Peptic Ulcer Disease

Pharmacotherapy I

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Suggested Readings

- Peptic Ulcer Disease (Chapter 20)

- Guidelines on the management of Helicobacter pylori
- infection. Am J Gastroenterol 2007;102:1808-1825.

- Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol 2009;104:728-738.

Learning Objectives

- Distinguish between NSAID and H. pylori induced PUD
- Explain the pharmacological and nonpharmacological treatment/prevention of PUD
- Counsel patients on anti-ulcer regimens
- Recommend appropriate pharmacotherapy for management of H. pylori ulcers
- Devise a monitoring plan for patients receiving ulcer drug treatment

Peptic Ulcer Disease

Chronic disorders with ulceration of mucosal lesions in upper GI tract

Erosion in the mucosa of the GI tract; usually acidic and painful

Most common sites: duodenum & stomach

Typically reoccurring disease

Occur when disrupt normal mucosal defense & healing mechanisms

Types

- Helicobacter pylori ® ambulatory patients
- NSAID ® ambulatory patients
- Stress related mucosal damage ® critically ill hospitalized pts

Risk Factors for PUD

- H. pylori
- NSAID use
- Cigarette smoking
  - May increase acid
- Stress
  - Stress itself or associated habits?
- Dietary factors
  - Cola, carbonated drinks, ETOH; may increase acid; relation to PUD??

Potential Causes

- Hypersecretion of gastric acid (Zollinger-Ellison Syndrome)
- Virus
- Vascular insufficiency
- Radiation
- Chemotherapy
- Idiopathic

	Condition	Site of Damage	Intragastric pH	Symptoms	Ulcer Depth	GI Bleed
H. Pylori	Chronic	D > G	More dependent	Epigastric pain	Superficial	Less severe
NSAID	Chronic	G > D	Less dependent	Often asymptomatic	Deep	More severe
SRMD	Acute	G > D	Less dependent	Asymptomatic	Most superficial	More severe

D = duodenum, G = gastric (stomach)

Case Presentation

- AA is a 44 YO WM who presents to clinic C/O of abdominal pain of about 6 weeks duration. The pain occurs daily and seems to be worse a few hours after meals. It also occurs during the night. The pain is relieved somewhat by eating or taking antacids. AA denies N/V, or weight loss.

- What questions would you ask the patient?

Questions to Ask

- Has he ever had pain like this before?
- Any other symptoms?
- Tried anything else besides antacids?
- Any other family members with similar symptoms?
- NSAID use?
- ETOH? Tobacco?

Etiology and Risk Factors of PUD

Helicobacter pylori

Corticosteroids (when used with NSAID)

Cigarette smoking

- Impairs ulcer healing, helps ulcers reoccur, ↑ ulcer risk
- Exact mechanism unknown
  - Reduce synthesis of prostaglandins
  - Delayed gastric emptying of solids & liquids
  - Increase acid secretion
  - Inhibit pancreatic bicarbonate secretion
  - Promote duodenogastric reflux
  - Proportional to amount of cigarettes smoked/day

Etiology and Risk Factors of PUD

- Genetics
- NSAIDs
- Bisphosphonates
- Alcohol (high concentration)
  - Not proven to cause PUD
  - Damage gastric mucosa and cause upper GI bleeding
- COPD (may be due to smoking)
- Chronic renal failure
- RA (may be due to NSAID use)

Pathophysiology

Aggressive Factors

- Gastric muscosal cells secrete pepsinogen
- Pepsinogen forms pepsin in acidic environment
- Combines with acid to form ulcer

Protective Factors

- Mucus and bicarbonate secretion
- Prostaglandins (integrity & repair)
  - Inhibit gastric acid secretion
    - mucus and bicarbonate secretion
    - Maintain mucosal blood flow
    - Prevent deep mucosal injury

Rapid mucosal blood flow, Remove H ions that cross gastric mucosa Rapid healing if damaged

Pathophysiology

Normal defense mechanisms protect esophagus, stomach, duodenum from acid and pepsin

- Disrupt barrier → ↑ acid & pepsin → mucosal injury & ulcers develop

Delayed gastric emptying: ↑ stomach exposure to acid, pepsin, refluxed contents of duodenum

Clinical Presentation

Cannot differentiate between gastric & duodenal based on signs & symptoms need endoscopy

Abdominal pain: (most common, does not define an ulcer)

- Epigastric, burning, vague discomfort, abdominal fullness, cramping

Duodenal ulcer

- Nocturnal pain awakens them (12am-3am)
- Occurs 1-3 hrs after meal & relieved by food

Gastric ulcer

- No set pattern
- Food increases pain

No one sign or symptom that differentiates H. pylori from NSAID ulcer

Antacids: immediate relief, short-acting

PUD
Other Signs and Symptoms

Heartburn	Belching	Bloating
Nausea	Vomiting	Anorexia
Periods of exacerbation and remission	**Asymptomatic patients diagnosed with ulcers**	Can have no symptoms if taking NSAIDs (analgesics) or way in which perceive pain (ex: elderly)

Alarm Symptoms

BLEEDING/ANEMIA

EARLY SATIETY

WEIGHT LOSS

DYSPHAGIA

ODYNOPHAGIA

RECURRENT VOMITING

FAMILY OR PERSONAL HX OF GI CANCER

Complications

- Upper GI bleeding (10-15%)
- Penetration – through the bowel wall
- Perforation – leakage of acid into the peritoneal cavity
- Gastric outlet obstruction

Case Presentation

- AA is a 42 YO WM who presents to the pharmacy complaining of abdominal pain for about 6 weeks duration. The pain occurs daily and seems to be worse a few hours after meals. It also occurs during the night. The pain is relieved somewhat by eating or taking antacids. AA denies N/V, or weight loss.

- Does AA have any of the alarm symptoms? What would you want to do next?

H. pylori-associated Ulcer Disease

Helicobacter pylori

- Spiral-shaped gram-negative bacteria
- Found between mucous layer & stomach epithelial cells or any location where gastric-type epithelium is located
- Initially able to survive in acidic gastric juice
- Produces urease
  - Urea LEADS TO ammonia and CO2
  - Local neutral environment
- Ammonia buffering protects it from acid
- Person-to-person transmission

Helicobacter Pylori Transmission

Modes of transmission

- Fecal-oral route through people or contaminated water, food
- Oral-oral route
- Gastro-oral route (vomiting or infected instrument-endoscope)

Infected household members may infect other members

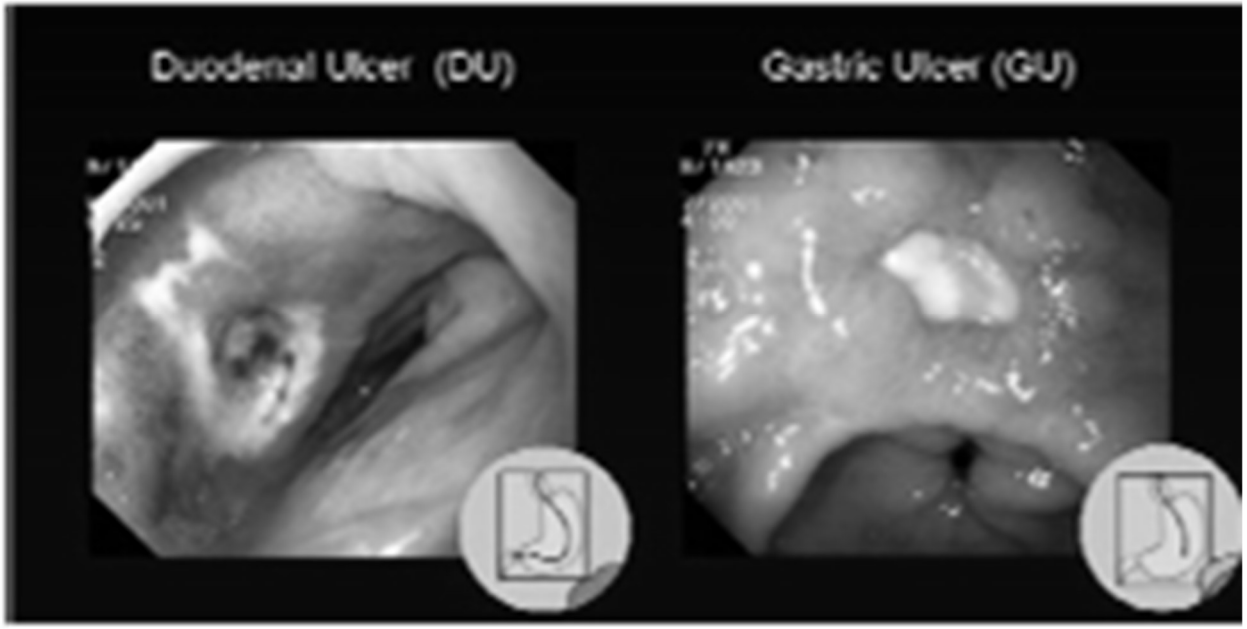
Risk factors: crowded living conditions, large amount of children, unclean water, raw vegetables

Helicobacter pylori

Mucosal injury:

- Direct mucosal damage
- Urea → ammonia toxic to gastric epithelial cells
- Adherence: increase toxin uptake into gastric epithelial cells

Diagnosis of H. pylori



- Invasive testing – requires endoscopy
- Noninvasive testing – no endoscopy

Invasive Testing - H. pylori

- Biopsy or rapid urease – test of choice
- Antibiotics, bismuth, PPIs may cause false (-)
- No antibiotics or bismuth X 4 weeks, PPIs X 2 weeks
- Culture – used in cases of treatment failure

Noninvasive Testing - H. pylori

Antibody testing (IgG)

- Fingerstick or blood test
- Does not distinguish active vs. previous
- Not affected by PPI, bismuth subsalicylate, abx

Urea breath test (UBT)

- Ingest urea with carbon isotope (13C or 14C)
- If urease present, urea is cleaved and labeled carbon excreted in CO_2
- Most accurate; ↓by antibiotics, bismuth, PPIs

Fecal antigen test (FAT)

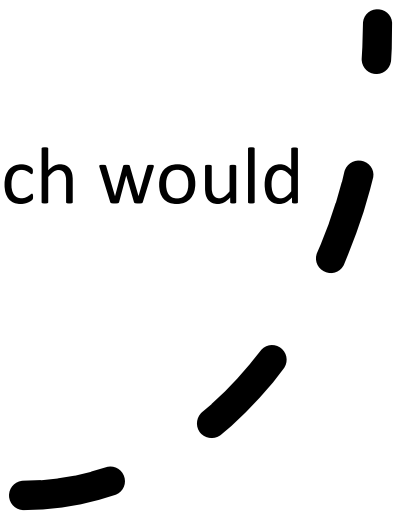
- Antigen detected in stool
- ↓ by antibiotics, bismuth, PPIs

Only test for H. pylori if you plan to treat!!

Case Presentation

- AA is a 42 YO WM who presents to clinic C/O of abdominal pain of about 6 weeks duration. The pain occurs daily and seems to be worse a few hours after meals. It also occurs during the night. The pain is relieved somewhat by eating or taking antacids. AA denies N/V, or weight loss.

- What diagnostic approach would be appropriate for AA?



Goals of Therapy

- Relieve ulcer symptoms
- Heal ulcer quickly
- Eradicate H. pylori
- Prevent ulcer recurrence
  - Recurrence rate very high if H. pylori not treated
- Prevent ulcer-related complications

Pharmacotherapy for H. pylori

Antibiotics – treat the infection

- Amoxicillin
- Clarithromycin
- Metronidazole
- Tetracycline

Bismuth subsalicylate (BSS)

Antisecretory agents – heal the ulcer

- PPI or H2RA

H. Pylori Treatment

Need to ask about previous antibiotic exposure
For 1st line treatment, clarithromycin triple therapy limited to pts with NO previous macrolide exposure history who live in areas with low clarithromycin resistance H. pylori isolates
4 drug regimens preferred
Clarithromycin, metronidazole: taste disturbances
Eradication: no organism 4 weeks after antibiotic therapy cessation
Do NOT substitute: H2RA for PPI, azithromycin or erythromycin for clarithromycin, ampicillin for amoxicillin, doxycycline for tetracycline
Do not use amoxicillin in penicillin allergic pts (use metronidazole)
Do not use metronidazole or tinidazole if consuming alcohol

About Antibiotics

Single antibiotics not effective

Consider resistance

- Clarithromycin (10-15%)
- Metronidazole (10-60%)
- Tetracycline/amoxicillin - uncommon

Common combinations

- Amoxicillin + clarithromycin
- Metronidazole + tetracycline

Consider allergies and ETOH use

Do not substitute

Role of PPIs in H. pylori

Preferred agents

Similar ulcer healing rates and symptom relief with all PPIs

May be used for maintenance of ulcer healing in high risk patients

PPIs – Dose for H. pylori

- Esomeprazole (NexiumTM) – 40mg daily
- Lansoprazole (Prevacid®) – 30mg BID
- Omeprazole (Prilosec®) – 20mg BID
- Pantoprazole (Protonix®) – 40mg BID*
- Rabeprazole (Aciphex®) – 20mg BID
- not FDA approved for H. pylori tx

H2 Receptor Antagonists

- Cimetidine (Tagamet®)
- Famotidine (Pepcid®)
- Nizatidine (Axid®)
- Ranitidine (Zantac®)
- Ulcer healing equivalent with equipotent doses
- All require renal dosage adjustment

Antacids

- Neutralize gastric acid
- Inactivate pepsin
- Al-antacids – activity against H. pylori
- For PRN use
- Chelates tetracycline

Preferred Regimens for H. pylori

Three-drug regimens

- First-line (cure rate 70-85%)
- Clarithromycin 500mg BID +
- Amoxicillin 1000mg BID +
- Proton pump inhibitor
- Duration 14 days
- FDA Approved

Penicillin allergic

- Clarithromycin 500mg BID +
- Metronidazole 500mg BID +
- Proton pump inhibitor
- Duration 14 days
- Not FDA approved

Quadruple Therapy

Usually reserved for second-line therapy or areas of clarithromycin resistance (>15%)

(BSS 525 mg + metronidazole 250mg + tetracycline 500mg) four times daily + PPI or H2RA X 10-14 days

Good if previous macrolide exposure or allergic to penicillin

High cure rate (80-90%), but high pill burden

Pylera

- 140 mg bismuth subcitrate
- 125 mg metronidazole
- 125 mg tetracycline
- Dosage – 3 caps four times daily PC and HS X 10d
- Must be given with PPI (omeprazole) twice daily

Counseling Points

Antibiotics

- finish therapy
- call MD if diarrhea

Bismuth subsalicylate – ASA allergy, black stools & tonque , constipation

Clarithromycin – metallic taste, GI upset

Metronidazole – avoid ETOH

Tetracycline – avoid dairy, antacids, photosensitivity

Case Presentation

- AA is a 42 YO WM who presents to clinic C/O of abdominal pain of about 6 weeks duration. The pain occurs daily and seems to be worse a few hours after meals. It also occurs during the night. The pain is relieved somewhat by eating or taking antacids. AA denies N/V, or weight loss.

- What regimen would be most appropriate for AA? What counseling points would you provide?

Other Therapies

Sequential therapy

- 5-7 days of PPI (standard dose) BID PLUS amoxicillin 1gm BID THEN
- 5 -7 days PPI BID, clarithromycin 500mg BID, and metronidazole 500 mg BID or tinidazole 500mg BID
- Needs validation
- PPI (standard or double dose) BID PLUS Amoxicillin 1-gram BID for 5-7 days followed by:
- PPI BID, Amoxicillin BID, Levofloxacin 500mg once daily, metronidazole 500mg BID or tinidazole 500mg BID for 5-7 day

Salvage therapy

- Bismuth-based 4-drug regimen (in patients previously treated with clarithromycin-based regimen)
- Levofloxacin 500mg daily + amoxicillin 1000mg BID + PPI for 10 days

Therapy selection

Ask These Questions:

- Penicillin (PCN) Allergy?
- Previous macrolide (MCL) exposure for any reason?

PCN Allergy: No, MCL exposure: No

- Bismuth quadruple, clarithromycin triple with amoxicillin

PCN Allergy: No, MCL exposure: Yes

- Bismuth quadruple, Levofloxacin triple, Levofloxacin sequential

PCN Allergy: Yes, MCL exposure: No

- Clarithromycin triple with metronidazole, Bismuth quadruple

PCN Allergy: Yes, MCL exposure: Yes

- Bismuth quadruple

NSAID-Induced Ulcers

Widely used drugs

Ulcers occur in 25% of chronic NSAID users

Risk greatest during the first month

Mechanism

- Direct irritation w/in 15 minutes
- Inhibition of prostaglandins

Enteric coating

H. pylori vs. NSAID-induced Ulcers

Characteristic	H. pylori-induced	NSAID-induced
Mechanism of injury	Direct mucosal damage, cytotoxins, adherence	PG inhibition, direct mucosal damage
Location	Duodenal > gastric	Gastric > duodenal
Ulcer depth	Superficial	Deep
Symptoms	Pain, may be related to food, nocturnal	Symptoms vary, may be asymptomatic
GI bleeding	Less severe	More severe

Prevention of NSAID-Induced Ulcers

- Use a COX-2 inhibitor instead of an NSAID
- Add a proton pump inhibitor
- Add misoprostol (synthetic PGE1 analog)
  - Dose: 200mcg three to four times daily
  - Produces diarrhea at all doses (limits use)
  - Pregnancy category X
- Add a high-dose H2RA
  - Double dose H2RA
  - Less effective than PPIs
- Assess GI risk to determine strategy

Prevention of NSAID Related Ulcer

Evidence suggests coxibs and NSAIDs (exception of full-dose naproxen) increase CV risk (refer to FDA warning slide)

Naproxen may be preferred since may have some cardioprotective properties (refer to FDA warning slide)

Consider testing for H. pylori and treat if positive, in all pts about to start long-term traditional NSAIDs regardless of risk status

All pts with history of ulcers who require NSAIDs should be tested for H. pylori, and treated if positive

Beneficial effect of COX-2 inhibitors negated when taking concomitant low-dose aspirin

Risk Factors for NSAID-Induced Ulcers

Prevention

Risk factors:

- Previous ulcer
- Older age (> 65 years)
- High-dose NSAIDs
- Other meds: Low-dose ASA, warfarin, clopidogrel, corticosteroids
- Helicobacter pylori

Determining Risk for NSAID GI Toxicity

Low risk – no risk factors , can treat with nonselective NSAID

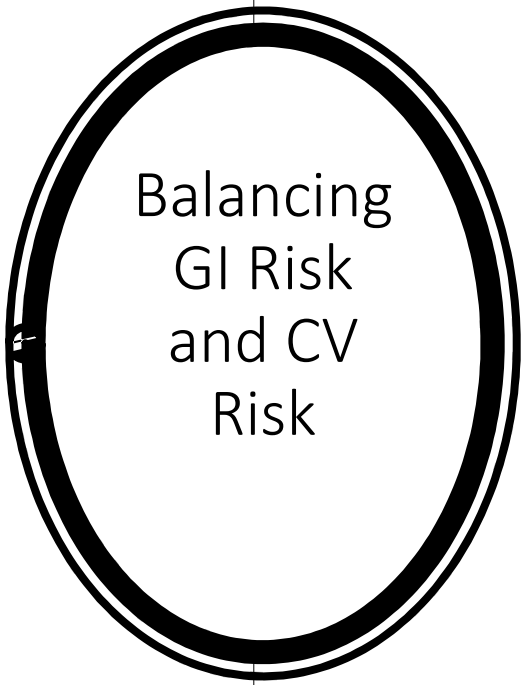
Moderate risk – 1-2 risk factors : COX-2 inhibitor alone or with nonselective NSAID plus misoprostol or PPI

- Age >65 years
- High dose NSAID therapy
- Previous hx of uncomplicated ulcer
- Use of ASA, corticosteroids, or anticoagulants

High risk - > 2 risk factors or history of previous complicated ulcer

- Alternative therapy, or if anti-inflammatory is absolutely necessary, COX-2 inhibitor with misoprostol or high-dose PPI

Stratify risk to determine prevention strategy



	Low GI risk	**Moderate GI risk**	**High GI risk**
Low CV risk	NSAID alone	COX-2 inhibitor OR NSAID + PPI/ misoprostol	Alternative tx OR COX-2 inhibitor + PPI/misoprostol
High CV risk needs low Dose ASA	Naproxen + PPI/misoprostol	Naproxen + PPI/misoprostol	Avoid NSAIDs or COX-2 inhibitors. Use alternate tx

Reducing Risk of NSAID Induced Ulcer

EC do not reduce GI bleeding (as a result it appears upper GI adverse effects are due to systemic effect)

Misoprostol or PPI

PPI better tolerated than misoprostol (PPI preferred med)

PPI and misoprostol > H2RA (not recommended)

CV Safety Issues – FDA Strengthened NSAID Rx Label 2015

- MI or stroke risk can occur in 1st weeks of taking NSAID, risk may increase with longer use
- Risk appears greater at higher doses
- Less clear that MI or stroke risk similar for all NSAIDs
- Not sufficient information to determine NSAID risk is definitely higher or lower than another NSAID
- With or without heart disease or risk factors for heart disease: can increase MI or stroke risk
- Have heart disease or risk factors: increased MI or stroke after NSAID use
- Treated with NSAIDs after 1st MI: more likely to die in 1st year after MI
- Increased heart failure with NSAID

Treatment of NSAID-Induced Ulcers

Discontinue or reduce dose of NSAID

Test for H. pylori and treat if positive

Antisecretory therapy

- PPIs preferred over H2RA (4 to 8-week tx)
  - Faster symptom relief
  - Better healing rates
- H2 receptor antagonists – 6 to 8 weeks
- Sucralfate – not recommended

Misoprostol (Cytotec)

Prostaglandin E1 analog

Slight reduction in acid secretion (dose:50-200mcg)

Cytoprotective effects (dose: > 200mcg)

Dose: 200mcg QID (200mcg TID if cannot tolerate higher dose)

- Dose ≤ 400mcg/day may compromise prophylactic effects

Adverse effects

- Diarrhea (most common): taking it with or after meals and HS may lessen it
- Headache
- Abdominal cramping
- Nausea
- Flatulence
- Uterine contractions (miscarriage): contraindicated in pregnancy

Negative pregnancy test within 2 weeks of starting therapy and need to confirm contraceptive measures

Avoid Mg antacids due to diarrhea side effects

Take Home Messages – H. pylori

Risks – bleeding

Treatment

- No single antibiotics
- Preferred = 2 antibiotics + PPI X 10-14 days
- Resistance with metronidazole, clarithromycin

Follow-up to assess eradication

Summary – NSAID Ulcers

Prevention is key

Prevention = dependent on level of risk

- PPI or misoprostol

Reduce or discontinue NSAID

Test for H. pylori and treat if +

Antisecretory therapy (PPI or H2RA)