Peptic ulcer disease

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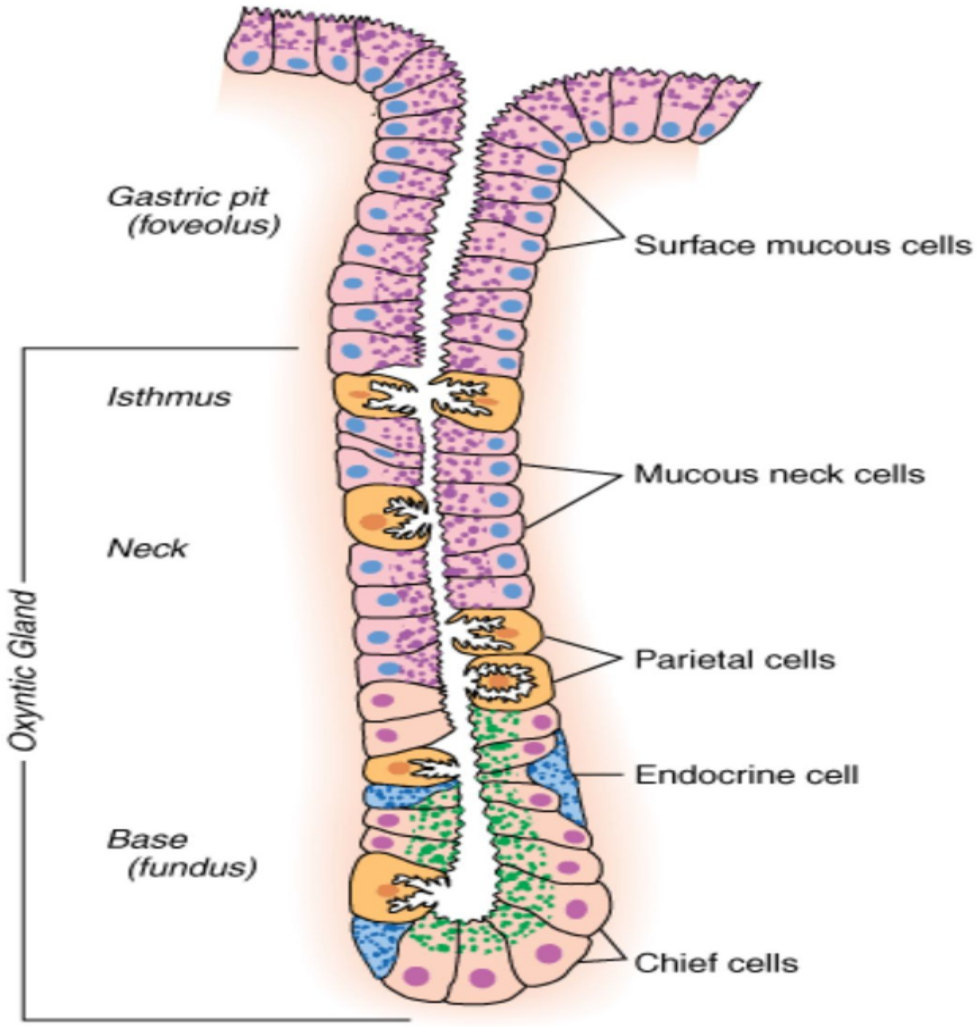
- *Ulcers* : breaks in the mucosal surface >5 mm, with depth to the submucosa

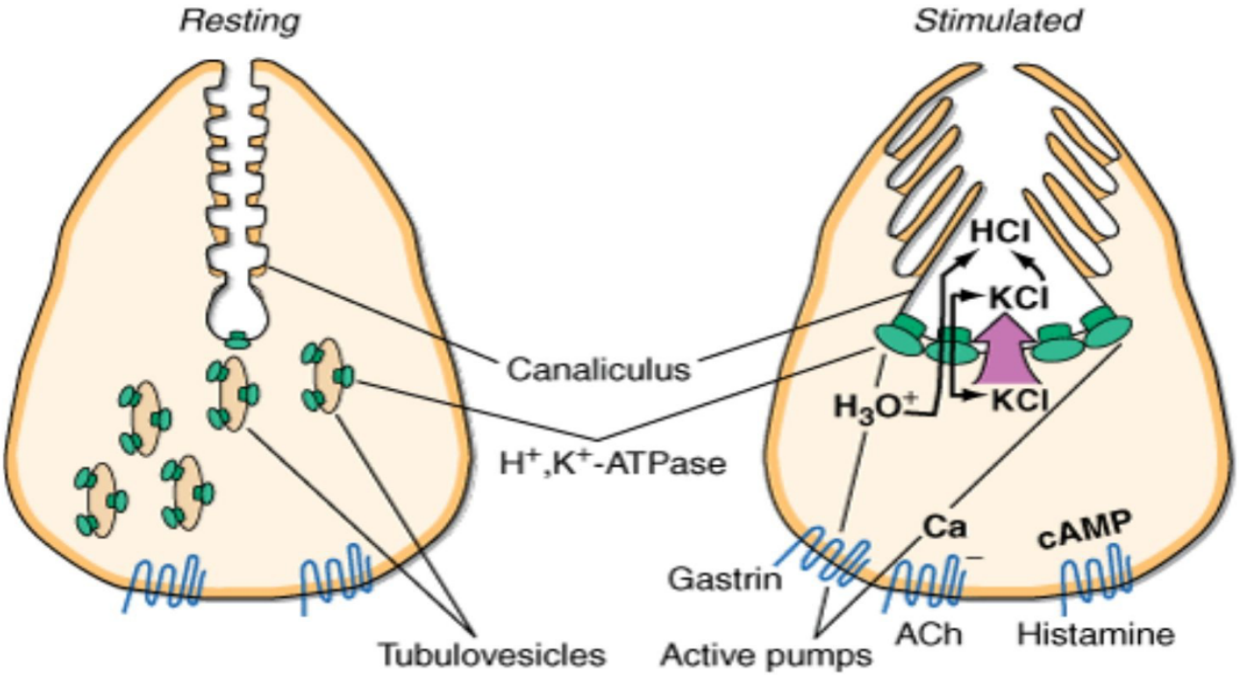
- Health care costs of ~$10 billion / year in the US
- Despite the constant attack on the gastroduodenal mucosa by noxious agents (acid, pepsin, bile acids, pancreatic enzymes, drugs, and bacteria), integrity is maintained by a system that provides mucosal defense and repair

Oxyntic Gastric Gland



Gastric parietal cell

undergoing transformation after stimulation

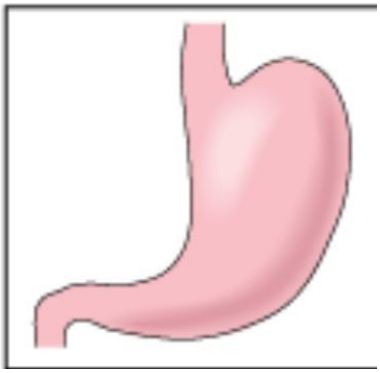


Epidemiology

- DUs occur in **6–15%** of the Western population.
- The **incidence of DUs declined** from 1960 to 1980 and has remained stable since then.
- The death rates, need for surgery, and physician visits have decreased over the past 30 years.
- This is likely related to the decreasing frequency of *Helicobacter pylori*
- Eradication of *H. pylori* has greatly reduced the recurrence rates.
- Peak incidence : sixth decade.
- More than half of GUs occur in males

- DUs occur most often in the first portion of duodenum (>95%) (~90% located within 3 cm of the pylorus).
- They are usually 1 cm in diameter
- Giant ulcer: >3 cm
- Ulcers depth at times reaching the muscularis propria.
- The base of the ulcer often consists of a zone of eosinophilic necrosis with surrounding fibrosis.
- Malignant DUs are extremely rare.

- GUs can represent a malignancy.
- Benign GUs are most often found distal to the junction between the antrum and the acid secretory mucosa (rare in fundus).
- Benign GUs associated with *H. pylori* antral gastritis
- NSAID-related GUs are not accompanied by chronic active gastritis (but have evidence of a chemical gastropathy)



Duodenal Ulcer

H. pylori & NSAID-induced injury account for the majority of DUs

Basal and nocturnal gastric acid secretion is increased

Bicarbonate secretion is decreased (*H. pylori* ?)

Gastric Ulcer

- Majority can be attributed to either *H. pylori* or NSAID-induced mucosal damage
- GUs that occur in the prepyloric area are similar in pathogenesis to DUs
- Impairment of mucosal defense
- Abnormalities in resting and stimulated pyloric sphincter pressure ?
- bile acids, lysolecithin, and pancreatic enzymes (duodenal gastric reflux) ?
- Delayed gastric emptying of solids ?

H. pylori & PUD

- Gastric infection with the bacterium *H. pylori* accounts for the majority of PUD
- *Development of gastric MALT lymphoma and gastric adenocarcinoma*
- Gram-negative microaerophilic rod
- Does not invade cells
- Contains multiple sheathed flagella

- Outer membrane protein (Hop proteins)
- Urease
- Vacuolating cytotoxin (Vac A)
- Cag pathogenicity island (cag-PAI).
- Cag A activates a series of cellular events in cell growth and cytokine production
- Urease produces ammonia from urea, an essential step in alkalinizing the surrounding pH
- Multiple strains of *H. pylori* exist and are characterized by their ability to express several of these factors
- Different diseases related to *H. pylori* infection can be attributed to different strains of the organism with distinct pathogenic features.

Epidemiology

- In developing parts of the world, 80% of the population may be infected by the age of 20,
- prevalence is 20–50% in industrialized countries

Risk factors:

- Poor socioeconomic status
- less education
- Birth or residence in a developing country,
- Domestic crowding,
- Unsanitary living conditions,
- Unclean food or water,
- Exposure to gastric contents of an infected individual

- Transmission of *H. pylori* occurs from person to person, following an oral-oral or fecal-oral route
- risk of *H. pylori* infection is declining in developing countries

- **Pathophysiology**
- associated with a chronic active gastritis
- *H. pylori* is present in only 30–60% of GUs and 50–70% of DUs
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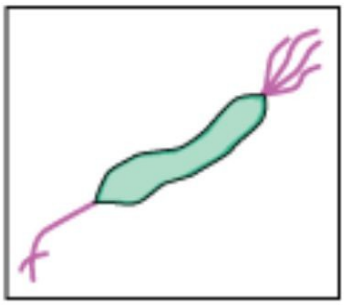
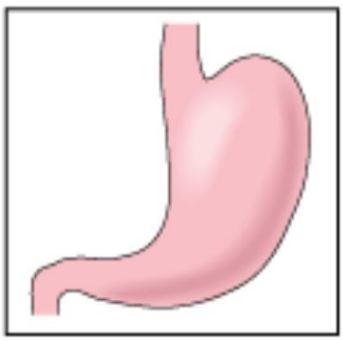


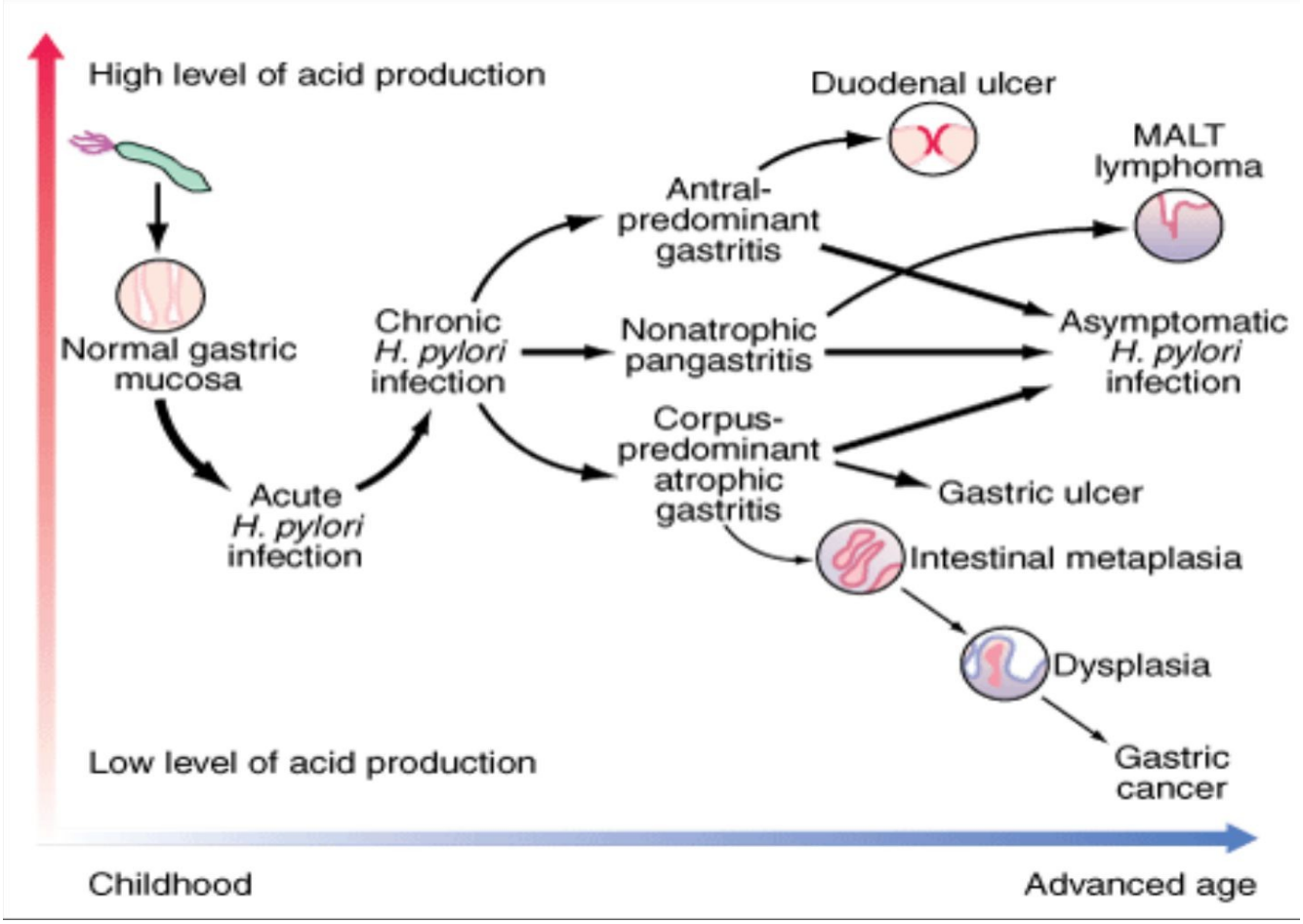


Bacterial factors
- Structure
- Adhesins
- Porins
- Enzymes
  (urease, vac A, cag A, etc.)

Host factors
- Duration
- Location
- Inflammatory response
- Genetics??

Chronic gastritis
Peptic ulcer disease
Gastric MALT lymphoma
Gastric cancer

Natural history of *H. pylori*



Development of Non-cardia cancer is a multistage and multifactorial process

H *pylori* infection

Superficial gastritis

- Atrophic gastritis + IM
- hypochlorhydria

Dysplasia & Cancer

NSAID-Induced Disease

- prescriptions written for NSAIDs was >111 million at a cost of $4.8 billion.
- The most common drug-related toxicities in the US: NSAIDs
- The spectrum of NSAID-induced morbidity ranges from:
- Nausea and dyspepsia (50–60%)
- Peptic ulceration (15–30% of individuals taking NSAIDs regularly)
- Bleeding or perforation (1.5% of users per year)

- > 80% of patients with serious NSAID-related complications did not have preceding dyspepsia
- No dose of NSAID is completely safe
- Enteric-coated are also associated with PUD

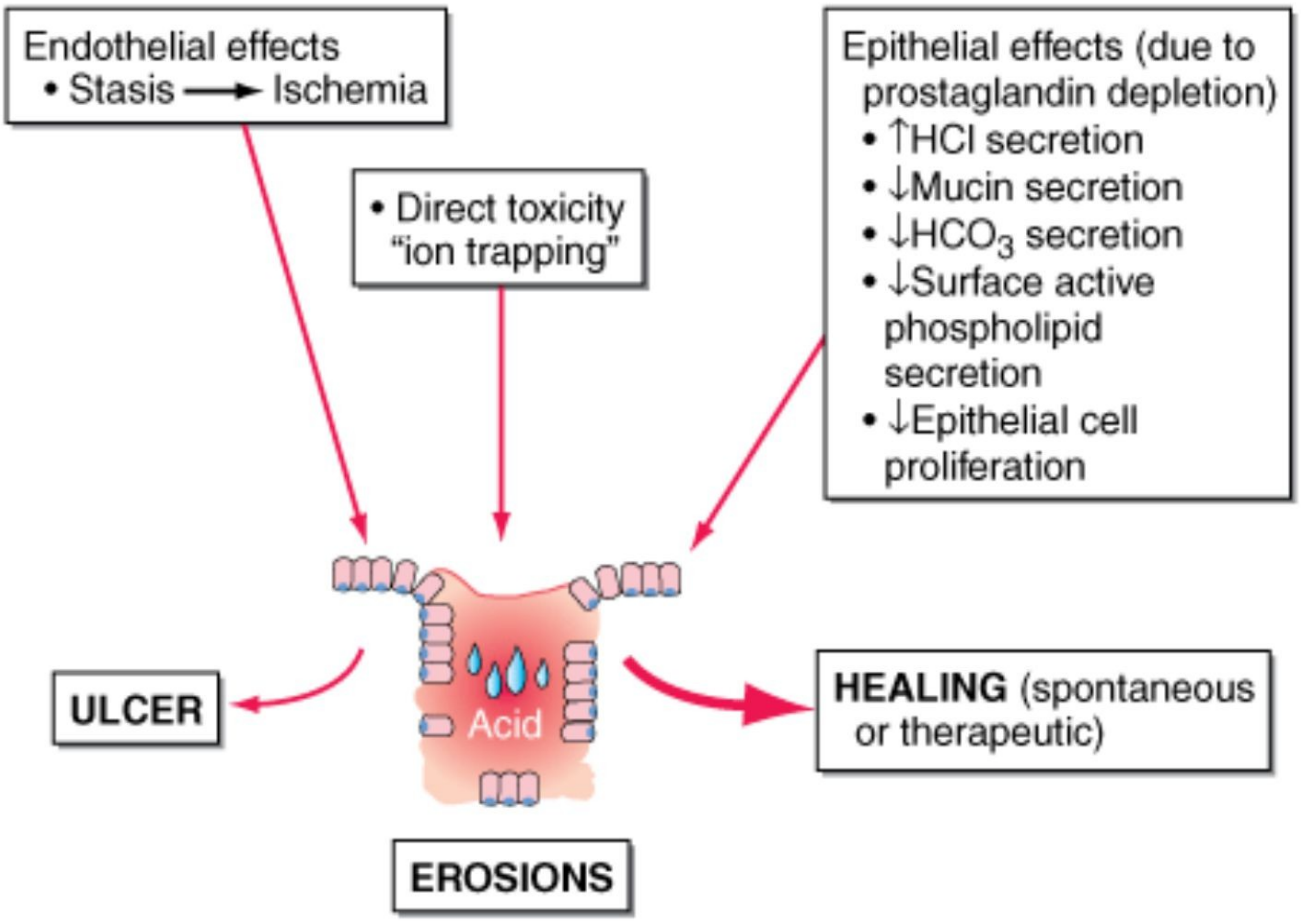
Established risk factors include:

- Advanced age,
- History of ulcer,
- Glucocorticoids,
- High-dose NSAIDs,
- Multiple NSAIDs,
- Anticoagulants,
- Serious or multisystem disease.

Possible risk factors include:

- *H. pylori*
- Smoking
- Alcohol

NSAIDs may induce mucosal injury



- **Genetic predisposition**
- First-degree relatives of DU patients are three times as likely to develop an ulcer
- Increased frequency in blood group O

- Psychological stress has been thought to contribute to PUD
- Diet has also been thought to play a role in peptic diseases

Strong association are :

- 1) Systemic mastocytosis,
- 2) Chronic pulmonary disease,
- 3) Chronic renal failure,
- 4) Cirrhosis,
- 5) Nephrolithiasis,
- 6) A1-antitrypsin deficiency.

Possible association are:

- 1) Hyperparathyroidism,
- 2) Coronary artery disease,
- 3) Polycythemia vera,
- 4) Chronic pancreatitis

Table 287-1 Causes of Ulcers Not Caused by *Helicobacter Pylori* and NSAIDs

Pathogenesis of Non-Hp and Non-NSAID Ulcer Disease

Infection

- Cytomegalovirus
- Herpes simplex virus
- *Helicobacter heilmanni*

Drug/Toxin

- Bisphosphonates
- Chemotherapy
- Clopidogrel
- Crack cocaine
- Glucocorticoids (when combined with NSAIDs)
- Mycophenolate mofetil
- Potassium chloride

Miscellaneous

- Basophilia in myeloproliferative disease
- Duodenal obstruction (e.g., annular pancreas)
- Infiltrating disease
- Ischemia
- Radiation therapy
- Sarcoidosis
- Crohn's disease
- Idiopathic hypersecretory state

Clinical Features

- *Abdominal pain* is common, but has a poor predictive value for the presence of PUD
- 10% of patients with NSAID-induced mucosal disease can present with a complication without antecedent symptoms
- Typical pain pattern in DU occurs 90 min to 3 h after a meal and is frequently relieved by antacids or food.
- Pain that awakes the patient from sleep (between midnight and 3 A.M.) is the most discriminating symptom, in two-thirds
- This symptom is also present in 1/3 of patients with NUD

- In GU, discomfort may actually be precipitated by food
- *Nausea* and *weight loss* occur more commonly in GU

possible explanations for pain include:

- Acid-induced activation of chemical receptors in the duodenum,
- Enhanced duodenal sensitivity to bile acids and pepsin,
- Altered gastroduodenal motility

- Dyspepsia that becomes constant, is no longer relieved by food or antacids, or radiates to the back may indicate a penetrating ulcer (to the pancreas).
- Sudden onset of severe, generalized abdominal pain may indicate perforation.
- Pain worsening with meals, nausea, and vomiting of undigested food suggest gastric outlet obstruction.
- Tarry stools or coffee-ground emesis indicate bleeding.

Physical Examination

- *Epigastric tenderness* is the most frequent finding (*predictive value of this finding is rather low*)
- *Tachycardia and orthostasis* suggest dehydration secondary to vomiting or active gastrointestinal blood loss.
- A severely tender, *board like abdomen* suggests a perforation.
- Presence of a *succession splash* indicates retained fluid in the stomach, suggesting gastric outlet obstruction.

PUD-Related Complications

Gastrointestinal Bleeding

- The most common complication
- In ~15% of PUD patients
- More often in individuals >60 y (likely due to the increased use of NSAIDs)

Perforation

- The second most common complication
- In 6–7% of PUD patients
- *Penetration* is a form of perforation in which the ulcer bed tunnels into an adjacent organ.
- DUs penetrate posteriorly into the pancreas, leading to pancreatitis,
- Whereas GUs tend to penetrate into the left hepatic lobe

Gastric Outlet Obstruction

- The least common complication
- In 1–2% of patients
- Obstruction secondary to inflammation and edema often resolves with ulcer healing.
- A fixed, mechanical obstruction secondary to scar formation in the peripyloric areas requires endoscopic (balloon dilation) or surgical intervention

Differential Diagnosis

- NUD, also known as *functional dyspepsia is typified by upper abdominal pain without the presence of an ulcer*
- Proximal gastrointestinal tumors,
- Gastroesophageal reflux,
- Vascular disease,
- Pancreaticobiliary disease (biliary colic, chronic pancreatitis),
- Gastroduodenal Crohn's disease

Investigations

Endoscopy

Radiology (Double-contrast barium)

H. pylori **detection**

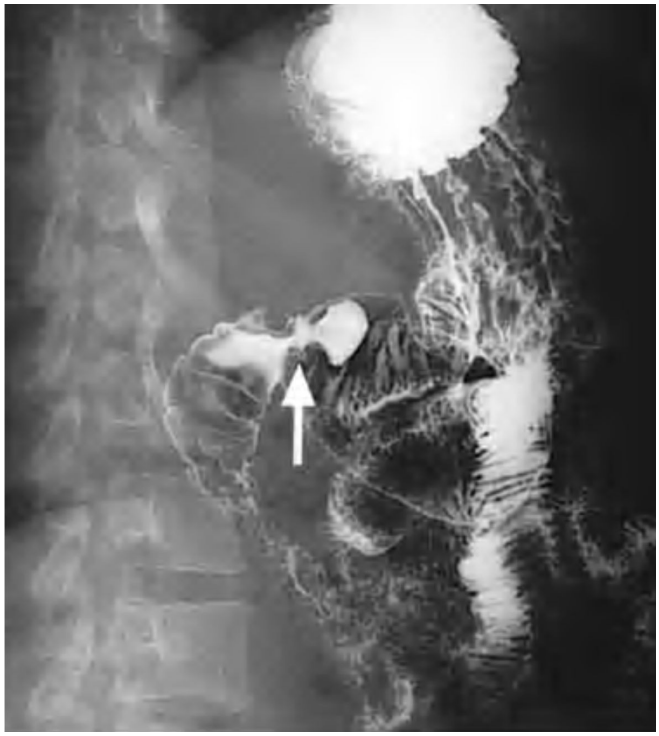
Diagnostic Evaluation

- In view of the poor predictive value of abdominal pain for the presence of an ulcer, documentation of an ulcer requires either a **radiographic** (barium study) or an **endoscopic procedure**

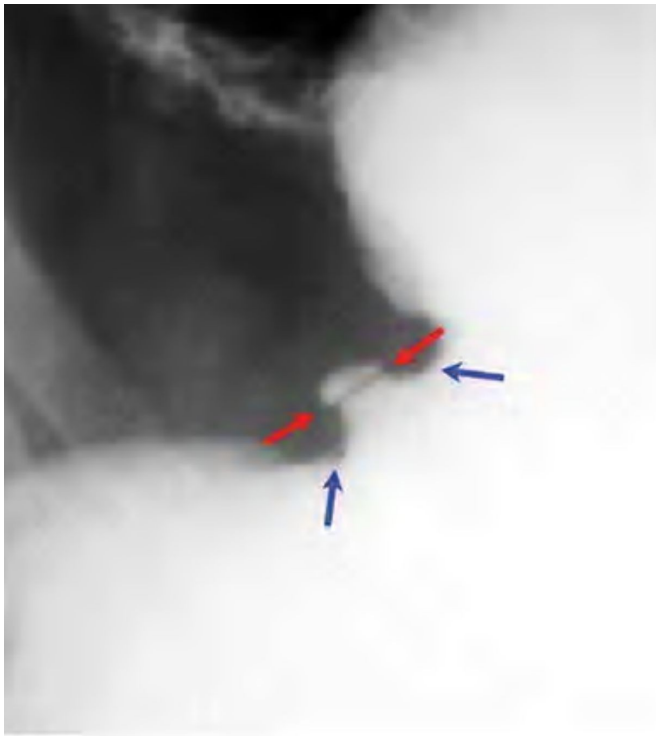
Double-contrast study

- Detection rates as high as 90%
- Sensitivity for detection is decreased in **small ulcers** (<0.5 cm), presence of **previous scarring**, or in **postoperative** patients
- Ulcers >3 cm in size or those associated with a mass are more often malignant.
- Up to 8% of GUs that appear to be benign by radiographic appearance are malignant by endoscopy or surgery.
- Radiographic studies that show a GU must be followed by endoscopy and biopsy

A benign duodenal ulcer



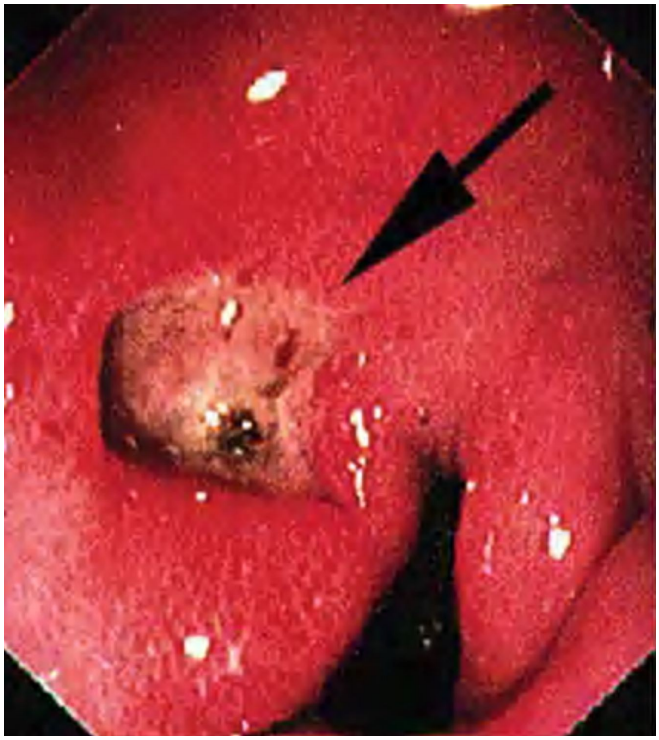
A benign gastric ulcer



Endoscopy

- The most sensitive and specific approach for examining the upper gastrointestinal tract
- Facilitates tissue biopsy to rule out malignancy (GU) or *H. pylori*
- Identifies lesions too small to detect by radiography
- Evaluates atypical radiographic abnormalities
- Determines if an ulcer is a source of blood loss

a benign duodenal ulcer



a benign gastric ulcer

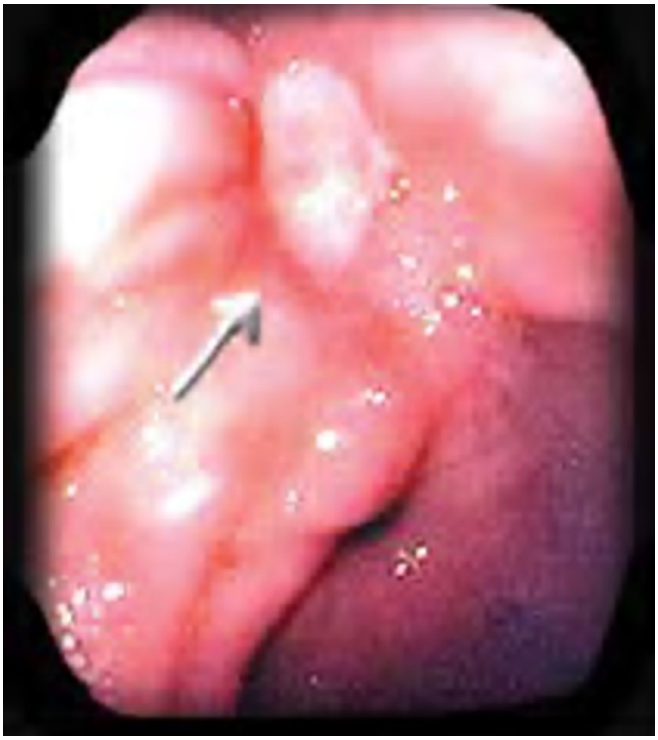


Table 287-2 Tests for Detection of *H. pylori*

Test	Sensitivity/Specificity, %	Comments
Invasive (Endoscopy/Biopsy Required)		
Rapid urease	80–95/95–100	Simple, false negative with recent use of PPIs, antibiotics, or bismuth compounds
Histology	80–90/>95	Requires pathology processing and staining; provides histologic information
Culture	—/—	Time-consuming, expensive, dependent on experience; allows determination of antibiotic susceptibility
Non-invasive		
Serology	>80/>90	Inexpensive, convenient; not useful for early follow-up
Urea breath test	>90/>90	Simple, rapid; useful for early follow-up; false negatives with recent therapy (see rapid urease test); exposure to low-dose radiation with ^{14}C test
Stool antigen	>90/>90	Inexpensive, convenient; not established for eradication but promising

- Serum gastrin and gastric acid analysis (sham feeding) may be needed in individuals with complicated or refractory PUD (Zollinger-Ellison Syndrome).
- Screening for aspirin or NSAIDs (blood or urine) may also be necessary in refractory H. pylori–negative PUD patients.

Treatment

Acid suppression
Eradication of *H. pylori*
Therapy/prevention of NSAID-induced disease

Table 287-3 Drugs Used in the Treatment of Peptic Ulcer Disease

Drug Type/Mechanism	Examples	Dose
Acid-suppressing drugs		
Antacids	Mylanta, Maalox, Tums, Gaviscon	100–140 meq/L 1 and 3 h after meals and hs
H_2 receptor antagonists	Cimetidine	400 mg bid
	Ranitidine	300 mg hs
	Famotidine	40 mg hs
	Nizatidine	300 mg hs
Proton pump inhibitors	Omeprazole	20 mg/d
	Lansoprazole	30 mg/d
	Rabeprazole	20 mg/d
	Pantoprazole	40 mg/d
	Esomeprazole	20 mg/d
Mucosal protective agents		
Sucralfate	Sucralfate	1 g qid
Prostaglandin analogue	Misoprostol	200 μg qid
Bismuth-containing compounds	Bismuth subsalicylate (BSS)	See anti-*H. pylori* regimens (Table 287-4)

Acid Neutralizing/Inhibitory Drugs

Antacids

- They are now rarely, used as the primary therapeutic agent
- Mixtures of aluminum hydroxide and magnesium hydroxide
- Should n
- Not be used in CRF, because of possible hypermagnesemia, and chronic neurotoxicity

H2 Receptor Antagonists

- Cimetidine, famotidine, and nizatidine have different potency,
- Inhibit basal and stimulated acid secretion
- Confusion and elevated levels of serum aminotransferases, creatinine, and prolactin
- **Tolerance** to H2 blockers
- Pancytopenia

Proton Pump (H+,K+-ATPase) Inhibitors

- Omeprazole, esomeprazole, lansoprazole, rabeprazole, and pantoprazole are benzimidazole derivatives that covalently bind and irreversibly inhibit H+,K+-ATPase
- The **most potent acid inhibitory agents**
- Maximum acid inhibitory effect between 2 and 6 h after administration
- It can take 2 and 5 days for gastric acid secretion to return to normal levels once these drugs have been discontinued

- Before a meal
- Gastrin levels return to normal levels within 1–2 weeks after drug cessation
- IF production is also inhibited, but vitamin B12-deficiency anemia is uncommon
- Interfere with absorption of drugs such as ketoconazole, ampicillin, iron, and digoxin
- Hepatic cytochrome P450 can be inhibited by omeprazole & lansoprazole

- ***Tenatoprazole***: longer half-life
- ***Potassium-competitive acid pump antagonists*** (P-CABs), inhibit gastric acid secretion via potassium competitive binding of the H+,K+-ATPase.

Cytoprotective Agents

Sucralfate

- Binding primarily to sites of active ulceration
- Promoting a trophic action by binding growth factors such as EGF
- Enhancing prostaglandin synthesis
- Stimulating mucous and bicarbonate secretion
- Enhancing mucosal defense and repair
- ***Avoid in CRF*** to prevent aluminum-induced neurotoxicity.
- Hypophosphatemia
- Gastric **bezoar** formation

- ***Bismuth***

- Ulcer coating;
- Prevention of further pepsin/HCl-induced damage;
- Binding of pepsin;
- Stimulation of prostaglandins, bicarbonate, and mucous secretion
- Black stools,
- Constipation,
- Darkening of the tongue
- Neurotoxicity

Prostaglandin Analogues

- Enhance mucous bicarbonate secretion,
- Stimulate mucosal blood flow
- Decrease mucosal cell turnover.
- The most common toxicity noted with this drug is diarrhea (10–30%).
- Uterine bleeding
- ***Contraindicated in pregnancy***

Therapy of *H. pylori*

- PUD who are found to be *H. pylori*–positive by serology or breath testing.
- Gastric MALT lymphoma
- Patients with GERD requiring long-term acid suppression?
- 14 days provides the greatest efficacy
- Promote ulcer healing,
- ***Prevent ulcer recurrence and complications***
- Diminished recurrent ulcer bleeding

Table 287-4 Regimens Recommended for Eradication of *H. pylori* Infection

Drug	Dose
Triple Therapy	
1. Bismuth subsalicylate *plus*	2 tablets qid
Metronidazole *plus*	250 mg qid
Tetracycline[a]	500 mg qid
2. Ranitidine bismuth citrate *plus*	400 mg bid
Tetracycline *plus*	500 mg bid
Clarithromycin or metronidazole	500 mg bid
3. Omeprazole (lansoprazole) *plus*	20 mg bid (30 mg bid)
Clarithromycin *plus*	250 or 500 mg bid
Metronidazole[b] *or*	500 mg bid
Amoxicillin[c]	1 g bid
Quadruple Therapy	
Omeprazole (lansoprazole)	20 mg (30 mg) daily
Bismuth subsalicylate	2 tablets qid
Metronidazole	250 mg qid
Tetracycline	500 mg qid

- The most complication with amoxicillin is pseudomembranous colitis (<2%)
- Tetracycline has been reported to cause rashes,hepatotoxicity and anaphylaxis
- ***Resistant to amoxicillin, and tetracycline is uncommon***
- Quadruple therapy
- ***Antibiotic-resistant strains are the most common cause for treatment failure in compliant patients***

- Second-line therapy include:
- (levofloxin, amoxicillin, PPI) for 10 days
- Then culture and sensitivity of the organism
- Cigarette smoking
- Sequential therapy:5 days of amoxicillin + PPI, followed by an additional 5 days of PPI + tinidazole + clarithromycin

- If *H. pylori* present, eradication is recommended for 14 days, followed by continued acid-suppressing drugs for 4–6 week
- ***Test of choice for documenting eradication is the urea breath test (UBT).***
- Stool antigen assay (off PPI)
- Multiple biopsies of a GU should be taken initially; even if these are negative for neoplasm, repeat endoscopy to document healing at 8–12 weeks should be performed, with biopsy if the ulcer is still present.
- ~ 70% of GUs eventually found to be malignant undergo significant (usually incomplete) healing.

- A ***GU that fails to heal after 12 weeks*** and a ***DU that does not heal after 8 weeks*** of therapy **should be considered refractory**
- Poor compliance
- Persistent *H. pylori* infection
- NSAID use
- Smoking
- Malignancy (For a GU)
- Hypersecretory state such as ZES, (fasting gastrin or secretin stimulation test)

- Ischemia
- Crohn's disease
- Amyloidosis
- Sarcoidosis
- Lymphoma
- Eosinophilic gastroenteritis
- Infection [CMV, tuberculosis, or syphilis].
- Higher dose is also effective in maintaining remission.
- Surgical intervention

Surgical Therapy

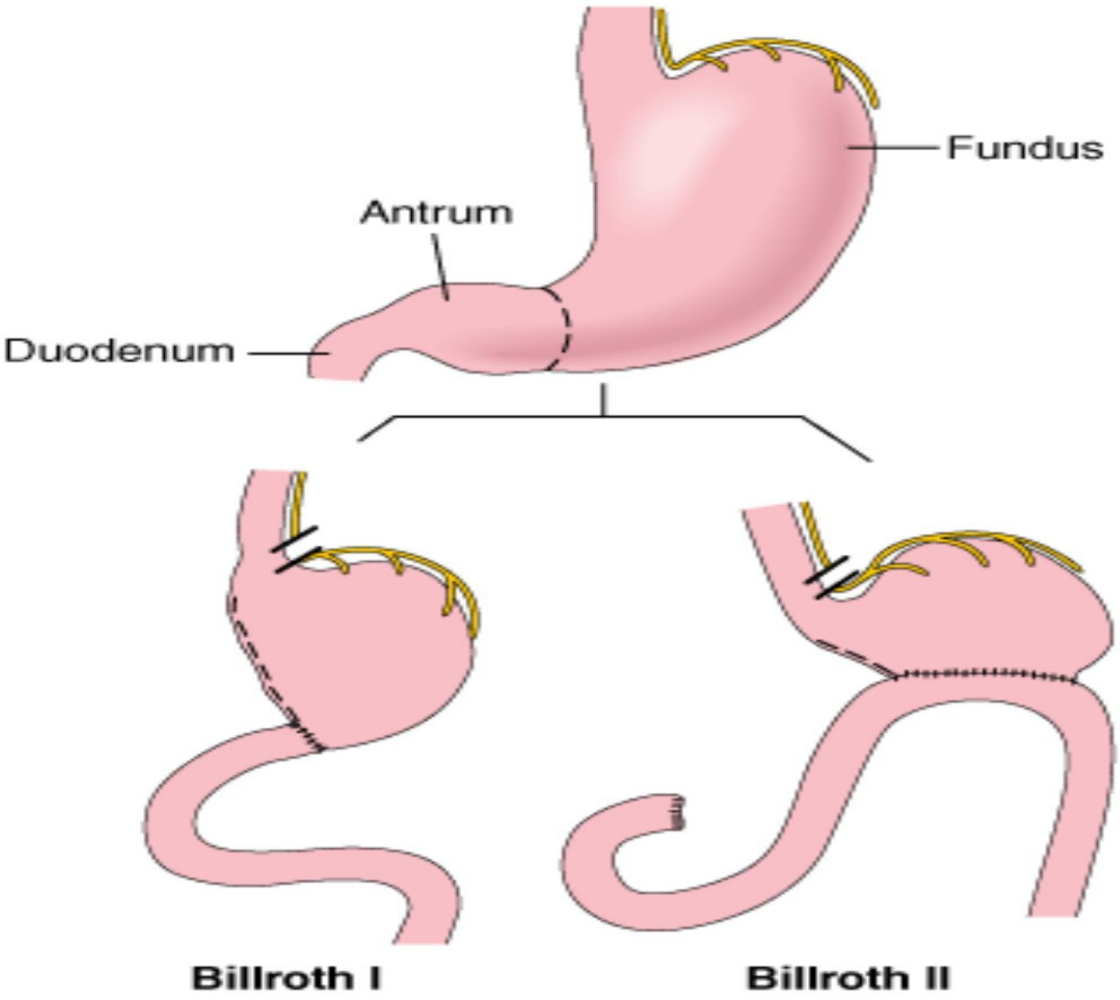
- Elective, for medically refractory disease,
- Or as urgent/emergent, for an ulcer-related complication

- GIB unresponsive or refractory to endoscopic intervention + IV PPI, will require surgery (~5% of transfusion-requiring patients)

Specific Operations for Duodenal Ulcers

- Surgical treatment is designed to decrease gastric acid secretion by *Vagotomy*

- 1) **vagotomy and drainage** (by pyloroplasty, gastroduodenostomy, or gastrojejunostomy to compensate for the vagotomy-induced gastric motility disorder)
- 2) **highly selective vagotomy** (which does not require a drainage procedure)
- 3) **vagotomy with antrectomy** in prepyloric ulcers and refractory to medical therapy (lowest rates of ulcer recurrence but the highest complication rate)


Fundus
Antrum
Duodenum
Billroth I
Billroth II

Operations for Gastric Ulcers

- Antrectomy (including the ulcer) with a Billroth I anastomosis is the treatment of choice for an antral ulcer.
- Vagotomy is performed only if a DU is present
- Ulcers located near the esophagogastric junction require subtotal gastrectomy with esophagogastrojejunostomy (Csende's procedure).

Surgery-Related Complications

- More aggressive surgical procedures have a lower rate of ulcer recurrence but a greater incidence of gastrointestinal dysfunction
- Recurrent Ulceration
- Afferent Loop Syndromes
- Dumping Syndrome
- Postvagotomy Diarrhea
- Bile Reflux Gastropathy
- Maldigestion and Malabsorption
- Gastric Adenocarcinoma


Thank you
Questions?