PEPTIC ULCER DISEASE

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Background

- Peptic: body part related to digestion and possesses an acidic lumen
- Gastric-related diseases: gastritis, erosions, PUD
- Peptic ulcer: defect in gastric or duodenal mucosal wall that extends through muscularis mucosa deep into submucosa
- Types of PUD (common causes):
  1) *Helicobacter pylori*-related 2) NSAID-related
  3) Stress-related mucosal damage (stress ulcer)

Background

- Uncommon causes for PUD: idiopathic, hypersecretory (e.g., Zollinger-Ellison), viral (e.g., CMV), vascular insufficiency (e.g., crack cocaine), radiation therapy, chemotherapy
- Most common causes are NSAIDs and *H. pylori*
- Most peptic ulcers recur
- Complications of PUD: GIB, perforation, gastric cancer
- Gastric ulcer more associated with malignancy than duodenal
- *H. pylori* infection's prevalence is ~ 50% worldwide
- No vaccine, exact source of infection unknown

Types of PUD

Characteristic	*H. pylori* Induced	NSAID Induced	SRMD
Condition	Chronic	Chronic	Acute
Site of damage	Duodenum > stomach	Stomach > duodenum	Stomach > duodenum
Symptoms	Usually epigastric pain	Often asymptomatic	Asymptomatic
Ulcer depth	Superficial	Deep	Most superficial
GIB	Less severe, single vessel	More severe, single vessel	More severe, superficial capillaries

DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach, 8th Ed*

Helicobacter Pylori

- Prevalence is highest in developing countries
- Risk increases with increased age, poor socioeconomic status during childhood
- Transmitted through gastro-oral or fecal-oral
- Transmission typically occurs during childhood and persists throughout life
- 10-20% of infected will develop PUD, 1% will develop gastric cancer
- Can manifest as duodenal ulcer, gastric ulcer, Mucosa-Associated Lymphoma Tissue (MALT), or gastric cancer

NSAIDs

- PUD in up to 30% of chronic NSAID users
- GIB or perforation in 1.5% of pts with ulcers
- Causes superficial mucosal damage within minutes of ingestion which heals on its own within a few days. Continuing leads to erosion
- Risk factors generally additive and include: advanced age, anticoagulant use, concomitant corticosteroid or SSRI use, hx PUD, multiple NSAIDs use, duration of use (> 1 mo), high dose use, cigarette smoker, presence of NSAID-related dyspepsia

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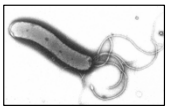
Pathophysiology

- Imbalance in homeostasis between offending factors (gastric acid and pepsin) and healing factors (mucosal sodium bicarb and PGs)
- Acid secretion from proton pumps in parietal cells is controlled by histamine, acetylcholine, and gastrin
- Acid secretion with NSAID use is normal, and slightly elevated with *H. pylori* infection
- Pepsinogen is converted to pepsin by acid
- With lack of proper mucosal protection, gastric acid and pepsin erode the mucosa

Pathophysiology: *H. pylori*

- With NSAIDs and *H. pylori*, primary mechanism for PUD is damage to *mucosal defense system*
- GNR, S-shaped, with flagella
- Produces urease to tolerate acidic environment
- Penetrates mucous gel barrier and acutely infects epithelial cells underneath
- Damage mechanism: 1) direct mucosal damage 2) chronic inflammation 3) hypergastrinemia



Pathophysiology: NSAIDs

- PGs:
  - Inhibit gastric acid secretion
  - Stimulate production of mucus, bicarb, phospholipid
  - Increase mucosal blood flow
  - Stimulate epithelial cell regeneration
- Mechanisms of injury
  1. Direct mucosal irritation:
     - Due to acidity of NSAIDs
     - Plays minor role in ulcer development
  2. Systemic inhibition of PG synthesis through COX-1:
     - Important PGs = PGE_1, PGE_2, PGI_2
     - Plays major role in ulcer development

Clinical Presentation and Diagnosis

- Dyspepsia: common in population but be suspicious in older pts or younger ones with alarming symptoms (GIB, IDA, wt. loss..)
- *H.pylori* test can help guide diagnosis
  - Endoscopic tissue biopsy, serologic testing, stool antigen test, urea breath test (first line)
- If *H. pylori* negative, a trial of PPI for 4-8 weeks vs. endoscopy can further guide diagnosis
- Complicated cases will present with GIB (melena, occult blood, hematemesis), perforation, or obstruction

Treatment of PUD: Non-Pharmacologic

- Risk factor avoidance
- Surgery in complicated or refractory cases (partial gastrectomy or vagotomy)
- Acute GIB: endoscopic hemostasis with clips, thermal therapy, epi injection..

Treatment of PUD: Pharmacologic *H. pylori*-related Ulcer

- Goal is to completely eradicate infection using ABX and allow ulcer healing with acid suppression
- Treatment is indicated if *H. pylori* positive and has PUD or hx of ulcer or related complication
- First line is PPI-based triple-drug regimen
  - PPI + clarithromycin + amoxi or metonidazole
  - e.g., lansoprazole 30 mg + clarithromycin 500 mg + metronidazole 500 mg (or amoxicillin 1 g) each given BID
- BID PPI preferred over QD
- PPIs are interchangeable
- Course of therapy: 10-14 days

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Treatment of PUD: Pharmacologic
H. pylori-Related Ulcer

- Second line is Bismuth-based 4-drug regimen, which have similar cure rates to 3-drug regimen
  - Bismuth + TCN or amox + metronidazole + PPI or H_2RA
  - e.g., bismuth subsalicylate 525 mg QID + metro 250 mg QID + amoxicillin 1 g BID + PPI BID
- Bismuth issues include frequency, salicylate accumulation in renal failure, AEs (constipation, tongue discoloration, N/V..)
- Confirmation through breath test or stool antigen
- Failure rate: 10-20% 2/2 antimicrobial resistance, non-adherence, or re-infection
- Failure → quadruple therapy x 14d

Treatment of PUD: Pharmacologic
NSAID-Related Ulcer

1. First line is to D/C NSAID and be treated with 4-8 wks of PPI, or until ulcer healed
2. If not possible to D/C NSAIDs then try to replace with safer alternative (e.g., paracetamol, COX-2 inhibitor) or reduce dose
3. If need to continue NSAIDs add PPIs (or H_2RAs or sucralfate as second line) to heal ulcer and prevent recurrence

- Prophylactic regimens are often required for pts on long-term NSAID or ASA
- PPIs are the most effective and tolerated agents for preventing DU and GU in pts on chronic NSAIDs

Prevention of NSAID-Induced Ulcer
Other Agents Used For Prophylaxis

- COX-2 inhibitors
  - Celecoxib is only one left on market
  - As effective as standard NSAIDs combined with PPI
  - Higher risk for serious CV events (MI and stroke)
  - Remains second line to standard NSAIDs + PPI
- H_2RAs
  - Less effective in preventing GU than DU
  - PPIs are preferred over H_2RAs

Prevention of NSAID-Induced Ulcer
Other Agents Used For Prophylaxis

- Misoprostol
  - Synthetic PGE_1 analog
  - Used to reduce risk of GU
  - May be superior to H_2RAs for prevention of NSAID-related ulcers
  - Given as 200 mcg QID
  - Inhibits acid secretion and promotes mucosal defense
  - Limited by common side effects (pain, flatulence, diarrhea)
  - C/I in pregnancy (abortifacient)

Prevention of NSAID-Induced Ulcer
Other Agents Used For Prophylaxis

- Sucralfate
  - Effective in treatment of NSAID-related ulcer if NSAID will be D/C'd, but not for prophylaxis on NSAID
  - Binds positively charged proteins in exudates from ulcer site, coats it and prevents exposure to gastric juices
  - Needs multiple daily dosing (BID-QID)
  - Interaction with warfarin, digoxin, FQ, ADEK vitamins, folate, iron, vitamin D analogs..
  - Can cause constipation, nausea, metallic taste, and Al toxicity in pts with renal dysfunction

Misc. Topics

- Stress Ulcer prophylaxis
  - Indicated in certain critical care pts (mechanically ventilated, burn > 25%..)
  - PO H_2RAs or PPI, IV if NPO
- Treatment of GIB
  1. Fluid resuscitation
  2. IV PPI x 72h to keep pH > 6
  3. Switch to PO or IV BID after 72h
  4. Switch IV to PO once able to take oral diet
  5. EGD to evaluate and treat source

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