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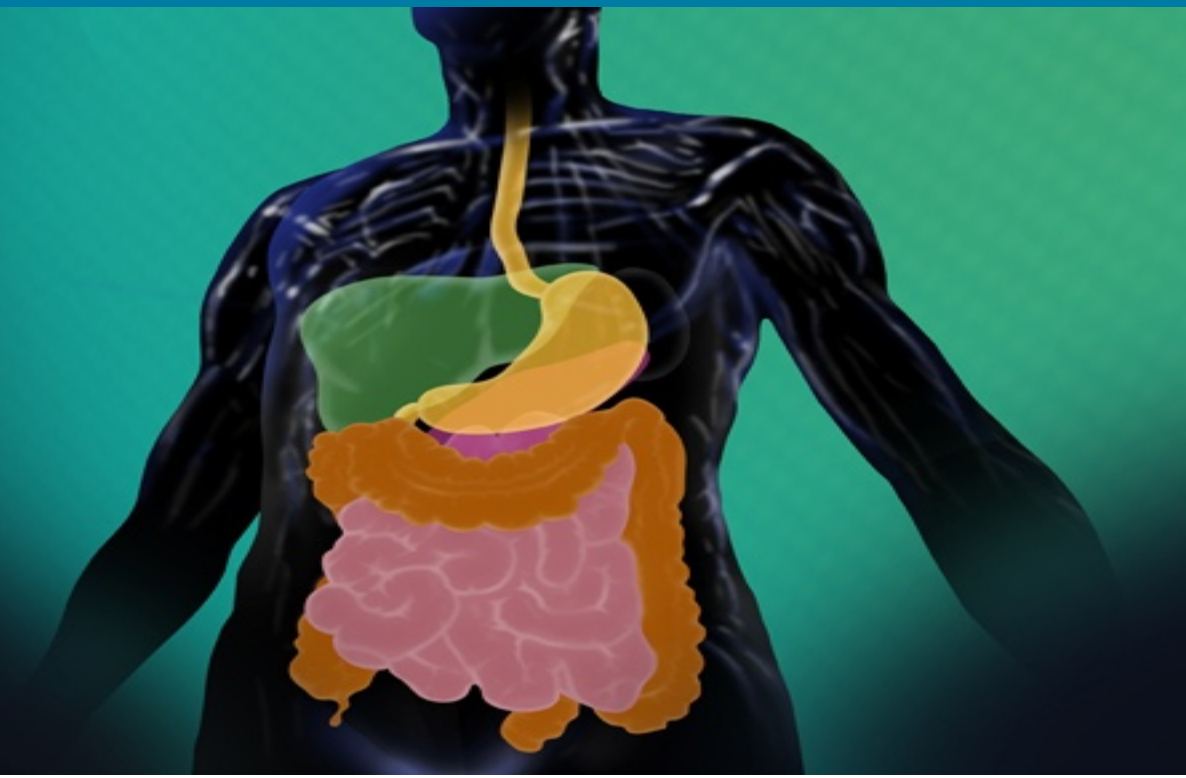
GERD, peptic ulcer disease, and celiac disease: updates from the upper GI tract



Updates in General Internal Medicine for Specialists
January 29, 2020

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Disclosures

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Consultant for Shire plc, Synergy, and Bayer Ag

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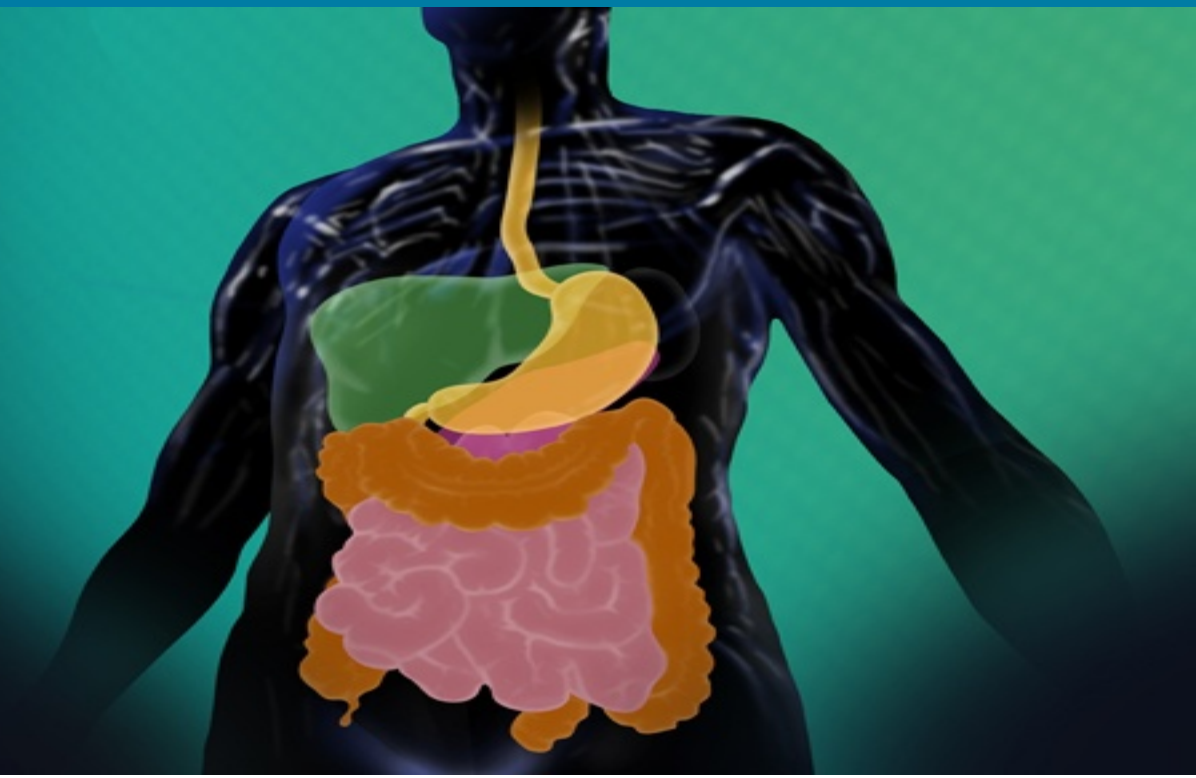
Part I: Gastroesophageal Reflux Disease (GERD)



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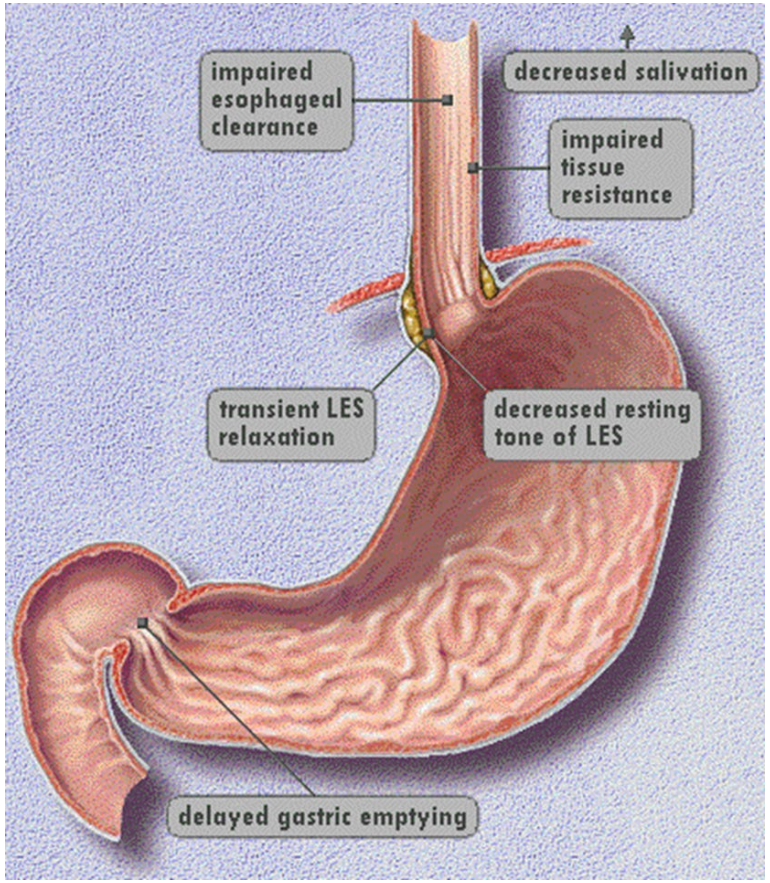
Definitions

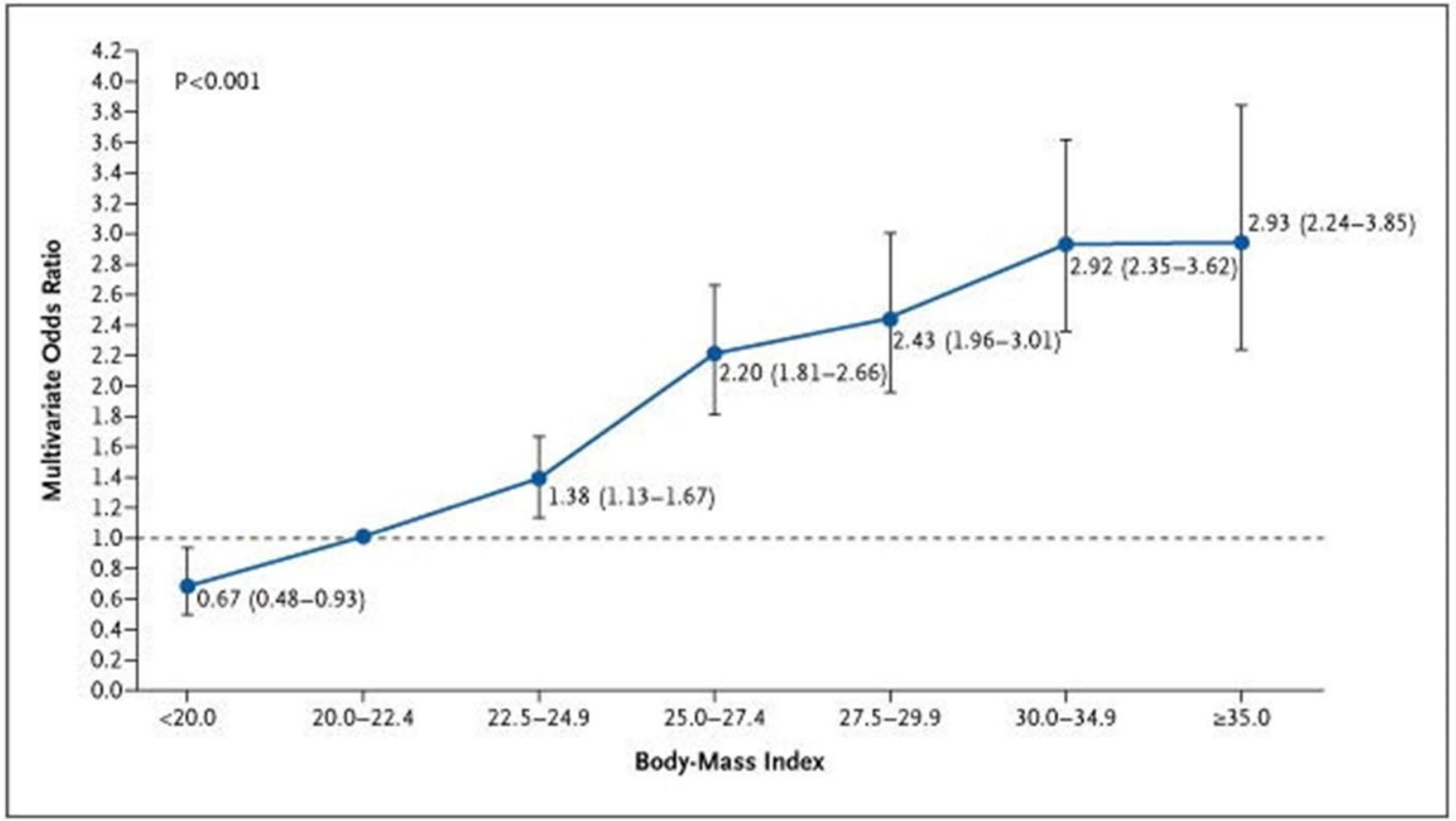
- GERD develops when the reflux of stomach contents causes symptoms/complications
  - Reflux that is not troublesome is not GERD
  - “Troublesome”: mild symptoms 2 or more times/week or severe symptoms 1 or more times/week
- Hallmark symptom of GERD is <u>heartburn</u>



Risk factors for GERD

- Obesity

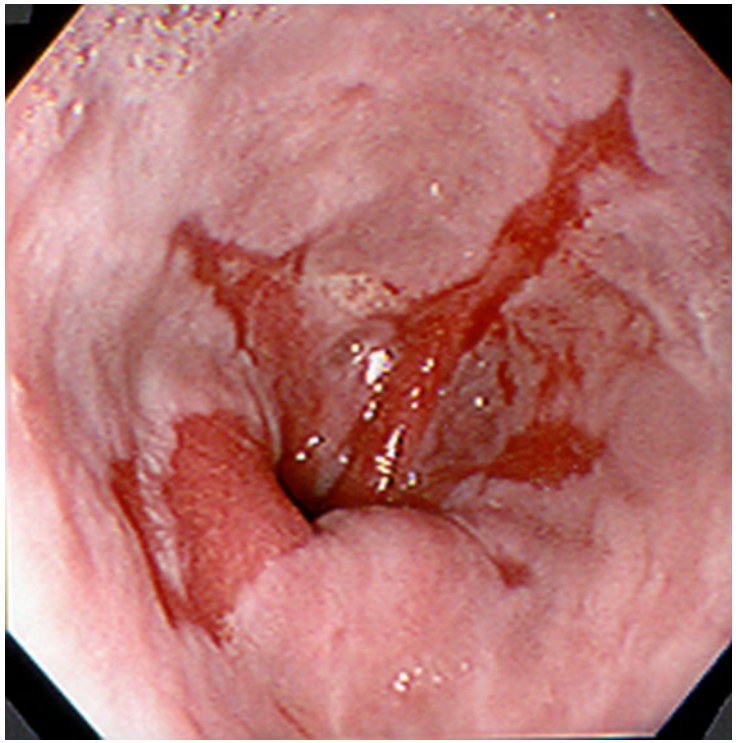
Risk factors for GERD



Risk factors for GERD

- Obesity
- Smoking
- Menopausal hormone therapy (formerly HRT)
- Asthma/COPD
- Connective tissue disease (i.e. scleroderma)
- Medications (bisphosphonates)

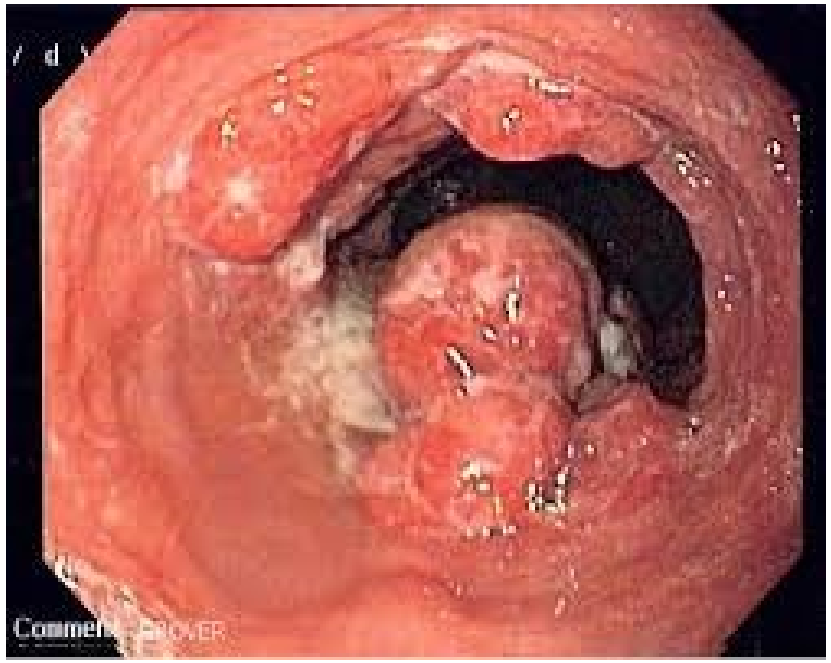
Typical complications



- Erosive esophagitis
- Barrett's esophagus
  - Risk of progression to adenocarcinoma:
    - 0.12-0.38% per year
  - Screening interval generally 3 years, but not evidence-based
  - Frequency/duration of sxs do not predict Barrett's

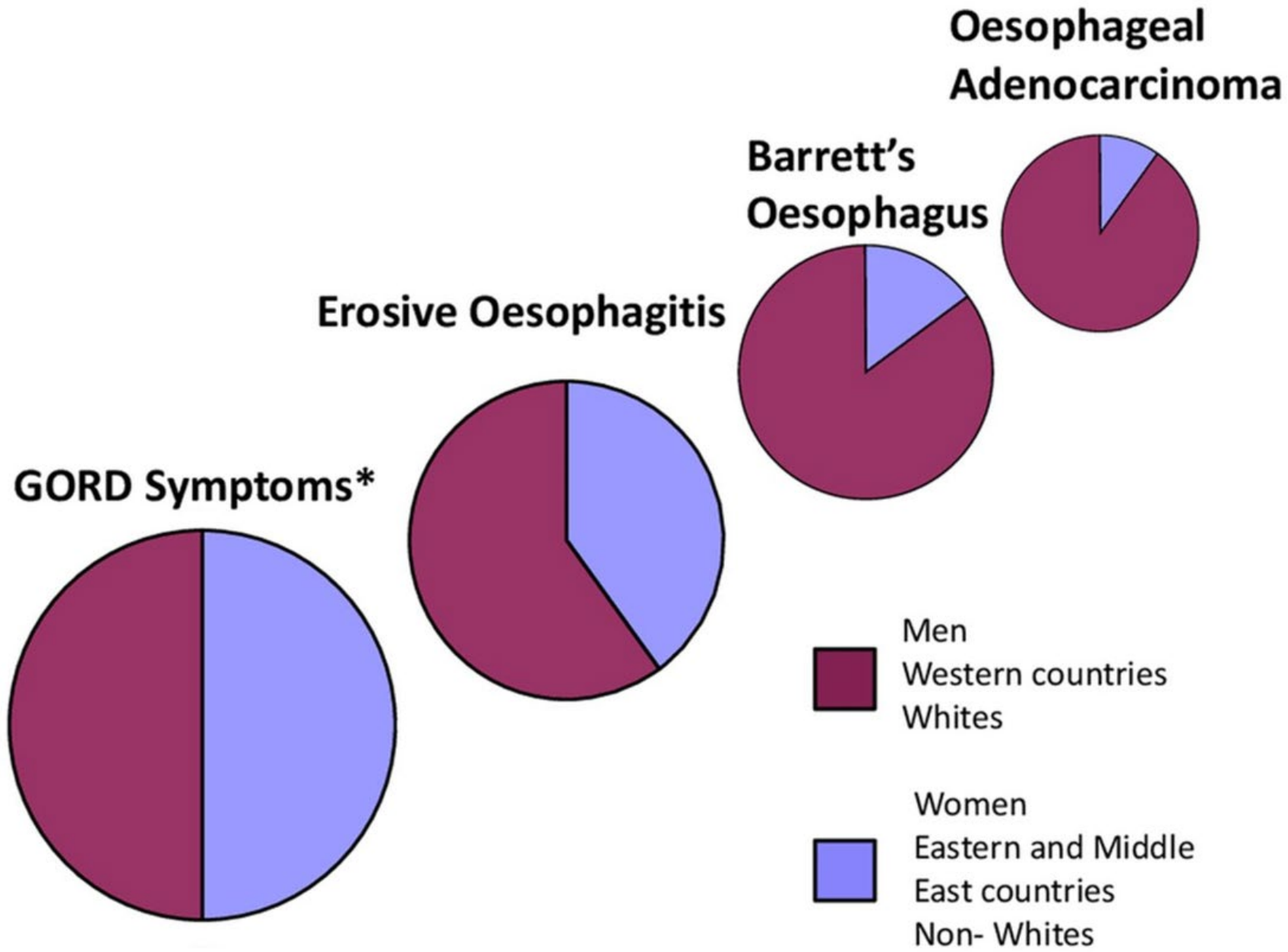
Mayo Clin Proc. 2014 Jul;89(7):973-984.

More serious complications



- Esophageal adenocarcinoma
  - Rates increasing rapidly in the western world
  - Increased risk with heartburn duration and frequency
  - Risk of development increases with age
  - Increasingly seeing in younger populations
  - Male-predominant (9:1)
  - White-predominant (5:1 compared to blacks)

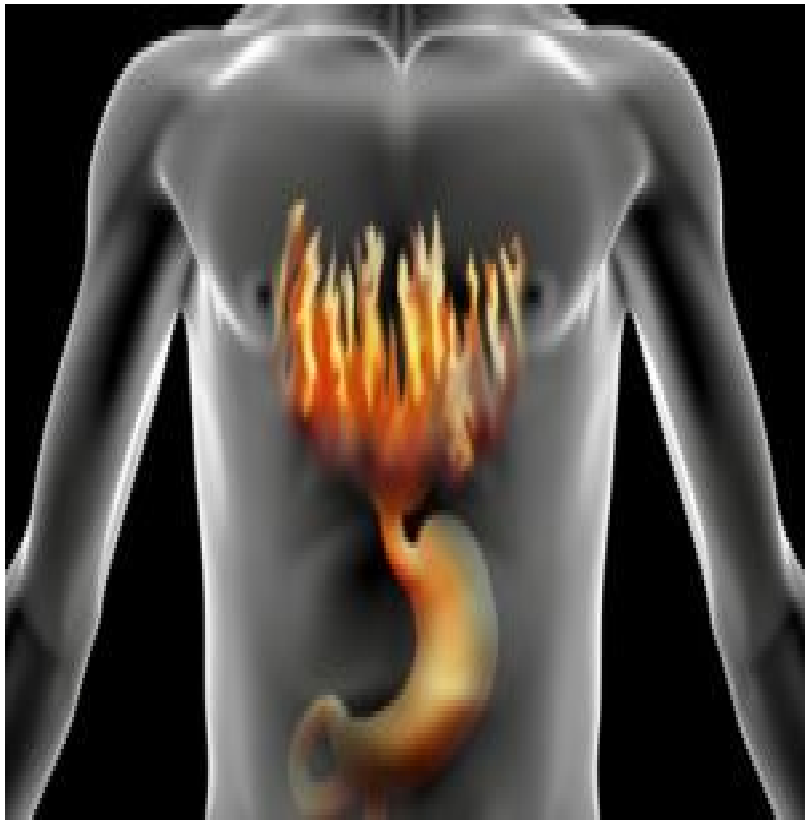
PLoS One. 2014 Jul 30;9(7):e103508.
Clin Gastroenterol Hepatol. 2016 Mar;14(3):338-347.e1.



Gut. 2014 Jul;63(7):1185-93.

GERD has atypical symptoms

- Chest pain
- Chronic cough
- Chronic laryngitis
- Asthma
- GERD often not the sole cause of atypical symptoms
- Atypical symptoms without concomitant heartburn/reflux unlikely to be due to GERD



Diagnostic testing

- Clinical diagnosis (young (<55 years old) with classic symptoms)
- No alarm symptoms
  - Weight loss
  - Bleeding
  - Dysphagia
  - Family history of esophageal or gastric cancer
- Diagnostic/therapeutic acid suppression
  - Best sensitivity in patients with classic heartburn or chest pain
- Barium swallow? (NO → reflux common in healthy pts)
- Laryngoscopy (NO → laryngeal irritation in 80% healthy pts)

Clin Gastroenterol Hepatol. 2017 Aug;15(8):1162-1172.

When to order an upper endoscopy

- Useful with any alarm symptoms
- Can evaluate for mucosal disease but beware
  - Presence of erosive esophagitis confirms GERD
  - EGD normal in 2/3 of patients with heartburn and regurgitation
- GERD symptoms to prompt EGD:
  - Refractory to treatment
  - Long duration of symptoms
  - Atypical symptoms, dysphagia
- Age threshold (>60 years old?)
- Keep pH testing in your back pocket
  - Cost benefit over prolonged PPI (>8 weeks) use

J Gastrointest Surg. 2014 Jan;18(1):26-33
Clin Gastroenterol Hepatol. 2017 Aug;15(8):1162-1172

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Management of GERD

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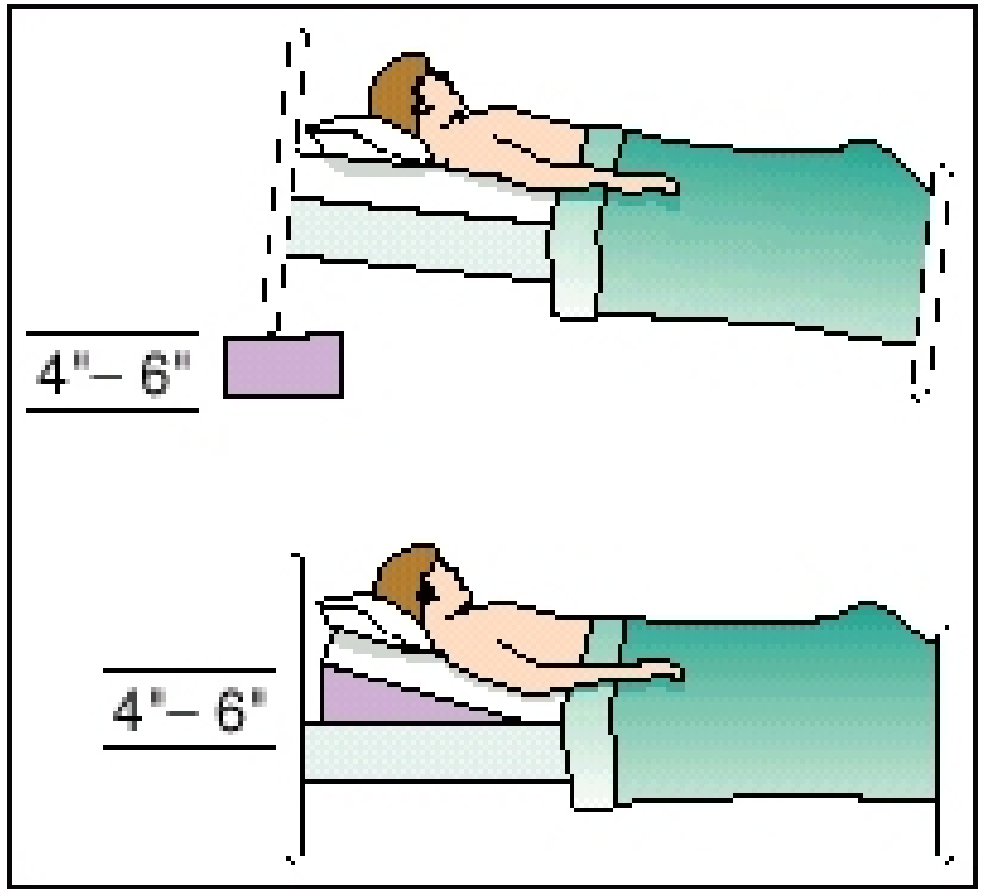
Lifestyle modification

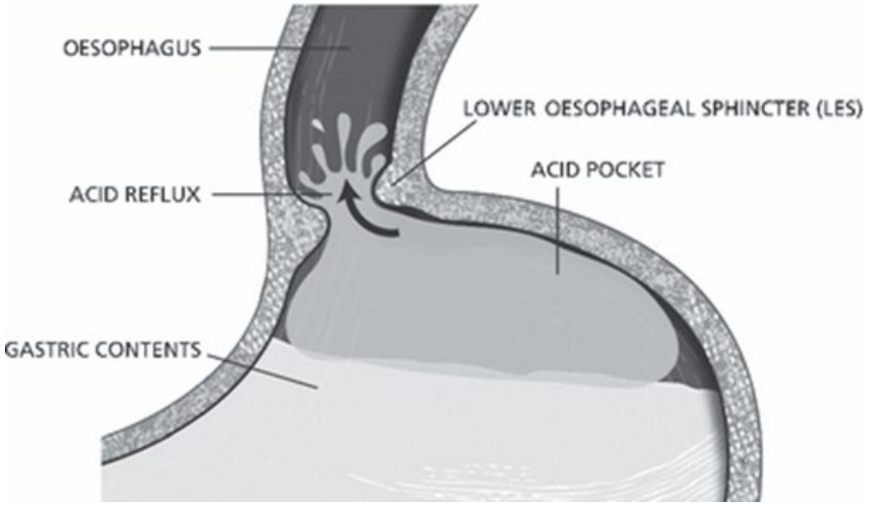
- Evidence for improvement is mostly anecdotal
- Weight loss and stopping smoking the only *proven* ways to reduce heartburn symptoms
- Weight reduction
  - Decrease in BMI of as little as 3.5 lbs/in^2 could result in a 40% decrease in symptom frequency
  - Differential effects of bariatric surgery based on type
    - Roux-en-Y (↓ reflux)
    - Sleeve gastrectomy (↑ reflux)
- Avoid late meals/raise head of bed (<u>most reflux in daytime</u>)
  - Only makes sense for nocturnal symptoms
- Trigger foods are *not* the cause of chronic GERD

N Engl J Med. 2006 Jun 1;354(22):2340-8.
Clin Gastroenterol Hepatol. 2016 Feb;14(2):175-82.e1-3.


4"– 6"
4"– 6"

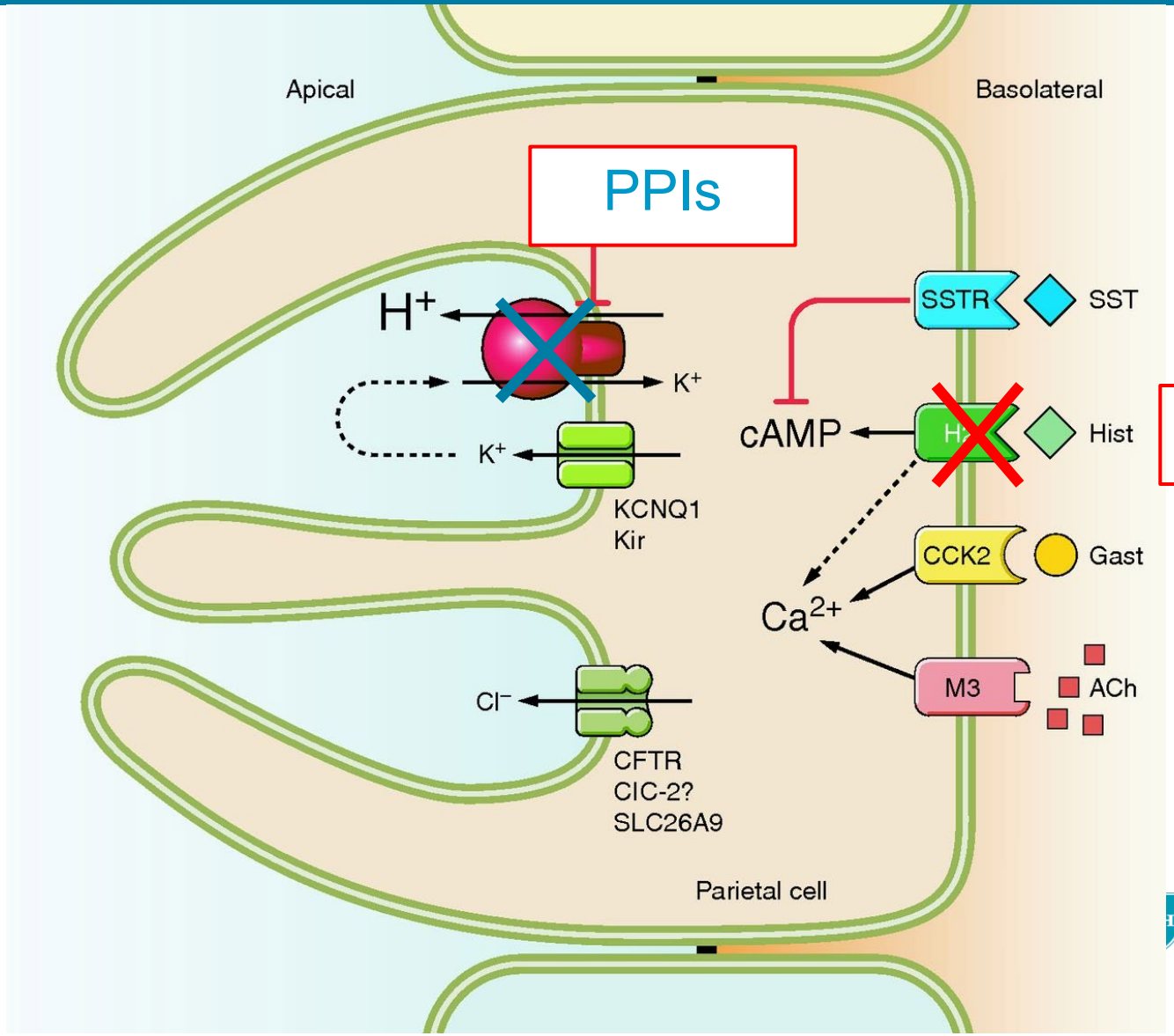
Antacids

- Generally useful for mild symptoms
- Work quickly for on-demand use
- The “acid pocket”
  - Post-prandial phenomenon where highly-acidic fluid sits on top of stomach
  - Alginate antacids (Gaviscon) form an “alginate raft” and can shrink or abolish the acid pocket
  - Rafts can push pocket below diaphragm
  - Alginates for post-prandial symptoms?



Aliment Pharmacol Ther. 2008 Feb 1;27(3):249-56

H2 receptor antagonists vs. PPIs



H2 receptor antagonists vs. proton pump inhibitors

- H2 receptor antagonists
  - Ranitidine, cimetidine, famotidine (generic, OTC)
  - Rapid action
  - Not influenced by meals
  - Weaker than PPI
  - Tachyphylaxis

- Proton pump inhibitors
  - Omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole
  - Needs to be taken prior to a meal
  - Even bid acid suppression is not complete

Proton pump inhibitor failure: what next?

- Most PPIs are basically the same (i.e. the most expensive drug is not going to be the difference maker)

Table 1. Potency of PPIs Based on OE

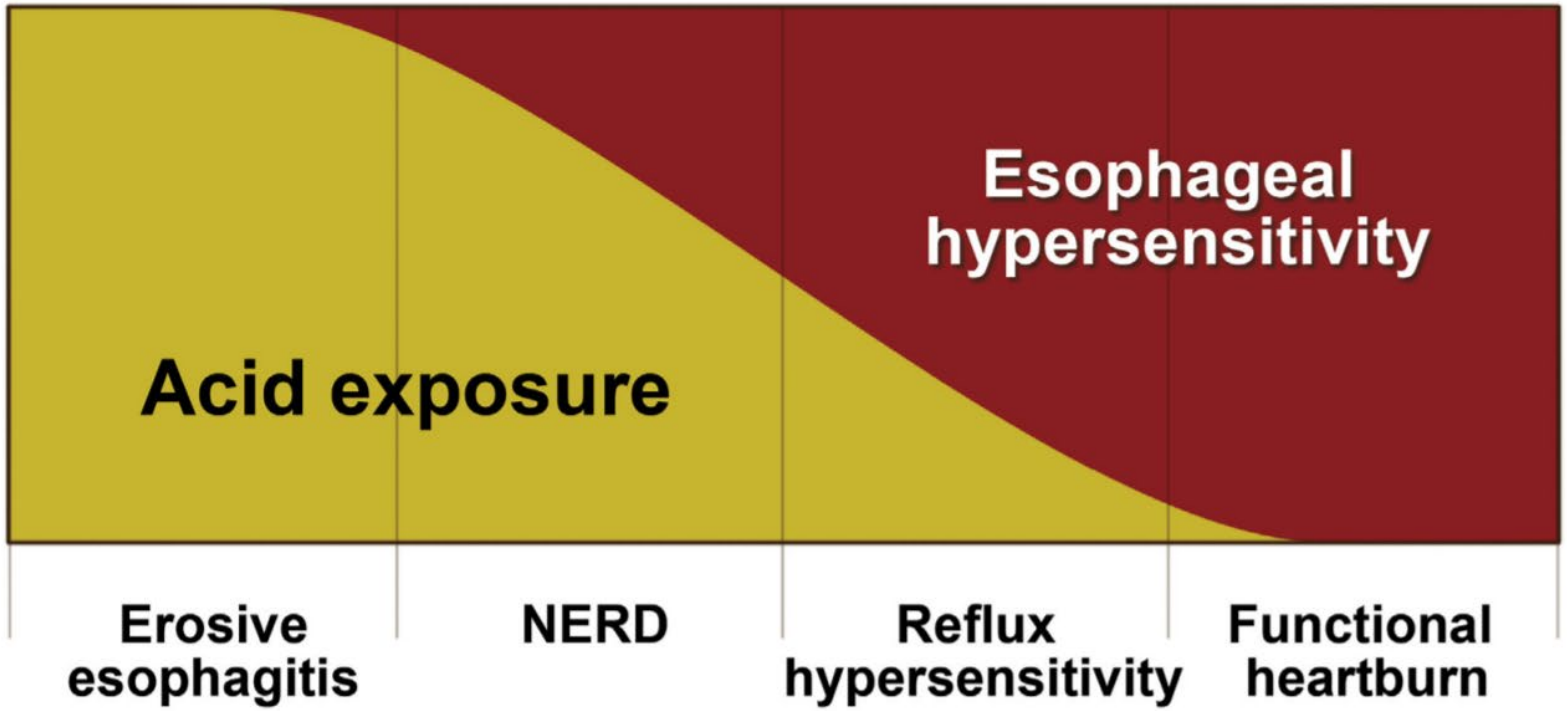
Drug at lowest available dosage	OE
Pantoprazole 20 mg	4.5 mg
Lansoprazole 15 mg	13.5 mg
Omeprazole 20 mg	20 mg
Esomeprazole 20 mg	32 mg
Rabeprazole 20 mg	36 mg

NOTE. PPIs are listed in order of increasing potency.[17]
OE, omeprazole equivalent; PPIs, proton pump inhibitors.

Proton pump inhibitor failure: what next?

- Dosing time
  - Essential that PPIs are taken at least 30 minutes before a meal
  - Ensure that PPI dosing times correspond to symptom times
- Insufficient dosing
  - Don’t be afraid to push dose twice daily dosing as a diagnostic/therapeutic trial…but don’t forget to d/c if no improvement
- Visceral hypersensitivity or functional heartburn
  - Exquisite sensitivity to normal amount of acidic reflux
  - Sensitivity to non-acid reflux (after neutralization by PPIs)

Proton pump inhibitor failure: what next?

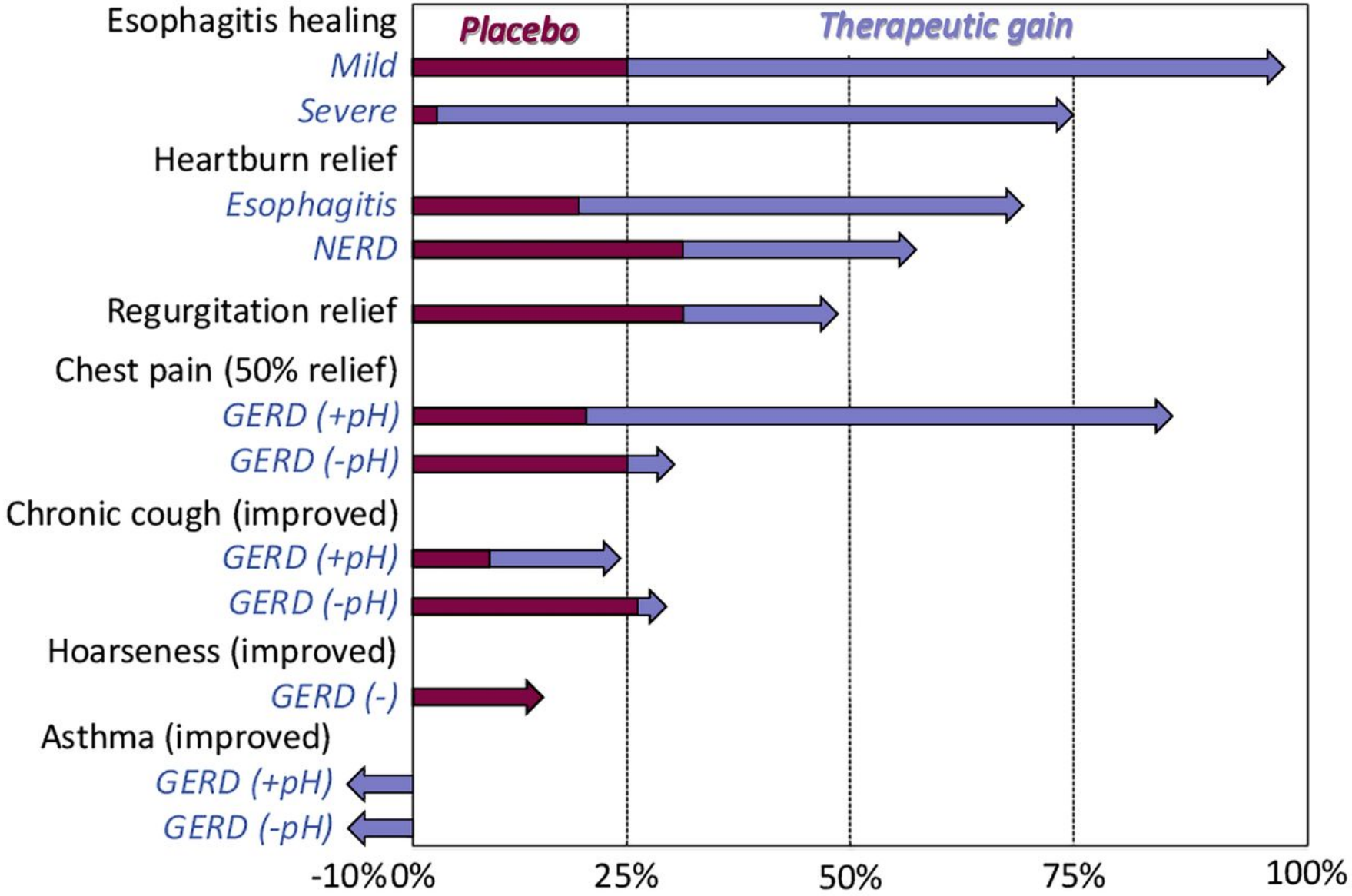


- Alternative diagnosis? (more on that later)
- Anti-reflux surgery (only for people who respond to PPIs)

Gastroenterology. 2016 Feb 15. pii: S0016-5085(16)00178-5.

PPI efficacy for potential manifestations of GERD

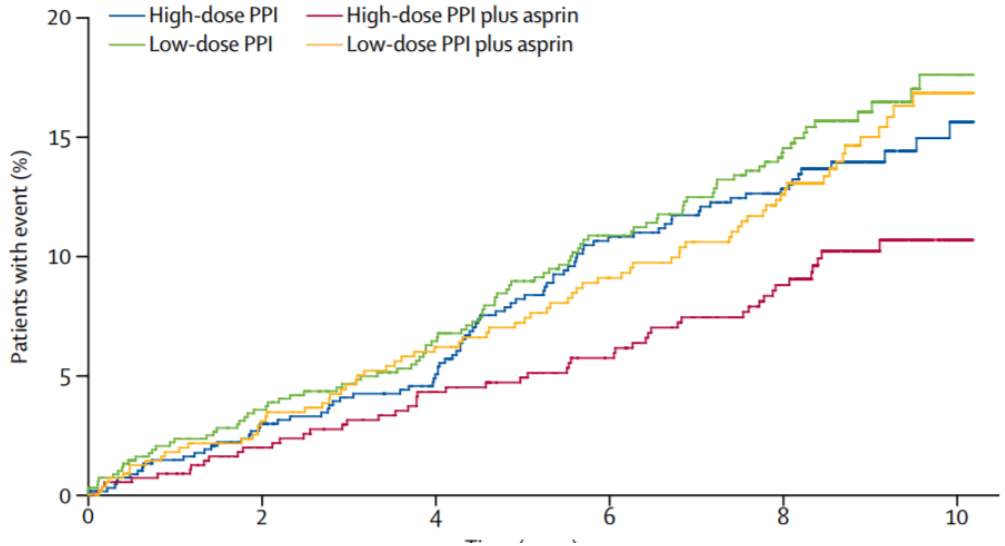
Estimates based on available RCT data



Gut 2014;63:1185-1193

Long-term treatment

- <u>Most true GERD patients require long-term treatment</u>
- GERD + esophagitis?
  - *Probably needs lifelong treatment*
- GERD w/ Barrett's esophagus?
  - *Benefit to lifelong treatment*
  - *Recent RCT showing benefit to PPI use over 9 years*
- GERD without esophagitis?
  - *Consider on-demand PPI therapy (!?!)*



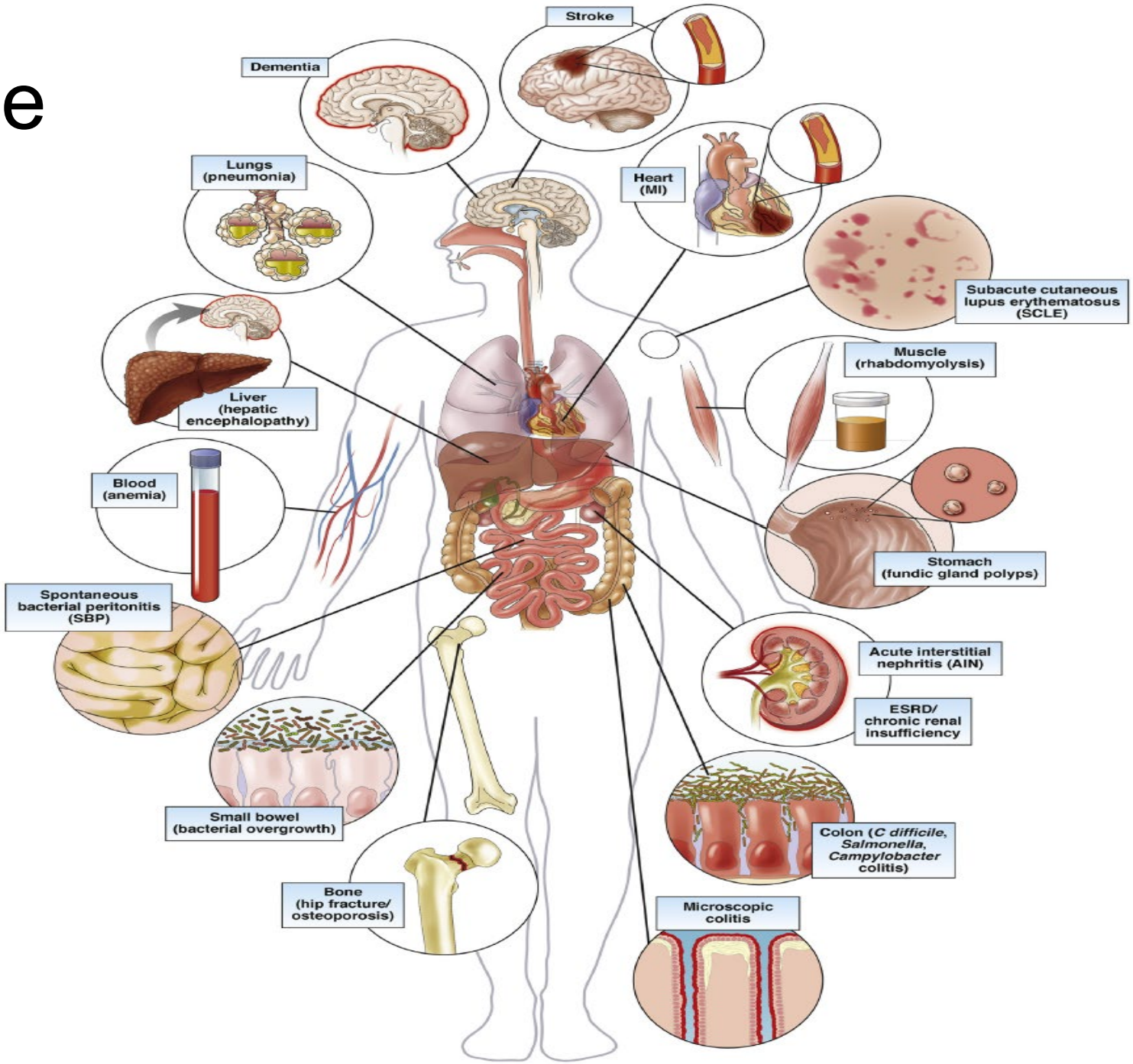
Gastroenterology. 2017 Mar;152(4):706-715.
Lancet. 2018 Jul 26.

Mitigating the risks of long-term PPI therapy

- Use lowest dose that is still effective at symptom control
  - Many patients inappropriately maintained on PPIs who don't need them
- Beware rebound acid hypersecretion w/ PPI stoppage and have strategy in place
  - Consider 1 week overlap with H2RA
- Know the risks of long-term PPI use but don't scare patients away who truly need them

Clin Gastroenterol Hepatol. 2018 Jun;16(6):800-808.e7.

Proposed side effects of proton pump inhibitors



Gastroenterology. 2017 Jul;153(1):35-48.

Putting risk in perspective with PPIs

- Absolute risk is actually quite small for all associations between PPIs and adverse effects
- One lottery ticket vs. two lottery tickets analogy

Table 3. Absolute and RRs for Adverse Effects Associated With Long-Term PPIs

Potential Adverse Effect	Relative Risk	Reference for Risk Estimate	Reference for Incidence Estimate	Absolute Excess Risk
Chronic kidney disease[a]	10% to 20% increase	Lazarus et al[48]	Lazarus et al[48]	0.1% to 0.3% per patient/y
Dementia[b]	4% to 80% increase	Haenisch et al[90]	Haenisch et al[90]	.07% to 1.5% per patient/y
Bone fracture[c]	30% to 4-fold increase	Yang et al[27]	Yang et al[27]	0.1% to 0.5% per patient/y
Myocardial infarction	No association in RCTs	—	—	—
Small intestinal bacterial overgrowth	2-fold to 8-fold increase	Lo et al[91]	None available	Unable to calculate
Campylobacter or *Salmonella* infection	2-fold to 6-fold increase	Bavishi et al[26]	Crim et al[92]	.03% to 0.2% per patient/y
Spontaneous bacterial peritonitis[d]	50% to 3-fold increase	Xu et al[93]	Fernandez et al[94]	3% to 16% per patient/y
Clostridium difficile infection[e]	No risk to 3-fold increase	Furuya et al[95]	Lessa et al[96]	0% to .09% per patient/y
Pneumonia	No association in RCTs	—	—	—
Micronutrient deficiencies[f]	60% to 70% increase	Lam et al[97]	Bailey et al[98]	0.3% to 0.4% per patient/y
Gastrointestinal malignancies	No association in RCTs	—	—	—

Gastroenterology. 2017 Jul;153(1):35-48.

Finally, some prospective data

Safety of Proton Pump Inhibitors Based on a Large, Multi-Year, Randomized Trial of Patients Receiving Rivaroxaban or Aspirin

- Large, multi-year RCT of people with CVD/PAD in trial of rivaroxaban, ASA, Pantoprazole
- Followed over 3 years with no increased risk of:
  - Pneumonia
  - Fractures, gastric atrophy
  - Chronic kidney disease,
  - Dementia
  - Cardiovascular disease
  - All-cause mortality

Gastroenterology

Gastroenterology. 2019 May 29. pii: S0016-5085(19)40974-8.

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Part II: Dyspepsia

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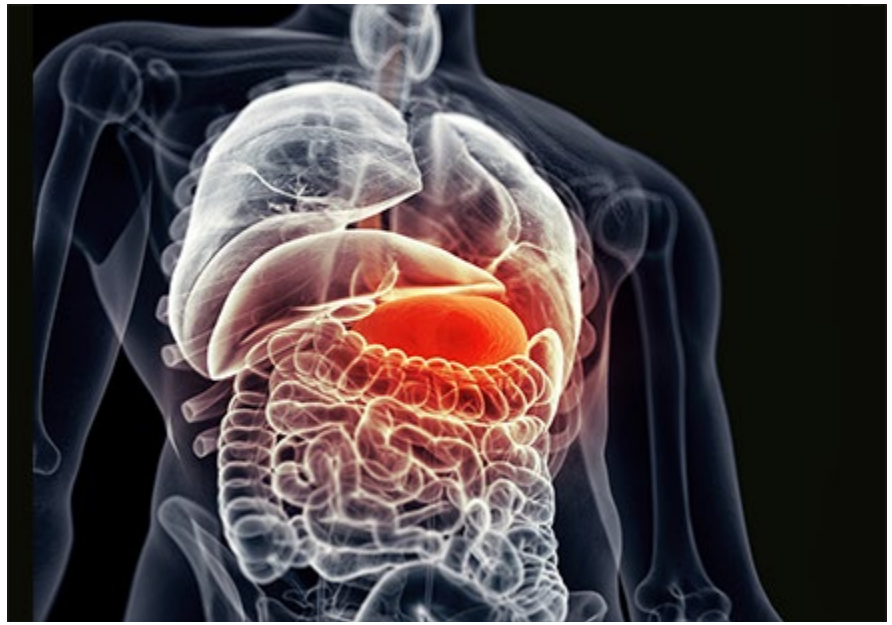
What is dyspepsia?



- Dyspepsia
  - Vague upper GI symptoms
  - Indigestion
- Differential diagnosis:
  - Peptic ulcer disease
  - Malignancy (rare)
  - Biliary pain
  - Drug-induced (NSAIDs)
  - Celiac disease
  - Chronic pancreatitis

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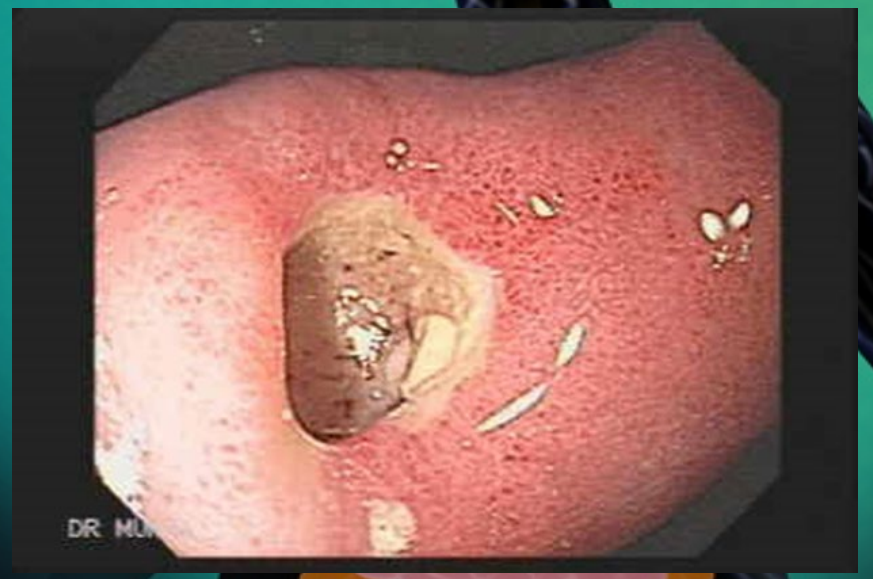
Peptic Ulcer Disease (PUD)



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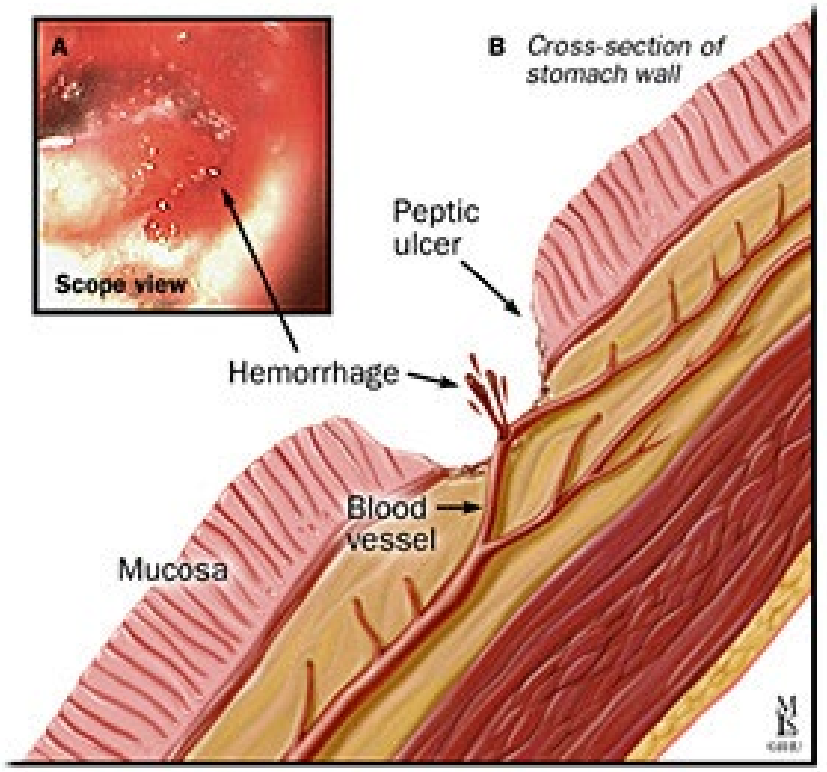
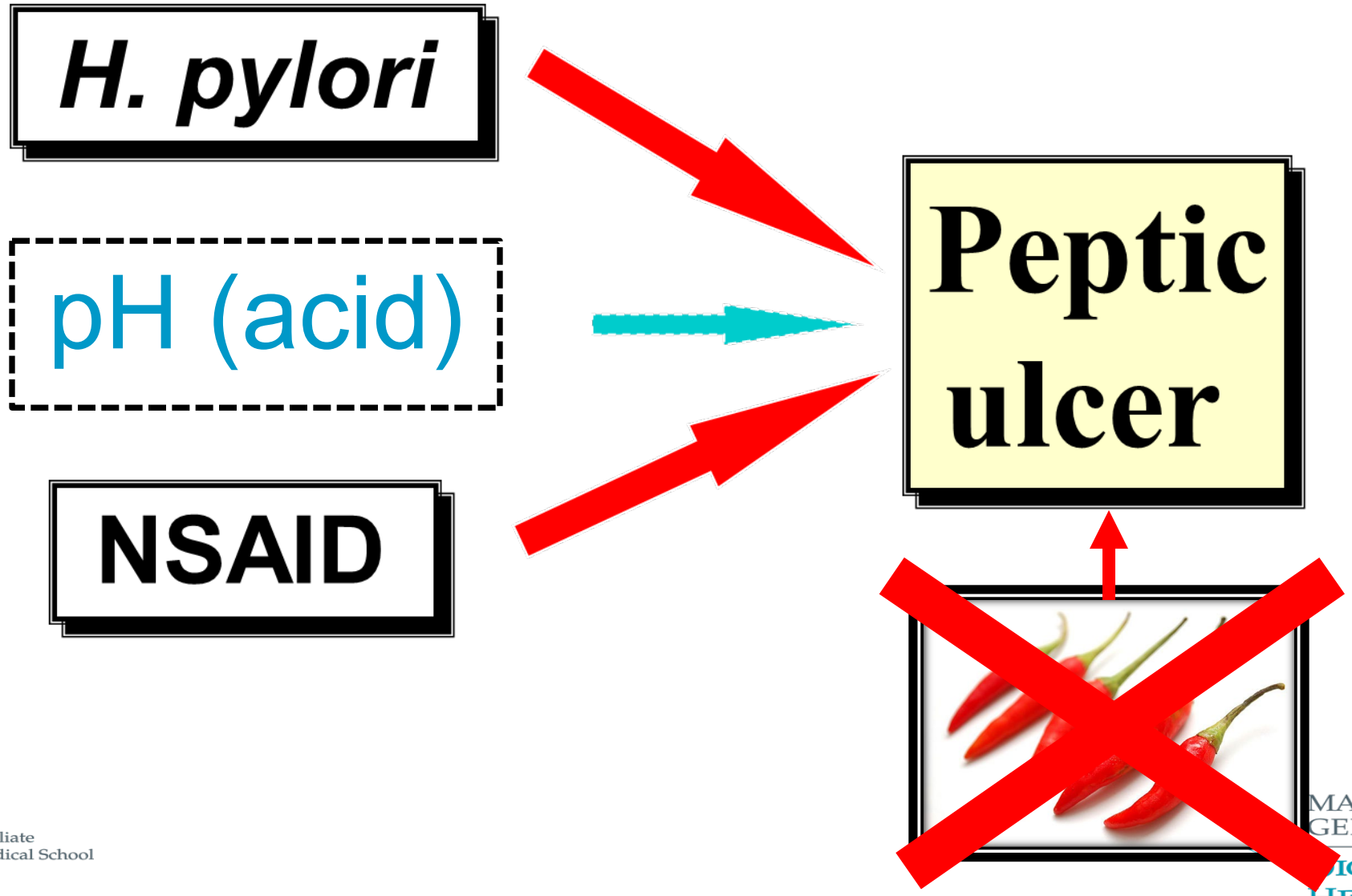
Symptoms of peptic ulcer disease

- Dyspepsia
  - Upper abdominal pain/burning
  - Vague abdominal discomfort
  - Nausea
  - Pressure/fullness
- Relationship to food (don't count on this)
  - Gastric ulcers worsened by food
  - Duodenal ulcers palliated by food
- Asymptomatic
- Gastrointestinal bleeding



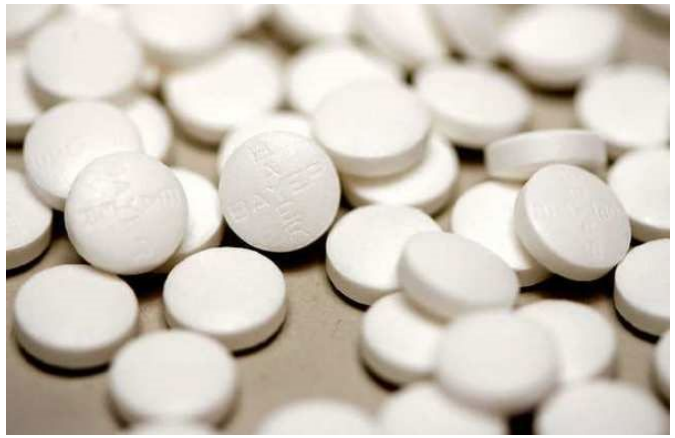
https://gi.jhsps.org/

Etiology of peptic ulcer disease



Risk of NSAID-induced ulceration

- NSAID use increases risk of gastric and duodenal ulcers by 5x
- Considered high-risk if ≥ 2 risk factors:
  - Age > 65 years old
  - High-dose NSAID therapy
  - Concurrent use of ASA (including low-dose), corticosteroids, or anticoagulants
  - Previous history of complicated ulcer
- Prevention of NSAID-induced ulceration
  - Minimize doses of NSAIDs
  - Treat H. pylori if positive
  - Standard-dose PPI
  - Misoprostol 800 mcg/day (similar efficacy to PPIs, ↑side effects)



Role of H. pylori infection

- Epidemiology
  - 10-15% of children under 12
  - 50-60% of adults over age 60
  - Decline in H. pylori infection in U.S.
  - Country of origin/ethnicity matters
    - >60% infection rate in Mexican-Americans
    - <30% in non-Hispanic whites
- Who to test?
  - All patients with gastric or duodenal ulcers
  - Patients who have gastric cancer resected or MALToma
  - Pts w/ uninvestigated dyspepsia
    - Small but real benefit compared to PPI or placebo

Gastroenterol Hepatol (N Y). 2012 Sep;8(9):623-5.

H. Pylori testing: which test to choose?

- Serology? BAD
  - Good NPV but poor PPV in low-prevalence populations (i.e. non-Hispanic Caucasian patients in U.S.)
    - Only 50% chance that + result is true
    - Not a good marker for infection clearance (can remain positive)
- Fecal antigen? BETTER
  - Need to wait 1 month s/p PPI use
- Urea breath test BEST
  - 95% sensitivity and specificity
  - Hold PPIs for at least 1 week prior to testing

Gastroenterol Hepatol (N Y). 2012 Sep;8(9):623-5.

Test and treat for new dyspepsia?

STRATEGY	COST/PATIENT	EFFECTIVENESS AT 1 YR
Test/treat → EGD	$1902	75%
PPI → EGD	$1628	78%
PPI → Test/treat → EGD	$1788	84%
Test/treat → PPI → EGD	$1680	84%

Gastroenterology. 2002 May;122(5):1270-85.

Treatment regimens for H. pylori

- First-line treatment (14 days)
  - PPI, clarithromycin 500 mg bid, amoxicillin 1000 mg bid
- H. pylori resistance rates are rising
- Clarithromycin resistance is assumed to be ≥ 15% in US so many patients will need quadruple therapy
  - PPI, bismuth subsalicylate, tetracycline, metronidazole
- Variety of second-line regimens
  - Avoid clarithromycin or metronidazole after 1st failure
  - High rates of resistance after initial treatment failure

Which patients need confirmation of eradication?

- All patients with peptic ulcer disease
- All patients with MALToma
- Do not confirm H. pylori eradication in functional dyspepsia unless recurrent symptoms
- REMINDER: never use serology to confirm H. pylori eradication

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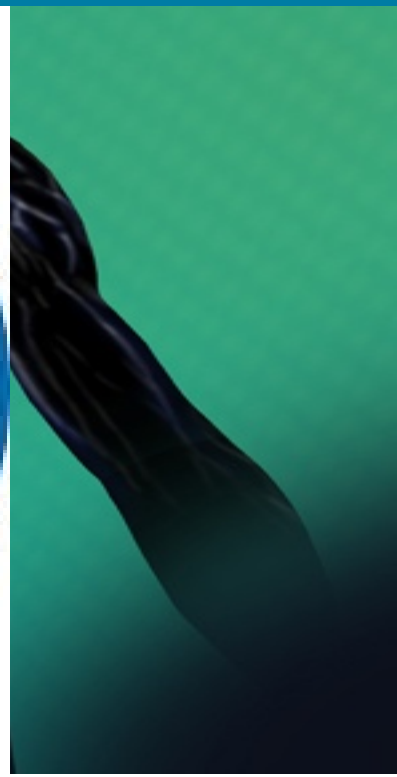
Part III: Celiac Disease



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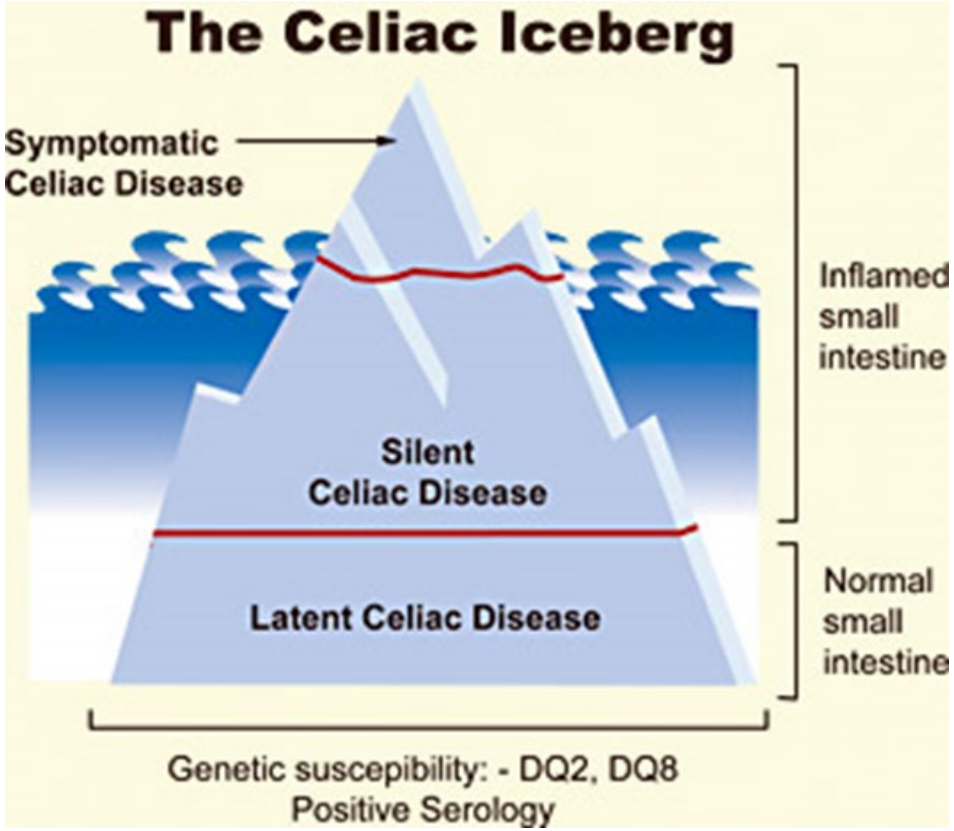
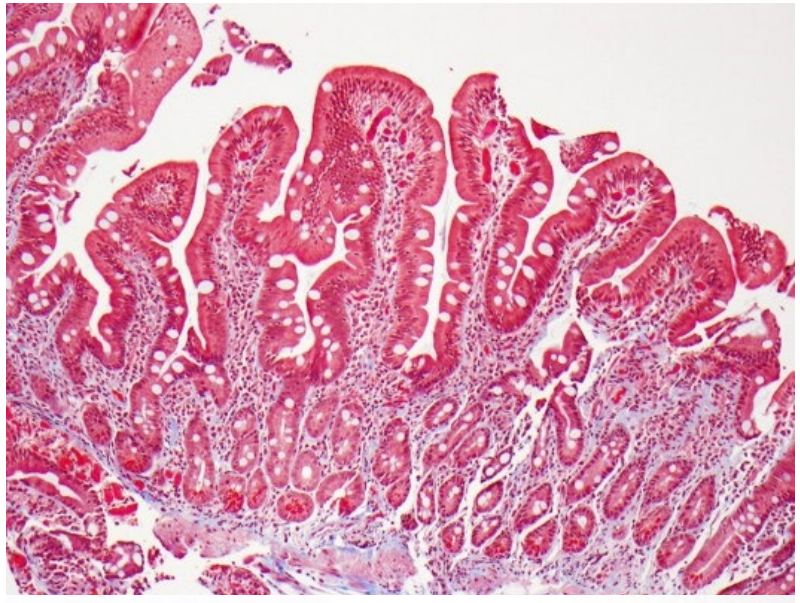
Celiac epidemiology

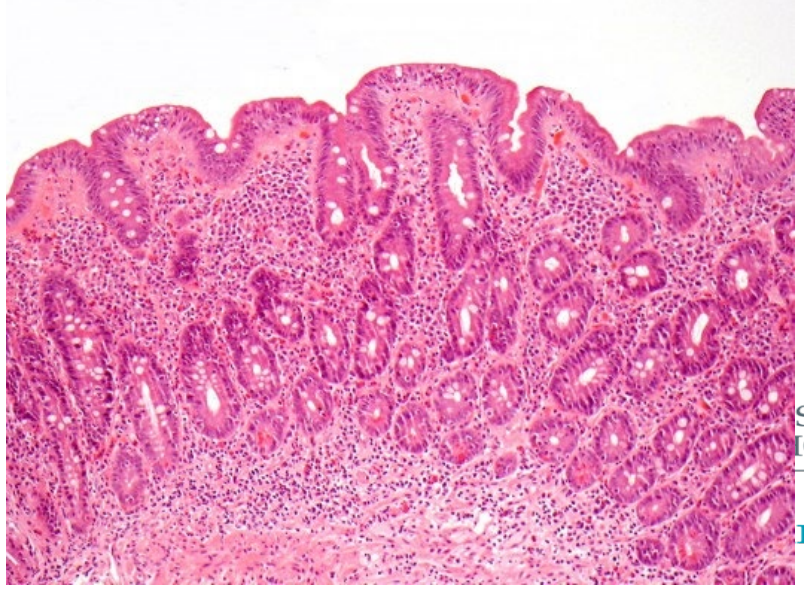


- Prevalence of 1:70-1:300
- Classically in pts of northern European descent
  - Can occur in non-whites in proper genetic background
- Prevalence increases with age
- Many cases are thought to be undiagnosed

Clinical presentation

- Classic presentation:
  - Villous atrophy with signs of malabsorption: steatorrhea, weight loss, vitamin deficiencies
- Atypical presentation:
  - Only minor GI complaints
  - Changes in dental enamel
  - Abnormal LFTs
  - Osteoporosis
  - Neurologic symptoms
  - Infertility
- Silent celiac disease





Who to test?

- ALWAYS test:
  - Patients w/ chronic GI sxs with a family history of celiac, personal history of autoimmunity or IgA deficiency
  - Chronic diarrhea
  - Dermatitis herpetiformis
  - Chronic iron deficiency anemia
- Risk of celiac
  - 1:22 in 1st-degree relatives
  - 1:39 in 2nd-degree relatives
  - 1:56 in symptomatic patients (classic symptoms)

Who to test?

- CONSIDER testing:
  - Irritable bowel syndrome
  - Unexplained abnormal LFTs
  - Iron deficiency anemia
  - Chronic fatigue
  - Recurrent aphthous ulcerations
  - Unexplained neuropathies/ataxia
  - Early-onset osteopenia
  - Infertility
  - IgA deficiency

Negative serologies adequately excludes celiac disease in these patients

How to test

Assay type	Sensitivity (%)	Specificity (%)
IgA Tissue Transglutaminase (TTG)	98 (78-100)	98 (90-100)
IgA/IgG Deamidated Gliadin Peptide (DGP)	97 (75-99)	95 (87-100)
Emdomysial Antibody (EMA)	95 (86-100)	99 (97-100)
~~IgA Anti-Gliadin Antibody (AGA)~~	~~85 (57-100)~~	~~90 (47-94)~~
~~IgG Anti-Gliadin Antibody (AGA)~~	~~85 (42-100)~~	~~80 (50-94)~~

- TTG IgA (with IgA level) single best test for celiac disease in adults
- DGP best test for those with IgA deficiency

How to test?

- Consider HLA DQ2/DQ8 testing for risk stratification in patients:
  - Already on a gluten-free diet
  - With negative serology but + family history
- HLA DQ2/DQ8 requisite for the development of celiac disease
  - Will not change, so no need to repeat
- All positive serologies should undergo EGD for confirmation as should those with strong clinical suspicion and negative serology

Testing for patients who are already gluten-free

- Baseline serologic testing +/- HLA testing
- Modified gluten challenge: 3g gluten/day x 2 weeks
- Full gluten challenge: 3g gluten/day x 8 weeks
- What does this translate to?
  - Typical slice of wheat bread contains about 5g of gluten
  - ½ slice of bread or a cracker/day

Celiac disease treatment

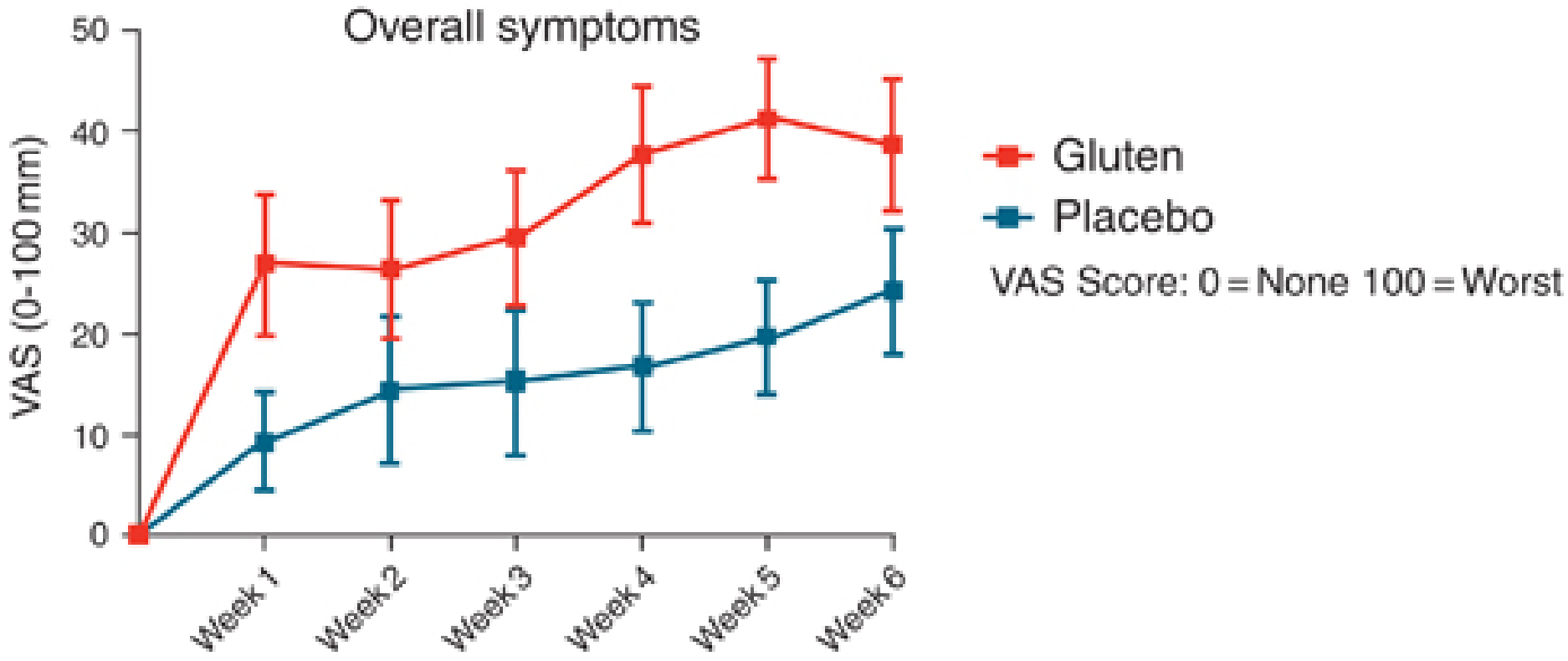
- Treatment
  - Lifelong gluten-free diet
  - Nutritional supplementation as needed
  - Very important to bring in nutrition early—invaluable in focusing on lifestyle changes, hidden gluten sources
  - Refractory cases will need immunotherapy
- Nutritional issues
  - Celiac disease can involve much of the small bowel from duodenum to ileum
  - Iron deficiency most common (duodenal site of absorption)
  - Think about osteoporosis—not unusual in premenopausal women with celiac disease (Vitamin D and calcium malabsorption)
  - Other nutrients (less common): B12, copper, zinc

I know the tests are negative, but I feel better “GF”

- Undiagnosed celiac is prevalent but not *that* prevalent
- Increasing popularity of going gluten-free in your patient population
  - Villainization of wheat products
  - Celiac prevalence is stable but people following a gluten-free diet has tripled
- Concept of non-celiac gluten sensitivity
- Gluten sensitive patients and nutrition
  - Lower intake of proteins, carbohydrates, fiber, and polyunsaturated fatty acids
  - Risk for nutritional deficiencies

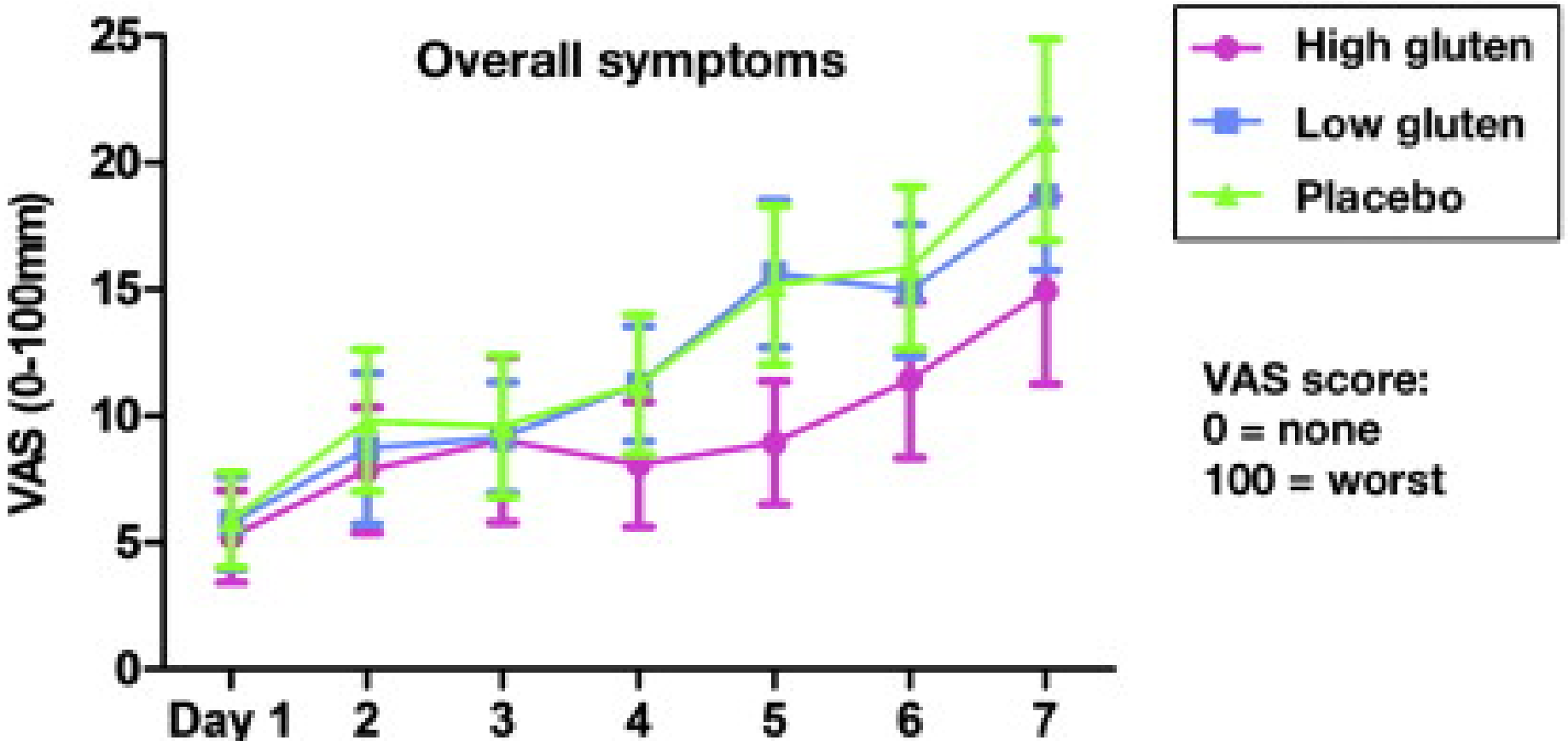
JAMA Intern Med. 2016 Sep 6.
Clin Gastroenterol Hepatol. 2016 Aug 21. pii: S1542-3565(16)30560-2.

Worsening of GI symptoms after introduction of gluten in patients without celiac disease



Am J Gastroenterol. 2011 Mar;106(3):508-14

Lack of differential effect of reintroduction of gluten, whey, or placebo on symptoms after lead-in FODMAP diet



Gastroenterology. 2013 Aug;145(2):320-8.e1-3.

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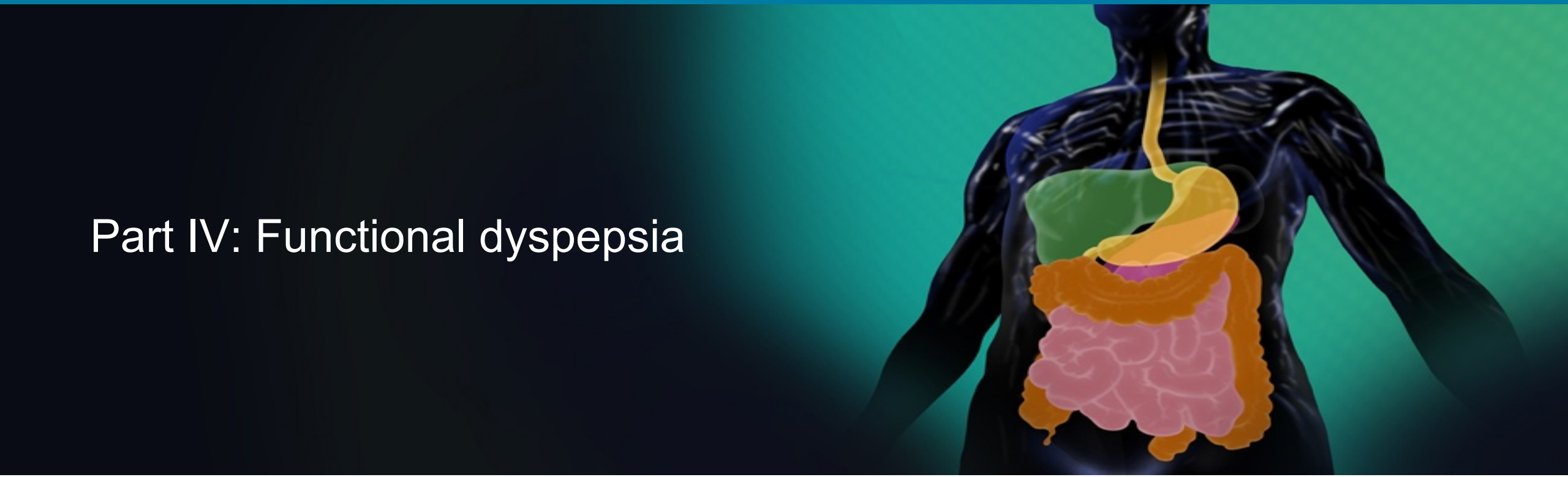
Part IV: Functional dyspepsia



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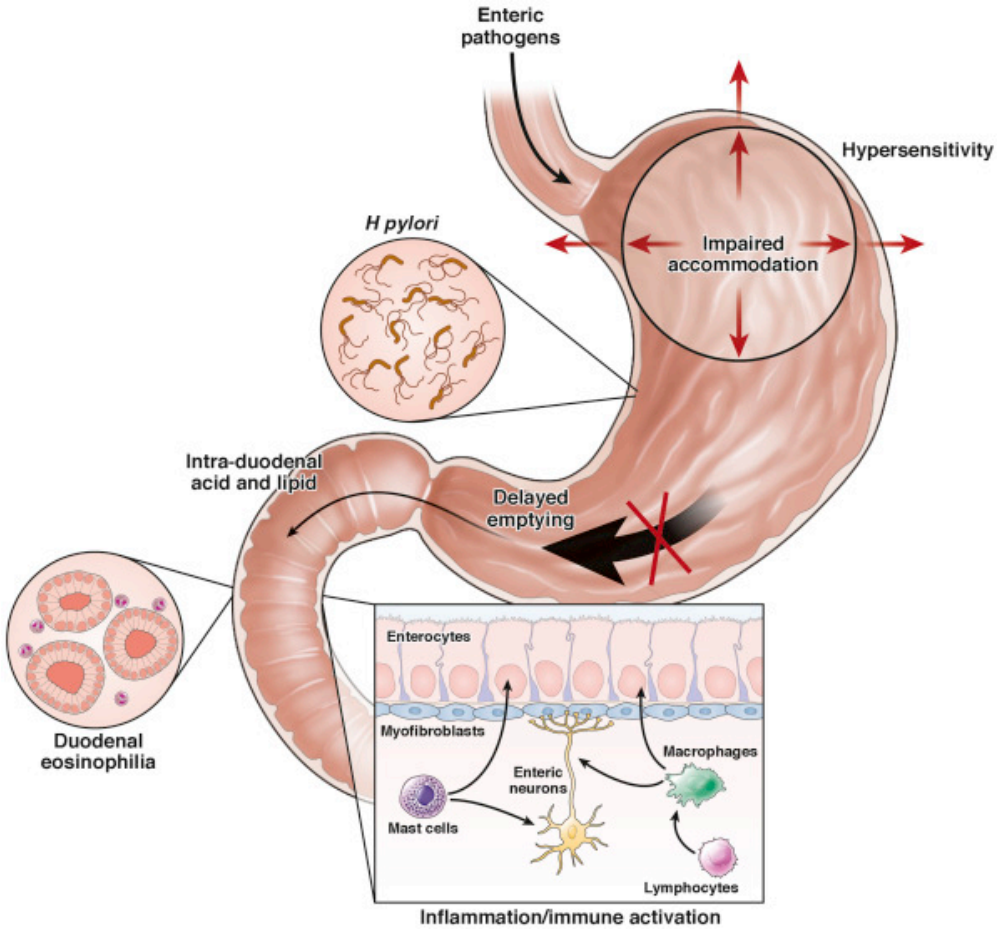
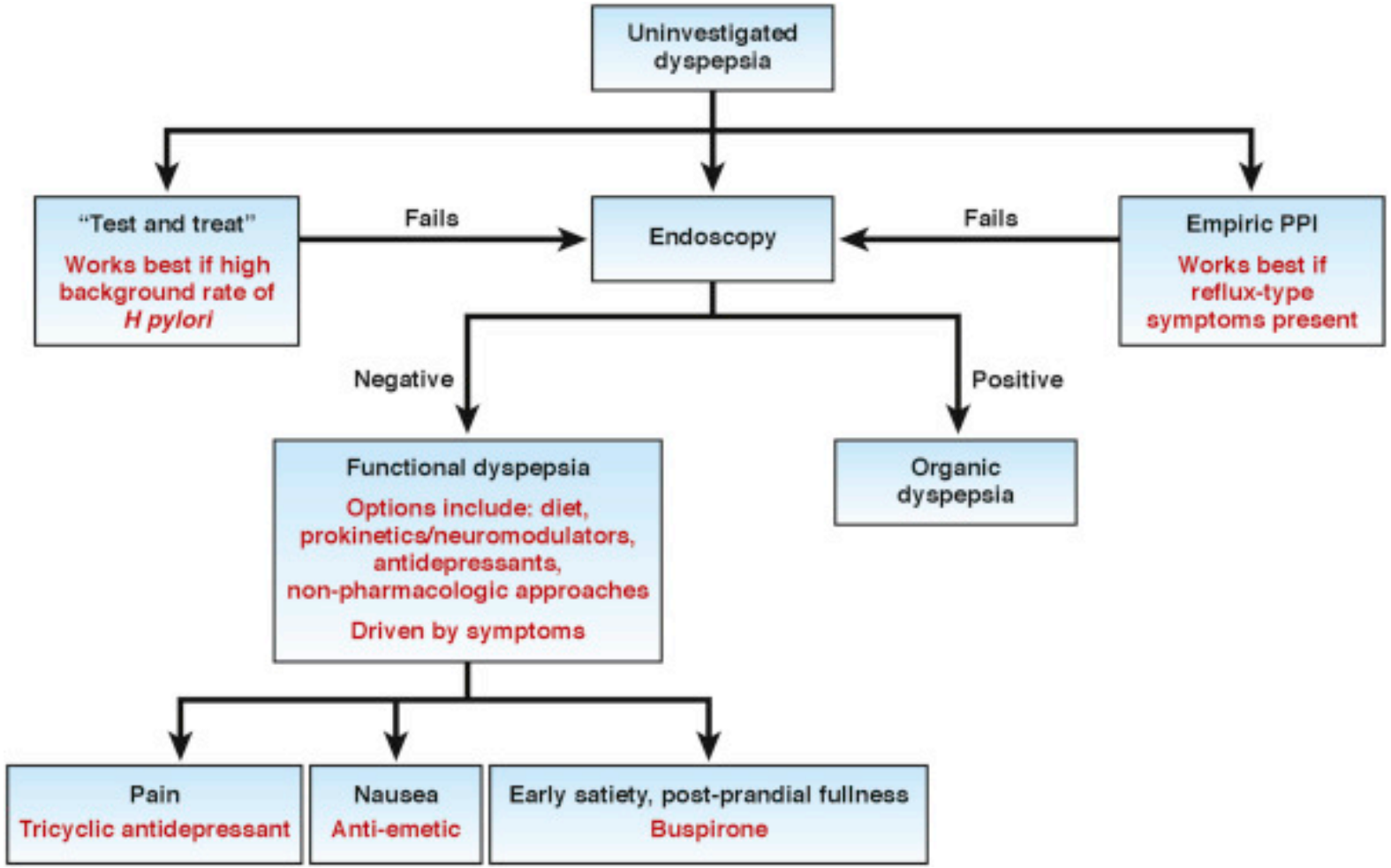
Functional dyspepsia—everything that's leftover

- No gold standard for diagnosis
- Upper GI symptoms without organic cause
  - Significant overlap with GERD and IBS
- Multifactorial:
  - Altered physiology (impaired accommodation, delayed emptying)
  - Psychosocial factors (anxiety/depression)
  - Inflammation



Clin Gastroenterol Hepatol. 2018 Apr;16(4):467-479.

Treating functional dyspepsia



Clin Gastroenterol Hepatol. 2018 Apr;16(4):467-479.

Key Points and Next Best Steps

- Key Points
  1. Most GERD patients need long-term treatment
  2. The absolute risks of long-term PPI use are low, but not zero
  3. H. pylori and NSAIDs are the cause of most peptic ulcer disease
  4. Tissue transglutaminase (with IgA level) is the best screening test for celiac disease among those consuming gluten
- Next Best Steps
  1. GI consultation should be considered for refractory GERD, but most of these cases are not truly GERD
  2. Best people to send for upper endoscopy:
     - GERD with alarm symptoms
     - New GERD over age 60
     - Malignancy surveillance after gastric ulcer
     - Positive celiac antibodies for confirmation

Thank you

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