Brigham and Women's Hospital
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Updates in Upper GI Disorders: GERD, Barrett's Esophagus, and *H. pylori*

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CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

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- Harvard Medical School
- Internal medicine residency @ Brigham and Women's Hospital (chief resident)
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- Associate Physician @ BWH
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- Clinical focus: general GI, *H. pylori*, celiac
- Program Director for fellowship in gastroenterology, hepatology & endoscopy
- Research focus: education, QI, CRC screening

Disclosures

I have no disclosures to report

I will discuss the use of medications for non-FDA approved indications

Learning Objectives

GERD

- Recognize the indications for EGD
- Review current and new treatments

Barrett's esophagus

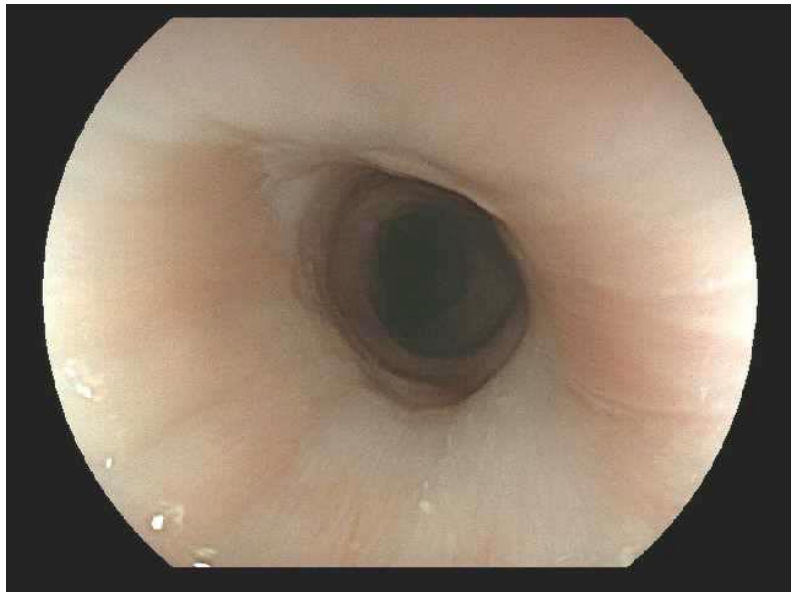
- Discuss screening recommendations
- Summarize treatment options

H. pylori

- Explain current treatment recommendations

Gastroesophageal Reflux Disease (GERD)

Indications for EGD in GERD



Not for diagnosis of GERD

- Most patients will have a normal esophagus

Used to diagnose complications, other causes for symptoms, and evaluate for malignancy

- Erosive esophagitis, Barrett's esophagus, strictures, eosinophilic esophagitis, esophageal cancer

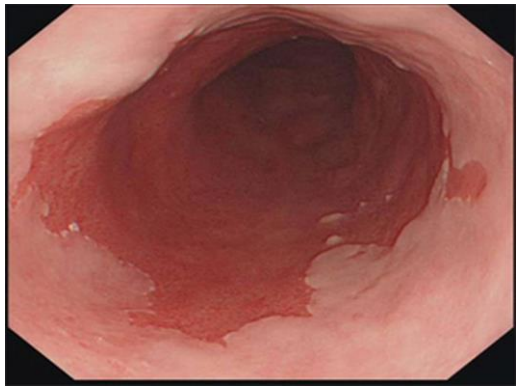
Indications for EGD in GERD

1. Alarm features

- New dyspepsia at age ≥60 years
  - No age criteria for GERD symptoms
- GI bleeding (overt, occult)
- Iron deficiency anemia
- Dysphagia, odynophagia
- Anorexia, weight loss, persistent vomiting
- Family history of upper GI cancer

Indications for EGD in GERD

1. Alarm features
2. GERD symptoms which
   - Do not respond to an 8 week trial of standard-dose PPI (ex. omeprazole 20mg daily)
   - Recur <3 months after stopping PPI
   - [Ideally do the EGD off PPI for 2-4 weeks to see if esophagitis is present]
3. Severe esophagitis (LA Grade C and D)
   - After PPI x 8-12 weeks to assess healing and r/o Barrett's



Katz PO, et al. ACG Clinical Guideline for the GERD. Am J Gastroenterol 2022.

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3. Severe esophagitis (LA Grade C and D)
   - After PPI x 2-3 months to assess healing and r/o Barrett's
4. Screen for Barrett's in patients with multiple risk factors
5. Abnormal upper GI tract imaging

Prescribing Proton Pump Inhibitors (PPI)

Optimal dosing

- 30-60 min before eating (breakfast and/or dinner)
- Avoid giving with H2-blockers (can give H2B at bedtime)

Overprescribed

- Clear indication in only 1/3 of patients

Similar efficacy

- Differences may relate to drug metabolism polymorphisms – can switch if needed

Possible adverse effects

- Most data is retrospective (residual confounding) – need more prospective data
- Few concerns are supported by consistent data demonstrating a causal relationship

Potential PPI Adverse Effects

GI issues

- *C. diff* and other enteric infections
- SBP in cirrhosis
- Small intestinal bowel overgrowth (SIBO)
- Microscopic colitis
- Possible increased risk of IBD
- ↑ gastrin and atrophy – but no clear increased risk of GI cancer

Renal

- AIN – idiopathic
- ? CKD – unclear mechanism

Bone fracture

- ? ↑ osteoclast activity, ↓ Ca absorption (Ca carbonate >> dietary)
- WHI study (2010) – PPI not associated with hip fracture, but was modestly associated with spine, wrist, and total fractures

Potential PPI Adverse Effects

Malabsorption

- Magnesium – check prior to long-term use, esp. if diuretics/elderly or hx arrhythmias/prolonged QTc – then check periodically/yearly
- Vitamin B12 – consider periodic/yearly monitoring
- Iron – no clear recommendation to monitor

Unclear significance

- Dementia
- CV/stroke events
- COVID-19
- Pneumonia

Drug interactions

- CYP2C19 metabolism
  - Omeprazole & esomeprazole the most
  - Pantoprazole the least
- Clopidogrel – no clear evidence of increased adverse effects
- Protease inhibitors – ↓ absorption

Prospective PPI Trial (2019)

- Large, prospective, randomized trial
- PPI (pantoprazole 40mg daily) vs placebo
- 17600 older patients (age >65, 78% men, 23% smokers)
  - Pts with stable CAD/PAD receiving rivaroxaban or ASA
- During median f/u of 3 years
  - No difference in pneumonia, hip fracture, CKD, dementia, COPD, gastric atrophy, or cancer
  - Enteric infections other than *C. diff* were more common in pts taking PPI (1.4% vs 1%, p 0.04)
  - *C. diff* 2x more common in pts taking PPI, but not statistically significant

Moayyedi P, et al. Gastroenterology 2019.

PPI – General Thoughts

- Overall safe and well-tolerated
- Possible safety issues – need more data
- Balance possible risk of PPI with risk of uncontrolled GERD (symptoms, bleeding, strictures, Barrett's)

- Consider discontinuing PPI w/ frequent symptom re-evaluation
- Use lowest dose needed
- Titrate down dose to avoid rebound acid hypersecretion
- Switch to H2-blockers when possible
- Maintenance PPI recommended if severe esophagitis and Barrett's

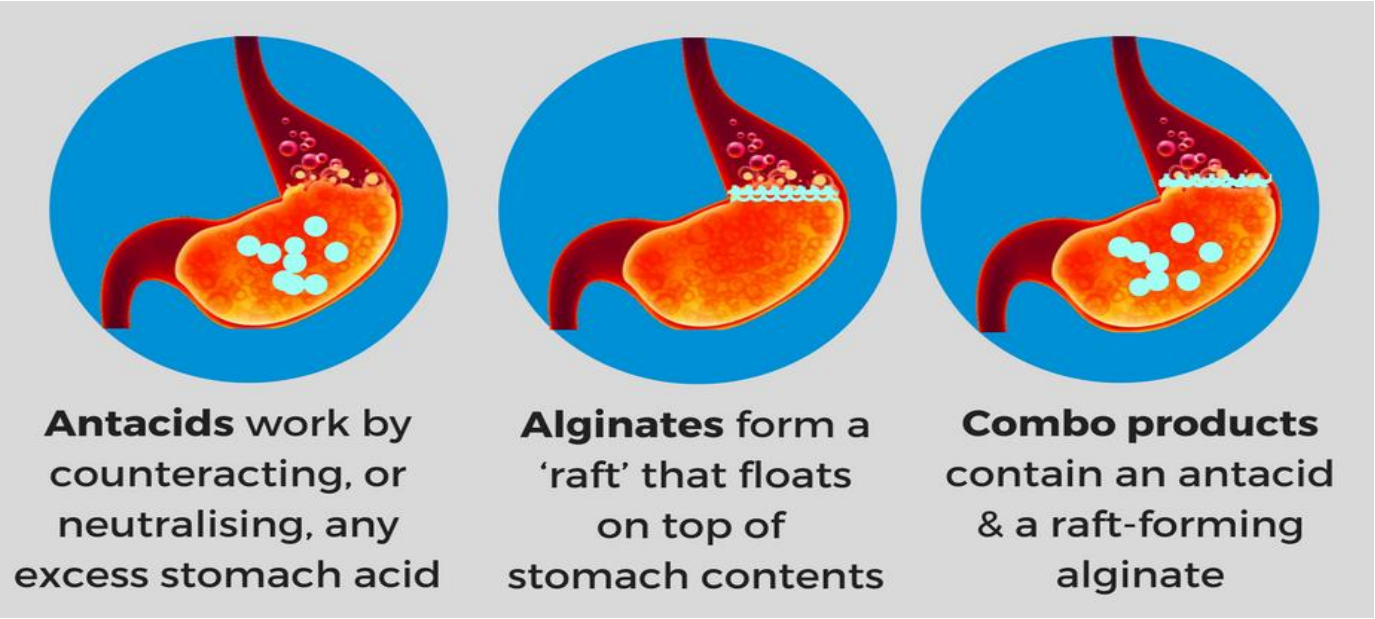
Vonoprazan – New Treatment for GERD

- Potassium-competitive acid blocker (PCAB)
  - May decrease intragastric pH and maintains it to a greater degree than PPI
  - Rapid onset and dosing independent of meals
- Erosive esophagitis – FDA approval 10/2023
  - RCT PCAB vs PPI (Laine, Gastro 2023)
  - Vonoprazan was noninferior and superior to the PPI lansoprazole in healing and maintenance of healing of erosive esophagitis (esp. more severe erosive esophagitis)
- Non-erosive GERD – FDA approval 7/2024
  - RCT PCAB vs placebo (Fass, Aliment Pharmacol Ther 2023; Laine, Clin Gastroenterol Hepatol 2024)
  - Vonozprazan more effective than placebo
- Adverse events - abdominal pain, dyspepsia, hypertension, UTI
  - Longer terms concerns may be similar to PPI, but less is known at this time
- Insurance coverage and cost still an issue
  - Usually need to document failure of PPI for acid-related reflux

Alginates

- Sodium alginate – polysaccharide derived from seaweed

- Forms a gel that floats above the food/liquid in the stomach
  - Neutralizes the postprandial acid pocket in the proximal stomach
  - Prevent reflux from entering the esophagus



https://www.peptest.co.uk/

Alginates

- Used in
  - Mild GERD
  - Refractory acid reflux (on PPI)
  - Non-acid reflux
- Dosing
  - Liquid, tablet
  - After meals and before bed
- Limited efficacy data
  - Mild GERD > refractory GERD or non-acid reflux
- Minimal side effects

Chiu CT, et al. Aliment Pharacol Ther. 2013.

Barrett’s Esophagus

Screening for Barrett's Esophagus

- Expert opinion, not based on RCT data
- A single screening EGD for patients with chronic GERD symptoms** and 3+ additional risk factors for Barrett's

Male sex	Age >50 years
White race	Obesity
Tobacco smoking	Hiatal hernia?
Family hx of Barrett's/esophageal adenocarcinoma in first- degree relative	

** 40% of patients with esophageal adenocarcinoma do not have chronic GERD symptoms

- If initial EGD is negative, repeating EGD for BE screening not recommended
- If EGD reveals severe esophagitis (LA Classification B/C/D) → repeat EGD after PPI for 2-3 months

Shaheen NJ, et al. Am J Gastroenterol. 2022

Novel Screening Modalities for Barrett's

- Swallowable, non-endoscopic capsule device combined with a biomarker
- Swallowed then withdrawn orally – obtaining esophageal cytology samples
- Can be performed in an office setting without sedation

- May make screening for Barrett's easier and more cost-effective
- More research is needed

PPI for Barrett's Esophagus - 2021 Meta-Analysis

- Meta-analysis of 12 studies (>155,000 patients) with Barrett's esophagus
- PPI use associated with a significantly lower risk of progression to high-grade dysplasia and/or esophageal cancer compared to no PPI (OR 0.47)
- Prospective studies needed

Chen Y, et al. J Cancer Res Clin Oncol. 2021;147:2681

Management of Barret's Esophagus

- PPI
  - Data suggests decrease progression to cancer
  - Generally recommend indefinitely at lowest dose to control GERD symptoms (including asymptomatic GERD)
- ASA/NSAIDs
  - May decrease progression to cancer
  - Not recommending solely for Barrett's
- Endoscopic surveillance
  - No dysplasia: 3-5 years
    - Segment ≥ 3cm in 3 years; segment < 3cm in 5 years (ACG Guidelines 2022)
  - Low-grade dysplasia (LGD): 6-12 months
  - High-grade dysplasia (HGD): 3 months
- Radiofrequency ablation – HDG, ? LGD

H. Pylori Treatment

H. pylori Treatment Guidelines

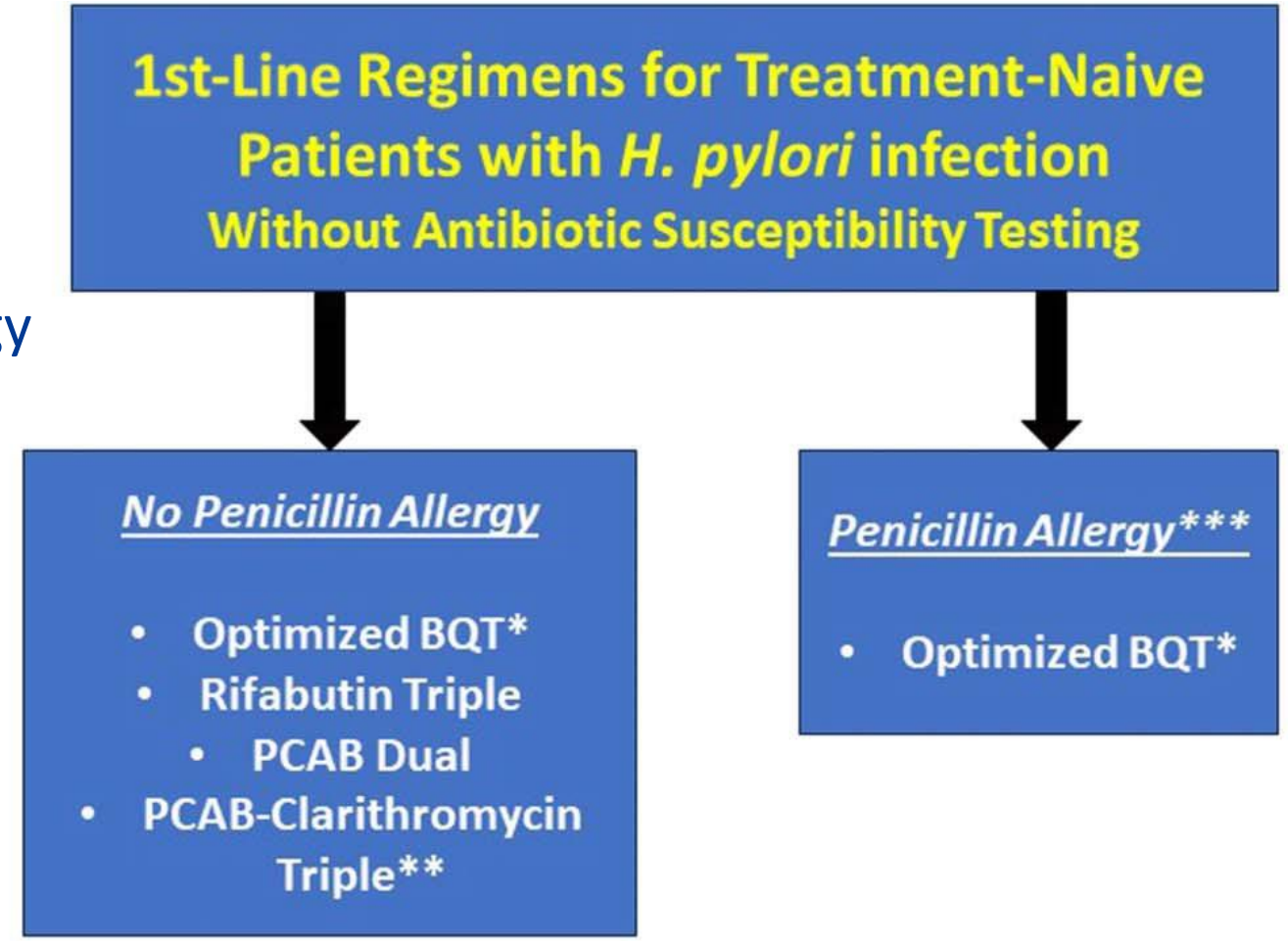
American College of Gastroenterology (ACG) **September 2024**

Bismuth quad therapy (BQT) - metronidazole, tetracycline, bismuth, PPI

Rifabutin triple – rifabutin, amoxicillin, PPI

PCAB dual – amoxicillin (higher dose), vonozopram

PCAB-clarithromycin triple – clarithromycin, amoxicillin, vonozopram
(only if the above are not available and no prior macrolide exposure)



BQT, bismuth quadruple therapy, PCAB, potassium-competitive acid blocker
*Includes appropriately dosed PPI, bismuth, nitroimidazole, and tetracycline (not doxycycline)
** Avoid in those with previous macrolide exposure
*** May require formal allergy testing

All regimens for 14 days

Chey WD, et al. Am J Gastroenterol 2024

First-Line Treatment Summary

- Eradication rates for *H. pylori* in the US have decreased to <80%, mainly due to rising rates of clarithromycin resistance (now up to 30%)

- Bismuth quad therapy (BQT) generally recommended as 1st line (eradication rate approx. 85%)
- Generally avoid clarithromycin-based regimens unless susceptibility is known

Other *H. pylori* Regimens

- In general
  - Clarithromycin, metronidazole, and levofloxacin should not be used again due to concern for resistance
  - Amoxicillin, tetracycline, and rifabutin can often be reused as resistance is rare
- Levofloxacin – resistance a concern given common general use (up to 40%)
  - Levofloxacin, amoxicillin, and PPI BID x 14 days
  - Generally avoid unless documented susceptibility
- Rifabutin (anti-TB drug) – H. pylori resistance rare (eradication rate 84% in US RCT)
  - Rifabutin, amoxicillin, and PPI BID x 14 days
  - ACG 2017 salvage therapy; ACG 2024 consider as first-line
  - Potential concerns
    - Cytopenias (less likely with short course), uveitis/myeloxicity (rare)
    - Drug-drug interactions (similar to rifampin)
    - May increase mycobacteria resistance
- PPI consideration – rapid CYP2C19 metabolizers are at increased risk of failure with standard doses of earlier PPIs
  - Consider esomeprazole and rabeprazole – bypass or are minimally metabolized by CYP2C19
  - Consider higher dose PPI

Consider Penicillin Allergy Testing

- Most patients with a history of penicillin (PCN) allergy do not have true PCN hypersensitivity
  - 5-10% of US population report PCN allergy →
  - 90% have negative skin testing and can tolerate PCN

- Consider referral for allergy testing after failure of a 1st line treatment to see if an amoxicillin-containing regimen can be given

Anti-Acid Therapy for *H. pylori* Treatment?

- Intragastric acid suppression is important for *H. pylori* eradication
  - High gastric pH promotes active replication of H. pylori, making it more susceptible to antibiotics
  - Higher gastric pH promotes stability of acid-labile antibiotics (amoxicillin, clarithromycin) → increases their concentrations in the stomach → may improve eradication
- PPI better than H2-blockers
- New PCAB (potassium-competitive acid blocker) better than PPI?
  - Decrease intragastric pH faster and maintains to a greater degree than PPI
  - Optimized dosing not impacted by meals (unlike PPI ideally 30-60 min before a meal)
  - Use of this instead of a PPI may improve *H. pylori* eradication rates

Potassium-Competitive Acid Blocker (PCAB): Vonoprazan

- Approved by FDA in 5/2022
- Chey, et al. (Gastro 2022) – first clinical trial from the US and Europe
  - Vonoprazan triple (with amoxicillin and clarithromycin) and dual (with amoxicillin) were superior to PPI-based triple therapy (80.8% and 77.2% vs 68.5%), especially in clarithromycin-resistant strains (65.8% and 69.6% vs 31.9%)
- Notes:
  - Vonoprazan-dual (amoxicillin)
    - Superior to PPI-triple (77% vs 69%) in all patients
    - 2 RCT in China – non-inferior to bismuth quad regimens (not the same as ours)
    - Simple and well-tolerated
  - Vonoprazan-triple (clarithromycin, amoxicillin)
    - Cure rate for PPI-triple therapy was 68% (we should be avoiding clarithromycin-based regimens)
    - Overall efficacy of vonoprazan-based triple therapy improved to 81%
    - Use this only if other regimens are not available
- Need more data
  - ? Replacing PPI with PCAB in BQT or rifabutin triple therapy
- Fewer concerns re side effects with short courses (vs chronic use in GERD)

Chey WD, et al. Gastroenterol 2022

Prevent Treatment Failures

- Think about resistance
  - Especially to clarithromycin, metronidazole, and levofloxacin
- Explain regimen & reinforce compliance
- Consider sensitivity testing after 2 failed regimens
  - Culture – requires EGD and special processing, increasingly available via commercial labs
  - Molecular testing – the future, but not widely available and insurance may not cover

Shah SC, et al. Gastroenterology 2021

Confirmation of *H. pylori* Eradication

- Who?
  - Anyone that has been treated, but especially PUD, gastric cancer/MALT
- Which tests?
  - Breath test or stool antigen; not serology
  - EGD if doing for another reasons (e.g. gastric ulcer follow-up, persistent dyspepsia)
- When?
  - Avoid false negatives due to bacterial suppression
    - 4-8 weeks after *H. pylori* treatment
    - Off antibiotics/bismuth for 4 weeks and PPI for 2 weeks

Summary

GERD

- EGD should be performed to diagnose complications, other causes for symptoms, and evaluate for malignancy – and should be repeated after an EGD shows severe esophagitis
- Be mindful about PPI therapy
- Vonoprazan a new possible treatment (instead of PPI) for refractory acid-related GERD

Barrett's esophagus

- Screening can be considered in patients with multiple risk factors
- PPI therapy is generally continued at lowest dose to control GERD symptoms

H. pylori treatment

- Review prior antibiotic exposure, more commonly using quadruple therapy
- Consider penicillin allergy testing to allow use of amoxicillin
- Vonoprazan a new possible treatment (instead of PPI)
- Consider sensitivity testing after 2 failed regimens

Selected References

GERD

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PCAB (Potassium-Competitive Acid Blockers)

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