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

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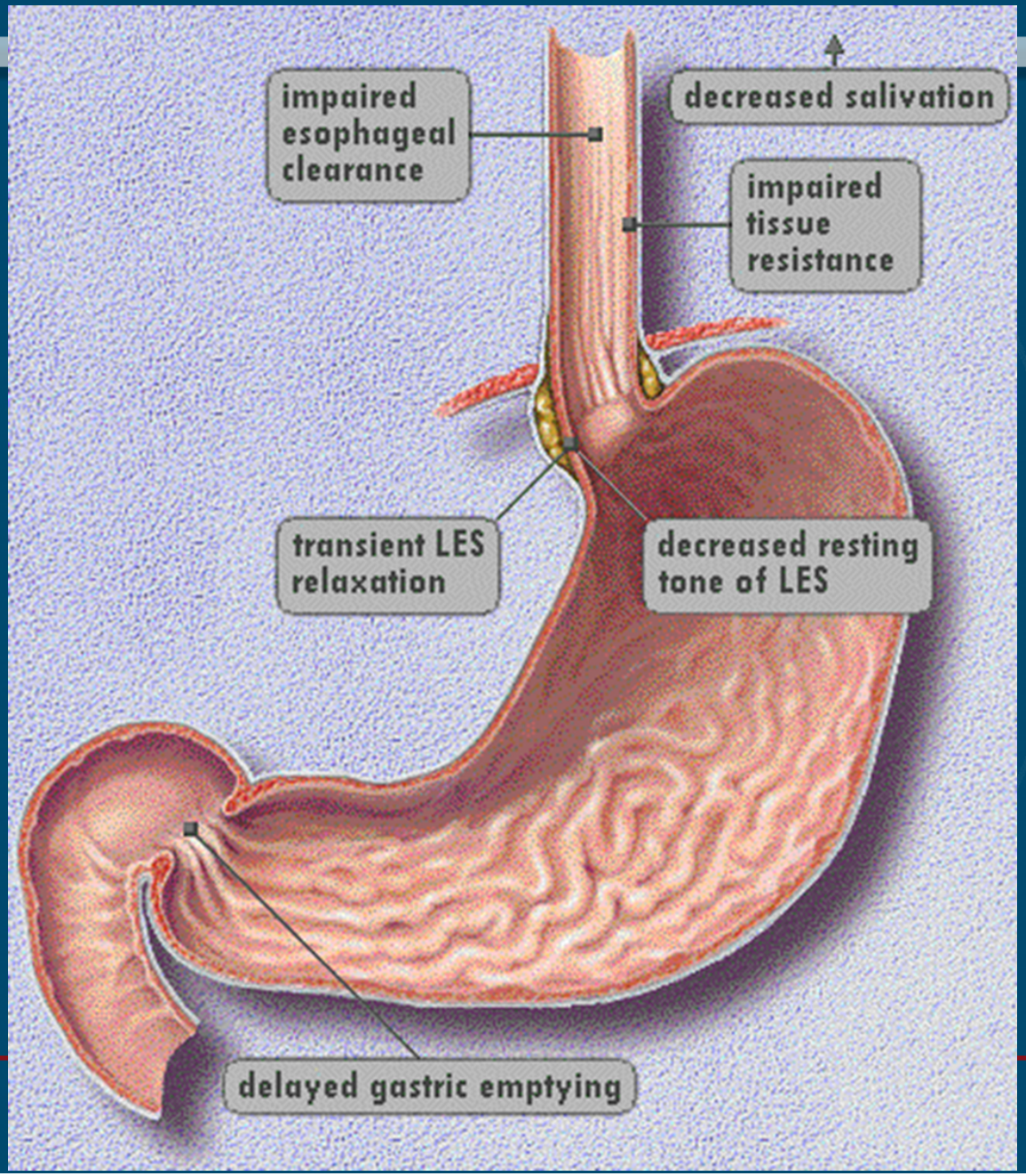
Gastroesophageal reflux disease (GERD)

Definitions

- GERD is a condition which 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 heartburn
- GERD is the most common GI diagnosis in your clinic

Am J Gastroenterol. 2006 Aug;101(8):1900-20

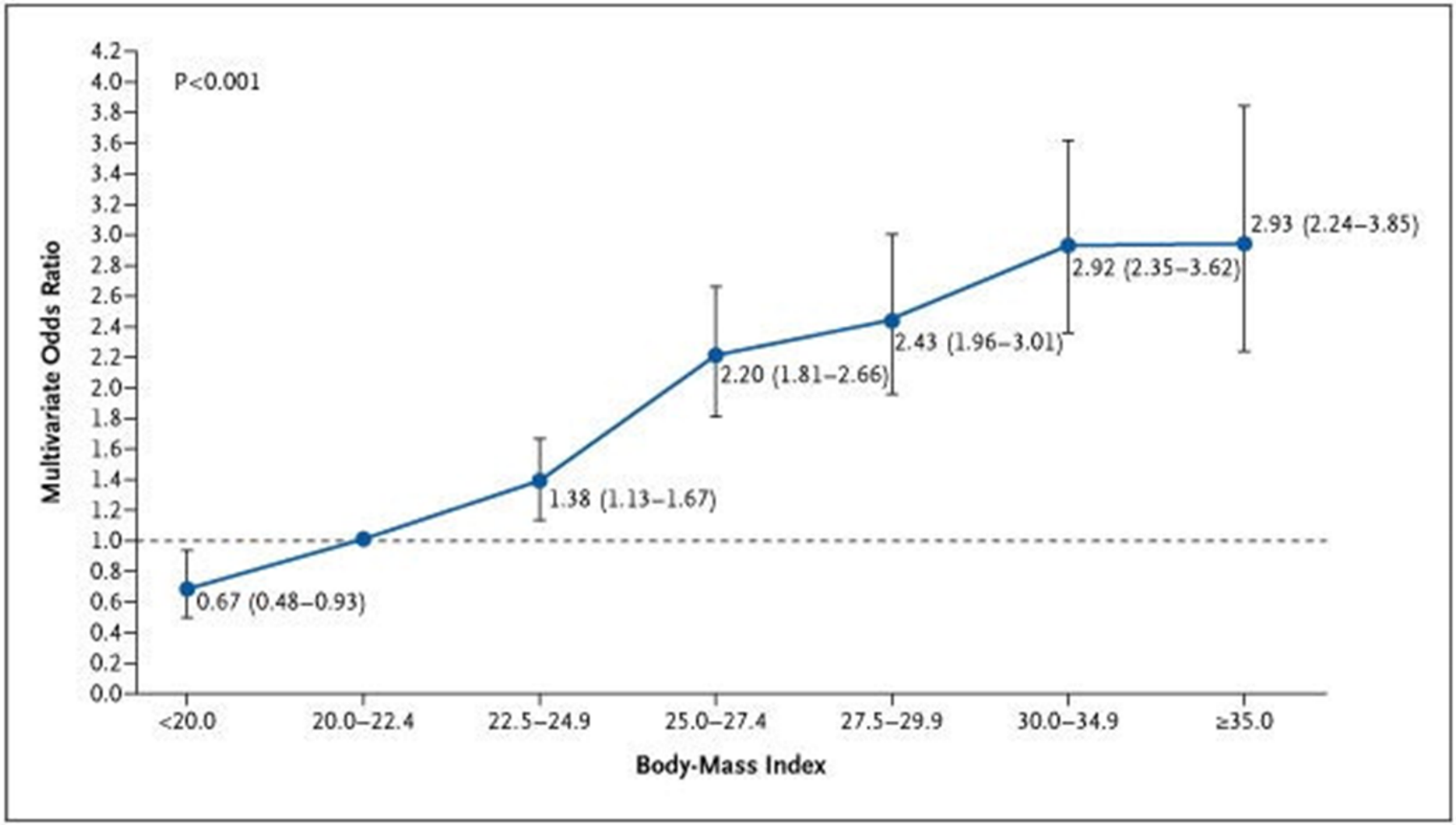
Pathophysiology



Risk factors for GERD

- Obesity

Risk factors for GERD

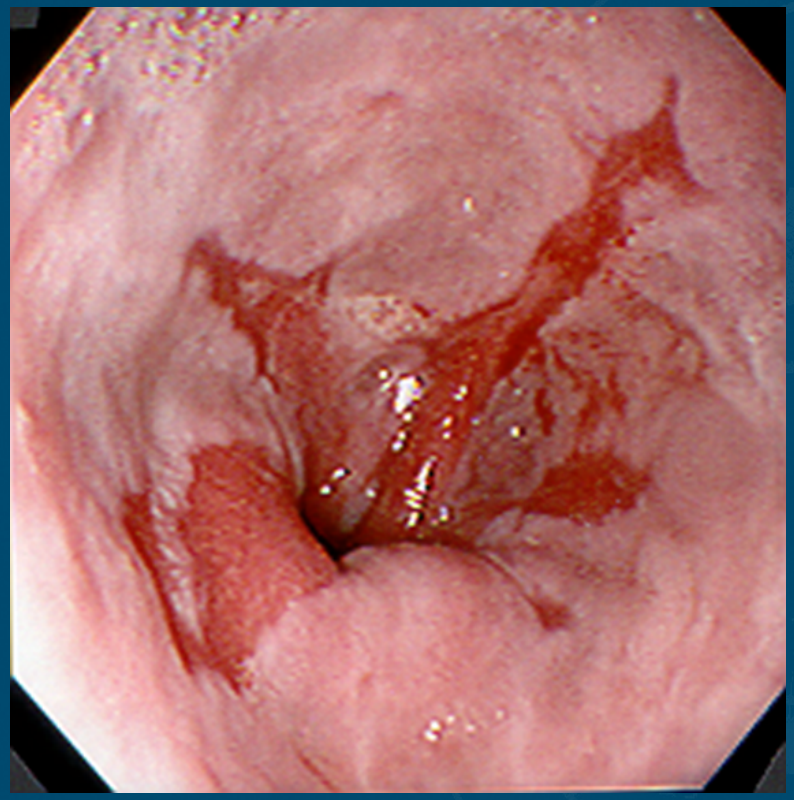


N Engl J Med. 2006 Jun 1;354(22):2340-8.

Risk factors for GERD

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

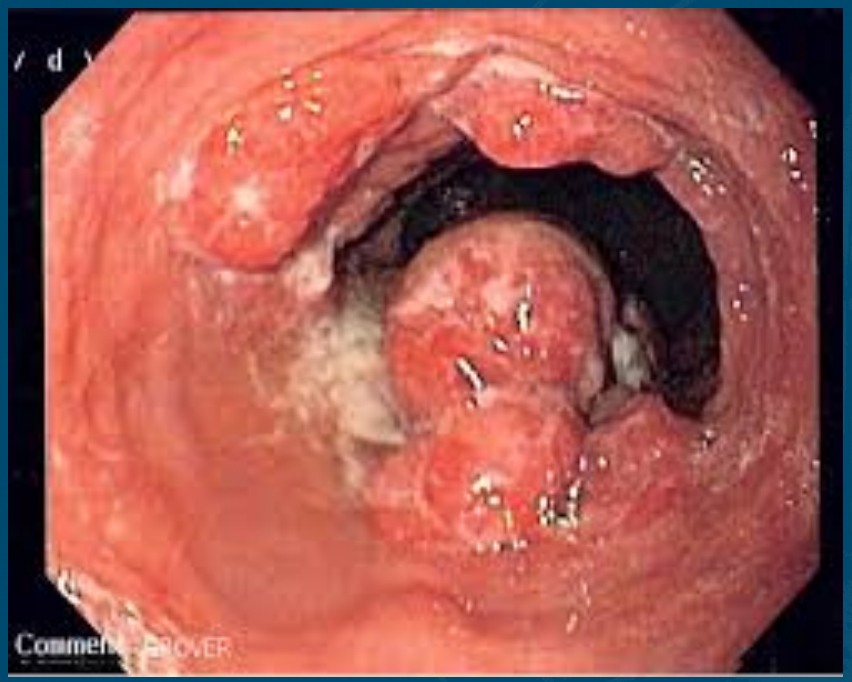
Typical complications



- 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

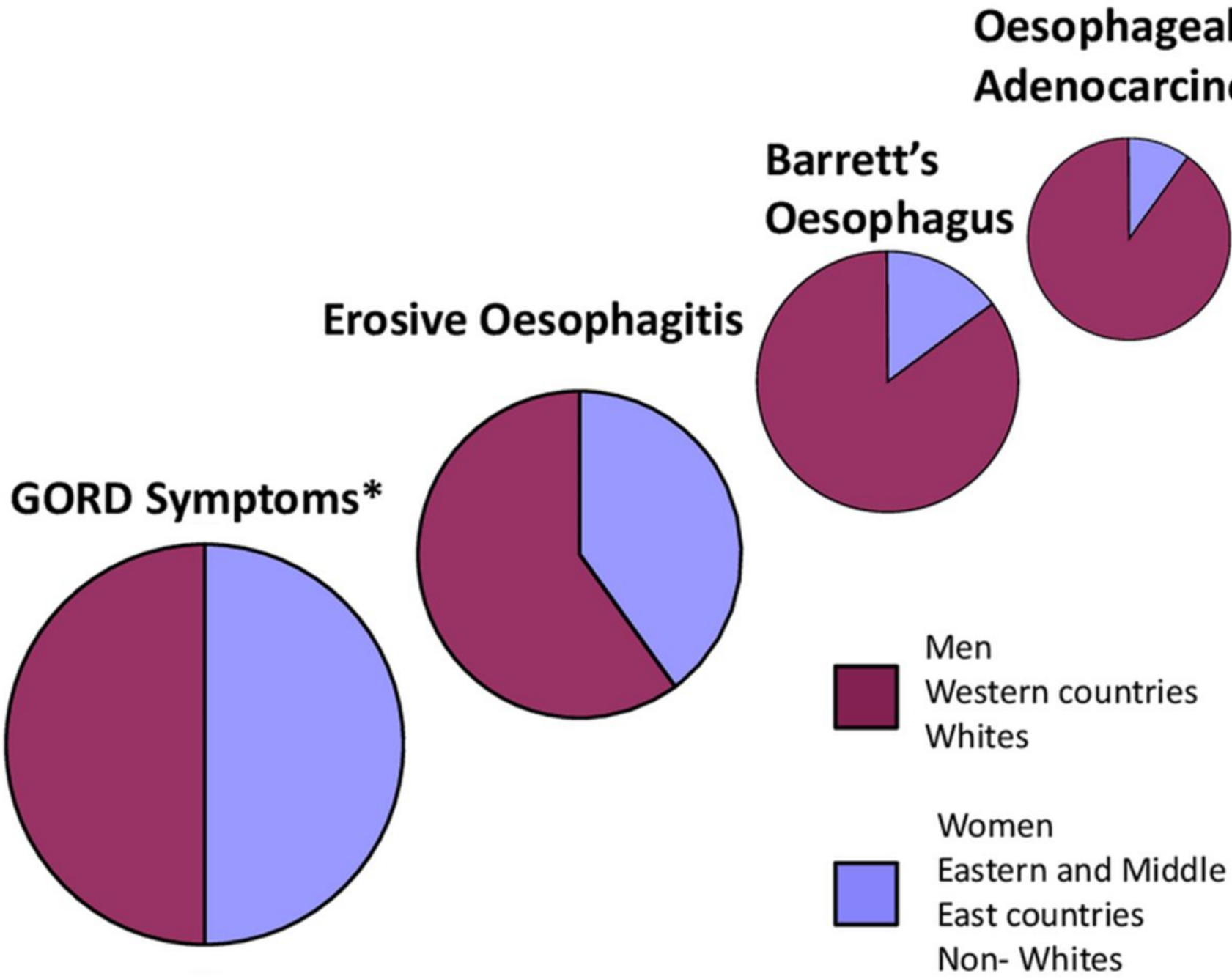
Mayo Clin Proc. 2014 Jul;89(7):973-984.

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)

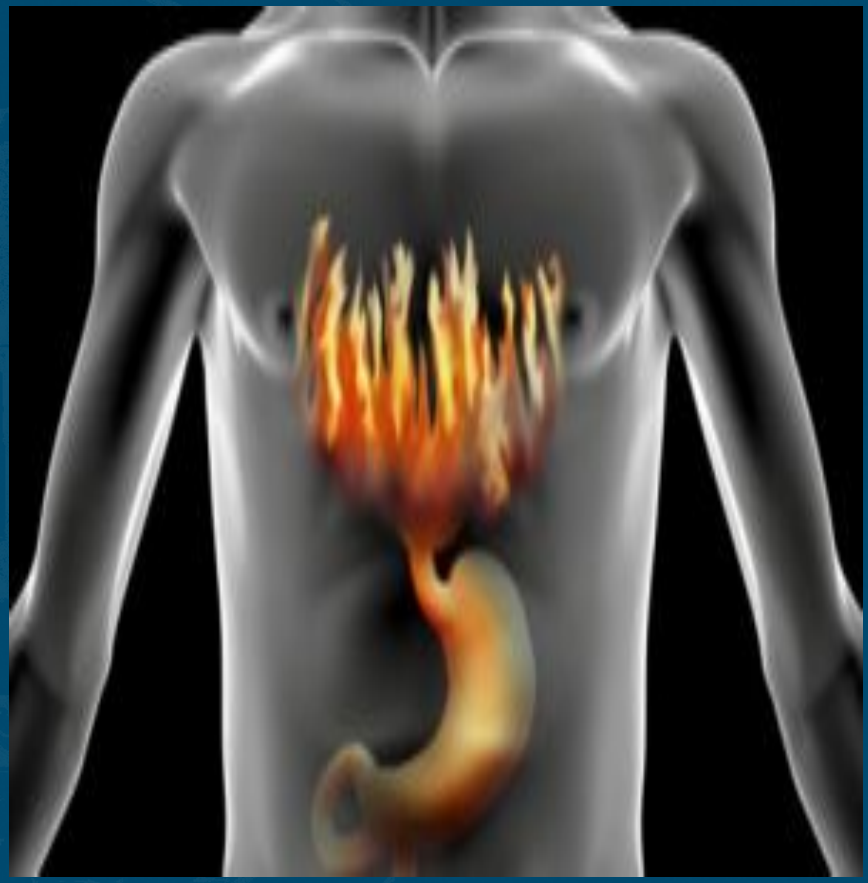
PLoS One. 2014 Jul 30;9(7):e103508.
Clin Gastroenterol Hepatol. 2016 Mar;14(3):338-347.e1.



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.

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 (>55 years old?)
- Keep pH testing in your back pocket
  - Cost benefit over prolonged PPI (>8 weeks) use

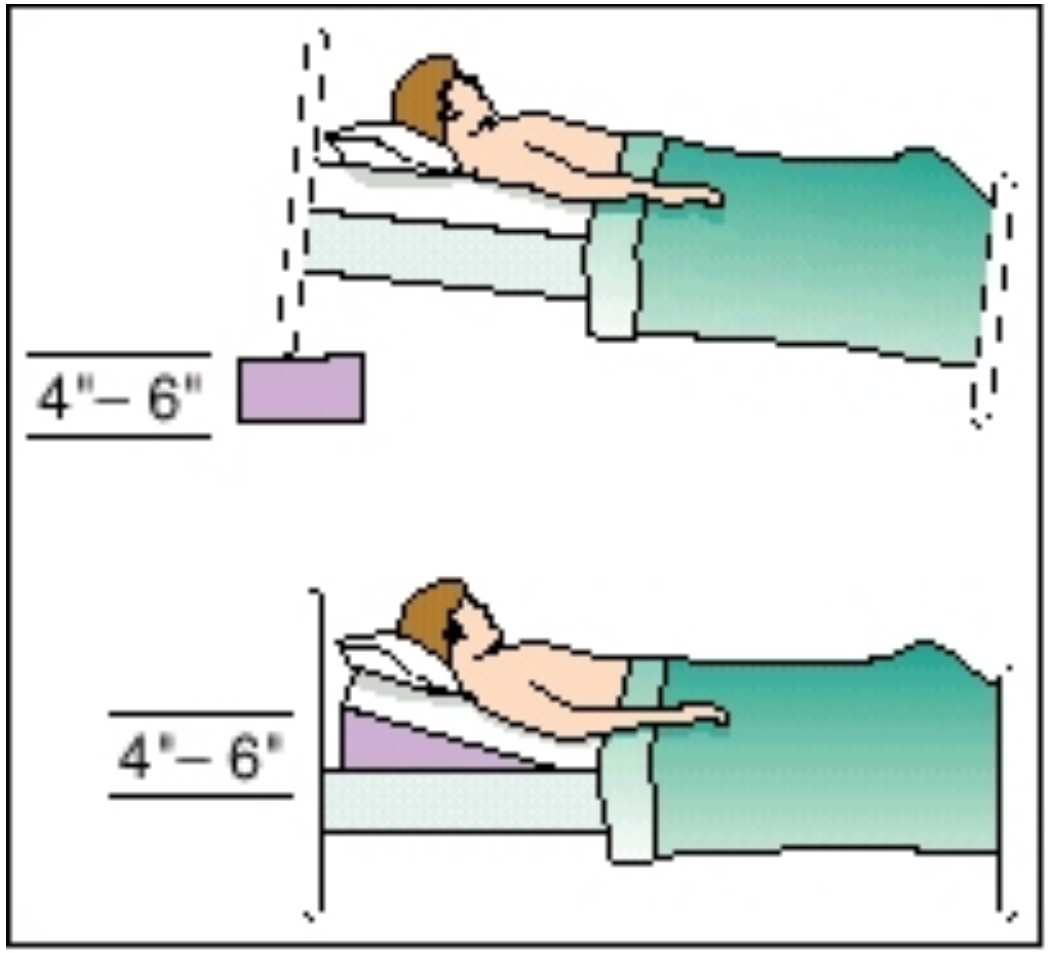
J Gastrointest Surg. 2014 Jan;18(1):26-33
Clin Gastroenterol Hepatol. 2017 Aug;15(8):1162-1172

MANAGING GERD

Lifestyle modification

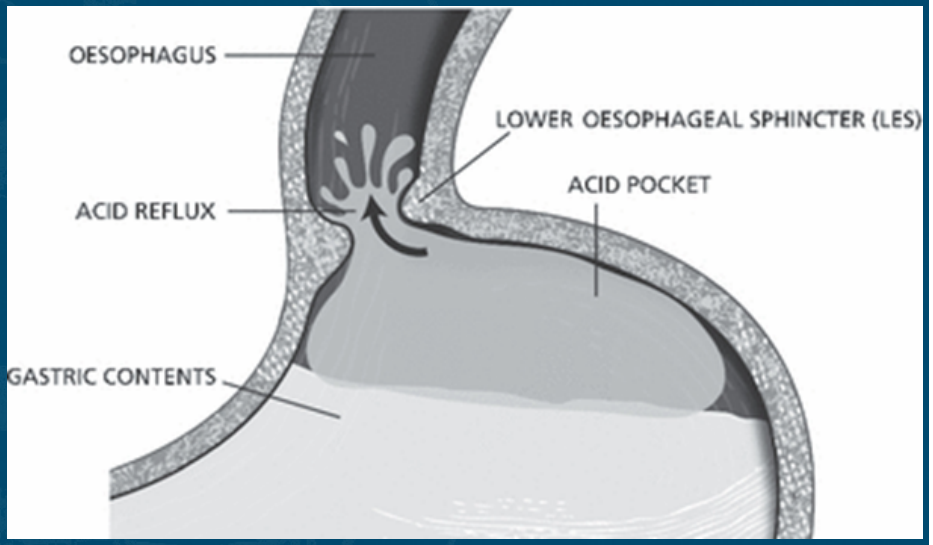
- Evidence for improvement is mostly anecdotal
- Weight loss and stopping smoking the only *proven* ways to reduce heartburn symptoms
- Weight reduction
  - Decrease in BMI of as little as 3.5 lbs/in^2 could result in a 40% decrease in symptom frequency
  - Differential effects of bariatric surgery based on type (Roux-en-Y vs. sleeve gastrectomy)
- Avoid late meals/raise head of bed (most reflux in daytime)
  - 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"

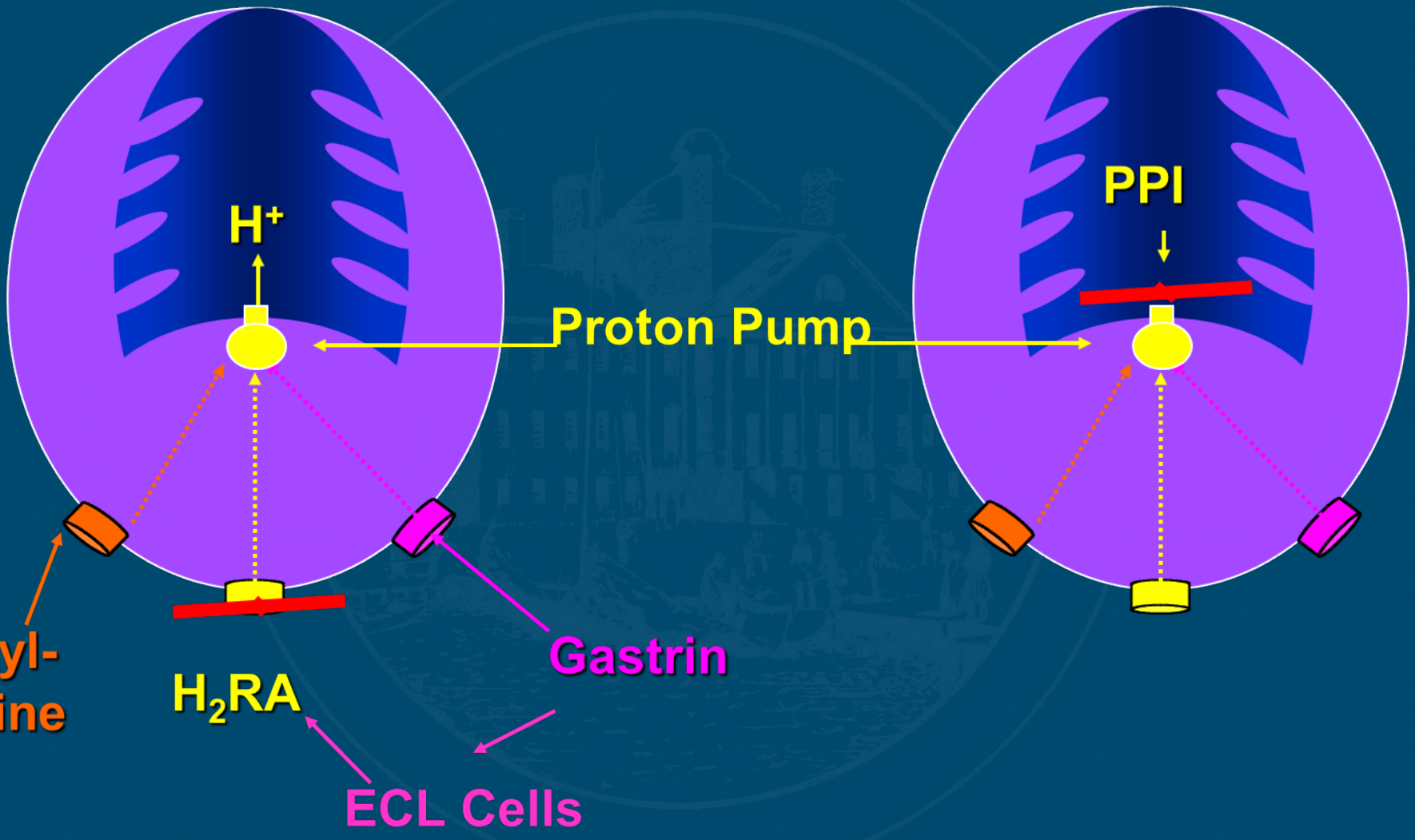
Antacids

- 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. PPIs

- H2 receptor antagonists
  - Ranitidine, cimetidine, famotidine (generic, OTC)
  - Rapid action
  - Not influenced by meals
  - Incomplete acid suppression
  - 25-40% symptom remission
  - Tachyphylaxis with consistent dosing

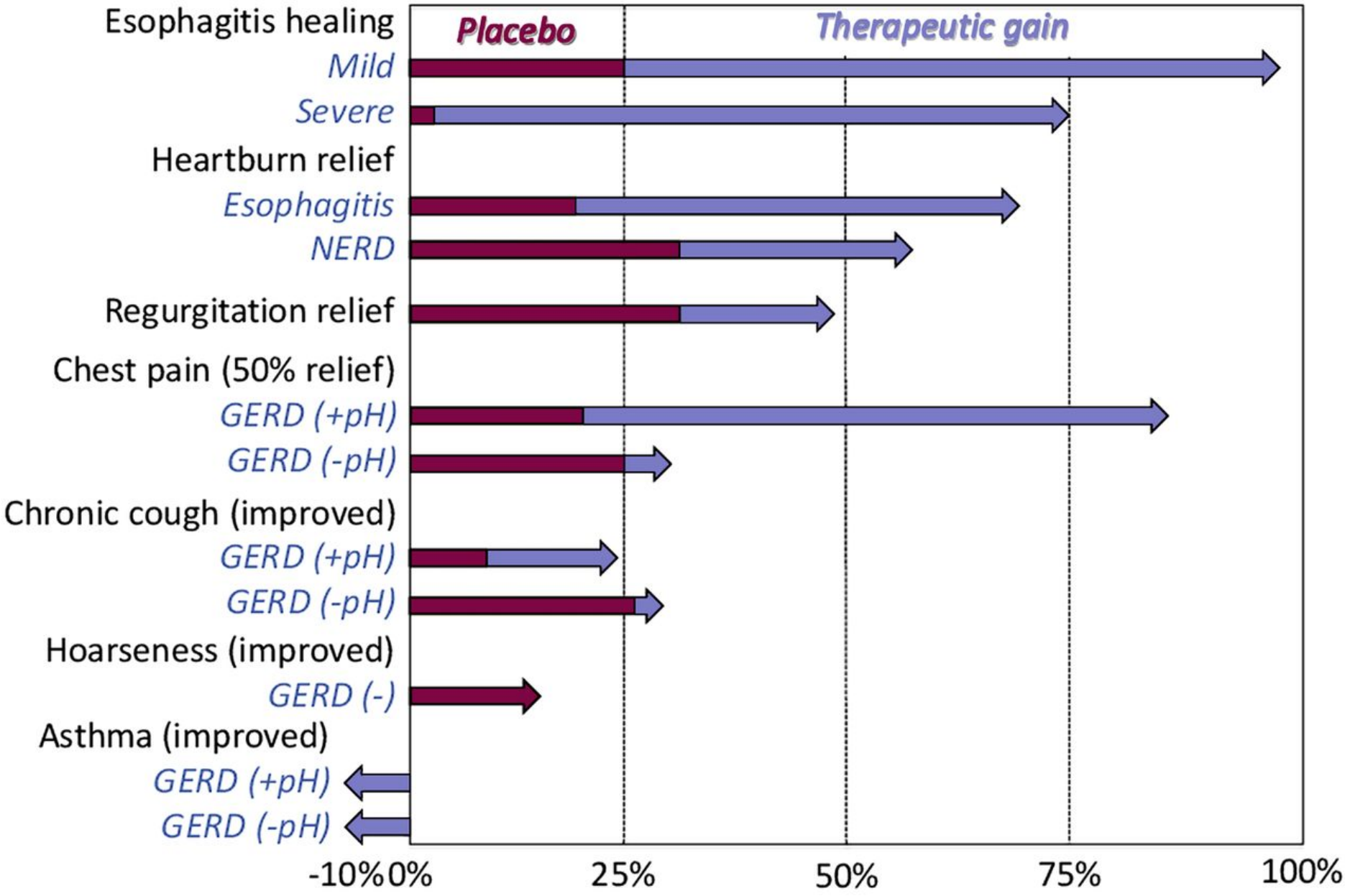
- Proton pump inhibitors
  - Omeprazole (generic, OTC), lansoprazole, rabeprazole, pantoprazole, esomeprazole (S isomer of omeprazole)
  - Needs to be taken prior to a meal
  - Even bid acid suppression is not complete

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 to 40 mg bid 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)
- Alternative diagnosis? (rumination syndrome)
- Anti-reflux surgery (only for people who respond to PPIs)

PPI efficacy for potential manifestations of GERD

Estimates based on available RCT data

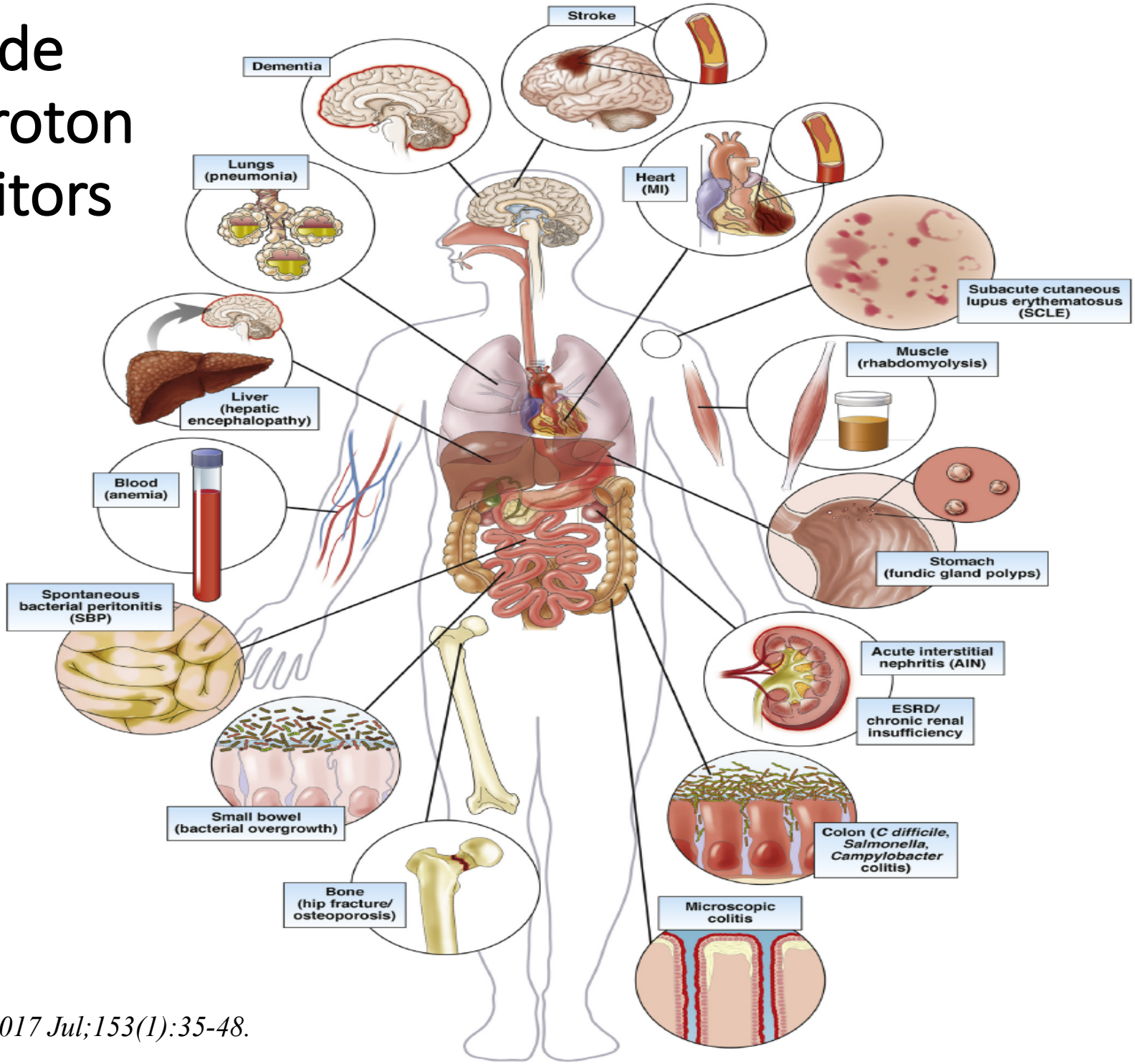


Gut 2014;63:1185-1193

Long-term treatment

- Most true GERD patients require long-term treatment
  - Use treatment that is least costly but still effective at controlling symptoms
- Know the risks of long-term PPI use but don't scare patients away who truly need them
- Beware of rebound hypersecretion when stopping PPIs
- Two epidemics:
  - Big one: Patients inappropriately maintained on PPIs who don't need them
  - Smaller one: Patients who need PPIs for symptom relief but they (or their providers) overly fearful of long-term side effects

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.

Back to the basics: making sense of recent associations

Table 2. Hill Criteria

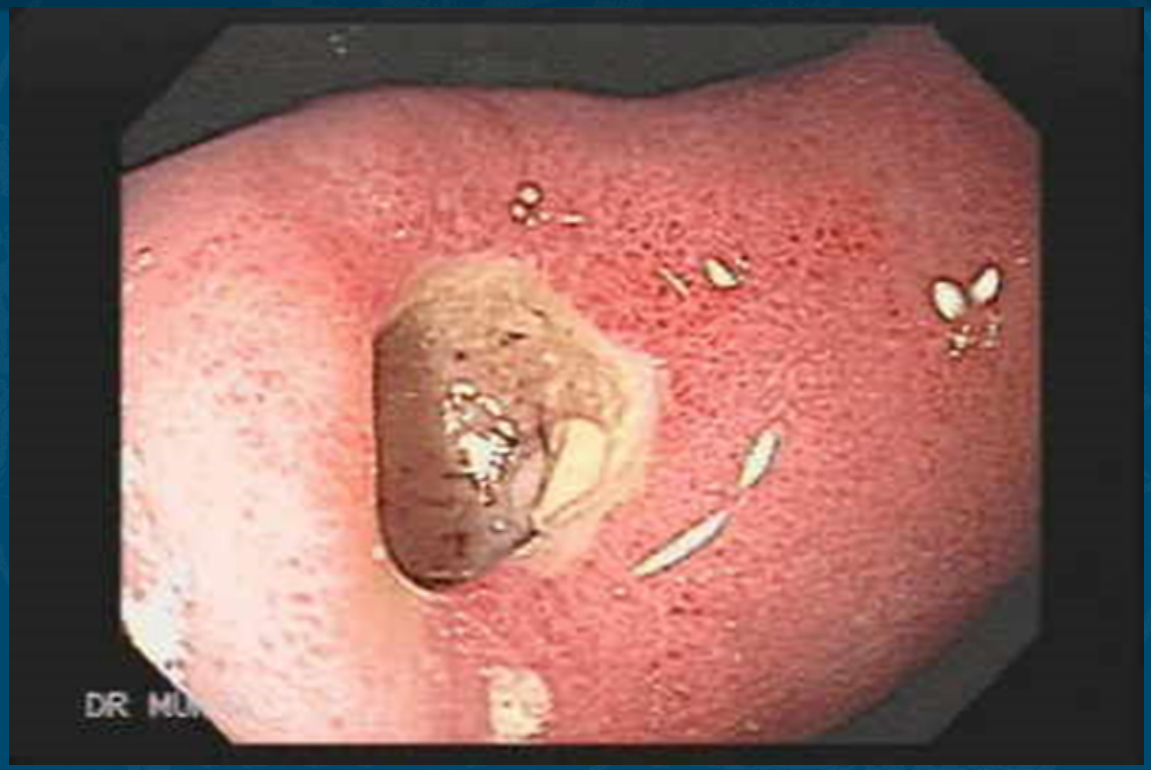
Strength of association	Is the association of high magnitude?
Consistency	Are the findings reproducible?
Specificity	Is the outcome predicted based only on the exposure to PPIs?
Temporality	Does the use of PPIs precede the observed outcome?
Biological gradient	Is there a direct relationship between dose or duration of PPI use and the outcome?
Biological plausibility	Is there a rational and theoretical basis for the proposed association?
Coherence	Any conflicts with what is known about the natural history and biology of the disease?
Experiment	Are the data based on experiments?
Analogy	Are there features of association similar to other associations judged to be causal?

Table 6. Application of the Hill Criteria to Some of the Proposed Associations With Long-Term PPI Therapy

Hill Criteria	Clopidogrel Interaction	Fracture	CAP	SBP	Bacterial Enteric Infection	*C difficile* Infection	Hypomagnesemia (ie, <1.6–1.8 mg/dL)	Severe Hypomagnesemia Syndrome	Rhabdomyolysis	AIN	SCLE	Renal Failure	Dementia	MI	Anemia	HE	FGPs
Strength	Weak	Weak	Weak	Weak	Moderate	Moderate	Weak	N/A[a]	Weak	Weak	Weak	Weak	Weak	Weak	Weak	Weak	High[h]
Consistency	No	No	No	No	Yes	No	Yes	Yes	No	No	No	No	No	No	No	No	Yes
Specificity	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	Yes
Temporality	Yes	Yes	No[b]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Biological gradient	No	No	No	No	Yes[c]	Maybe	No	N/A	No	No	No	No	No	No	No	No	No
Plausibility	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No	No	Possible	Yes[i]	Yes	Yes
Coherence	No[d]	No[e]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A
Experiment	No	No	No	No	No	No	No	Yes[f]	No	Yes[g]	No	No	No	No	No	No	Yes
Analogy	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No

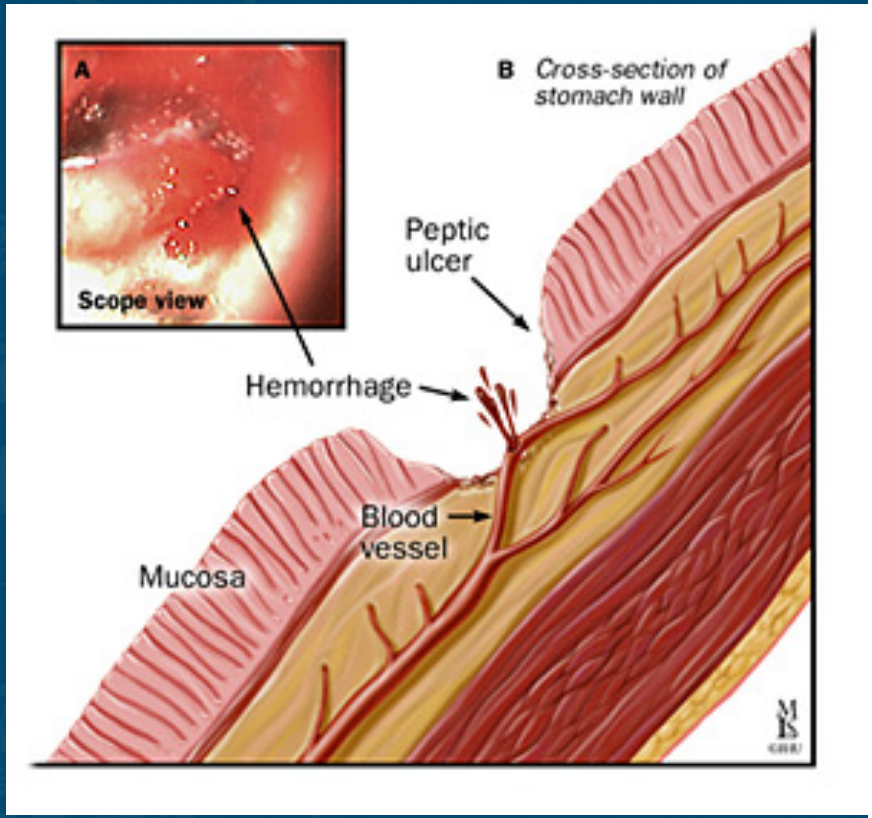
Gastroenterology. 2017 Jul;153(1):35-48.

PEPTIC ULCER DISEASE



Symptoms of peptic ulcer disease

- Dyspepsia
  - Upper abdominal pain/burning
  - Vague abdominal discomfort
  - Nausea
  - Pressure/fullness
- Relationship to food
  - Gastric ulcers worsened by food
  - Duodenal ulcers palliated by food
- Asymptomatic
- Gastrointestinal bleeding



https://gi.jhsps.org/

Etiology of peptic ulcer disease

H. pylori

pH (acid)

NSAID

Peptic ulcer

NSAIDs and ulcers

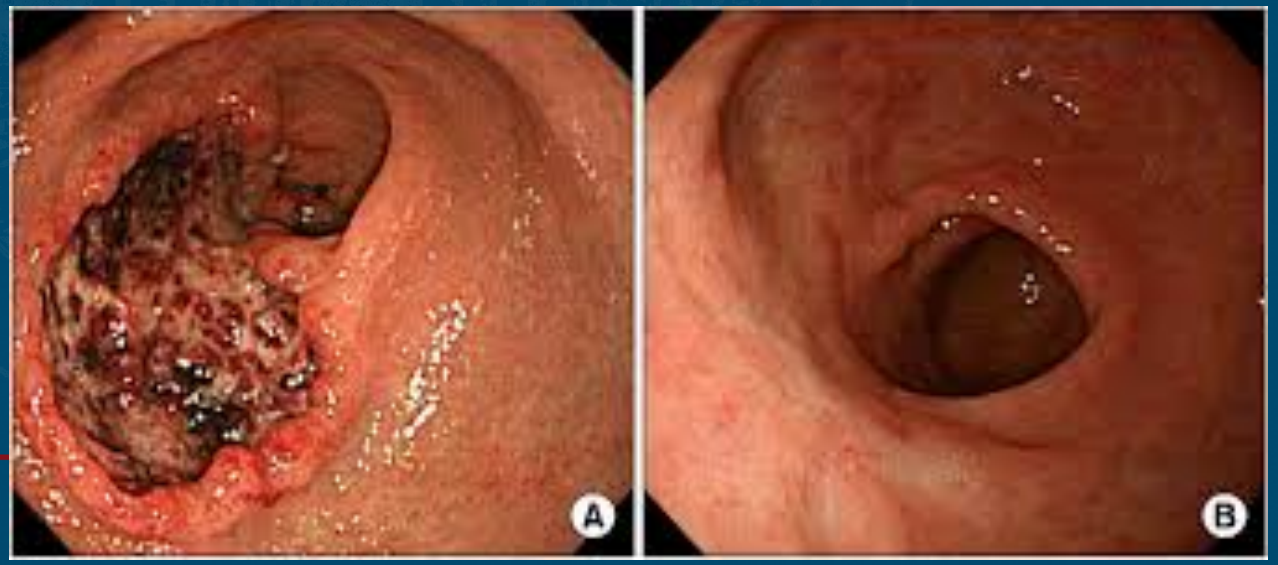
- NSAID use increases risk of gastric and duodenal ulcers by 5x
- 0.5-2% risk of ulcer per patient per year
- Risk can increase to as high as 9% if multiple risk factors:
  - Dose and duration of NSAID therapy
  - Anticoagulant or steroid use
  - Age
  - History of past peptic ulcer
  - H. pylori (acts synergistically with NSAIDs)

Risk of NSAID-induced ulceration

- 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)
  - High-dose H2RA (less effective)

Aftercare of patients with peptic ulcer disease

- Patients admitted for bleeding ulcers on ASA for CAD should have ASA restarted within 1st week after endoscopic therapy (should also continue PPI)
- Any patient with a solitary gastric ulcer without definitive etiology
  - May be indicative of gastric cancer
  - Follow up endoscopy in 4-8 weeks to confirm healing and biopsy for malignancy



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/ functional 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

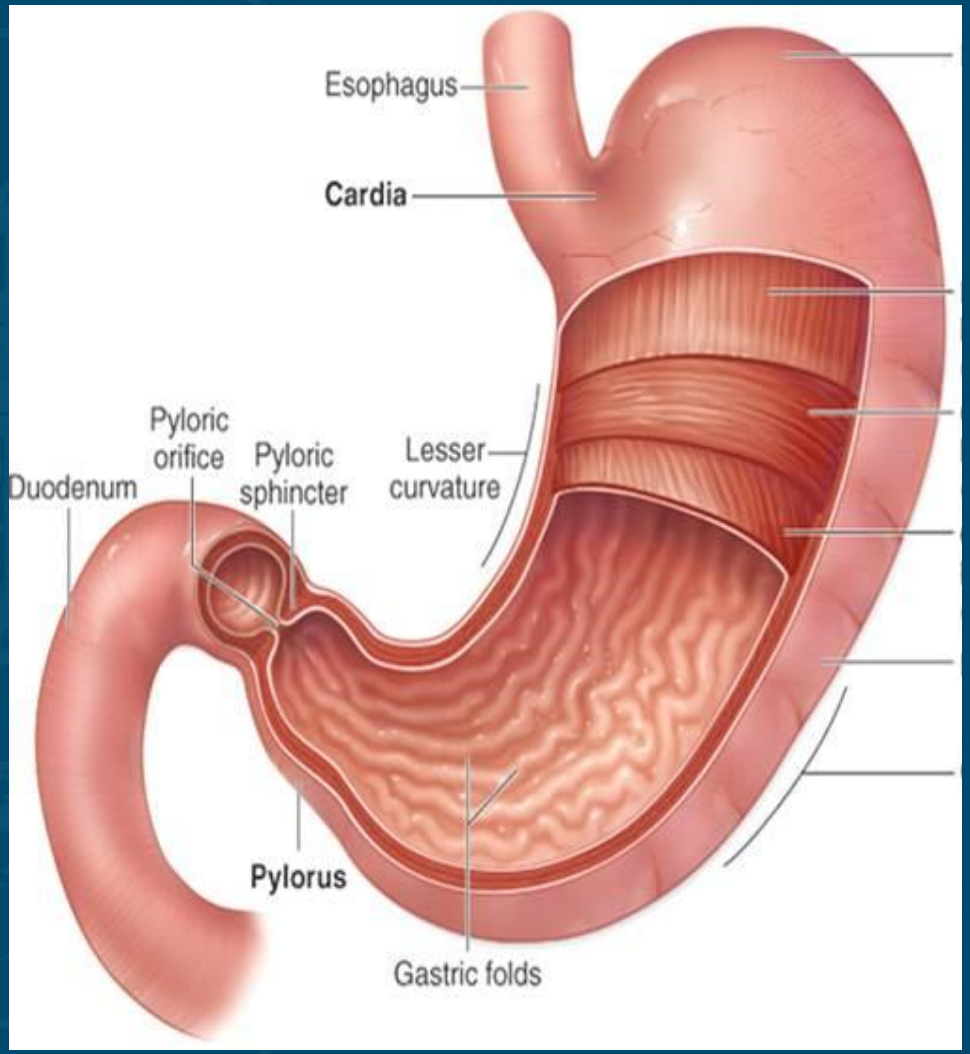
- First-line treatment (14 days)
  - PPI, clarithromycin 500 mg bid, amoxicillin 1000 mg bid
- H. pylori resistance rates are rising
- Clarithromycin resistance is assumed to be ≥ 15% in US so many patients will need quadruple therapy
  - PPI, bismuth subsalicylate, tetracycline, metronidazole
- Variety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

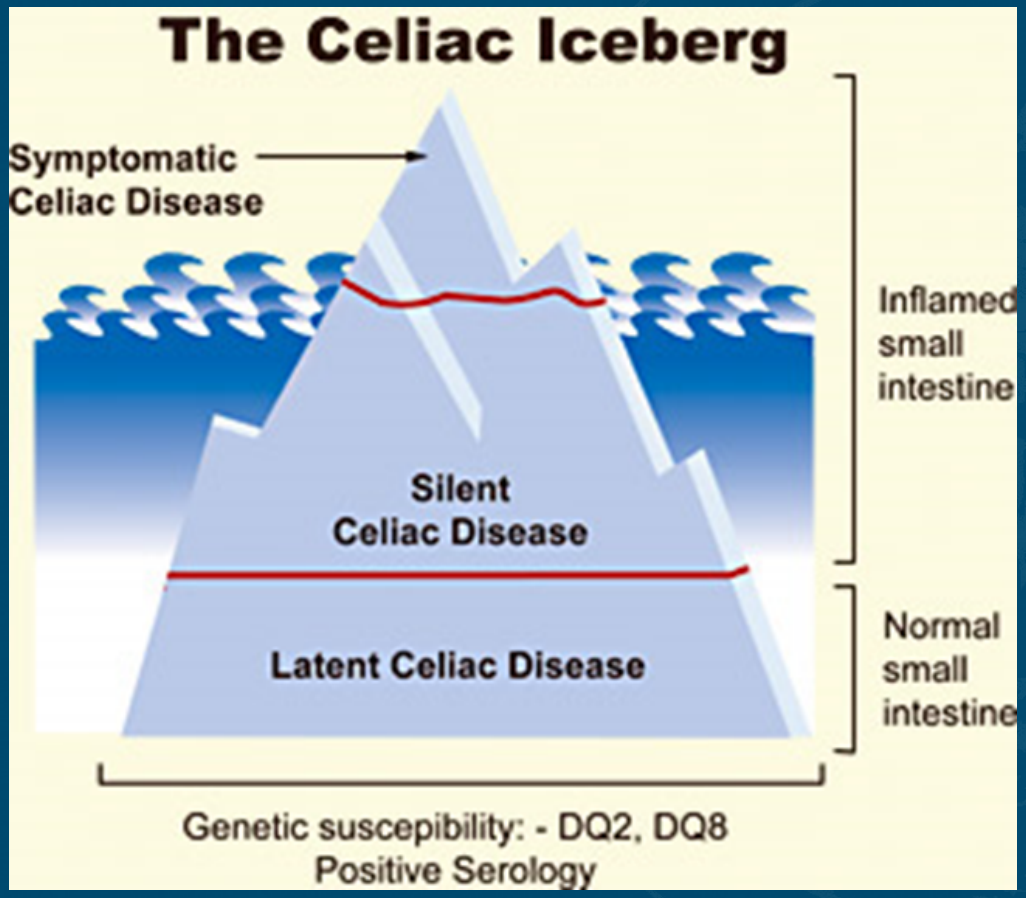
No H. pylori, no ulcer, still dyspeptic—now what?

- Think functional GI disease!
- Gastroparesis
  - Delayed exit of foods
  - Nausea AND vomiting
  - Worse with fat, roughage
  - Dx by gastric emptying scan
- Functional dyspepsia
  - Impaired gastric accommodation
    - Dyspepsia within a few bites
- Chronic nausea
  - Chronic nausea w/o vomiting



CELIAC DISEASE

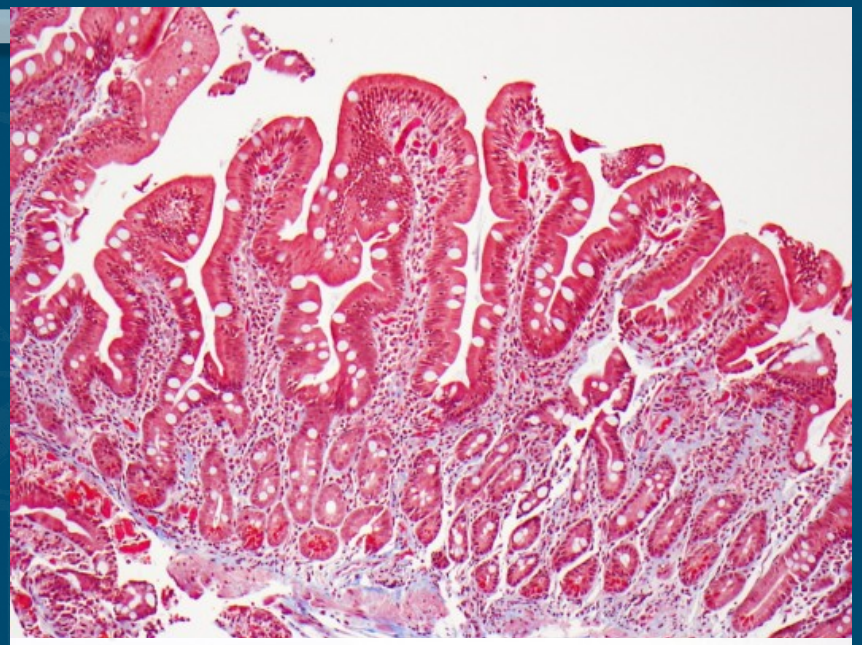
Celiac epidemiology

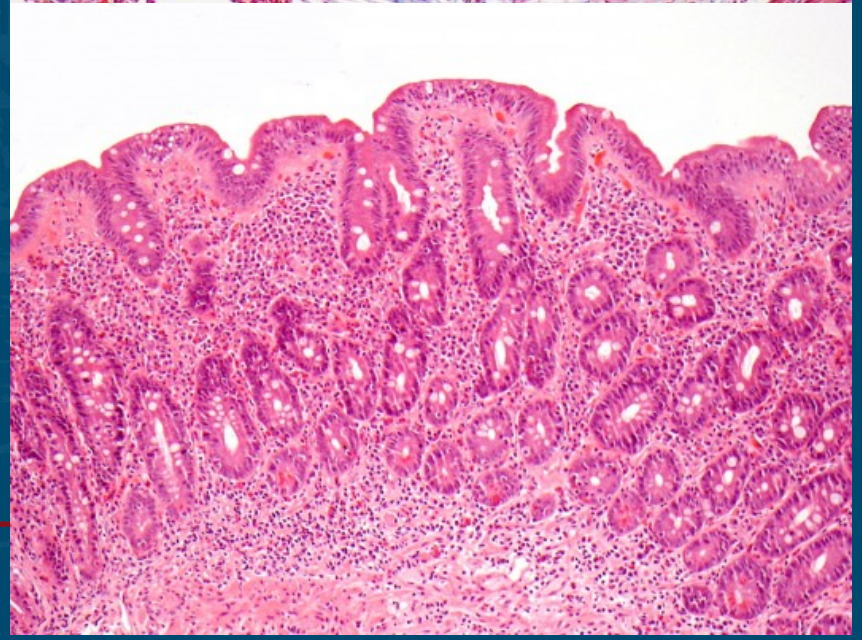


- Prevalence of 1:70-1:300
- Classically in pts of northern European descent
  - Can occur in non-whites in proper genetic background
- Prevalence increases with age
- Many cases are thought to be undiagnosed

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

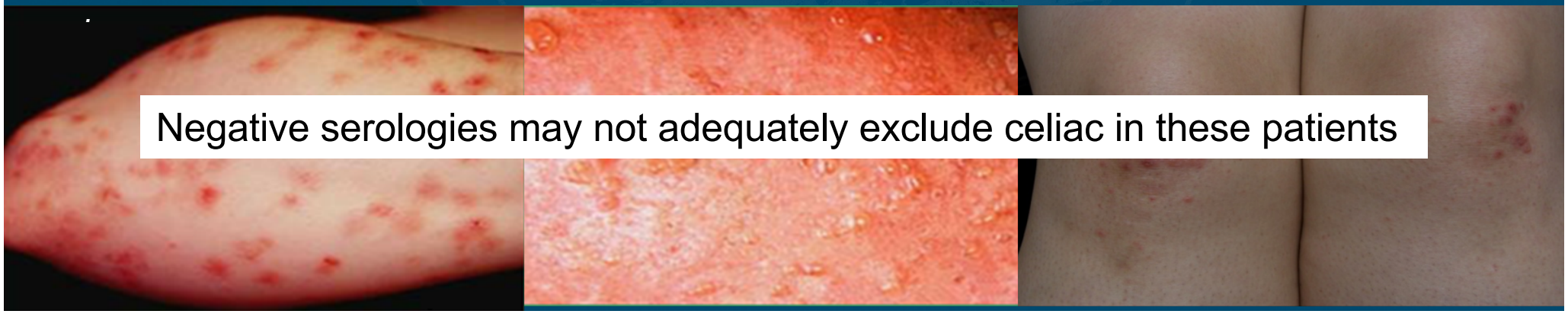




Who to test?

- 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)

Arch Intern Med. 2003;163(3):286.



Negative serologies may not adequately exclude celiac in these patients

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

Nutritional issues in celiac disease

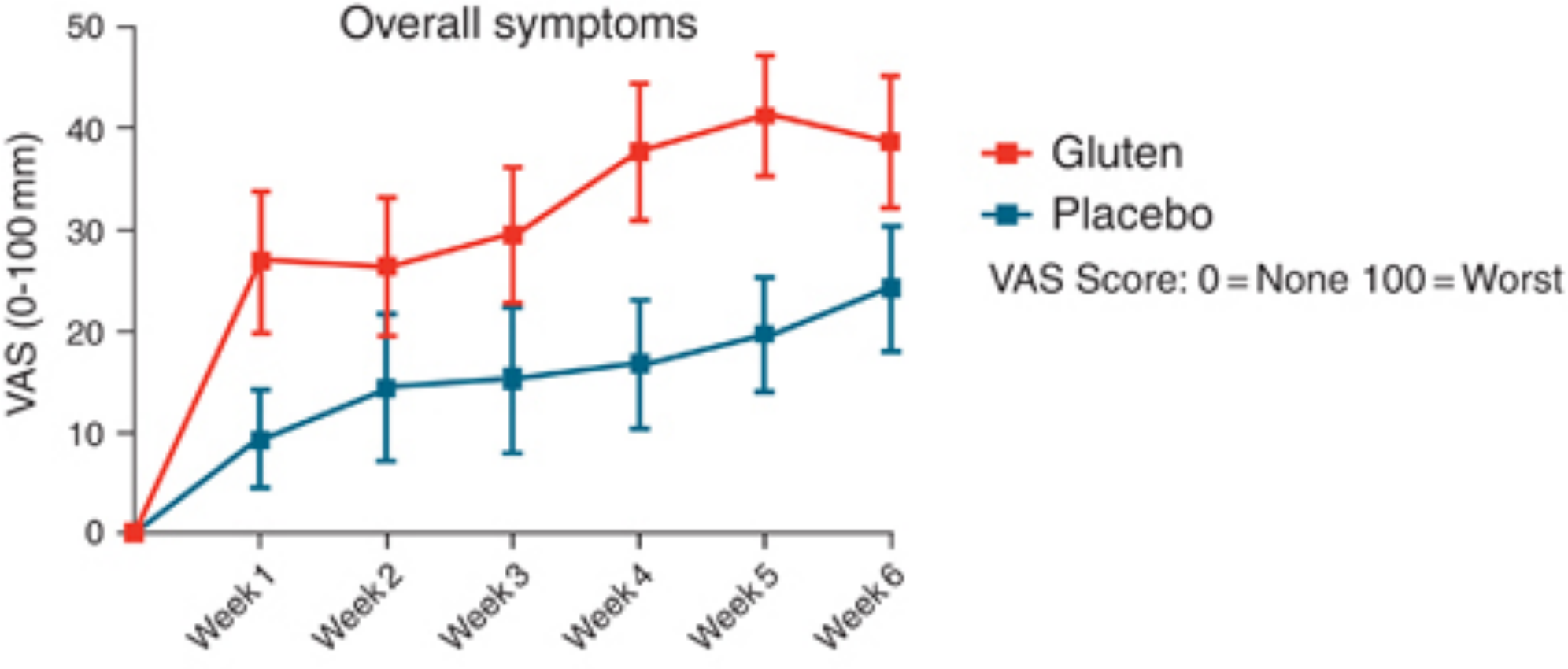
- Celiac disease can involve much of the small bowel from duodenum to ileum
- Iron deficiency most common (duodenal site of absorption)
- Think about osteoporosis—not unusual in premenopausal women with celiac disease (Vitamin D and calcium malabsorption)
- Other nutrients (less common): B12, copper, 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

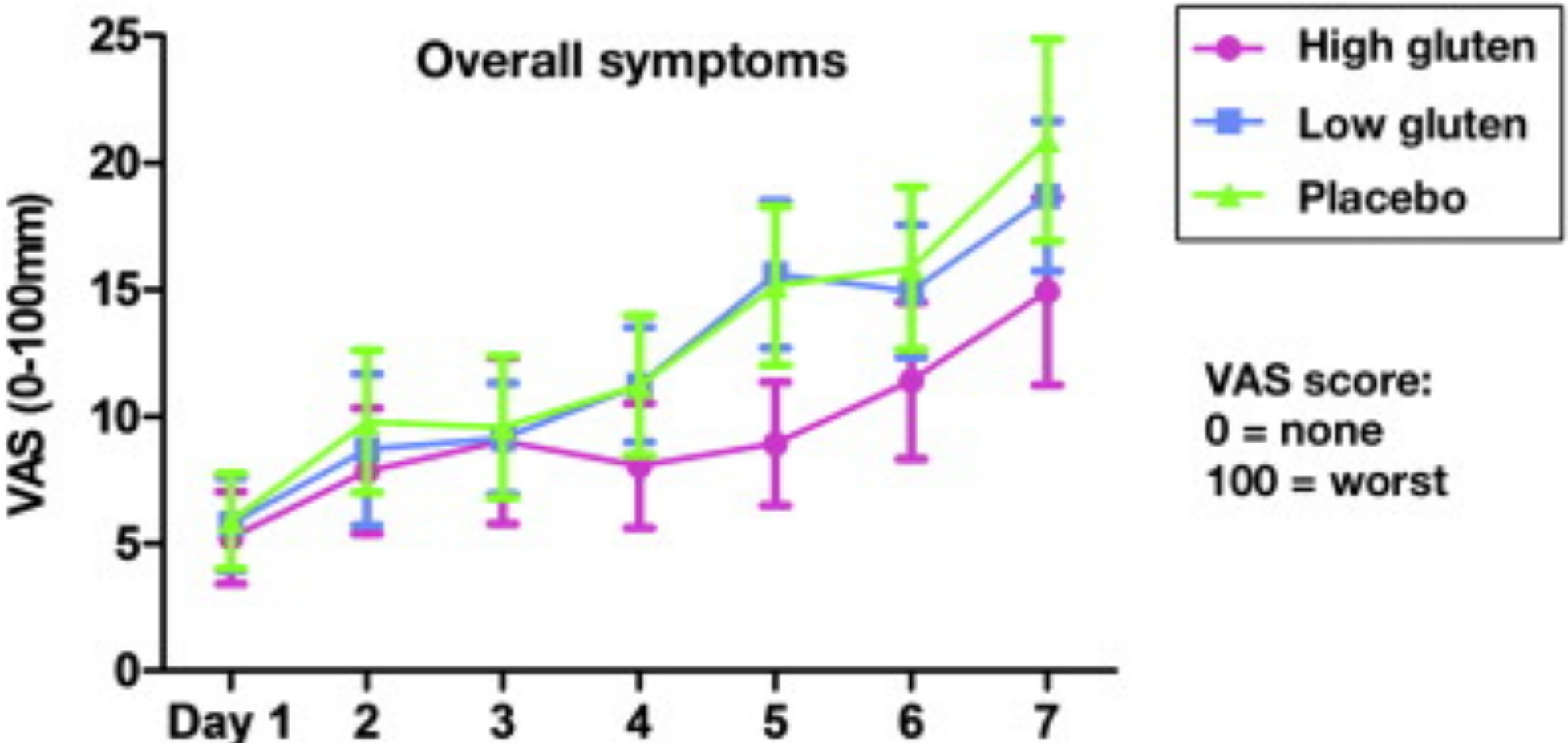
JAMA Intern Med. 2016 Sep 6.
Clin Gastroenterol Hepatol. 2016 Aug 21. pii: S1542-3565(16)30560-2.

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



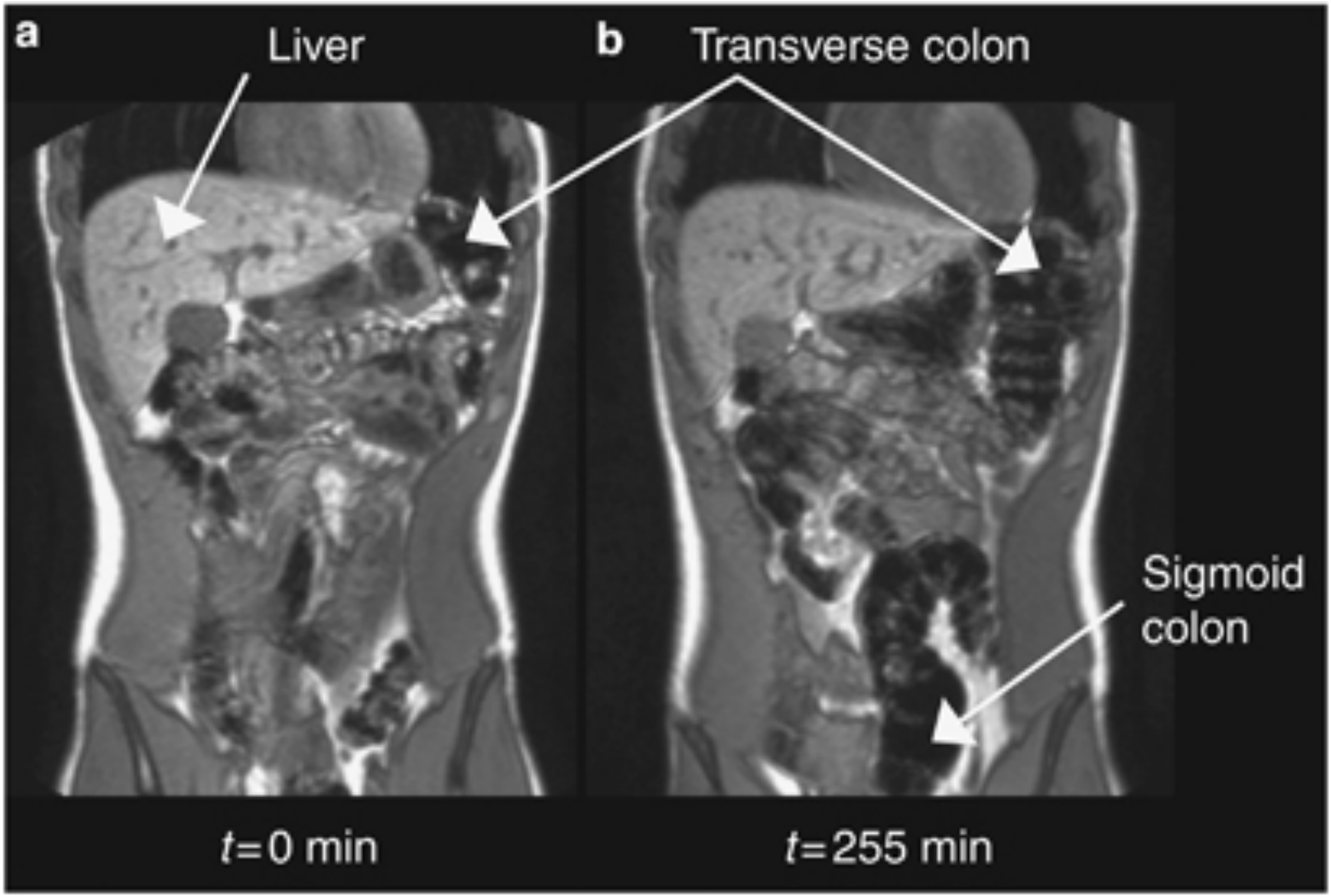
Am J Gastroenterol. 2011 Mar;106(3):508-14

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.

FODMAPs draw water and gas into the intestine



Am J Gastroenterol. 2014 Jan;109(1):110-9.

Wait a minute: foods high in FODMAPs

excess fructose	lactose	fructans	galactans	polyols
fruit apple, mango, nashi, pear, tinned fruit in natural juice, watermelon **sweetners** fructose, high fructose corn syrup, concentrated fruit sources, large servings of fruit, dried fruit, fruit juice **honey** corn syrup, fruisana	**milk** milk from cows, goats or sheep, custard, ice cream, yogurt **cheeses** soft unripened cheeses, such as cottage cheese, cream, mascarpone, ricotta	**vegetables** asparagus, beetroot, broccoli, brussel sprouts, cabbage, eggplant, fennel, garlic, leek, okra, onion, shallots, spring onion **cereals** wheat and rye **fruit** custard apple, persimmon, watermelon **misc.** chicory, dandelion, inulin	**legumes** baked beans, chickpeas, kidney beans, lentils	**fruit** apple,apricot, avocado, blackberry, cherry, lychee, nashi, nectarine, peach, pear, plum, prune, watermelon **vegetables** cauliflower, bell pepper, mushroom, sweet corn **sweetners** sorbitol, mannitol, isomalt, maltitol, xylitol

Treatment for celiac disease and wheat sensitivity

- Celiac disease
  - 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
- Non-celiac wheat/gluten sensitivity
  - Consider empiric low-FODMAP trial for motivated patients who do not have complete response to gluten removal
  - Validate their symptoms—symptoms and response to diet are real, but medical explanation lags behind

Thank you

Questions?

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