Gastroesophageal Reflux Disease: Evidence-Based Approach

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Dr. Heidelbaugh is a family physician who has 20 years of academic teaching experience. His specialty topics include gastrointestinal disorders, men's health, and primary care urology. He is a member of the American Gastroenterological Association guideline panels for irritable bowel syndrome, inflammatory bowel disease, and Lynch syndrome. He is the co editor and co author of the textbook ROME IV: Functional Gastrointestinal Disorders for Primary Care and Non GI Clinicians, published through the Rome Foundation. In addition, he is the consulting editor of Primary Care: Clinics in Office Practice and the president elect of the American Society for Men's Health. Dr. Heidelbaugh believes that increasing awareness and education about gastrointestinal and men's health issues is an important trend in medical education, clinical practice, and research.

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Learning Objectives

1. Distinguish between gastroesophageal reflux, dyspepsia, or GERD in patients who present with typical and atypical symptoms.
2. Screen patients with asthma for symptoms of GERD.
3. Educate parents of infants and children with GERD or dyspepsia on effective feeding strategies and safe medication use.
4. Select appropriate imaging studies to confirm the diagnosis of GERD from dyspepsia and appropriately interpret test results for patients.
5. Develop collaborative treatment plans for patients with GERD or dyspepsia to include lifestyle modifications and effective medication use, and ensure patient compliance with treatment.

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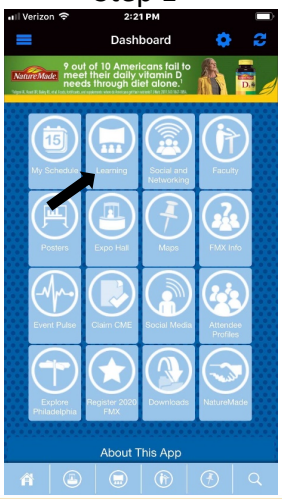
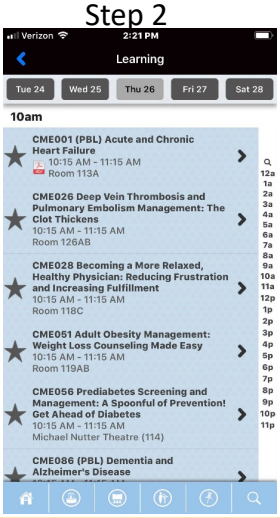
Audience Engagement System

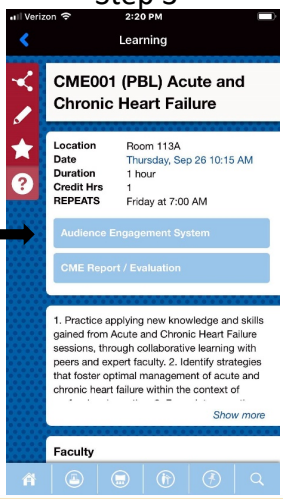
Step 1



Step 2



Step 3



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"*Thought depends absolutely on the stomach, but in spite of that, those who have the best stomachs are not the best thinkers…*"

- Voltaire, 1770

Pathophysiology of GERD

- **Disorder of excessive acid secretion** in the stomach (*or is it too little???*)
  - Conventional anti-secretory therapy is aimed at raising gastric pH via decreasing gastric acid production
- **Transient lower esophageal sphincter relaxations (TLESRs)** allow for reflux of gastric contents into esophagus causing a burning sensation
  - *Smoking, alcohol, caffeine, carbonated beverages, large meals, fatty meals, spicy meals, stress, anxiety, depression, etc., etc., etc.*

Pathophysiology of GERD

- **Lower esophageal dysmotility / prolonged relaxation vs. contraction of the esophagus**
- **Visceral hypersensitivity**
- **GERD** is differentiated from **dyspepsia** and **peptic ulcer disease**:
  - Intermittent gnawing/aching epigastric pain that may improve with meals
  - Lack of heartburn and regurgitation
  - GERD shouldn't be bloody…
  - Most common referral to gastroenterology: **"*refractory GERD*"**

Dyspepsia

- Classically confused with "refractory GERD"
  - Most common cause of GI referral from primary care
- Up to 1/3 of GERD cases don't have classical symptoms of heartburn and regurgitation - ***So, how do we know ?***
- 60% of cases are due to **peptic ulcer disease**
  - NSAIDs, ASA (yes, even enteric coated…)
  - *H. pylori*, although incidence is decreasing
  - History of conflicting guidelines with respect to GERD
- 40% of cases are due to **functional dyspepsia**
  - VERY challenging to treat, may overlap with other diagnoses
  - No proven effective pharmacotherapy

Talley NJ. Gastroenterology 2005;129(5): 1753-1755.

Poll Question 1

Which of the following is a proposed mechanism to explain functional dyspepsia?

1. Delayed gastric emptying
2. Chronic upper gastrointestinal infections
3. Insensitivity to gastric acid
4. Hyperdistensible stomach
5. Decreased acid secretion

Functional Dyspepsia

Current Theories for Causality:

- Hyperactive acid secretion
- Delayed stomach emptying
- Stiff stomach that doesn't expand easily to accommodate food
- Hypersensitivity to stomach acid or expansion

Potential Theories:

- Accelerated stomach emptying
- Abnormal responses to food by the duodenum
- Poor coordination between the upper and lower parts of the stomach
- Abnormal processing of internal organ activity by the brain and nerves
- Abnormal stomach contractions
- Acute or chronic infections
- Altered neurohormonal responses to meals

Infantile GERD

- "*The happy spitter*"
- Increased amounts of vomiting or persistent projectile (forceful) vomiting - - -> **R/O pyloric stenosis**
- Vomiting fluid that is green, yellow or coffee grounds/blood
- Difficulty breathing after vomiting or spitting up
- Food refusal that causes weight loss or poor weight gain
- Pain related to eating
- Difficult or painful swallowing

Acid reflux (GER and GERD) in infants. NIDDK. Available at: https://www.niddk.nih.gov/health-information/digestive-diseases/acid-reflux-ger-gerd-infants, Accessed June 5, 2019.

Infantile GERD - Diagnosis

- "Test and treat"
  - Histamine-2 receptor antagonists
  - Proton pump inhibitors
  - Prokinetics (erythromycin)
  - Antacids (maalox, gaviscon)
  - Cytoprotective agents (carafate, cytotec)
- Barium swallow or upper GI series
- pH probe
- Upper endoscopy
- Gastric emptying study

Acid reflux (GER and GERD) in infants. NIDDK. Available at: https://www.niddk.nih.gov/health-information/digestive-diseases/acid-reflux-ger-gerd-infants, Accessed June 5, 2019.

Infantile GERD - Treatment

- Parental education and reassurance!
- Smaller, more frequent feedings throughout the day
- Change feeding schedules ("*discuss with the child's doctor first*")
- Elevate the head of the baby's crib or bassinet
  - DO NOT RECOMMEND BABY SLEEPING PRONE - - -> INCREASES RISK OF SIDS
- Hold the baby upright for 30 minutes after a feeding
  - Burping, special bottles may help
- Thicken bottle feedings with cereal ("*not without doctor's supervision*")
- Try solid food ("*discuss with the child's doctor first*")
- Medications (previous slide)
- Surgery (fundoplication)

Acid reflux (GER and GERD) in infants. NIDDK. Available at: https://www.niddk.nih.gov/health-information/digestive-diseases/acid-reflux-ger-gerd-infants, Accessed June 5, 2019.

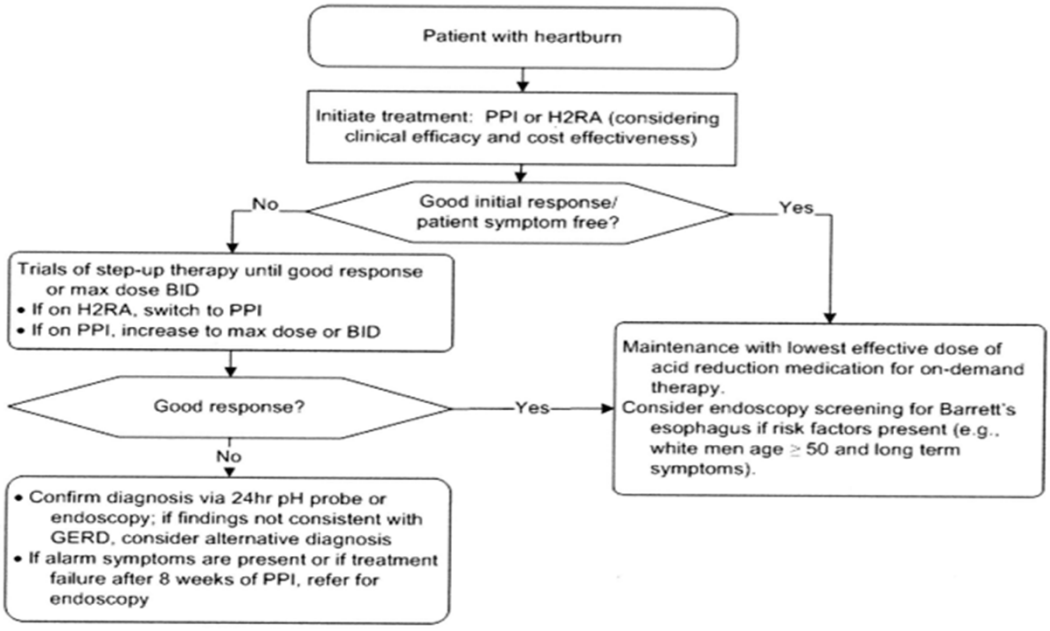
Classification and Risk

- NERD (non-erosive reflux disease)
  - 90+% of cases
- Erosive esophagitis
  - Los Angeles (LA) Classification A - D
- Barrett's esophagus (BE)
- Esophageal adenocarcinoma (EAC)

Poll Question 2

Which of the following is considered the "gold standard" test for diagnosing GERD?

1. Upper endoscopy
2. Esophageal manometry
3. 24-hr pH probe
4. Barium swallow
5. There isn't one



Gastroesophageal Reflux Disease. University of Michigan Health System. http://www.cme.med.umich.edu/pdf/guideline/GERD12.pdf

Diagnosis

- No gold standard test exists for the diagnosis of GERD
- EGD is to assess complications; > 50% will be normal!
- Presumptive diagnosis of GERD can be established with typical symptoms of heartburn and regurgitation
  - Consider empiric trial of PPI **[SOR A]**
- Patients with non-cardiac chest pain suspected due to GERD should be investigated and cardiac causes excluded **[SOR B]**
- Barium radiographs should not be performed to diagnose GERD (but may discover complications…) **[SOR A]**
- Upper endoscopy is not required for typical GERD symptoms, but recommended in presence of alarm symptoms and for screening high risk patients **[SOR A]**

Katz PO, et al. Guidelines for the Diagnosis and Management of GERD. Am J Gastroenterol 2013;108:308-328.

Diagnosis

- Routine endoscopic biopsy of distal esophagus is not required to diagnose GERD **[SOR B]**
- Esophageal manometry has no role in the diagnosis of GERD and should only be used for pre-operative evaluation **[SOR C]**
- Ambulatory esophageal reflux monitoring (pH probe) is the only test that can assess reflux symptom association **[SOR B]**
- Ambulatory esophageal reflux monitoring is indicated prior to consideration of surgical therapy, and in evaluation of patients refractory to AST **[SOR C]**
- Screening for *H. pylori* is not recommended in patients with GERD; treatment is not required as anti-reflux therapy **[SOR C]**

Katz PO, et al. Guidelines for the Diagnosis and Management of GERD. Am J Gastroenterol 2013;108:308-328.

Diagnosis

- An empiric trial of acid suppression therapy for 4 to 8 weeks can identify patients with GERD who do not have alarm symptoms "test and treat" **[SORT A]**
- Acid suppression may be helpful in the evaluation of patients with atypical or extraesophageal manifestations of GERD **[SORT B]**
- Lifestyle modifications should be recommended throughout the treatment of GERD, but there is no evidence-based data to support efficacy (*it's never been randomized…*) **[SORT C]**
  - Avoid smoking, alcohol, caffeine, fatty meals, spicy or citrus foods
  - Elevate head of bed 6-8 inches (not just pillows…)
  - Avoid eating 3-4 hours prior to recumbency

Katz PO, et al. Guidelines for the Diagnosis and Management of GERD. Am J Gastroenterol 2013;108:308-328.

Alarm Symptoms

- Black or bloody stools
- Choking
- Chronic cough
- Dysphagia
- Early satiety
- Hematemesis
- Hoarseness
- Iron deficiency anemia
- Odynophagia
- Weight loss

Gastroesophageal Reflux Disease. University of Michigan Health System. http://www.cme.med.umich.edu/pdf/guideline/GERD12.pdf

Poll Question 3

Which of the following is the most common extraesophageal manifestation of GERD?

1. Asthma
2. Diarrhea
3. Hoarseness
4. Globus sensation
5. Non-cardiac chest pain

Extra-Esophageal Manifestations

- Nasopharyngeal
  - Globus sensation
  - Granulomas
  - Hoarseness - 78%
  - Laryngitis (recurrent)
  - Polyps
  - Sinusitis
  - Sore or burning throat
  - Throat clearing
  - Ulcerations
- Respiratory
  - Asthma (microaspiration) - 82%
  - Bronchitis
  - Chronic cough
  - Interstitial fibrosis
  - Pneumonia
- Cardiac
  - Chest pain (non-cardiac) - 50%
- Other
  - Dental erosions
  - Halitosis

Gastroesophageal Reflux Disease. University of Michigan Health System. http://www.cme.med.umich.edu/pdf/guideline/GERD12.pdf

Pharmacologic Treatment

- H2-receptor antagonists (H2RAs), PPIs, and prokinetics have proven efficacy in the treatment of GERD **[SORT A]**
- PPI's should be taken 30 – 60 minutes prior to a meal (the first meal of the day) to optimize effectiveness **[SORT B]**
- Non-erosive reflux disease (NERD):
  - *Step-up* (H2RAs followed by a PPI if no improvement) and *step-down* (PPI followed by the lowest dose of acid suppression) therapy are equally effective for both acute treatment and maintenance **[SORT A]**
  - *Step-down* therapy (transitioning from a twice daily or once daily PPI to the least potent and lowest effective dose of anti-secretory therapy) has not been shown to change the natural history of GERD-related disease but may decrease pharmacy costs **[SORT B]**

Katz PO, et al. Guidelines for the Diagnosis and Management of GERD. Am J Gastroenterol 2013;108:308-328.

Pharmacologic Treatment

- Documented Erosive Esophagitis:
  - Initial PPI therapy is the treatment of choice for acute and maintenance therapy for patients with documented erosive esophagitis **[SORT A]**
- Pharmacy costs for step-down treatment are mainly medications, while step-up treatment requires more frequent endoscopy **[SORT A]**
- On demand (patient-directed) therapy is the most cost-effective strategy **[SORT A]**

Katz PO, et al. Guidelines for the Diagnosis and Management of GERD. Am J Gastroenterol 2013;108:308-328.

Lifestyle Modifications [SORT C]

- Avoid spicy, fatty, citrus foods
- Avoid acidic and carbonated beverages
- Avoid smoking, alcohol, caffeine, chocolate
- Avoid large meals
- Elevate head of bed 3-4 inches
- Avoid recumbency 3-4 hours after eating
- Avoid tight clothing around waist

Katz PO, et al. Guidelines for the Diagnosis and Management of GERD. Am J Gastroenterol 2013;108:308-328.

Treatment for Atypical GERD

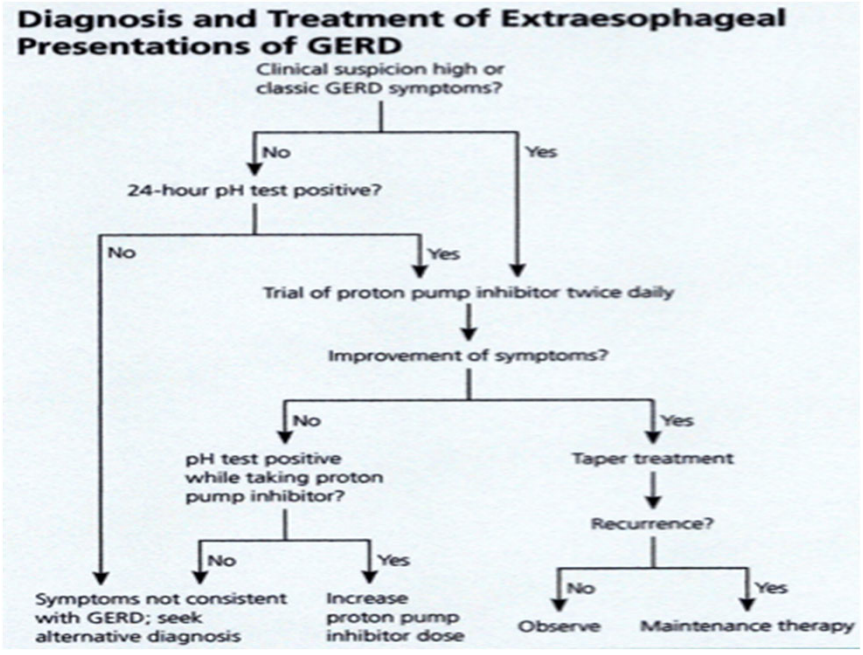
- Aggressive acid reduction using PPIs twice daily before meals for three to four months is the standard treatment for atypical GERD and may be the best way to demonstrate a causal relationship between GERD and extraesophageal symptoms **[SORT B]**
- Randomized trials have not shown significant benefit for twice daily treatment with a PPI for laryngeal symptoms **[SORT B]**

Katz PO, et al. Guidelines for the Diagnosis and Management of GERD. Am J Gastroenterol 2013;108:308-328.

Treatment for Atypical GERD

- In patients with moderate to severe persistent asthma and symptoms of GERD, BID PPI therapy for 24 weeks reduces:
  - Asthma exacerbations and improves quality of life
  - Does not reduce symptoms, albuterol use, or pulmonary function **[SORT B]**
- Patients with chronic cough have a high likelihood of GERD and should be prescribed a trial of antisecretory therapy, even when they have no reportable GI symptoms **[SORT B]**
- PPI therapy reduces symptoms of noncardiac chest pain and may be useful as a diagnostic test in identifying abnormal esophageal reflux **[SORT B]**

Katz PO, et al. Guidelines for the Diagnosis and Management of GERD. Am J Gastroenterol 2013;108:308-328.



Richter JE. Aliment Pharmacol Ther 2005;22(suppl 1):78.

Surgical Treatment

- Anti-reflux surgery is an alternative modality in the treatment of GERD in patients who have documented chronic reflux with recalcitrant symptoms **[SORT A]**
- Surgery has a significant complication rate (10-20%)
- Resumption of pre-operative medication treatment is common (> 50%) and will likely increase over time
- Alternative endoscopic modalities (*e.g. Stretta procedure*) are less invasive and have fewer complications, but have lower response rates than anti-reflux surgery, and have not been shown to reduce acid exposure **[SORT C]**

Katz PO, et al. Guidelines for the Diagnosis and Management of GERD. Am J Gastroenterol 2013;108:308-328.

CAM Options

- Demulcents
  - Licorice (*Glycyrrhiza glabra)*
  - Marshmallow (*Althea officinalis)*
  - Slippery elm (*Ulmus fulva, Ulmus rubra)*
- Ginger (*Zingiber officinal)*
- Apple Cider Vinegar
- Probiotics
- Digestive enzymes
- Relaxation, transcendental meditation, biofeedback
- Acupuncture

Follow-Up and Surveillance

- If symptoms remain unchanged in a patient with a prior normal endoscopy, repeating endoscopy is not recommended **FOR 10 YEARS [SORT C]** – *what about patient-directed direct access endoscopy ?*
- Patients with warning signs and symptoms suggesting complications from GERD should be referred to a gastroenterologist **[SORT C]**
- Further diagnostic testing (e.g. EGD, pH monitoring) should be considered in patients who do not respond to acid suppression therapy and in patients with a chronic history of GERD who are at risk for complications **[SORT C]**
  - Esophageal strictures, webs, rings
  - Barrett's esophagus
  - Esophageal adenocarcinoma

Katz PO, et al. Guidelines for the Diagnosis and Management of GERD. Am J Gastroenterol 2013;108:308-328.

Follow-Up and Surveillance

- Chronic reflux has been suspected to play a major role in the development of Barrett's esophagus, yet it is unknown if outcomes can be improved through surveillance and medical treatment **[SORT C]**
- Antisecretory therapy has been shown to reduce the need for recurrent dilation from esophageal stricture formation **[SORT A]**

Katz PO, et al. Guidelines for the Diagnosis and Management of GERD. Am J Gastroenterol 2013;108:308-328.

Poll Question 4

Which population represents the highest risk for development of Barrett's esophagus?

1. Asian men
2. African American men
3. Hispanic men
4. Caucasian men
5. Middle Eastern men

Barrett's Esophagus

- "*Change in the distal esophageal epithelium of any length that can be recognized as columnar type mucosa at endoscopy and is confirmed to have intestinal metaplasia by biopsy of the tubular esophagus*"
- Screening for BE is controversial
  - Lack of documented impact on mortality from EAC **[SOR B]**
- The large number of patients that lack reflux symptoms but have Barrett's esophagus provides a diagnostic challenge
- The highest yield for BE is in older (age 50 or more) Caucasian males with longstanding heartburn

AGA Medical Position Statement on Management of Barrett's Esophagus
https://doi.org/10.1053/j.gastro.2011.01.030

Barrett's Esophagus

- The grade of dysplasia determines the appropriate surveillance interval; any grade of dysplasia by histology should be confirmed by an expert pathologist
- Any mucosal irregularity, such as nodularity or ulcer, is best assessed with endoscopic resection for a more extensive histologic evaluation and exclusion of cancer
- For patients with BE, the goal of pharmacologic acid suppression with agents such as the PPIs is to control reflux symptoms
- **Proton pump inhibitors do not cure Barrett's esophagus!**

AGA Medical Position Statement on Management of Barrett's Esophagus
https://doi.org/10.1053/j.gastro.2011.01.030

Barrett's Esophagus

Onset < 30 years	OR 4.09 (95% CI 2.75-6.54)	OR 31.4 (95% CI 13.0-75.8)
Onset 30-49 years	OR 6.93 (95% CI 1.43-11.7)	OR 6.29 (95% CI 3.48-11.4)
Onset 50-79 years	OR 4.51 (95% CI 2.43-8.37)	OR 5.03 (95% CI 2.72-9.29)

- Based upon weekly reported symptoms
- Risk of BE increases linearly with earlier age of onset of GERD symptoms
- Age at symptom onset may direct primary care clinicians in deciding which patients with GERD symptoms to refer for endoscopic screening for BE

Thrift AP et al. Am J Gastroenterol 2013

Esophageal Adenocarcinoma

- GERD symptoms are “relative risks” for EAC
- Absolute incidence of EAC in patients with GERD is unknown
- Screening for EAC should not be performed in men younger than 50 years or in women at any age because of very low incidences of cancer, regardless of the frequency of GERD symptoms
- Incidence of EAC in men < 50 yrs with GERD symptoms is 1.0/100,000; incidence of colorectal cancer is 6.7X greater
- Incidence of EAC in men > 70 yrs with weekly GERD symptoms is 60.8/100,000; incidence of colorectal cancer is 3X greater
- Incidence of EAC in women with GERD is similar to that of breast cancer in men (3.9/100,000 at 60 yrs)

Rubenstein JH, et al. Am J Gastroenterol 2010

H. Pylori Diagnosis

- ELISA IgG - *“once positive, always positive”*
  - Sensitivity - 85% / Specificity - 79%
- Stool Antigen
  - Sensitive / Specificity - 90%
  - False negatives - antibiotics, bismuth, PPIs
  - Test for eradication 8-14 weeks after treatment
- ^{13}C / ^{14}C Urea Breath Test
  - Accurate for pre- or post-Rx testing
  - Sensitive / Specificity - 90%
  - False negatives
    - Antibiotics or bismuth within 2 to 4 weeks
    - PPIs within 1 to 2 weeks – High dose H2RAs

Chey WD, et al. Am J Gastroenterology 2017

H. Pylori Treatment

Regimen	Drugs (doses)	Dosing Frequency	Duration (Days)	FDA approval
Clarithromycin Triple	PPI (standard or double dose) Clarithromycin (500 mg) Amoxicillin (1 grm) or Metronidazole (500 mg TID)	BID	14	Yes*
Bismuth Quadruple	PPI (standard dose) Bismuth subcitrate (120-300 mg) or subsalicylate (300 mg) Tetracycline (500 mg) Metronidazole (250-500 mg)	BID TID or QID	10-14	No**
Concomitant	PPI (standard dose) Clarithromycin (500 mg) Amoxicillin (1 grm) Nitroimidazole (500 mg)^	BID	10-14	No

Chey WD, et al. Am J Gastroenterology 2017

H. Pylori Treatment

Regimen	Drugs (doses)	Dosing Frequency	Duration (Days)	FDA approval
Bismuth Quadruple	PPI (standard dose) Bismuth subcitrate (120-300 mg) or subsalicylate (300 mg) Tetracycline (500 mg) Metronidazole (500 mg)	BID QID QID TID or QID	14	No**
Levofloxacin Triple	PPI (standard dose) Levofloxacin (500 mg) Amox (1 grm)	BID QD BID	14	No
Concomitant	PPI (standard dose) Clarithromycin (500 mg) Amoxicillin (1 grm) Nitroimidazole (500 mg)	BID BID BID BID or TID	10-14	No
Rifabutin triple	PPI (standard dose) Rifabutin (300 mg) Amox (1 grm)	BID QD BID	10	No
High-dose dual	PPI (standard to double dose) Amox (1 grm TID or 750 mg QID)	TID or QID TID or QID	14	No

Chey WD, et al. Am J Gastroenterology 2017

H. Pylori Treatment

Sequential	PPI (standard dose) + Amoxicillin (1 grm) PPI, Clarithromycin (500 mg) + Nitroimidazole (500 mg)^	BID BID	5-7 5-7	No
Hybrid	PPI (standard dose) + Amox (1 grm) PPI, Amox, Clarithromycin (500 mg), Nitroimidazole (500 mg)^	BID BID	7 7	No
Levofloxacin Triple	PPI (standard dose) Levofloxacin (500 mg) Amox (1 grm)	BID QD BID	10-14	No
Levofloxacin Sequential	PPI (standard or double dose) + Amox (1 grm) PPI, Amox, Levofloxacin (500 mg QD), Nitroimidazole (500 mg)^	BID BID	5-7 5-7	No
LOAD	Levofloxacin (250 mg) PPI (double dose) Nitazoxanide (500 mg) Doxycycline (100 mg)	QD QD BID QD	7-10	No

Chey WD, et al. Am J Gastroenterology 2017

H. Pylori Treatment

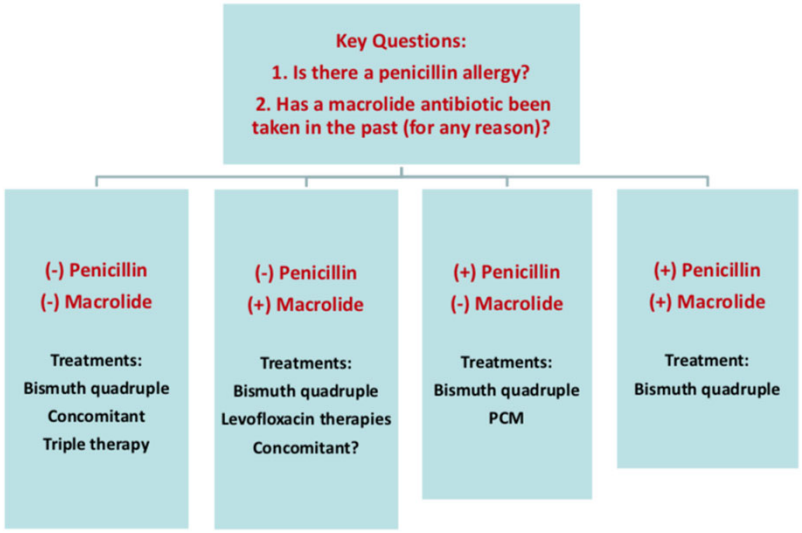
Antibiotic Resistance of *H. pylori:*

Single Center Data from the Houston VAMC

Antibiotic	Resistance Rate (%)
Metronidazole	20
Clarithromycin	16
Levofloxacin	31
Tetracycline	<2
Amoxicillin	<2

Shiota et al Clin Gastroenterol Hepatol 2015

H. Pylori Treatment



Chey WD, et al. Am J Gastroenterology 2017

Scope of the PPI Problem

- Many patients begin with a self-directed trial of OTC anti-secretory therapy (AST)
- Most will consult their PCP due to persistence of symptoms or to obtain reimbursement for prescribed anti-secretory therapy
- "Refractory GERD" remains most common referring diagnosis from primary care to gastroenterology (non-procedural)

American Academy of Family Physicians 2009
National Ambulatory Care Medical Survey 2008

Scope of the PPI Problem

- Since they are superior, patients are often started on PPIs and left on them until…
- What are our endpoints in treatment?
- PPIs are commonly used in non-ICU settings for stress ulcer prophylaxis – *little evidence to support this*
- These practices cost millions (preventable)
- "Knee jerk" phenomenon of prescribing
  - "Nobody uses H2RAs any more, PPIs are much better"
  - "My attending told me to use PPIs…"
  - The concept of "automatic refills"

The **REAL** Problem

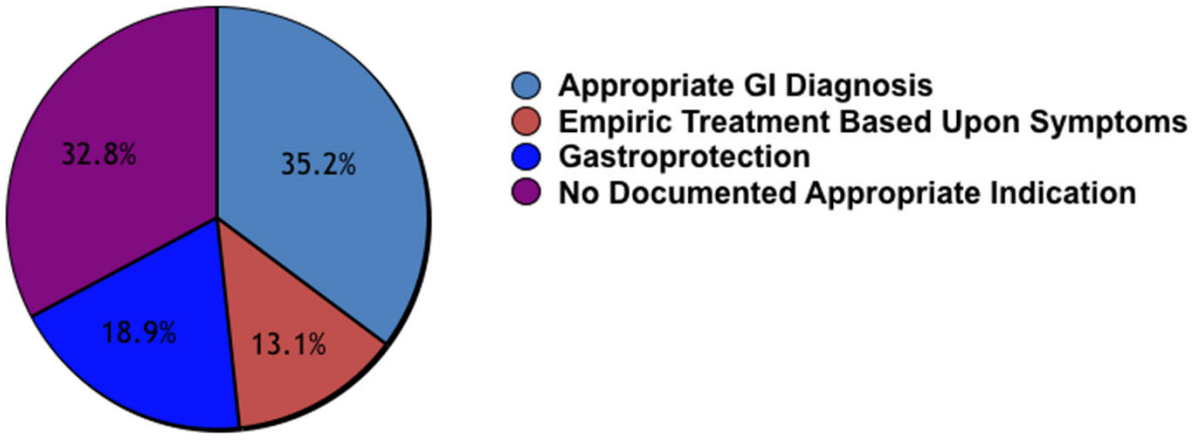
- Clinicians often leave patients on PPI therapy indefinitely without readdressing:
  - If patient takes PPI daily
  - If patient needs to take PPI daily
  - If patient has breakthrough or alarm symptoms suggestive of advanced upper gastrointestinal disease
  - If patient can avoid symptoms without it
- THESE ARE SAFE MEDICATIONS

PPI Overutilization in Ambulatory Care

- What is the prevalence and economic impact of inappropriate PPI utilization in the ambulatory care (primary care) setting?
- Retrospective cohort study of 946 patients in a VA setting who were receiving PPI therapy
- Patients categorized according to appropriateness of PPI therapy
- Costs and adverse events were charted

Heidelbaugh JJ et al. Am J Managed Care 2010

PPI Overutilization in Ambulatory Care



Heidelbaugh JJ et al. Am J Managed Care 2010

PPI Overutilization in Ambulatory Care

- 48.6% of patients across all 4 categories received PPIs without re-evaluation
  - 1034 patient/years of PPI use
- Total cost of inappropriate PPI use
  - $233,994 based on OTC PPI costs
  - $1,566,252 based on AWP costs
- Adverse events
  - 6 cases of community-acquired pneumonia
  - 1 case of *Clostridium difficile*-associated colitis
  - No reported cases of vitamin or mineral deficiency
  - No reported cases of hip fracture

Heidelbaugh JJ et al. Am J Managed Care 2010

Poll Question 5

Which of the following is the most likely sequela from chronic use of PPIs?

1. Renal insufficiency
2. Dementia
3. Clostridium difficile-associated diarrhea
4. Osteoporosis
5. Community-acquired pneumonia

Potential Risks of PPI Therapy

- Excessive pharmacy costs when left unmonitored! *(now OTC)*
- Community-acquired pneumonia
- *Clostridium difficile*-associated diarrhea
- Bone fractures, mostly hip (? Osteoporotic)
- Vitamin B12, calcium, zinc deficiencies
- Interactions with clopidogrel (omeprazole / + or -)
- Renal insufficiency / failure / chronic kidney disease
- Heart disease
- Dementia
- Decreases magnesium (FDA warning), contraindicated in pregnancy…
  - Data from ALL studies was extracted retrospectively
  - Cannot prove direct cause-and-effect relationship

Heidelbaugh JJ, et al. Gastroenterology and Hepatology 2009

Risks Associated with Long-term PPI Use

Adverse effect	Relative risk/odds ratio (95% CI)	Quality of evidence	Practice recommendations
Likely causative			
Hypomagnesemia[3]	1.43 (1.08-1.88)	Low	Check serum magnesium levels in symptomatic patients
Vitamin B_{12} deficiency[5]	1.65 (1.58-1.73)	Low	Check CBC every 2 y and vitamin B_{12} every 5 y
Small-intestine bacterial overgrowth[6]	2.28 (1.24-4.21)		
Duodenal/jejunal aspirate	7.59 (1.81-31.89)	Low	Unclear clinical importance
Glucose hydrogen breath test	1.93 (0.69-5.42)		No recommendation to check for SIBO while using PPIs
Association unclear			
Bone fractures[8]	1.26 (1.16-1.36) for hip fractures 1.33 (1.15-1.54) for fractures at any site	Low	BMD screen per national guidelines Calcium and vitamin D intake per RDA recommendations
Clostridium difficile infection[14]	1.74 (1.47-2.85)	Low	No recommendations Cautious use of antibiotics
Chronic kidney disease[19]	1.50 (1.14-1.96)	Very low	Check serum creatinine level annually
Dementia[24]	1.44 (1.36-1.52)	Very low	No recommendations
Unlikely causative			
Community-acquired pneumonia[28]	1.27 (1.11-1.46)	Very low	No recommendations

BMD = bone mineral density; CBC = complete blood cell count; PPI = proton pump inhibitor; RDA = Recommended Dietary Allowance; SIBO = small intestine bacterial overgrowth.

Nehra AK, et al. Mayo Clin Proc 2018

"*The benefits of your efforts are not always <u>oblivious</u>*"

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Fortune Cookie # 2235

Practice Recommendations

- Diagnose and manage non-erosive reflux disease (NERD) via a test and treat strategy with anti-secretory therapy, and implementation of lifestyle and dietary modifications
- Minimize the likelihood of development of advanced disease (e.g. esophageal strictures, Barrett's esophagus, and esophageal adenocarcinoma) with appropriate diagnosis and management of GERD via atypical or extraesophageal symptoms
- Consider testing for *H. pylori* in patients with dyspepsia (not GERD) and use current diagnostic and treatment algorithms to foster eradication
- Use anti-secretory therapy with H2RAs or PPIs according to evidence-based guidelines, including frequent reassessment of GERD and related symptoms, to minimize over-utilization and potential adverse risks of pharmacotherapy

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Questions

FMX

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