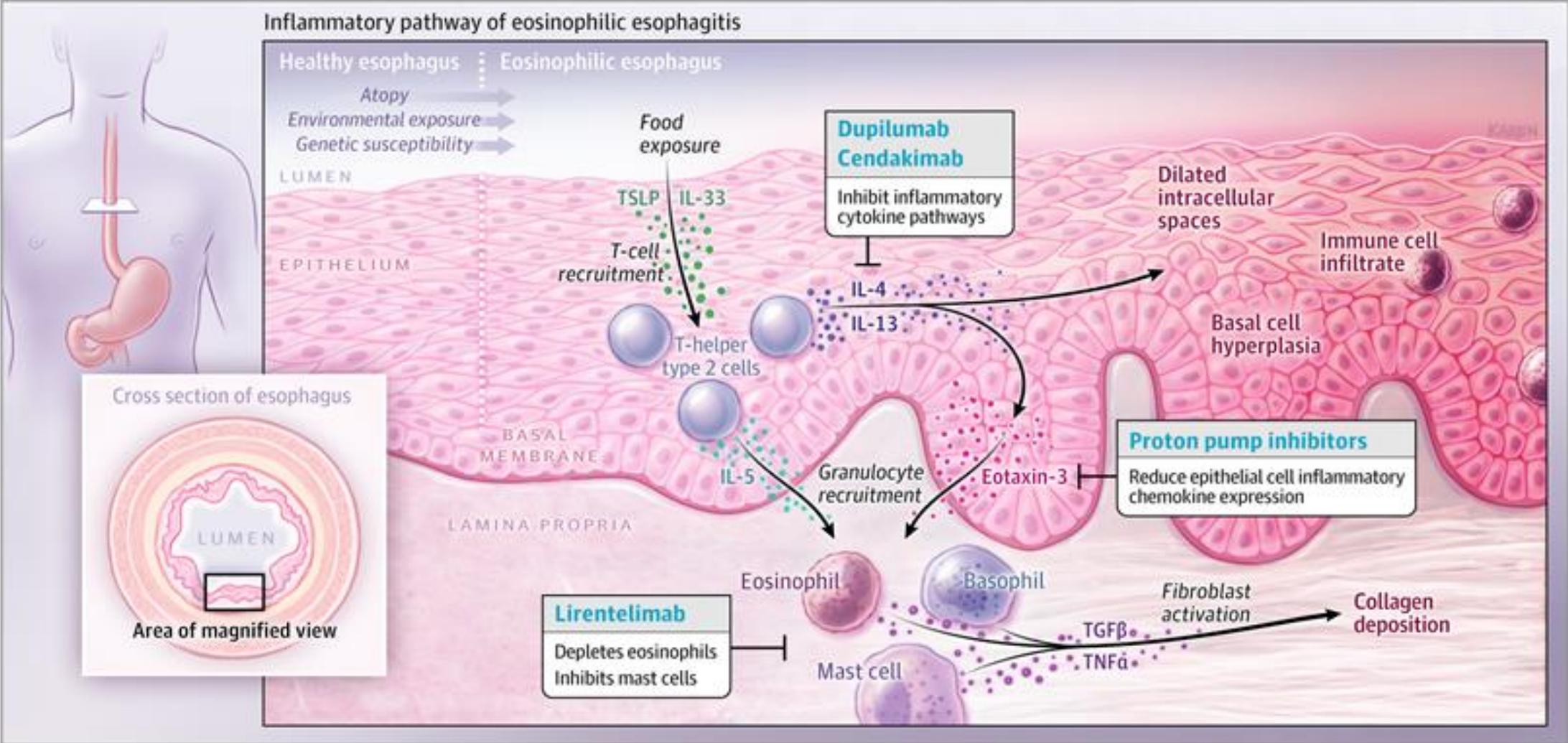
Endoscopic Appearance



Normal Esophagus



EoE Pathophysiology



EoE Treatments

EoE is an allergic/inflammatory disorder of the esophageal mucosa which over time can lead to fibrosis and esophageal narrowing. As such, which of the following would be expected to improve dysphagia symptoms in EoE?

- A. Endoscopic dilation
- B. Swallowed topical steroids
- C. A novel medication that blocks Interleukins involved in eosinophil recruitment
- D. Avoiding identified allergens
- E. All of the above

As such, which of the following would be expected to improve dysphagia symptoms in EoE?

Endoscopic dilation

Swallowed topical steroids

A novel medication that blocks Interleukins involved in eosinophil recruitment

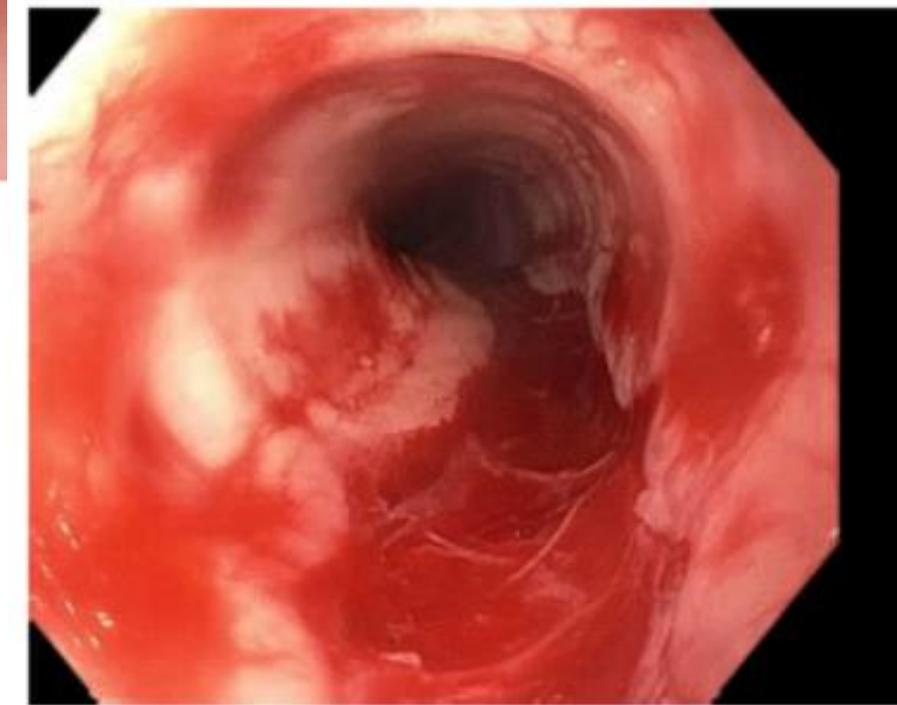
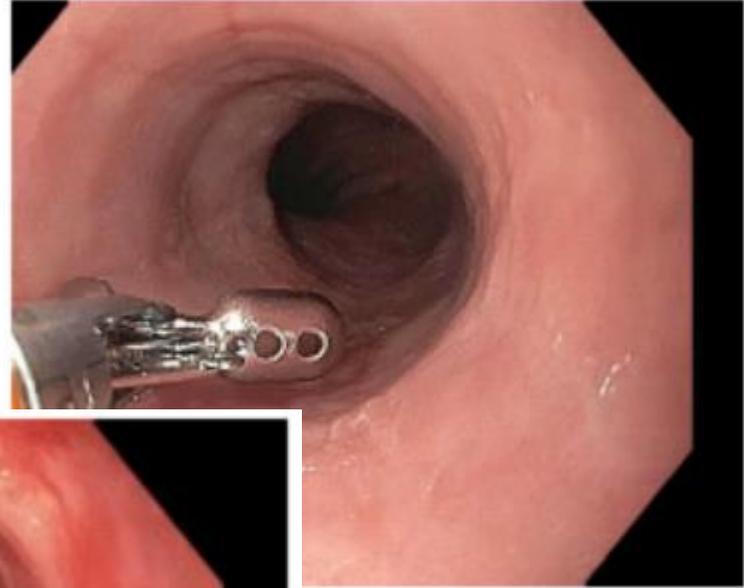
Avoiding identified allergens

All of the above

EoE Treatment

- “3 D’s”: Drugs, Diet and Dilation

Dilation in EoE



Drugs

- Proton Pump Inhibitors (PPIs)
- Steroids: topical >>> systemic
 - Several randomized trials revealing decreased esophageal eosinophilia and improved symptoms
- Biologics: target eosinophil recruitment
 - Dupilumab: Blocks IL-4 and IL-13
 - 1st FDA approved Rx for EoE



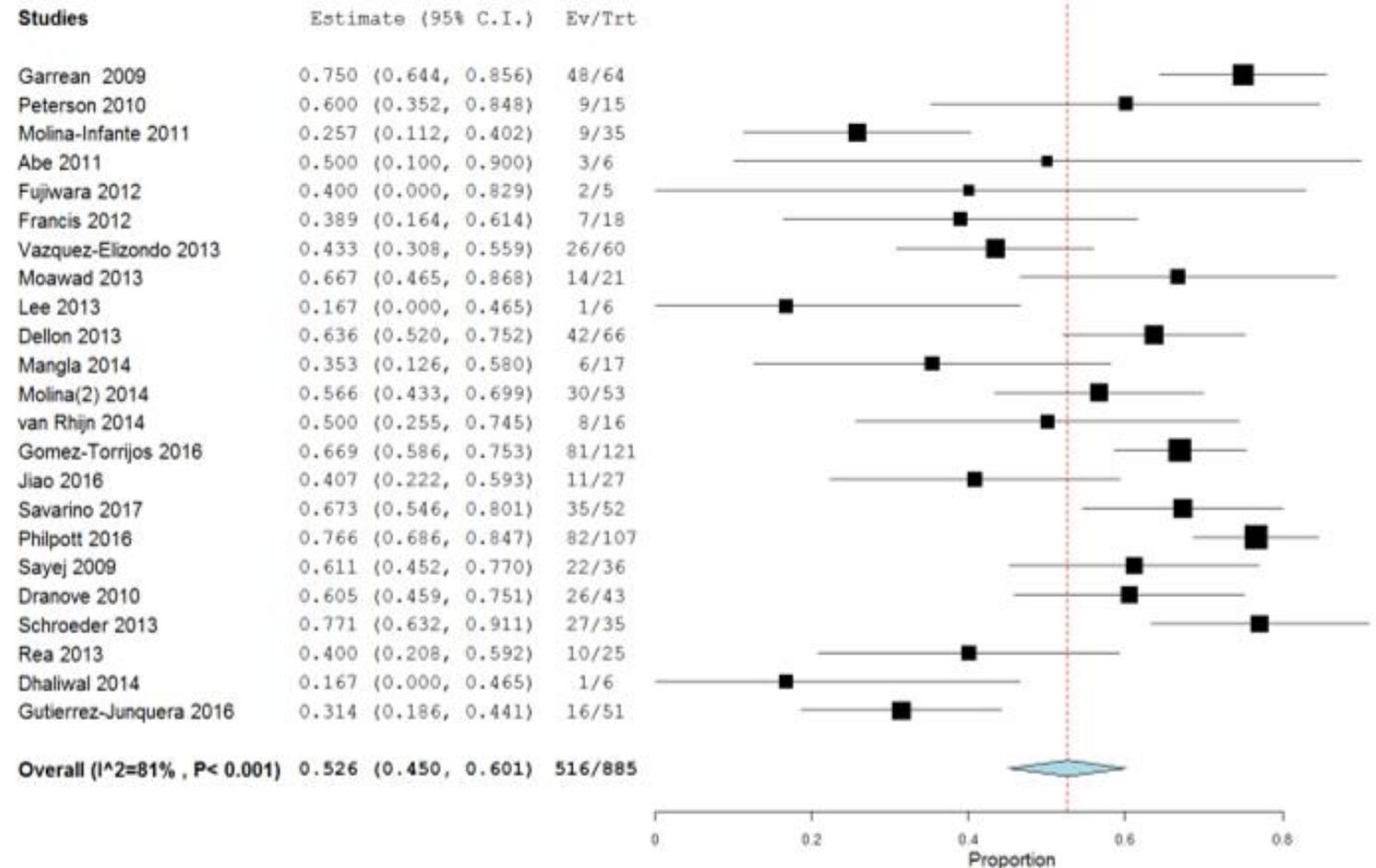
AGA Guidelines: Management of Eosinophilic Esophagitis

Proton Pump Inhibition

Recommendation: In patients with symptomatic esophageal eosinophilia, the AGA/JTF suggests using proton pump inhibition (conditional recommendation, very low quality evidence).

42% achieving histologic response

Forest plot for not achieving histologic remission

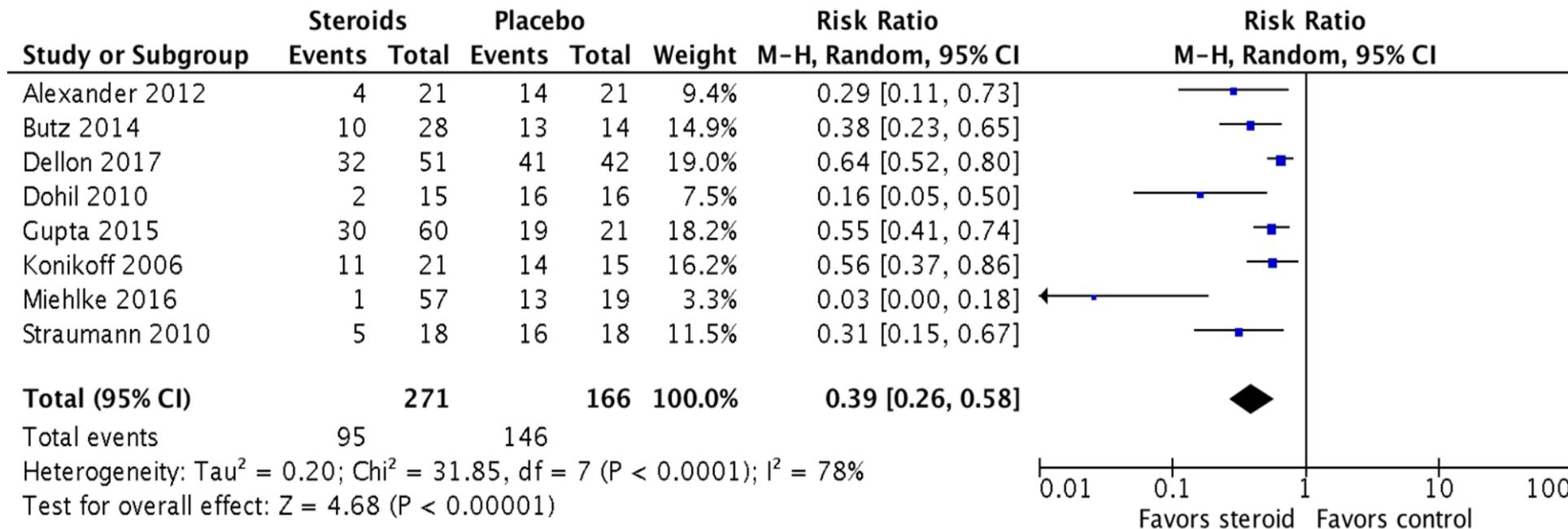


AGA Guidelines: Management of Eosinophilic Esophagitis

Corticosteroid Therapy: Topical Corticosteroids

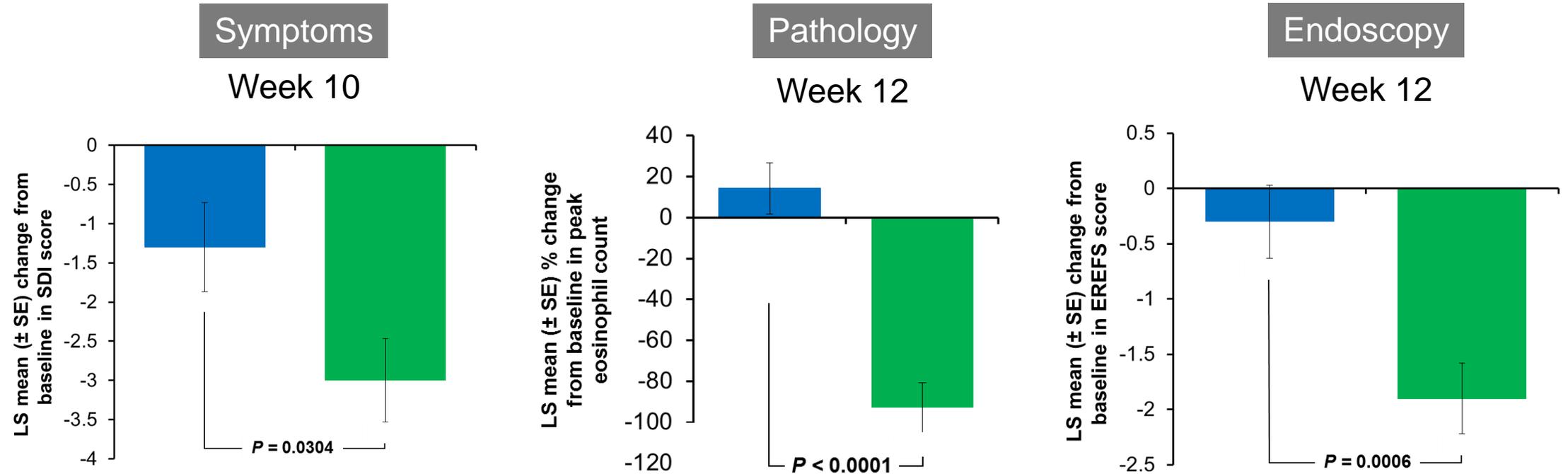
Recommendation: In patients with EoE, the AGA/JTF recommends topical steroids over no treatment (strong recommendation, moderate quality evidence).

Forest plot for not achieving histologic remission



65% achieving histologic response

Dupilumab (Anti-IL4R) reduced dysphagia, esophageal eosinophilia and endoscopic activity in a phase 2 study in adults with EoE



■ Placebo (n/N = 14/24)

■ Dupilumab 300 mg every week (n/N = 17/23)

LS=Least Squares; SDI=Straumann Dysphagia Index, Eosinophilic Esophagitis Endoscopic Reference Score SE=Standard Error

Case 4

- EGD reveals endoscopic features of EoE and esophageal biopsies with > 100 eosinophils/HPF
- Patient would like to avoid chronic medications and has heard that dietary therapy is possible in EoE
- What would you recommend?
 - A. Refer to Allergist for food allergy testing
 - B. Eliminate meats and breads as those cause most symptoms
 - C. Eliminate dairy only
 - D. Eliminate dairy, wheat, eggs, soy, tree nuts and seafood

What would you recommend?

Refer to Allergist for food
allergy testing

Eliminate meats and breads as
those cause most symptoms

Eliminate dairy only

Eliminate dairy, wheat, eggs,
soy, tree nuts and seafood

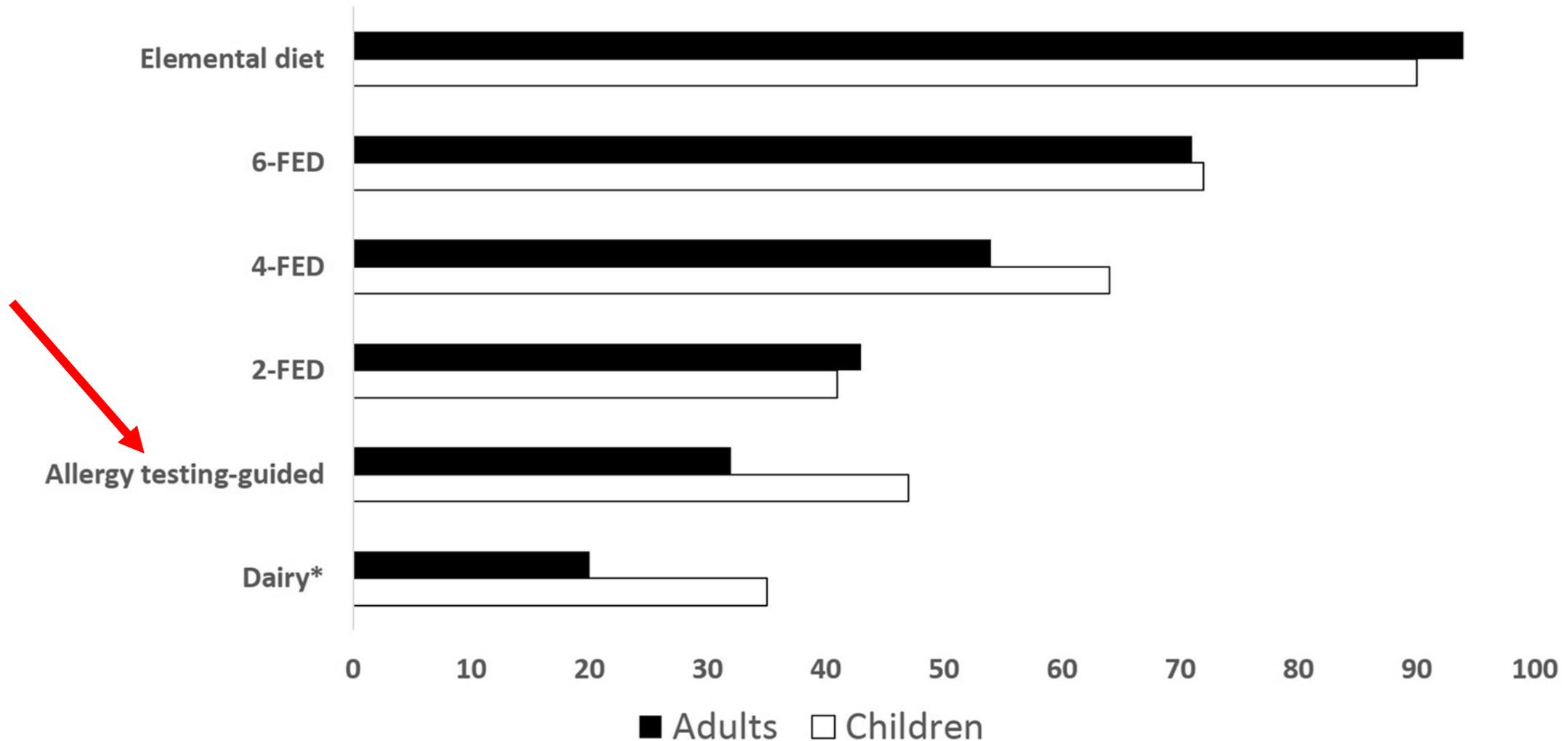
Dietary Therapy in EoE

- Elemental Diet (allergen-free) effective in children
- More practical: Empiric food elimination diet
- Eliminates most common food allergens:

Elimination Diets: What to Eliminate

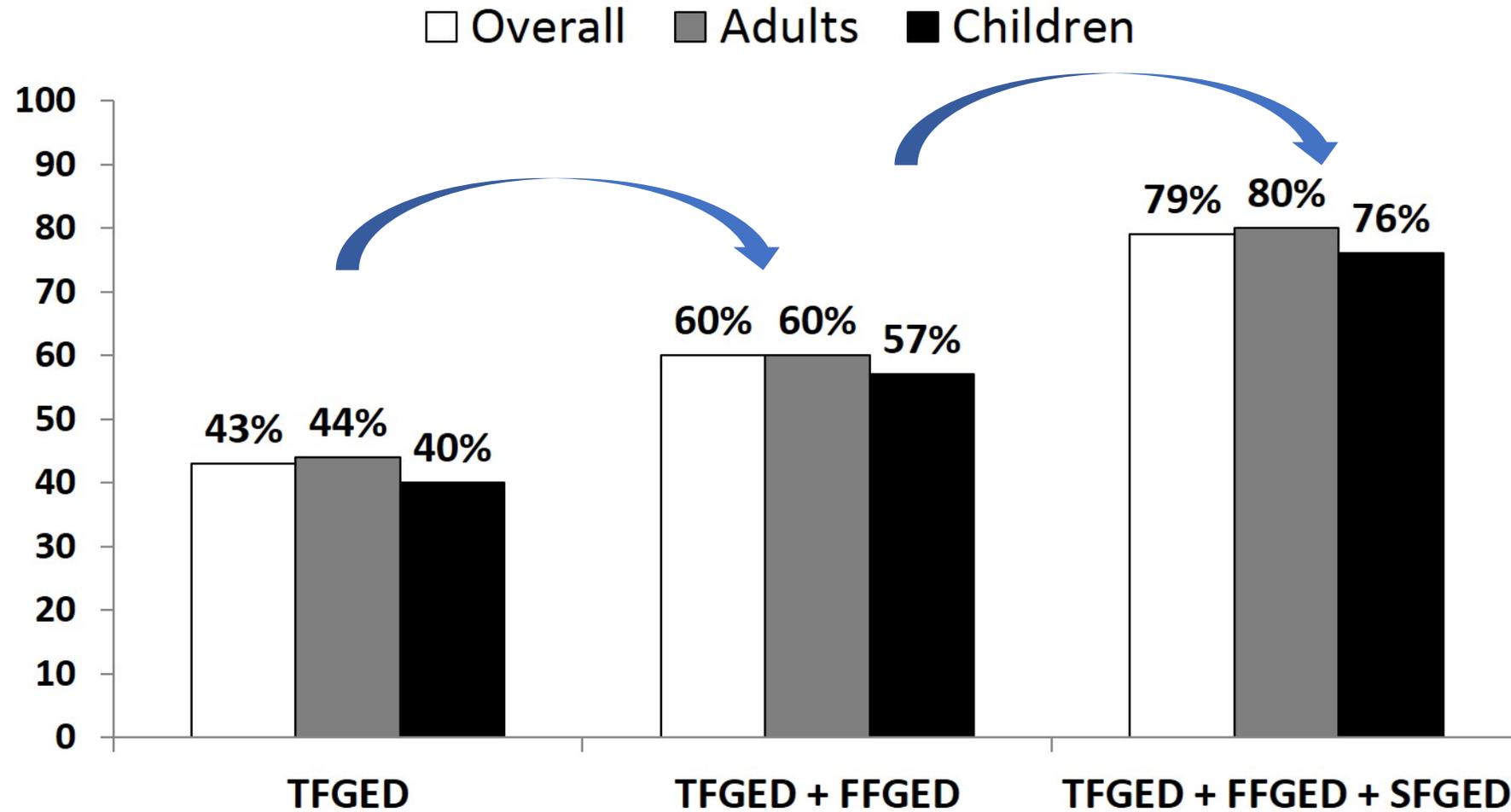
	6-Food (SFED)	4-Food (FFED)	2-Food	1-Food
Cow's milk	✓	✓	✓	✓
Wheat	✓	✓	✓	
Egg	✓	✓		
Soy	✓	✓		
Peanut/tree nut	✓			
Fish/Seafood	✓			

Comparison of diet therapies for EoE in children and adults



2-4-6 Step Up Diet for EoE

Histologic remission (< 15 eos/HPF)



Case 5: A different patient

25 yo diagnosed with EoE. On no planet do they want to avoid dairy and wheat. Undergoes dilation with improvement in symptoms. 8 week trial of daily PPI (or swallowed fluticasone) leads to resolution of esophageal eosinophilia on follow-up endoscopy.

What would you recommend next?

- A. Continue medical treatment indefinitely
- B. Use medical treatment as needed for recurrence of symptoms
- C. Stop treatment and repeat endoscopy with symptom recurrence to confirm return of esophageal eosinophilia

What would you recommend next?

Continue medical treatment
indefinitely

Use medical treatment as needed for
recurrence of symptoms

Stop treatment and repeat endoscopy
with symptom recurrence to confirm
return of esophageal eosinophilia

Rationale for maintenance therapy in EoE

EoE is a chronic disease

- Symptoms and esophageal eosinophilia persist without treatment
 - Untreated cohorts;* placebo arms of clinical trials
- Children do not “grow out” of EoE** and EoE is not (yet) curable
- Near universal recurrence if treatment is stopped
 - Randomized withdrawal studies#
 - Observation off-treatment after initial response##
 - Similar data for stopping dietary elimination

*Straumann AM, et al. *Gastroenterology*. 2013;145(6):1230-6.e1-2

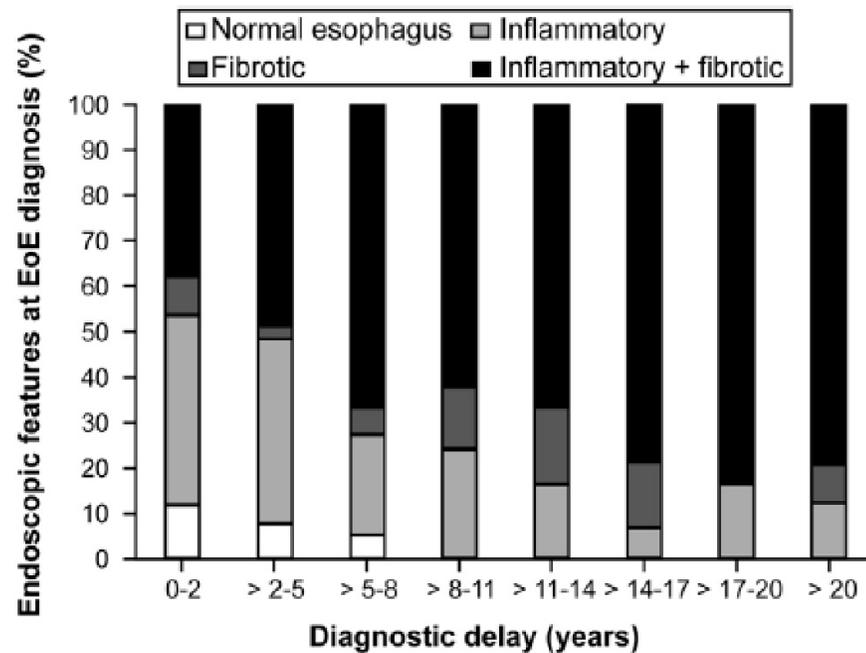
**Ruffner MA. *JACI*, 2018

#Straumann A, *Clin Gastroenterol Hepatol*. 2011;9(5):400-9.e1; Lucendo A, Presented at *DDW*. 2017

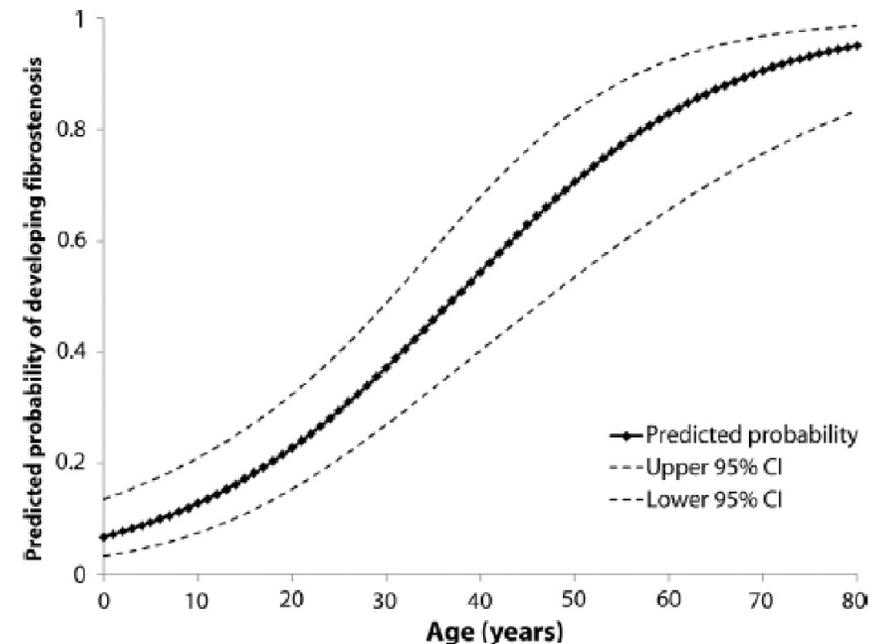
##Dellon ES, et al. *Clin Gastroenterol Hepatol*. 2020;18(7):1483-1492.e2; Greuter T, et al. *Am J Gastroenterol*. 2017;112(10):1527-1535

EoE natural history

Diagnostic delay and fibrostenosis – consistent results in 4 studies

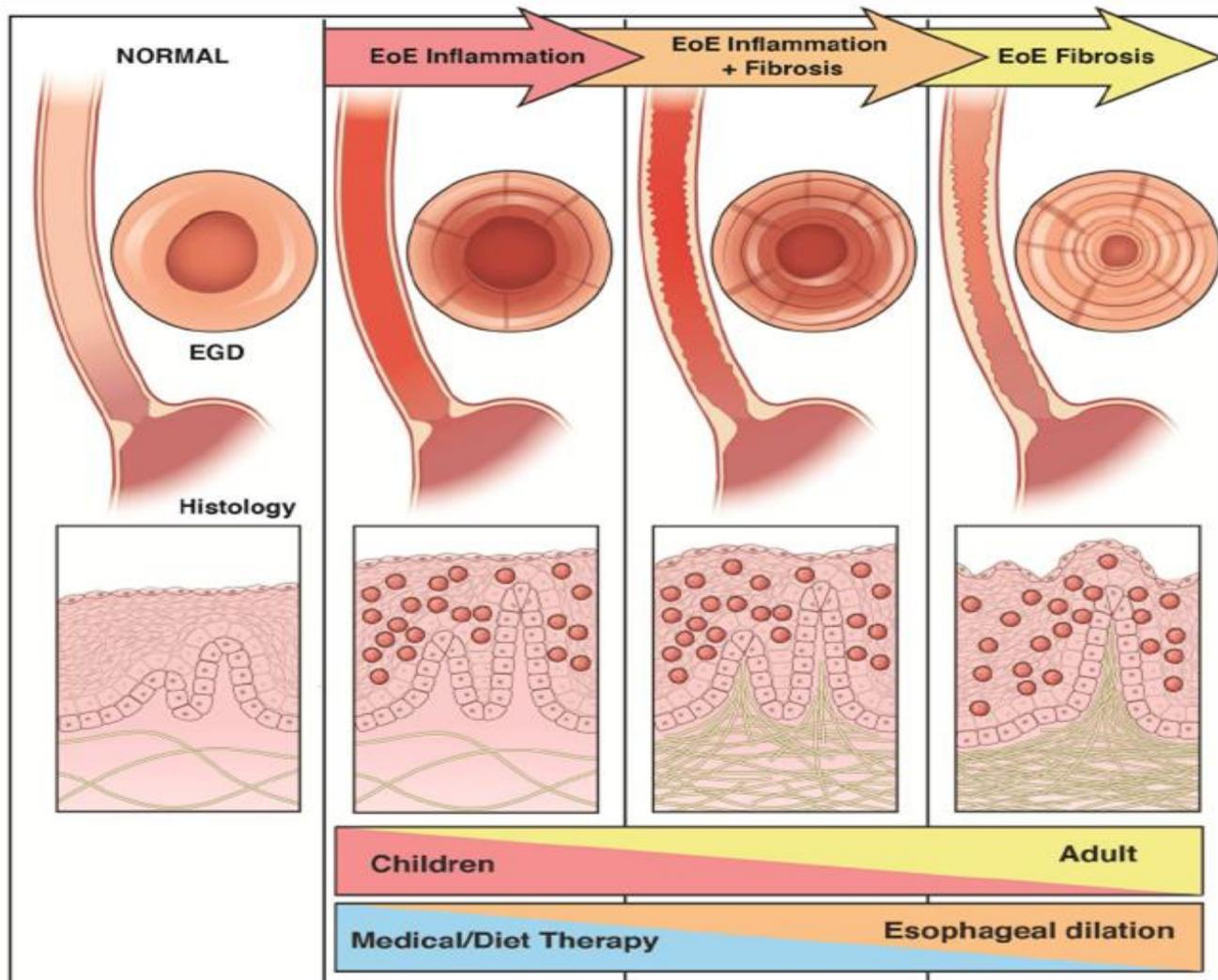


Prevalence of fibrotic features increased **from 47%** (diagnostic delay-2 years) **to 88%** (diagnostic delay, >20 years)



Every ten year increase in age, odds of fibrostenotic phenotype **more than doubled**

EoE as a Continuum From Inflammation to Fibrosis



Inflammation leads to fibrosis over time

- Explains different symptoms in children vs adults

Diagnostic delay leads to greater rates of stricture

- Necessitates both anti-inflammatory and dilation treatments in some patients

Rationale for maintenance therapy in EoE

EoE is a chronic disease

- Symptoms and esophageal eosinophilia persist without treatment
 - Untreated cohorts;* placebo arms of clinical trials
- Children do not “grow out” of EoE** and EoE is not (yet) curable
- Consider reduction in corticosteroid dose with prolonged use
- Near universal recurrence if treatment is stopped
 - Randomized withdrawal studies#
 - Observation off-treatment after initial response##
 - Similar data for stopping dietary elimination

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Summary

- Pathologic reflux can be confirmed or refuted with ambulatory pH monitoring
- In patients who are unable to come off medical therapy or have atypical symptoms (less likely to be GERD) consider objective testing with endoscopy and pH monitoring OFF PPI
- Antireflux procedures are an option for pathologic GERD
- Functional disorders can mimic GERD and are treated differently
- EoE is a chronic allergic inflammatory disease
- EoE treatments include PPIs, topical steroids, Dupilumab and dietary therapy

Questions & Discussion (I hope)

- Situations for BID PPI
- Other GERD treatments
 - Nighttime H2RA
 - Alginates
 - Elevating head of bed
 - Prokinetics/Gastroparesis treatments
- Role of esophageal manometry in GERD
- Loss of response to treatment in EoE (or GERD)
- When to screen for GERD complications (Barrett's)
- Surveillance endoscopy in EoE/GERD
- Burden of endoscopy

