Peptic Ulcer Disease (PUD)

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Peptic Ulcer Disease: Objectives

- Identify the primary causes and risk factors of peptic ulcer disease (PUD)
- Recommend drug therapy for patients with H. pylori and/or with NSAID-induced (PUD)
- Recommend primary and secondary PUD prophylaxis
- Describe patient counseling pearls for prophylactic and treatment drug regimens for PUD

Peptic Ulcer Disease

- Acid-related erosion or ulceration of the GI tract extending into the muscularis mucosae
  - NSAID-induced
  - *Helicobacter pylori* associated
  - Stress-related
- Predominately found in stomach and duodenum
- Complications include gastric or duodenal bleeding, perforation, and gastric outlet obstruction

Epidemiology

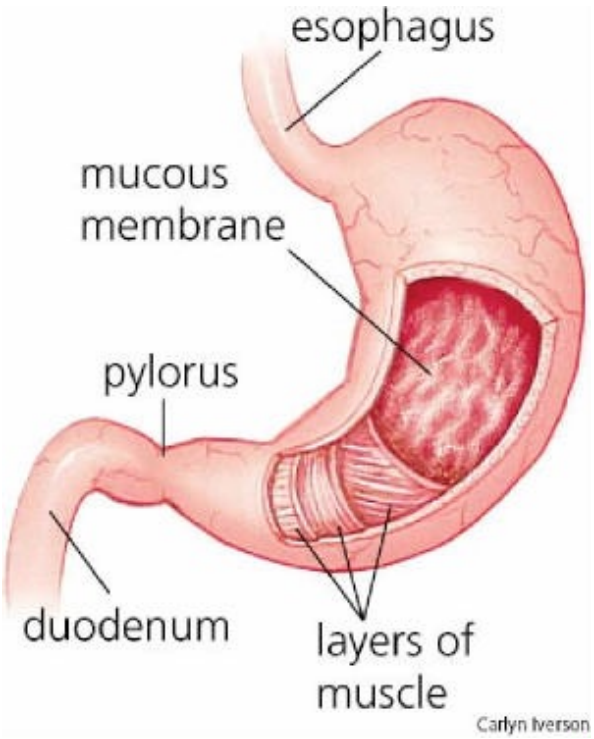
- Within U.S. ~4.6 million affected annually
- ~10% of U.S. population will have evidence of duodenal ulcer during their lifetime

- 35-40% of U.S. population is infected with *Helicobacter pylori*
  - 20% of these develop gastroduodenal disorders in their lifetime

- ~40% of elderly patients take NSAIDs

Peptic ulcer. OMICS International. Available at https://www.omicsonline.org/united-states/peptic-ulcer-peer-reviewed-pdf-ppt-articles/; Malik TF, Gnanapandithan K, Singh K. Peptic ulcer disease. *StatPearls [Internet]*. 2021 Jan.

Anatomy of the Stomach

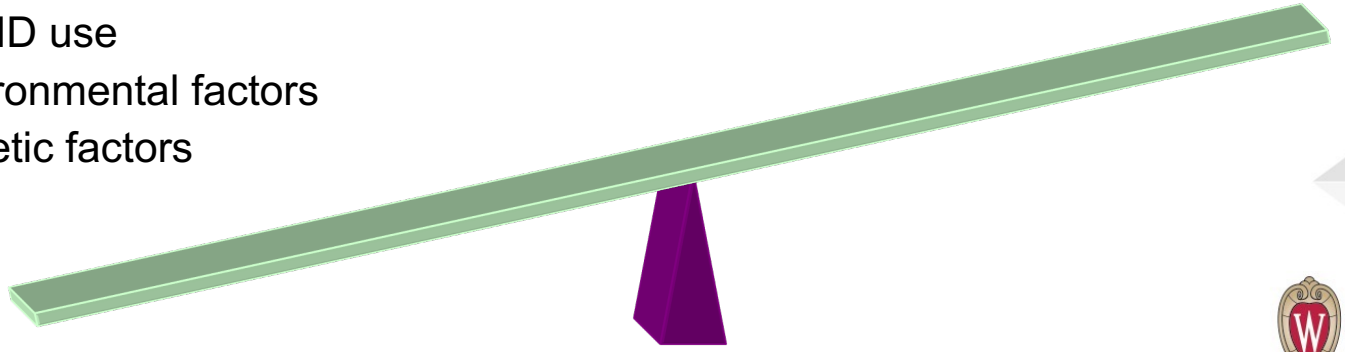


http://habibsanatomy.tripod.com/sitebuildercontent/sitebuilderpictures/.pond/a4stomac.jpg.w300h373.jpg.

PUD: Aggressive and Defensive Factors

- Aggressive
  - Acid
  - Pepsin
  - Smoking
  - Alcohol (high concentrations)
  - *Helicobacter* infection
  - NSAID use
  - Environmental factors
  - Genetic factors

- Defensive
  - Prostaglandins (blood flow)
  - Bicarbonate
  - Mucus
  - Growth factors



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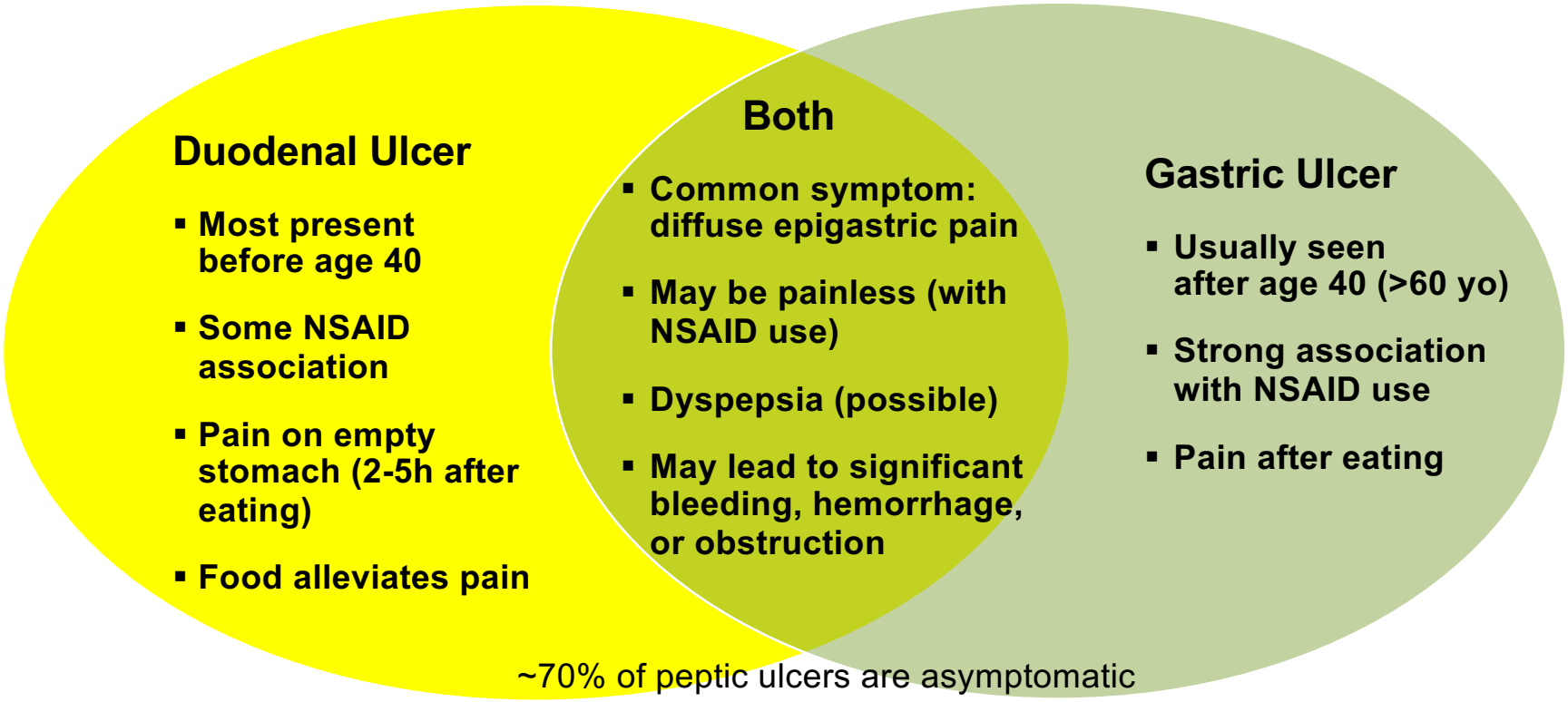
PUD: Presentation



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PUD: Alarm Symptoms

- Bleeding
  - Hematemesis
  - Melena
- Unexplained iron deficiency anemia
- Early satiety
- Unexplained weight loss

- Progressive dysphagia or odynophagia
- Palpable mass or lymphadenopathy
- Recurrent emesis
- Family h/o GI cancer

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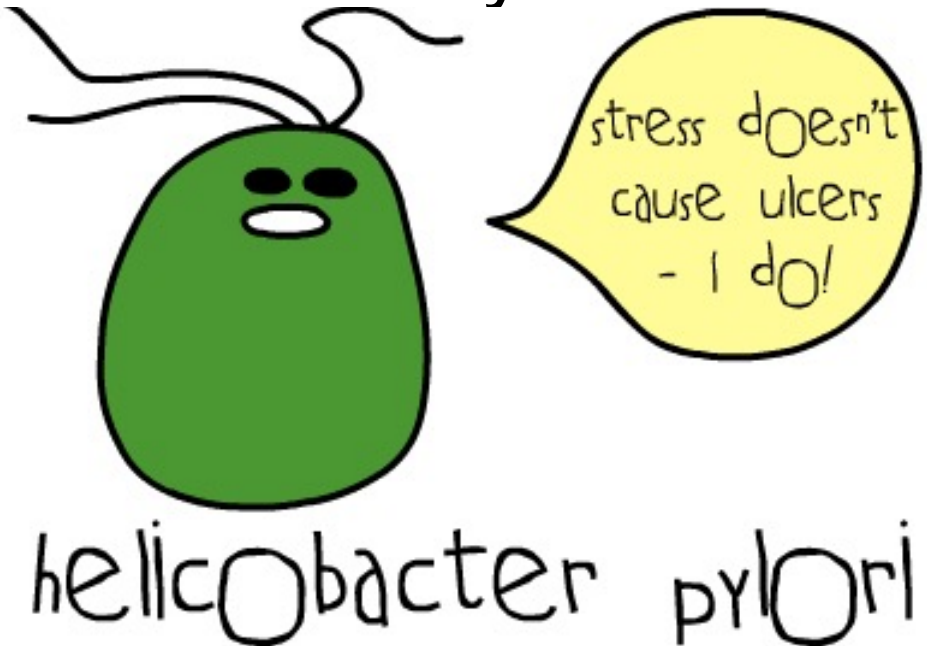
PUD: Diagnosis

- Routine lab tests are not useful
- Upper endoscopy
  - Allows direct visualization of the ulcer and any erosions/site of bleeding and biopsy if needed
    - Duodenal ulcers: ok to defer if no alarm symptoms
    - Gastric ulcers: recommended for all but ok to defer until post-treatment if no alarm symptoms

PUD: Primary Causes



Non-steroidal Anti-inflammatory Drugs

http://ilovebacteria.com/helicobacter.htm

http://jeffreysterlingmd.com/2013/08/14/straight-no-chaser-ulcers-i-cant-believe-you-ate-the-whole-thing/.

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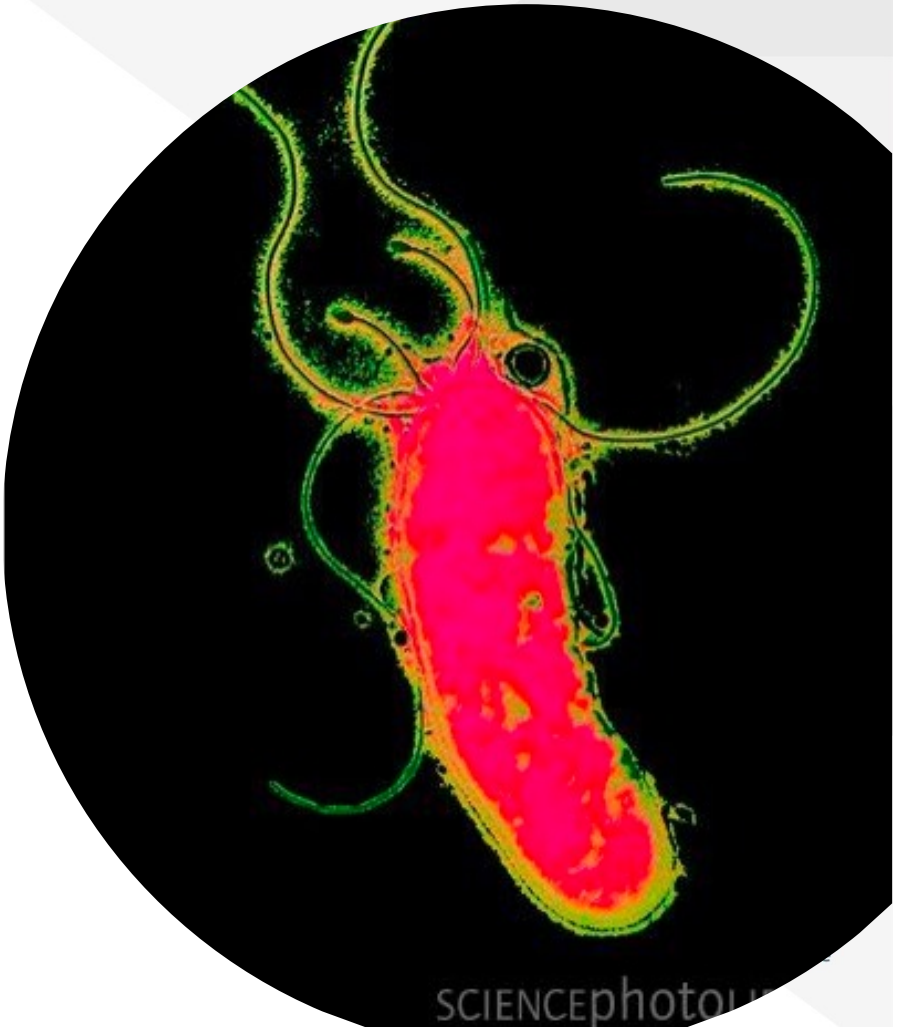
Helicobacter pylori

- Gram-negative rod, lives in stomach mucus layer
- 1–6 sheathed flagella
- Urease producing (pH ~7.0)
- Secretes cytokines (gastrin-releasing peptide)
- Complications
  - Gastric mucosa-associated lymphoid tissue (MALT) lymphoma
  - Gastric adenocarcinoma
  - Gastritis



http://www.sciencephoto.com/media/11114/enlarge.

H. Pylori Fun Facts

- Which of the following is correct?
  - A. George Bush and Pope John Paul II were both diagnosed with a bleeding ulcer 2/2 *H. pylori*
  - *B.* *H. pylori* is classified as a Class-I carcinogen (the same class as cigarette smoke)
  - C. A M.D. inoculated himself with *H. pylori* in the hopes he would prove it would cause ulcers
  - D. 2005 Nobel Prize in medicine or physiology was awarded to the two individuals who discovered *H. pylori* in 1982
  - E. All of the above

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http://www.nobelprize.org/nobel_prizes/medicine/laureates/2005/marshall-lecture.pdf

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Risk Factors for *H. pylori* Infection

- Year of birth
- Birth or residence in a developing country
- Institutionalization
- Crowded or unsanitary living conditions
- Low socioeconomic status
- Unclean food or water

Crowe SE. *Helicobacter pylori* Infection. *N Engl J Med*. 2019; 380:1158-1165.

PUD: Who Needs *H. pylori* Testing…

- All diagnosed with PUD (even if taking NSAIDs)
- Patients initiating chronic NSAID therapy
- Eradication of infection verification: minimum of 4 weeks POST-TREATMENT and 1-2 weeks post completion of PPI therapy

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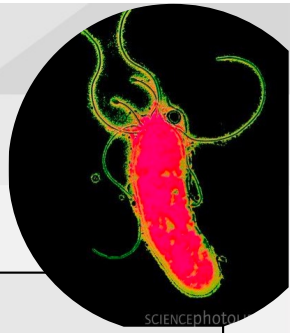
Crowe SE. *Helicobacter pylori* Infection. *N Engl J Med*. 2019; 380:1158-1165.

H. pylori Diagnostic Testing

Endoscopic Testing	Advantages	Disadvantages
1. Histology	Excellent sensitivity and specificity **Use if on PPI, abx,** or bismuth	$$$; requires infrastructure and trained personnel
2. Rapid urease testing (biopsy)	Inexpensive w/ rapid results; excellent specificity; very good sensitivity in selected pts **Rec'd in pts not on a PPI or abx**	Sensitivity significantly reduced in post-treatment setting; **affected by PPIs, abx,** and bismulth
3. Culture	Excellent specificity; allows determination of abx sensitivities	$$$; difficult to perform; not widely available; marginal sensitivity
4. Polymerase chain reaction	Excellent sensitivity and specificity; allows determination of abx sensitivities	Not standardized across labs; not widely available

Chey WD, et a. ACG Clinical Guideline. *Am J Gastroenterol*. 2017; 112:212-238.



H. pylori Diagnostic Testing

Nonendoscopic Testing	Advantages	Disadvantages
1. Antibody testing	Inexpensive; widely available very good NPV	Not rec'd after H. pylori therapy
2. Urea breath tests	Identifies active infection; excellent NPV and PPV regardless of prevalence; useful before and after H. pylori therapy **Rec'd in pts w/ acute GI bleeds**	**Affected by PPIs, abx, and bismulth**
3. Fecal antigen test	Identifies active infection; excellent NPV and PPV; useful before and after H. pylori therapy	Not as well validated as UBT in post-treatment setting but appears reliable before and after therapy; **affected by PPIs**, abx, bismulth, **and active bleeding (bld in stool decreases specificity)**

Chey WD, et a. ACG Clinical Guideline. *Am J Gastroenterol*. 2017; 112:212-238.

Risk Factors for NSAID-induced Ulcers and Upper GI Complications

Risk factors are additive*	
Age > 65	*Helicobacter pylori* infection
Previous peptic ulcer or complication	Concomitant use of: • NSAID + low dose Aspirin • Oral bisphosphonates • Corticosteroids • Anticoagulant or coagulopathy • Antiplatelet drugs (e.g. clopidogrel) • SSRIs
Multiple NSAID use	
Selection of NSAID (COX-1 vs -2)	
NSAID-related dyspepsia	
Aspirin (incl. 81mg dose)	
Cigarette smoking	Concomitant debilitating disorders • CV disease • Rheumatoid arthritis
Alcohol consumption	

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PUD Treatment

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Goals of Therapy

- Relieve symptoms and prevent complications
- Treat underlying etiology and heal lesions
  - Eradicate *H. pylori*
  - Discontinue NSAIDs (if able)
  - Anti-secretory therapy (PPIs)
- Prevent recurrence
  - Minimize ADEs
  - Provide long-term acid suppression in complicated disease

H. Pylori Eradication

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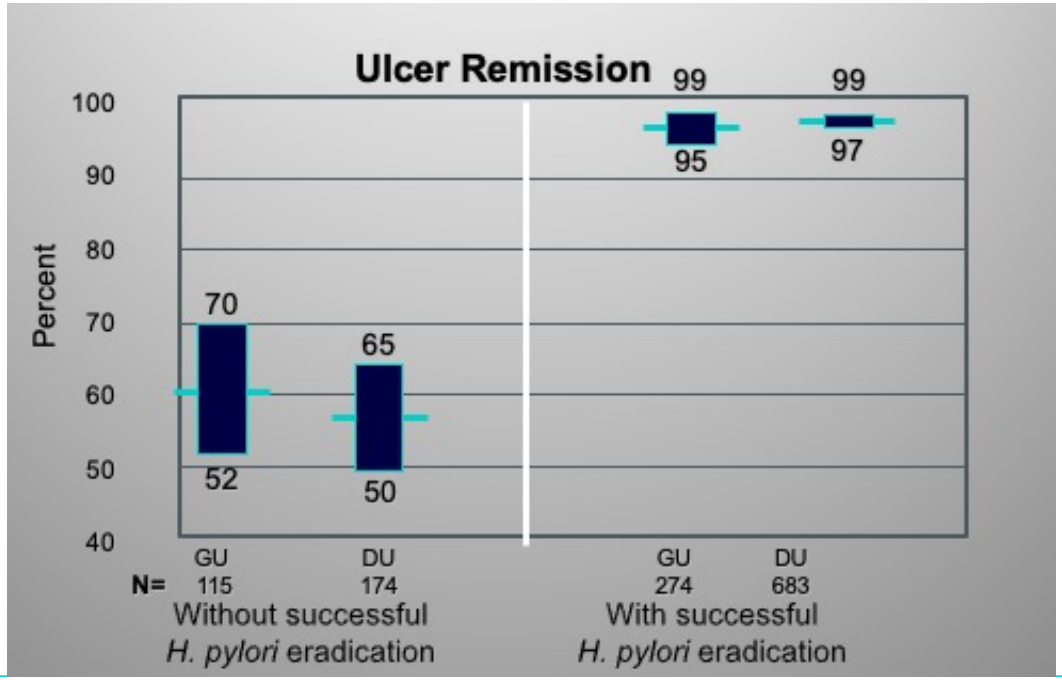
Meta-analysis of DU and GU Remission With *H. pylori* Eradication Regimens

Eradication of *H. pylori* results in sustained ulcer remission



Adapted from Leodolter A, et al. *Aliment Pharmcol Ther*. 2001;15:1949-1958.

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Determinants of *H. pylori* Eradication

- Choice of regimen
  - Complicated, multi-drug, high prevalence of adverse events
- Patient adherence
- Sensitivity of *H. pylori* strain - main factor affecting efficacy
  - Avoid classes of abx already used
    - Amoxicillin (PCN)
    - Clarithromycin (macrolide)
    - Levofloxacin (FQ)

Antibiotic	U.S. Resistance Rate	World-wide Resistance Rate
Amoxicillin	1-2%	11.2%
Clarithromycin	15-29%	17.2%
Levofloxacin	31%	16.2%
Metronidazole	20-44%	26.7%
Tetracycline	1-2%	5.9%
Multidrug	15%	9.6%

Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of *Helicobacter pylori* Infection. *Am J Gastroenterol*. 2017; 112:212-238.; Shiota S, Redy R, Alsarraj A et al. *Clin Gastroneterol Hepatol*. 2015;13:1616-1624.

H. pylori Treatment Challenges

- Nature of the organism
  - Dormant forms (increase gastric pH; extend duration of therapy)
- High bacterial load (use multiple antibiotics)
- Emerging resistance (use multiple antibiotics, increase dose/frequency of metronidazole)
- Gastric environment (dose PPIs more frequently)

Graham DY, Fischbach L. *Gut* 2010;59:1143-53.

Recommended *H. pylori* 1st-line Regimens (listed in recommended order)	DOT	Eradication Rate
(Clarithromycin triple therapy) PPI bid + clarithromycin 500mg bid + (amoxicillin 1gm bid OR metronidazole 500mg tid)	14d	81%
(Bismuth-based quadruple therapy) PPI bid + bismuth subsalicylate 525mg 4x/d + metronidazole 500mg tid to 4x/d + tetracycline 500mg 4x/d	14d	85%
(Concomitant therapy) PPI bid + amoxicillin 1gm bid + clarithromycin 500mg bid + metronidazole 500mg bid	14d	91-94%

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Crowe SE. *Helicobacter pylori* Infection. *N Engl J Med*. 2019; 380:1158-1165.; Chey WD, et al. *Am J Gastroenterol*. 2017; 112:212-238.

Alternative *H. pylori* First-Line Treatment Regimens	Rx	Eradication Rate
(**Sequential therapy**) PPI bid + amoxicillin 1gm bid followed by: PPI bid + clarithromycin 500mg bid + metronidazole 500mg bid	7d, then 7d (14d)	87%
(Hybrid therapy) PPI bid + amoxicillin 1 gm bid followed by: PPI bid + amoxicillin 1gm bid + clarithromycin 500mg bid + metronidazole 500mg bid	7d, then 7d (14d tot)	89%
(Levofloxacin triple therapy) PPI bid + levofloxacin 500mg daily + (amoxicillin 1gm bid OR metronidazole 500mg bid)	10-14d Best tolerated	90%
(Levofloxacin sequential therapy) PPI bid + amoxicillin 1gm bid followed by: PPI bid + amoxicillin 1gm bid + levofloxacin 500mg daily + metronidazole 500mg bid	5-7d, then 5-7d	87%

Crowe SE. *Helicobacter pylori* Infection. *N Engl J Med*. 2019; 380:1158-1165.; Chey WD, et al. *Am J Gastroenterol*. 2017; 112:212-238.

Key Questions:

1. Penicillin (PCN) allergy?
2. Previous macrolide (MCL) exposure for any reason?

PCN allergy: No MCL exposure: No	PCN allergy: No MCL exposure: Yes	PCN allergy: Yes MCL exposure: No	PCN allergy: Yes MCL exposure: Yes
• Clarithromycin triple w/ amoxicillin • Quadruple • Concomitant	• Quadruple • Levofloxacin triple • Levofloxacin sequential	• Clarithromycin triple w/ metronidazole • Quadruple	• Quadruple

Shiota S, et al. *Clin Gastroneterol Hepatol*. 2015;13:1616-1624.; Chey WD. *Am J Gastroenterol.* 2007;102:1808-25.

PPI Dosing for Treatment of *H. pylori* (ACG guidelines)
Lansoprazole 30mg po bid
Omeprazole 20mg po bid
Pantoprazole 40mg po bid
Rabeprazole 20mg po bid
Esomeprazole 40mg po ***daily***

- Bid PPI dosing is for duration of *H pylori* treatment only

Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of *Helicobacter pylori* Infection. *Am J Gastroenterol*. 2017; 112:212-238.

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

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Discontinue NSAIDs

- All patients with peptic ulcers should be advised to avoid NSAIDs
  - Including aspirin
- Consult with physician (in few situations NSAIDs may need to be continued)

Case Break Part I

- 32 year-old female presents to clinic with c/o upper abdominal pain after eating large meals, heartburn, and nausea. Symptoms have been present ~ 2 weeks. Pt reports OTC ibuprofen used prn.
- PMH: asthma, recent steroid burst
- MEDS: albuterol prn, Advair 50/250 mcg bid
- NKDA
- Urea breath test: (+) and pt is diagnosed with *H. pylori* PUD

Case Break Part I

- Which of the following regimens will you recommend for H. pylori treatment ?
  A. Lansoprazole 30mg bid + bismuth subsalicylate 525mg 4x/day + metronidazole 500mg 4x/day + tetracycline 500mg 4x/day
  B. Omeprazole 20mg bid + clarithromycin 500mg bid + amoxicillin 1 gm bid
  C. Omeprazole 20mg bid + levofloxacin 500mg daily + metronidazole 500mg bid
  D. Pantoprazole 40mg bid + amoxicillin 1000mg bid x 7 days, THEN pantoprazole 40mg bid + clarithromycin 500mg bid + metronidazole 500mg bid

Heal Lesions with Anti-secretory Therapy (PPIs)

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Antisecretory Therapy

PPI Dosing for Treatment of PUD (Antisecretory therapy)
Dexlansoprazole 30-60 mg daily
Esomeprazole 20-40 mg po daily
Lansoprazole 30 mg po daily
Omeprazole 20-40 mg po daily
Pantoprazole 40 mg po daily
Rabeprazole 20 mg po daily

- All administered daily before breakfast

Gisbert JP et al. *Helicobacter*. 2007;12:279.

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Duration of Therapy: Antisecretory Therapy

- Duration dependent on ulcer characteristics and complications (bleeding, perforation, gastric outlet obstruction)

- Non-complicated ulcer (small ulcer w/o bleeding or continued symptoms)
  - DOT: 14 days (d/c post antibiotic for *H. pylori* (+) ulcers)
- Complicated ulcers (bleeding, perforation, or gastric outlet obstruction)
  - Consider initial IV PPI (see acute GI Bleed lecture)
  - BID PPI x 4 weeks, then daily PPI
  - Complicated gastric ulcers: 8-12 weeks total PPI therapy
    - Must verify healing via endoscopy prior to d/c of PPI
  - Complicated duodenal ulcers: 4-8 weeks total PPI therapy
- Continued NSAID (including aspirin) therapy
  - Maintenance daily antisecretory therapy x 2-5 years (taper PPI)

Gisbert JP et al. *Helicobacter*. 2007;12:279.; Malfertheiner P, et al. Gut. 2012;61:646.

Case Break Part II

- How long should our patient receive anti-secretory therapy?

A. 14 days of *H. pylori* treatment

B. 14 days after *H. pylori* treatment has been concluded

C. 4 weeks total

D. 8 weeks total

Primary and Secondary Prophylaxis for PUD

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Primary and Secondary Prophylaxis of NSAID-Associated Gastroduodenal Ulcers

High Risk	Moderate Risk (1-2 risk factors)	Low Risk
• H/o complicated ulcer	• Age >65 years	• No moderate or high risk factors
• 3 or more moderate risk factors	• High dose NSAID therapy	
	• H/o uncomplicated ulcer	
• Dual antiplatelet therapy	• Concurrent use of ASA (incl: low dose), corticosteroids, or anticoagulants	

- Prophylaxis is recommended in pts at moderate- to high-risk of GI toxicity

Lanza FL, et al. *Am J Gastroenterol*. 2009;104:728.; Bhatt DL, et al. *J Am Coll Cardiol*. 2008;52:1502.

Primary PUD Prophylaxis for Patients Taking NSAIDs (and aspirin)

Drug Class	Note
PPIs	Effective in primary and secondary prophylaxis
Misoprostol	Effective in primary and secondary prophylaxis; Limited by adverse effects (cramping and diarrhea)
H_2RAs	Alternative when PPIs and misoprostol cannot be used

Prophylaxis of For Individuals on Chronic NSAID Therapy

	Gastrointestinal Risk	
CV Risk	Moderate	High
Low CV risk	NSAID + PPI or misoprostol	Alternative therapy - OR – COX-2 inhibitor + PPI/misoprostol
High CV risk	Naproxen + PPI or misoprostol	Avoid NSAIDs or COX-2 inhibitors. Use alt rx. If NSAID required: • If CV risk > GI risk: naproxen + aspirin + PPI or misoprostol • If GI risk > CV risk: COX-2 inh + PPI or misoprostol

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Lanza FL, et al. *Am J Gastroenterol*. 2009;104:728. Chapter 33. Peptic Ulcer Disease and Related Disorders. Love BL, Mohorn PL. Pharmacotherapy. 10th ed.

Patient Case Break III

- Which of the following GI risk classifications is our patient?

A. Low
B. Medium
C. High

Patient Case Break IV

- Which of the following is most appropriate for our patient regarding her follow-up?

A. No follow-up needed

B. Yes – f/u 4 weeks post-treatment for endoscopy and visualization of healing ulcer(s)

C. Yes – f/u in 4 weeks post-treatment for confirmation of *H. pylori* eradication

D. Yes – f/u in 8 weeks for medication evaluation and counseling

Role of Pharmacist in PUD Management

- Identify pts at risk for NSAID-associated ulcers
- Patient counseling (medication regimen)
  - Administration, adverse effects, therapy completion
  - Discourage ethanol (metronidazole)
  - Advise re: stool color change (bismuth)
  - Provide calendars, pill boxes if needed
- Encourage compliance (provide follow-up calls)
- If eradication therapy fails, recommend alternative therapy

Main Points

1.

2.

3.

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Questions

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