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

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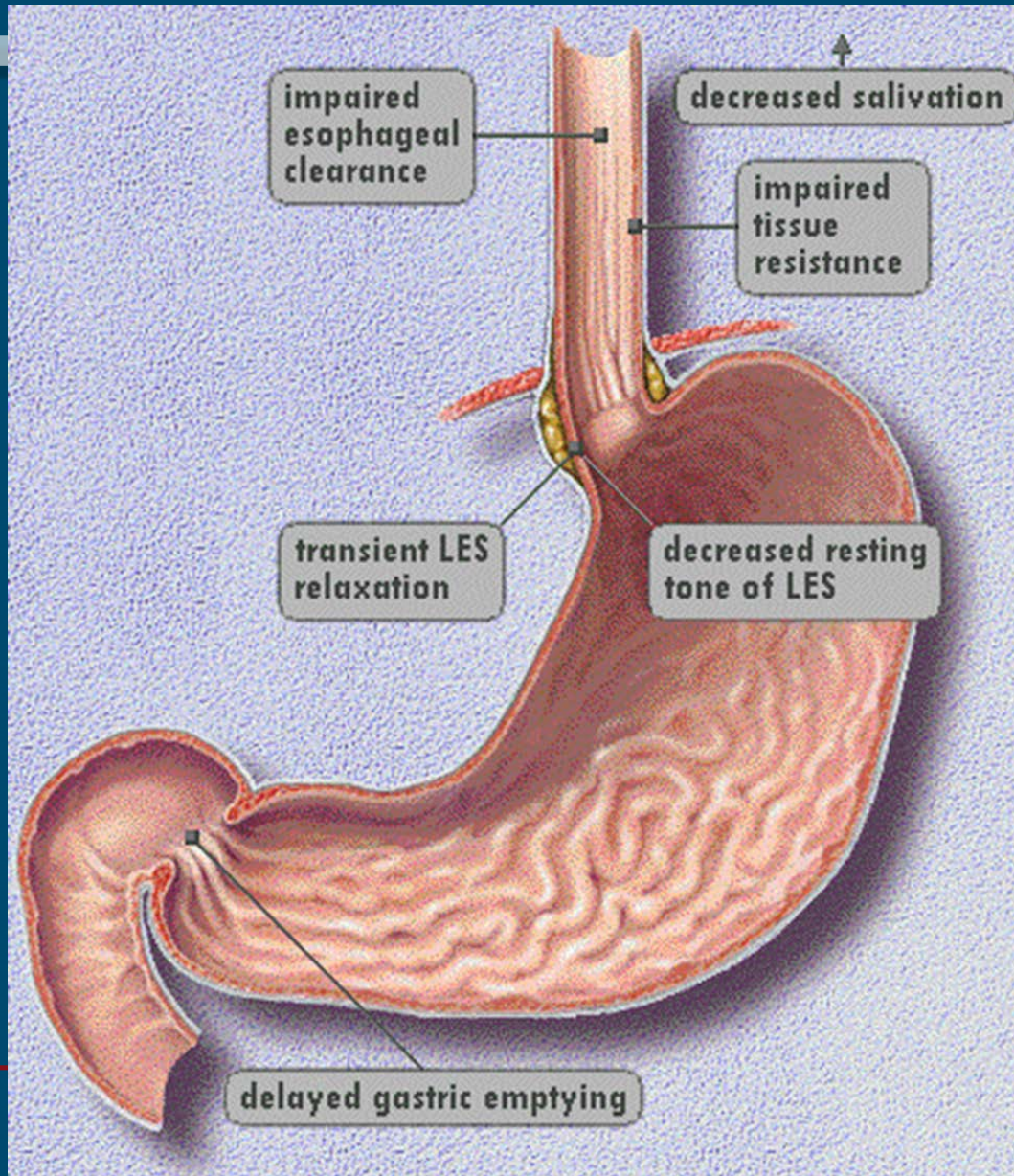
# Definitions

- 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
- Most feared complication is esophageal carcinoma





# Pathophysiology



# Risk factors for GERD

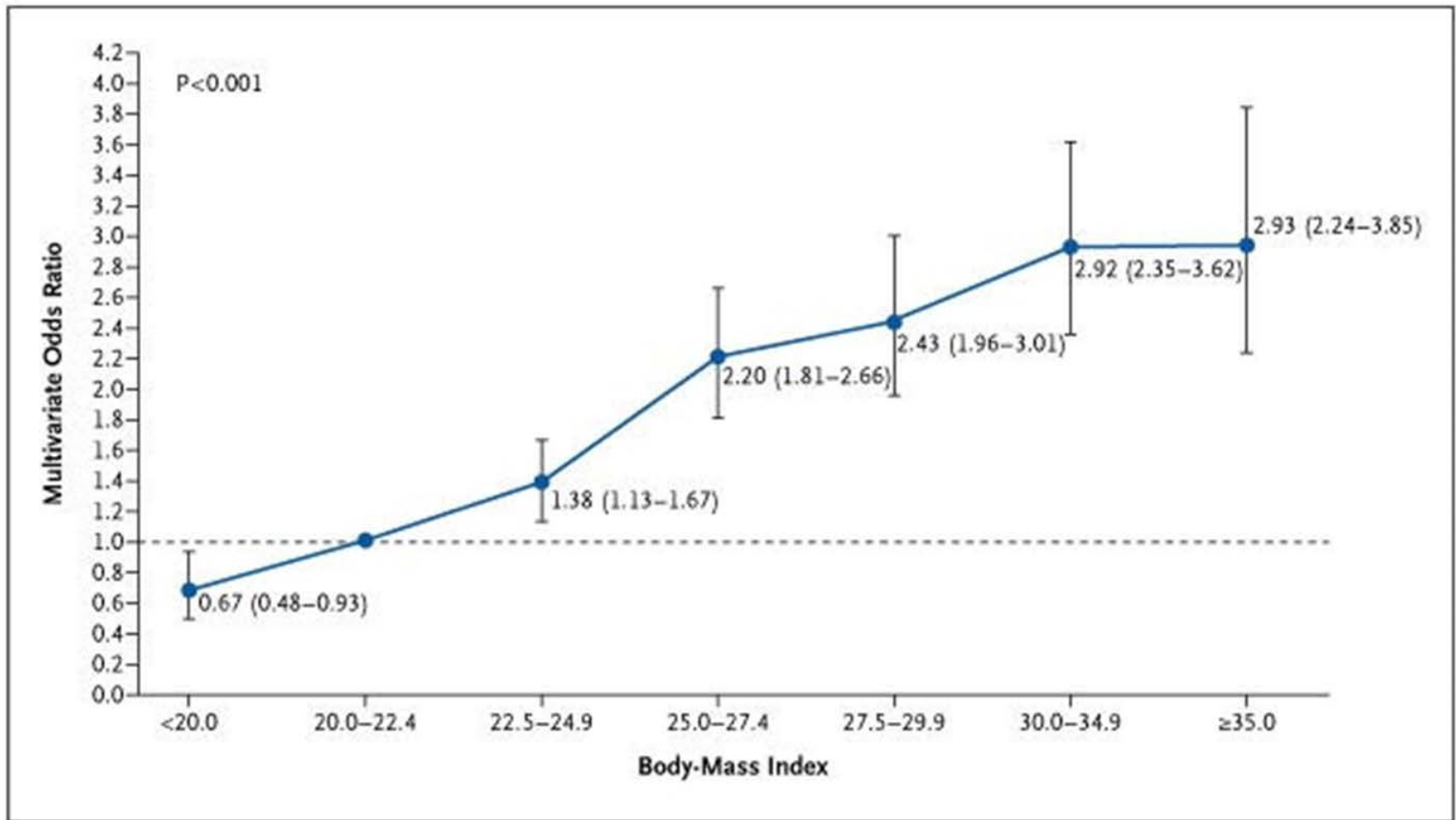


- Obesity





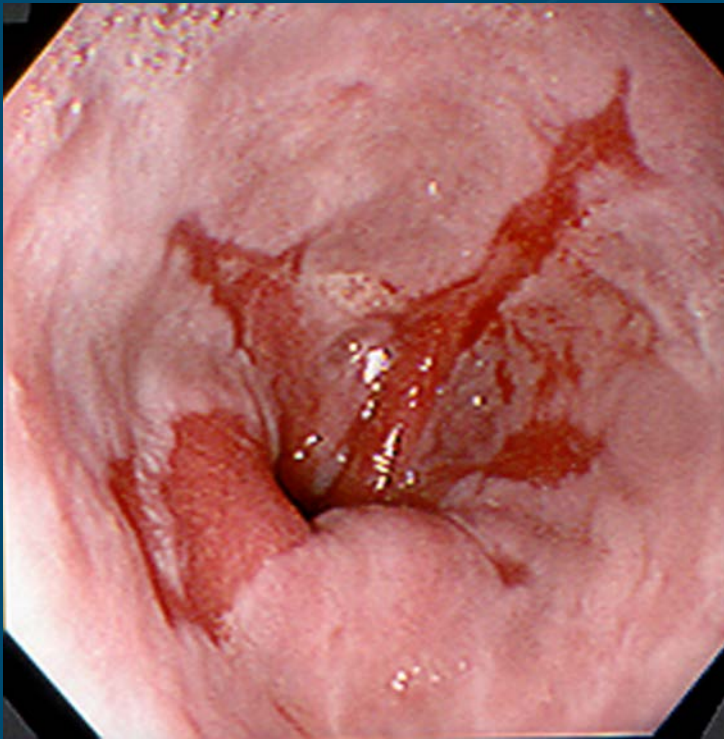
# Risk factors for GERD



# 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
  - Epithelial transformation
  - Risk of progression to adenocarcinoma:
    - 0.12-0.38% per year
  - Screening interval generally 3 years, but not evidence-based
  - Ablation of dysplastic Barrett's prevents progression to adenocarcinoma
  - Frequency/duration of sx's do not predict Barrett's



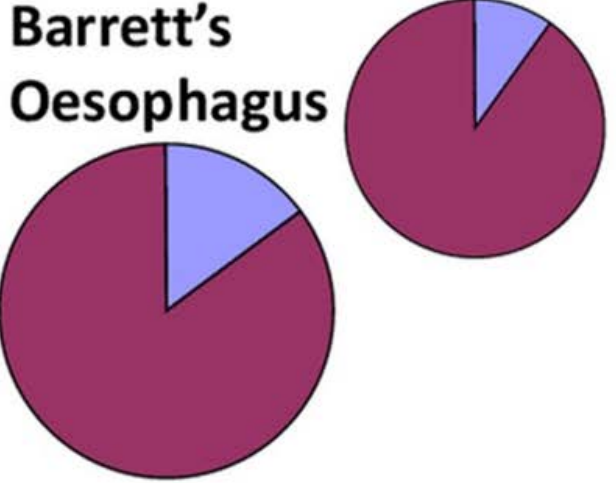
# More serious complications



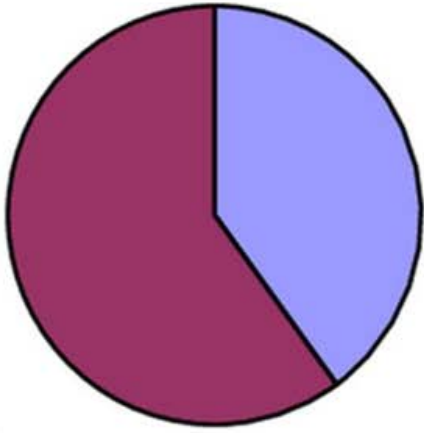
- Esophageal adenocarcinoma
  - Rates increasing rapidly in the western world
  - Increased risk with heartburn duration and frequency
  - Risk of development increases with age
  - Increasingly seeing in younger populations



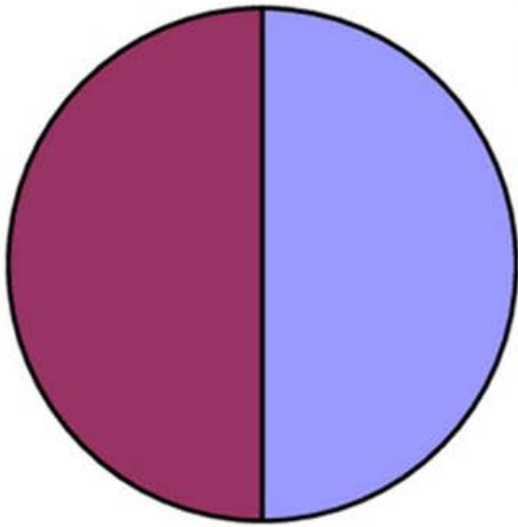
# Oesophageal Adenocarcinoma



## Erosive Oesophagitis



## GORD Symptoms\*



- Men
- Western countries
- Whites
- Women
- Eastern and Middle East countries
- Non- Whites

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

# GERD has atypical symptoms

- Chest pain
  - Often indistinguishable from ischemic cardiac 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

- Diagnostic/therapeutic acid suppression
- Barium swallow?
  - Not recommended unless dysphagia
- Clinical diagnosis
  - Young (<50 years old)
  - Classic symptoms
  - No alarm symptoms
    - Weight loss
    - Bleeding
    - Dysphagia
    - Family history



# Upper endoscopy

- Useful with any alarm symptoms
- Can evaluate for mucosal disease
- Symptoms refractory to treatment
- Long duration of symptoms, troublesome symptoms
- Atypical symptoms
- Age threshold (>50 years old?)
- Keep pH testing in your back pocket
  - Cost benefit over prolonged PPI (>8 weeks) use

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A faint, circular background image showing a dam structure with water flowing through it. In the foreground, several people are visible, some standing and some sitting, possibly engaged in an activity related to the dam or the water. The image is rendered in a light blue color against the dark blue background.

# MANAGING GERD

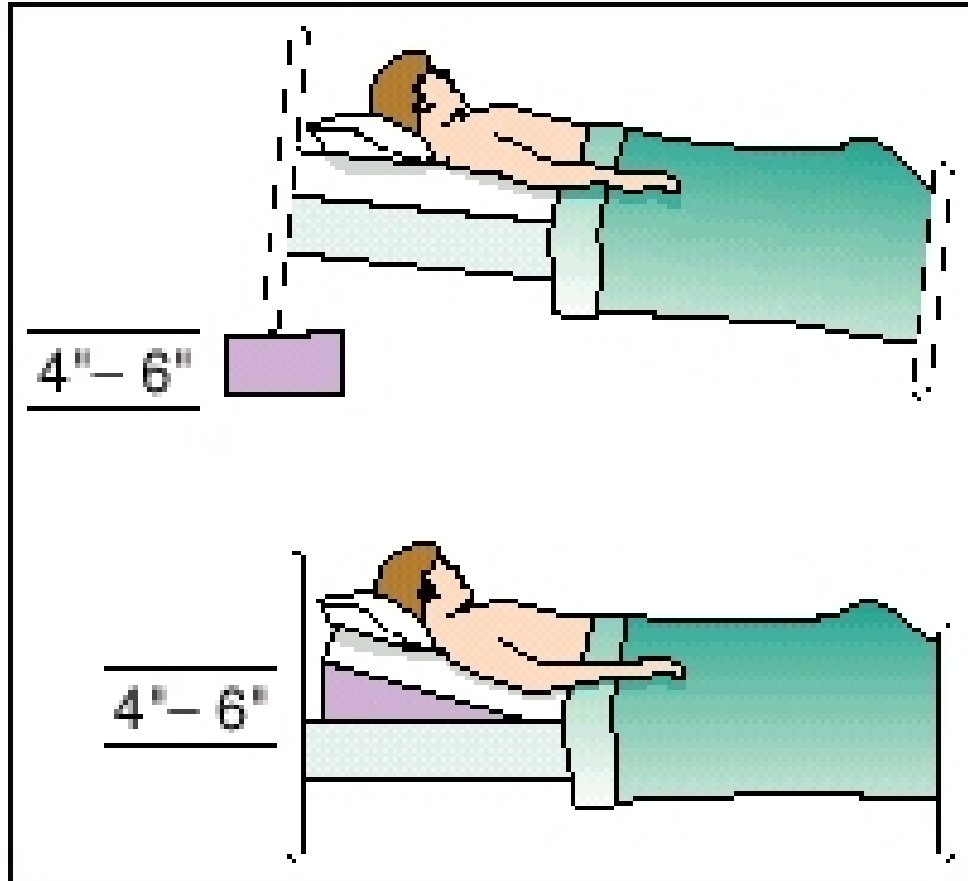
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# Lifestyle modification

- Evidence for improvement is mostly anecdotal
- Avoid foods that in the experience of the patient cause symptoms
- Weight reduction
  - Decrease in BMI of as little as 3.5 lbs/in<sup>2</sup> could result in a 40% decrease in symptom frequency
  - Effects of bariatric surgery
    - Gastric bypass with Roux-en-Y decreases reflux
    - Sleeve gastrectomy can increase reflux
- Avoid late meals/raise head of bed
  - Probably makes sense only for nocturnal symptoms

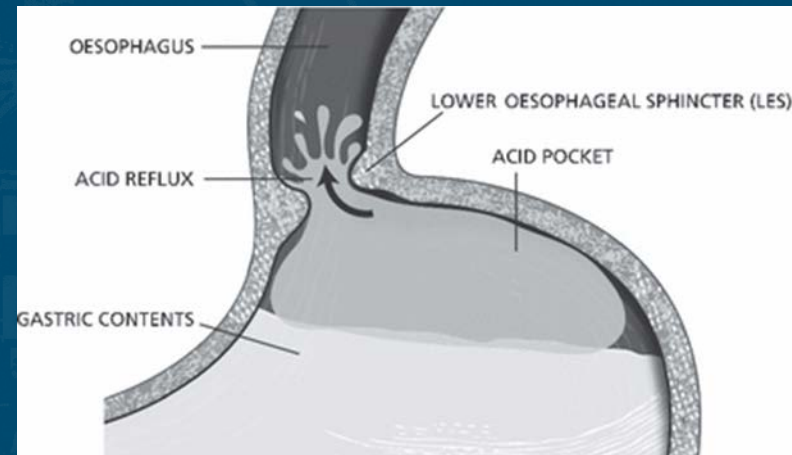




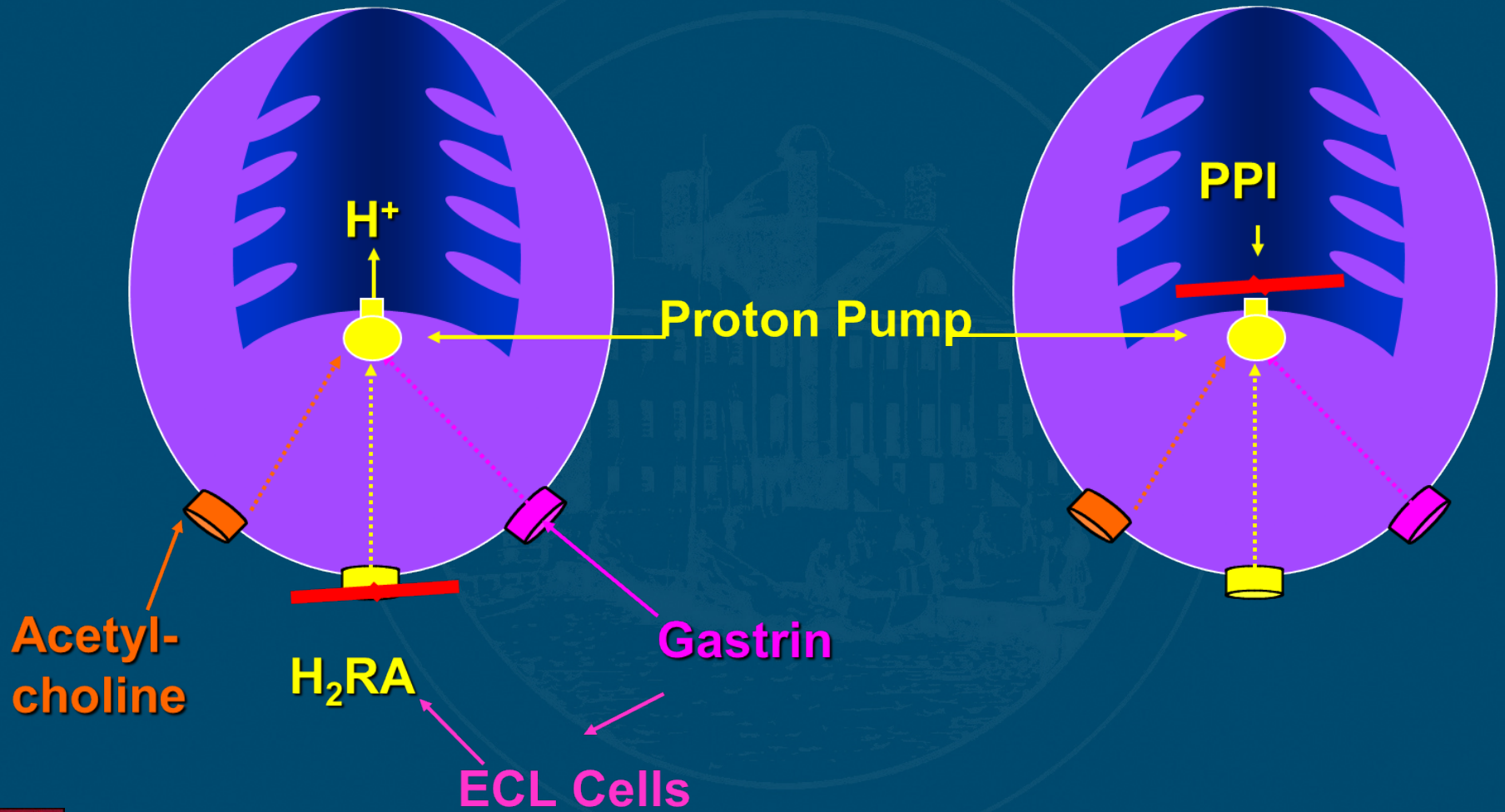


# Antacids

- 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 the stomach contents
  - Reflux events involve movement of acid pocket into esophagus
  - Alginate antacids (Gaviscon) form an “alginate raft” and can shrink or abolish the acid pocket
  - Rafts can push pocket below diaphragm
  - Consider alginates for post-prandial symptoms



# H2RAs vs. PPIs





# H2RAs 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

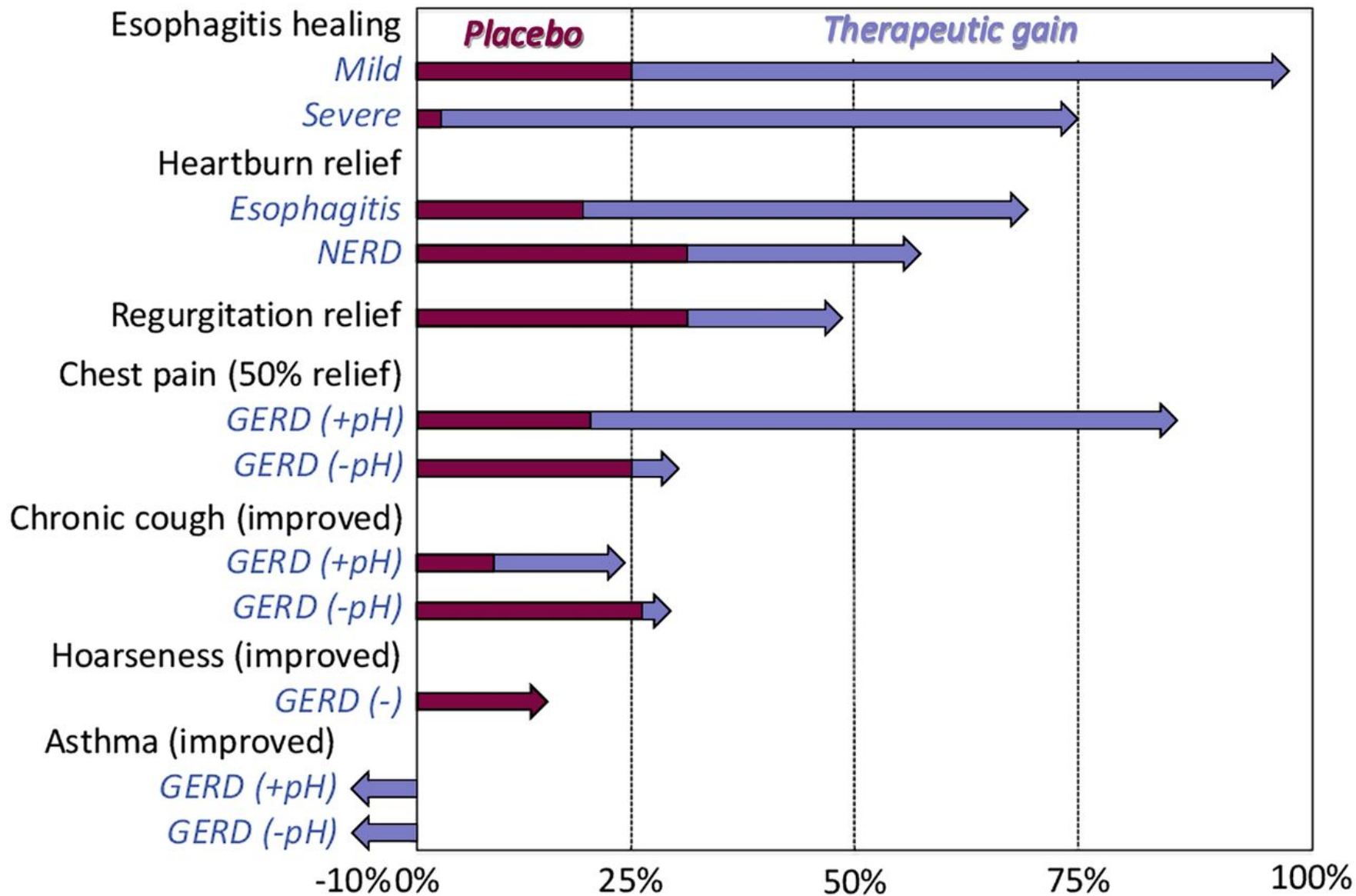
# Long-term treatment

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- Most 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
- 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) are overly fearful of long-term side effects

# PPI efficacy for potential manifestations of GERD

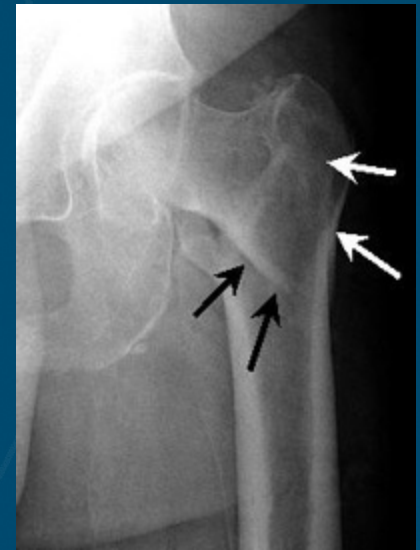
*Estimates based on available RCT data*





# Side effects of proton pump inhibitors

- Common: headache, diarrhea
- 1.5 times increased risk of infectious gastroenteritis
- 2 times risk of *Clostridium difficile* infection
- 1.4 times increased risk of hip fracture
  - Presumably due to calcium malabsorption
  - Use calcium citrate in patients on PPIs
  - Data quality is poor
- Potential (small) for vitamin B12 deficiency



# Clopidogrel and PPIs

- PPIs inhibit CYP2C19 *in vitro* and *ex vivo*
  - CYP2C19 is important part of activation pathway for clopidogrel
- Concern for decreased efficacy of clopidogrel in persons taking omeprazole
- Large clinical trials and meta-analyses have failed to demonstrate increased CV events (?underpowered)
- FDA black box warning remains
- Interaction less severe with pantoprazole (Protonix), lansoprazole (Prevacid), dexlansoprazole (Dexilant)



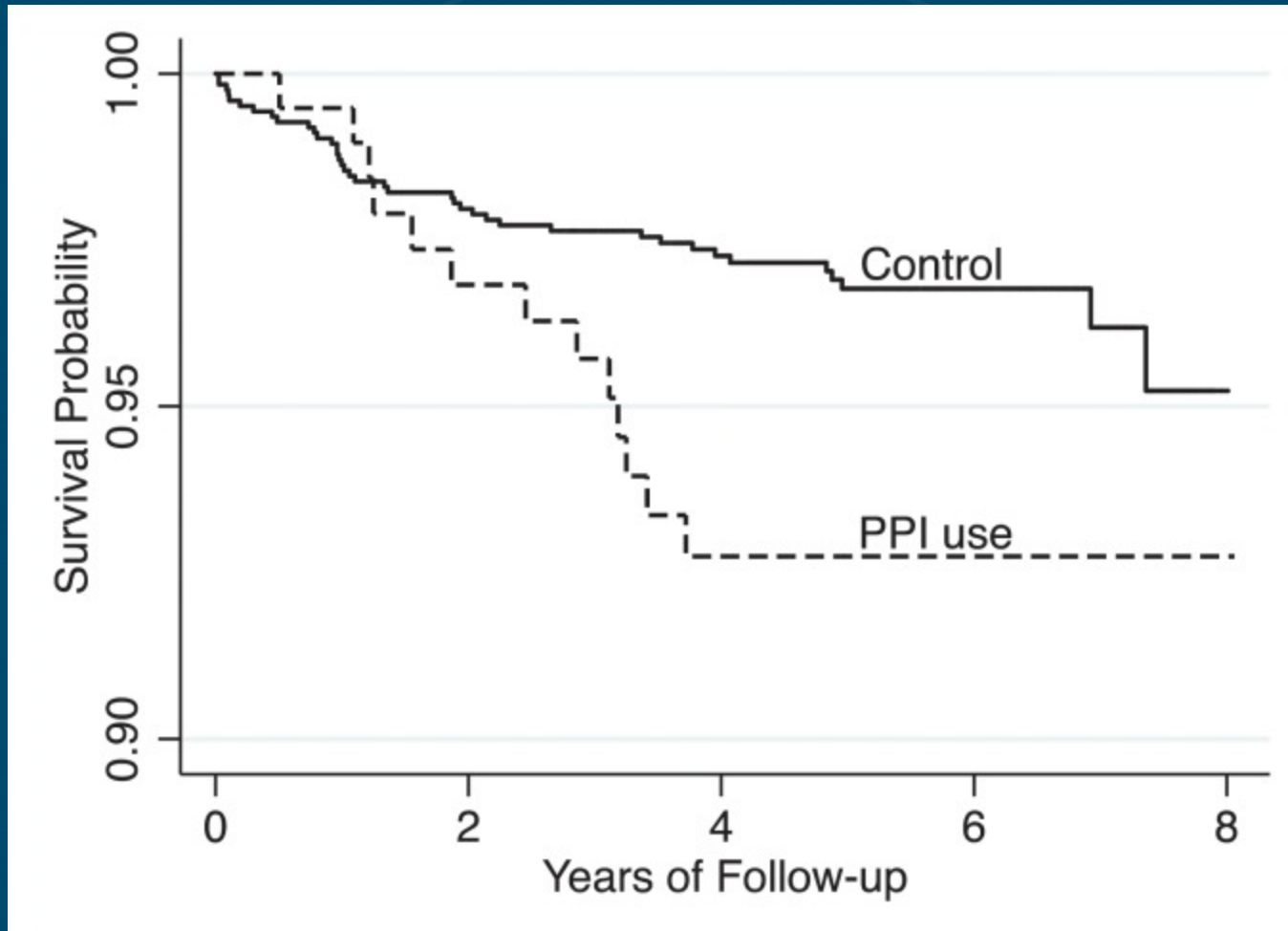
# PPIs and risk of myocardial infarction

- Recent data mining study found that PPI use associated with 1.16x w/ MI
- Survival analysis in a prospective cohort found 2x increase in association w/ CV mortality
- For every 4,000 patients treated with a PPI, 1 would develop a MI
- Observational data:
  - Did not account for comorbidities (DM, obesity, CAD, etc.)
  - No dose response noted
  - Not seen with all PPIs, only some





# PPIs and risk of myocardial infarction



# 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 (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)



# PEPTIC ULCER DISEASE

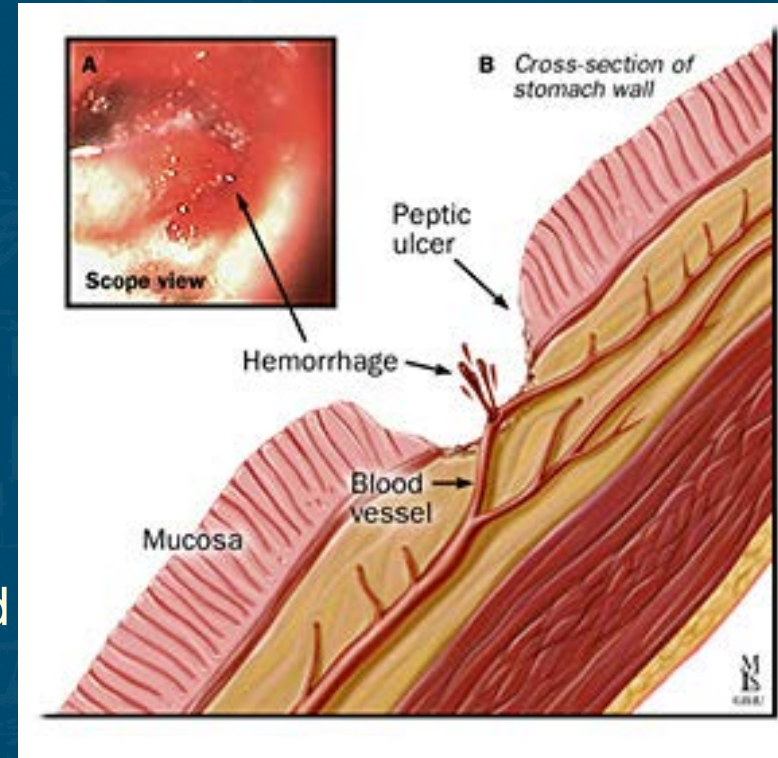
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# Symptoms of peptic ulcer disease

- 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



# 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 5 times
- 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)

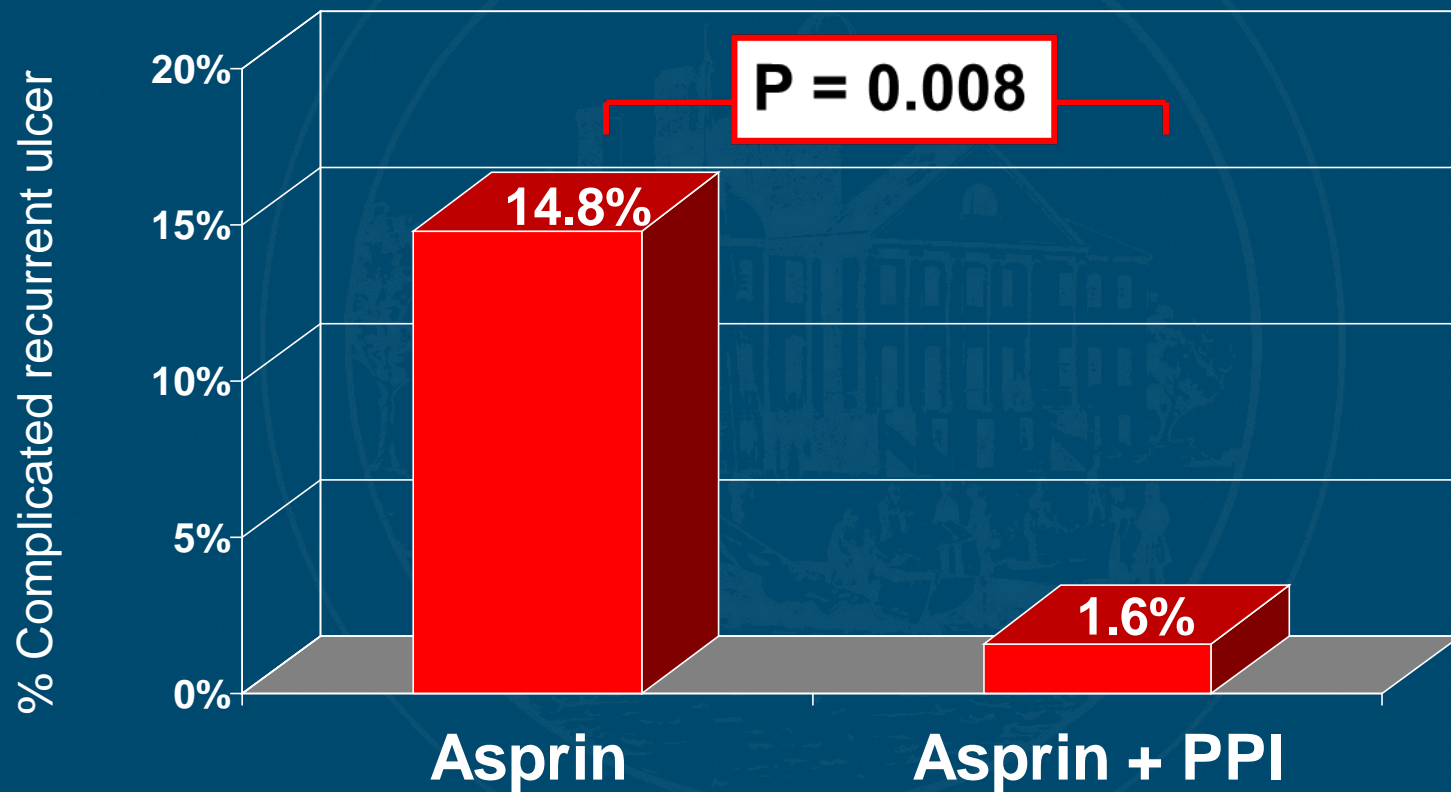




# Risk of NSAID-induced ulceration

- Considered high-risk if  $\geq 2$  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)

# Prophylaxis against NSAID-induced ulceration



# 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 ca resected or MALToma
  - Pts w/ functional dyspepsia
    - Small but real benefit compared to PPI or placebo











## H. Pylori testing: which test to choose?

- Serology? **BAD**
  - has good NPV but poor PPV in low-prevalence populations (i.e. 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



# 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%

# Treatment regimens for H. pylori

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- First-line treatment (7-10 days)
  - PPI
  - Clarithromycin 500 mg bid
  - Amoxicillin 1000 mg bid
- H. pylori resistance rates are rising
- Variety of second-line regimens
  - Avoid clarithromycin or metronidazole after 1<sup>st</sup> failure
  - high rates of resistance after initial treatment failure



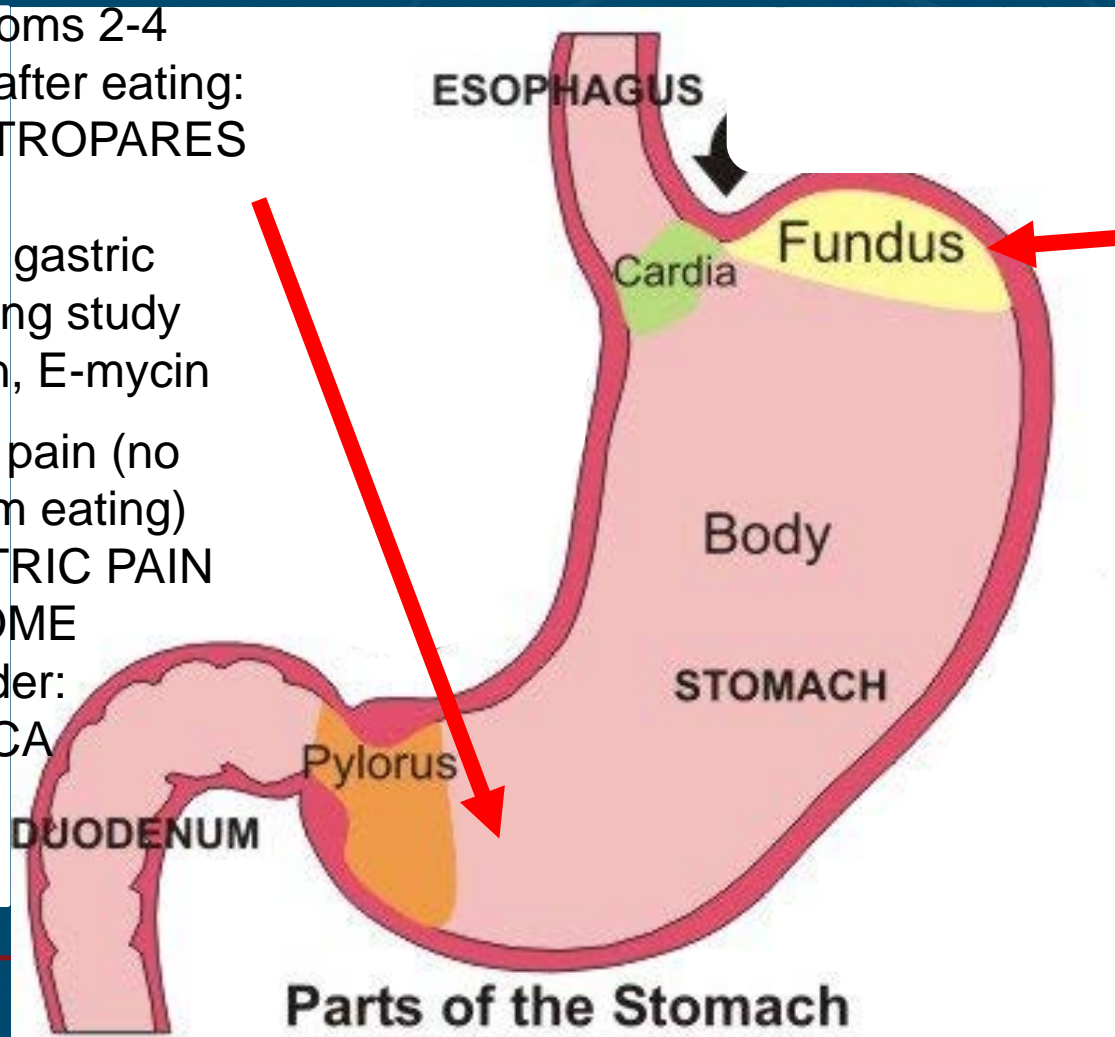
# No ulcer, no H. pylori, still dyspeptic, what now?

- Think functional dyspepsia, gastroparesis

- Symptoms 2-4 hours after eating:  
?GASTROPARESIS
- Obtain gastric emptying study
- Reglan, E-mycin

Constant pain (no effect from eating)  
EPIGASTRIC PAIN SYNDROME

- Consider:
  - TCA



- Symptoms within 1<sup>st</sup> bites → 1 hour after eating  
IMPAIRED FUNDIC ACCOMMODATION
- Consider:
  - Gabapentin
  - Buspirone

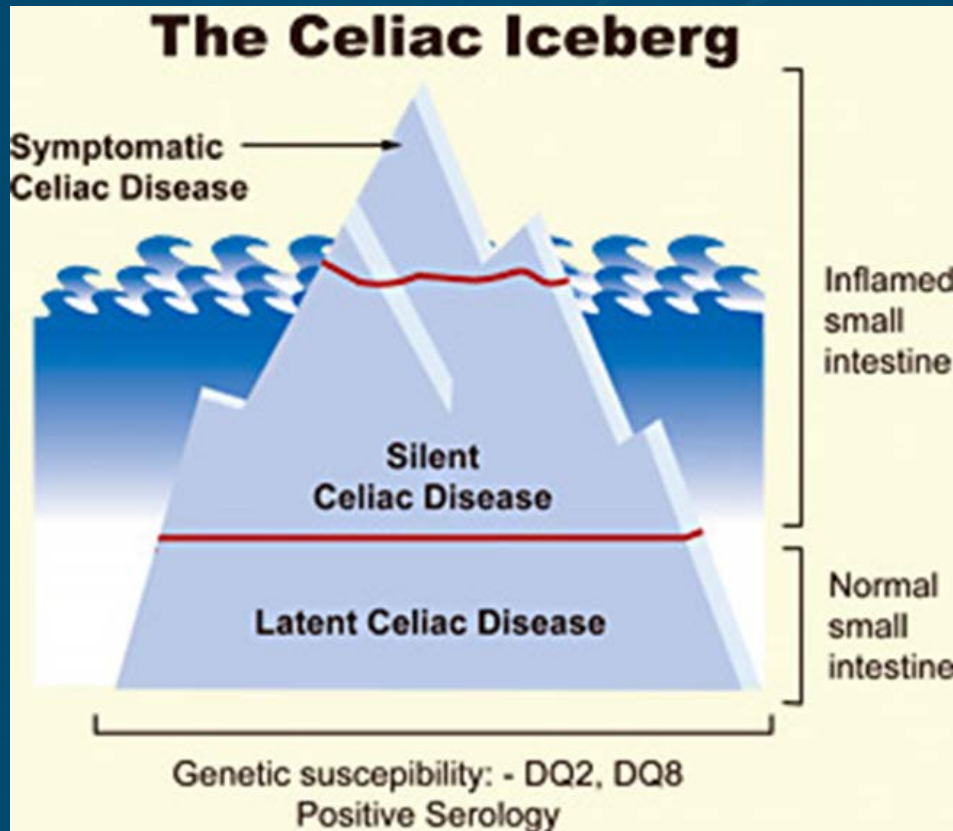


# CELIAC DISEASE

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# Celiac epidemiology

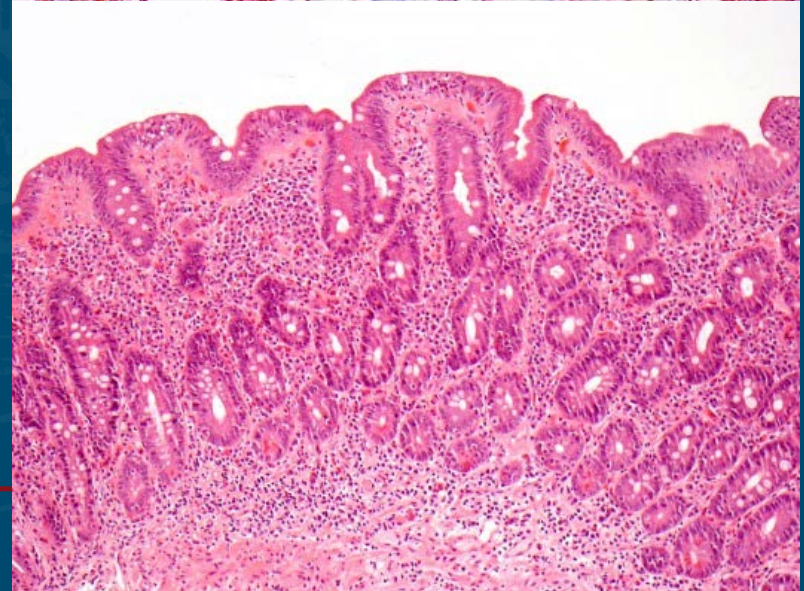
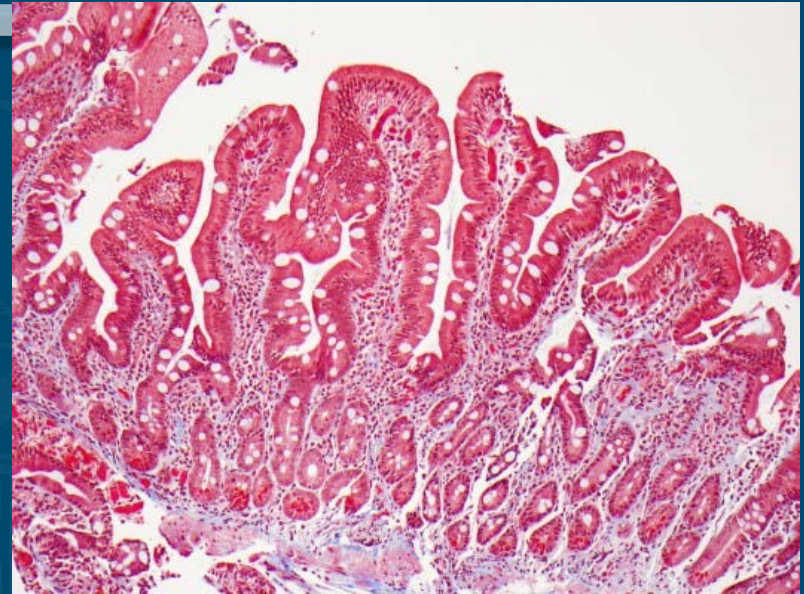


- Prevalence of 1:70-1:300
- Classically in pts of northern European descent
  - Can occur in non-whites in proper genetic background
- Prevalence increases with age
- Many cases are thought to be undiagnosed



# 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 1<sup>st</sup>-degree relatives
  - 1:39 in 2<sup>nd</sup>-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)
Emondysial Antibody (EMA)	95 (86-100)	99 (97-100)
<del>IgA Anti-Gliadin Antibody (AGA)</del>	<del>85 (57-100)</del>	<del>90 (47-94)</del>
<del>IgG Anti-Gliadin Antibody (AGA)</del>	<del>85 (42-100)</del>	<del>80 (50-94)</del>

- 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

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- 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

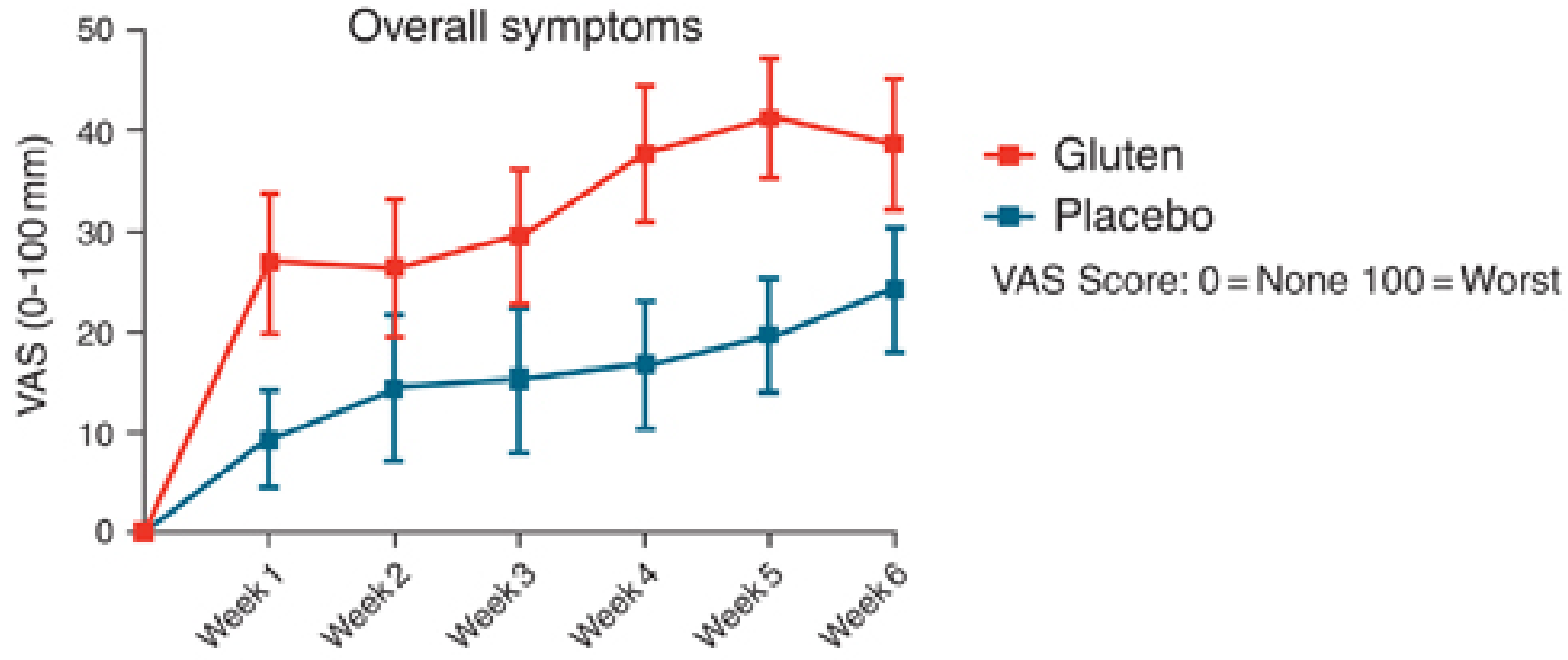


# I know the tests are negative, but I feel better “GF”

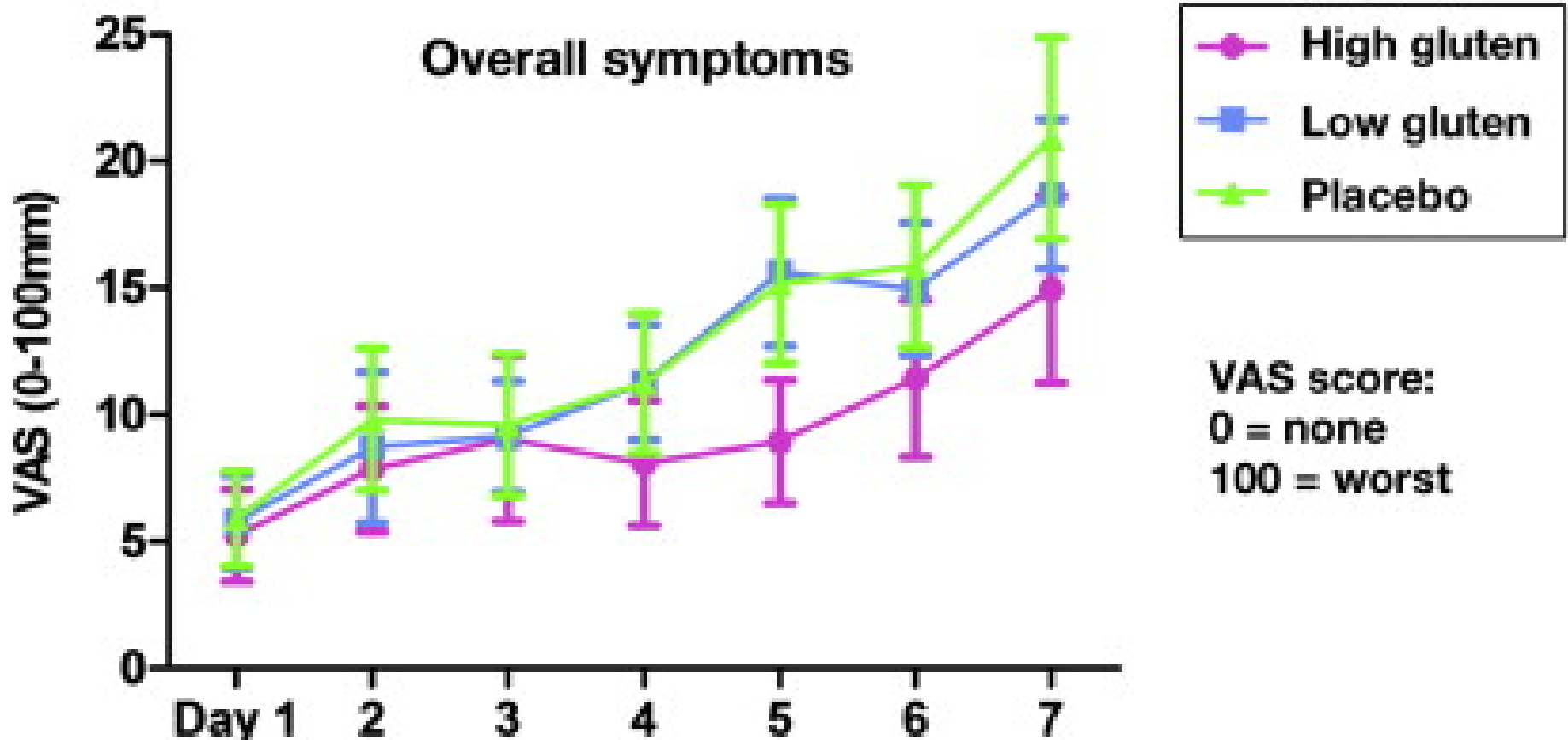


- Undiagnosed celiac is prevalent but not *that* prevalent
- Increasing popularity of going gluten-free in your patient population
- Villainization of wheat products
  - ?increasing gluten content in foods
  - Changes in intestinal microbiome
- Concept of non-celiac gluten sensitivity
  - More appropriately called non-celiac wheat sensitivity

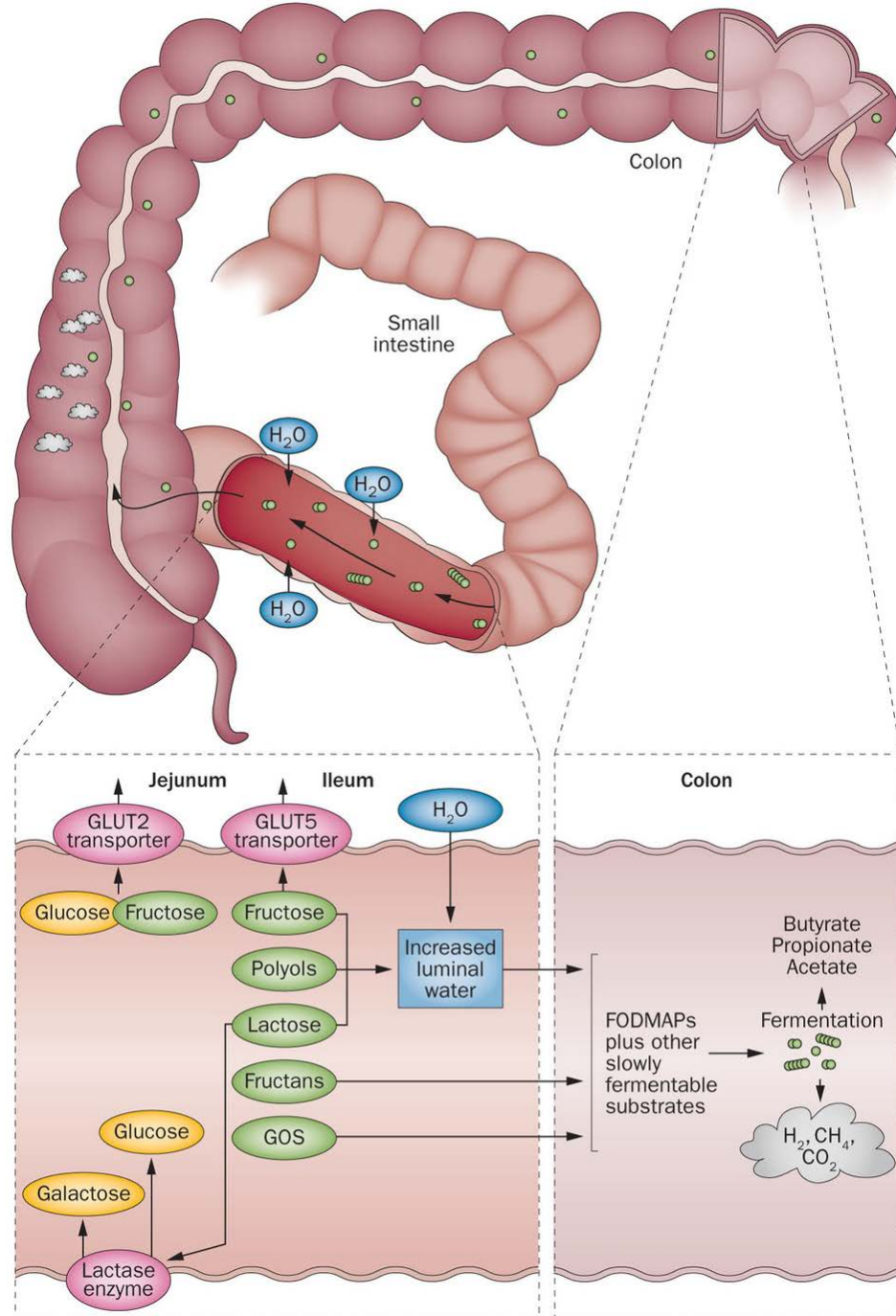
# Worsening of GI symptoms after introduction of gluten in patients without celiac disease



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







# Foods high in FODMAPs

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

# 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 sensitivity
  - Consider empiric 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





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Thank you  
Questions?

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