**Peptic ulcer disease**

* Peptic ulcer disease (PUD) refers to a defect in the gastric or duodenal mucosal wall that extends through the muscularis mucosa into the deeper layers of the submucosa.
* PUD is a significant cause of morbidity and is associated with substantial health care costs.
* Although there are many etiologies of PUD, the three most common are (a) H. pylori infection, (b) use of nonsteroidal anti-inflammatory drugs (NSAIDs), and (c) stress-related mucosal damage (SRMD).
* Complications of PUD include GI bleeding, perforation, and obstruction.
* Complications of untreated or undiagnosed H. pylori infection include gastric cancer and PUD.

**EPIDEMIOLOGY AND ETIOLOGY**

Factors that influence the incidence and prevalence of H. pylori infection include age, ethnicity, sex, geography, and socioeconomic status.

**1. Helicobacter Pylori**

* H. pylori is usually contracted in the first few years of life and tends to persist indefinitely unless treated.
* The infection normally resides in the stomach and is transmitted through ingestion of fecal-contaminated water or food.
* The organism causes gastritis in all infected individuals, but fewer than 10% actually develop symptomatic PUD.

**2.Nonsteroidal Anti-Inflammatory Drugs**

* Peptic ulceration occurs in up to 30% of chronic NSAID (including aspirin) users, with GI bleeding or perforation occurring in 1.5% of patients who develop an ulcer. Ulcer related complications result in hospitalizations and deaths
* Risk factors NSAID-induced PUD and complications are generally additive.
* Corticosteroid therapy is not an independent risk factor for ulceration but increases PUD risk substantially when combined with NSAID therapy.
* Whether H. pylori infection is a risk factor for NSAID-induced ulcers remains controversial; however, H. pylori and NSAIDs act independently to increase ulcer risk and ulcer related bleeding and also appear to have synergistic effects. Risk Factors for Ulcers and GI Complications Related to NSAID Use:
	+ Age older than 60 years
	+ Concomitant anticoagulant use
	+ Preexisting coagulopathy (elevated INR or thrombocytopenia)
	+ Concomitant corticosteroid or selective serotonin reuptake inhibitor therapy
	+ Previous PUD or PUD complications (bleeding/perforation)
	+ Cardiovascular disease and other comorbid conditions
	+ Multiple NSAID use (eg, low-dose aspirin plus another NSAID)
	+ Duration of NSAID use (> 1 month)
	+ High-dose NSAID use
	+ NSAID-related dyspepsia
	+ Cigarette smokers

**3.Stress-Related Mucosal Damage**

* SRMD occurs most frequently in critically ill patients due to mucosal defects caused by gastric mucosal ischemia and intraluminal acid.
* The ulcers are usually superficial, but SRMD may also penetrate into the submucosa and cause significant GI bleeding.
* Physiologically stressful situations that lead to SRMD include sepsis, organ failure, prolonged mechanical ventilation, thermal injury, and surgery.
* Critical care patients with the specific characteristics listed above are at highest risk.

**4.Zollinger–Ellison Syndrome**

* Zollinger–Ellison syndrome (ZES) is caused by a gastrin-producing tumor called a gastrinoma.
* The resulting gastric acid hypersecretion causes diarrhea and malabsorption.
* Ulcers tend to be numerous and have a high risk of perforation and bleeding.
* Treatments include surgical resection when feasible and high dose oral proton pump inhibitor (PPI) therapy.

**5.Other Causative Factors**

* Cigarette smoking is associated with a higher prevalence of ulcers in H. pylori-infected patients.
* The detrimental effects of smoking on the gastric mucosa may involve increased pepsin secretion, duodenogastric reflux of bile salts, elevated levels of free radicals, and reduced prostaglandin-2 (PG2) production, resulting in decreased mucus and bicarbonate secretion.
* Although psychosocial factors such as life stress, personality patterns, and depression may influence PUD prevalence, a clear causal relationship has not been demonstrated.
* Dietary factors such as coffee, tea, cola, alcohol, and spicy foods may cause dyspepsia but have not been shown to independently increase PUD risk.

**PATHOPHYSIOLOGY**

* Ulcers related to H. pylori infection more commonly affect the duodenum (duodenal ulcers), whereas NSAID-related ulcers more frequently affect the stomach (gastric ulcers).
* However, ulcers may be found in either location from either cause.
* Ulcer formation in the GI tract results from disrupted homeostasis between factors that break down food (eg, gastric acid and pepsin) and those that promote mucosal defense and repair (eg, bicarbonate, mucus secretion, and PGs).

**Gastric Acid and Pepsin**

* Hydrochloric acid and pepsin are the primary substances that cause gastric mucosal damage in PUD.
* Three different stimuli (eg, histamine, acetylcholine, and gastrin) cause acid secretion through interactions with the histaminic, cholinergic, and gastrin receptors on the surface of parietal cells.
* Gastric acid output occurs in two stages:

(a) basal acid output during fasting, and

 (b) maximal acid output in response to meals.

1. **Basal acid secretion** follows a circadian cycle and is modulated by the effects of acetylcholine and histamine on parietal cells
2. **Food increases gastric acid secretion** in two ways: (1) vagus nerve stimulation in response to sight, smell, or taste; and (2) stomach distention during the gastric and intestinal phases of acid secretion
* After stimulation by histamine, acetylcholine, and gastrin, acid is secreted by the H+-K+-ATPase+ (proton) pump, located on the luminal side of parietal cells.
* Acid secretion in PUD is usually normal or only slightly elevated. NSAID ingestion does not usually affect acid secretion, whereas H. pylori infection often slightly increases acid output.
* Pepsinogen released from chief cells in the body of the stomach is converted to pepsin in an acidic environment; pepsin initiates protein digestion and collagen proteolysis and serves as a signal for the release of other digestive enzymes such as gastrin and cholecystokinin.
* The proteolytic activity of pepsin appears to influence ulcer formation.

**Mucosal Defense and Repair**

* Several normal processes prevent mucosal damage and subsequent ulcer formation.
* The buffering action of the mucus/phospholipid and bicarbonate barrier shields the gastric epithelial surface from gastric acid.
* This allows an acidic environment in the gastric lumen but a near neutral pH on the epithelial lining.
* PGs inhibit gastric acid secretion and protect gastric mucosa by stimulating mucus, bicarbonate, and phospholipid production.
* PGs also increase mucosal blood flow and stimulate epithelial cell regeneration.
* **Damage to the mucosal defense system is the primary method by which H. pylori and NSAIDs cause peptic ulcers.**

**» Helicobacter pylori**

* H. pylori, a gram-negative rod, is found on the surface of the gastric epithelium.
* Flagella provide motility that allows the organism to penetrate the mucous gel barrier and infect epithelial cells.
* Cellular invasion by H. pylori is necessary for an active infection.
* The organism survives in the acidic **milieu of the stomach by producing urease, an** enzyme that hydrolyzes urea in gastric juice into carbon dioxide and ammonia.
* H. pylori may cause gastroduodenal mucosal injury through

(a) direct mucosal damage, (b) alterations in host inflammatory responses, and (c) hypergastrinemia and elevated acid secretion.



**Nonsteroidal Anti-Inflammatory Drugs**

 **NSAIDs can cause gastric mucosal damage by two mechanisms:**

(1) direct irritation of the gastric epithelium, and

 (2) systemic inhibition of endogenous mucosal PG synthesis.

* **Direct irritation occurs because NSAIDs are weak acids.** Less acidic agents, such as nonacetylated salicylates, may confer decreased GI toxicity.
* Direct irritant effects contribute to NSAID-induced gastritis but play a minor role in the development of NSAID-induced PUD.
* **Systemic inhibition of PG synthesis is** the primary means by which NSAIDs cause PUD. NSAID inhibition of PG production by blocking the cyclooxygenase-2 (COX-2) enzyme produces beneficial analgesic and anti-inflammatory effects.
* However, NSAIDs may also **block the COX-1 enzyme**, which produces PGs that provide gastroprotection. NSAIDs given parenterally (eg, ketorolac) and rectally (eg, indomethacin) have an incidence of PUD similar to oral NSAIDs.
* **Topical NSAIDs (eg, diclofenac) are unlikely t**o cause PUD because very low serum concentrations are achieved. The antiplatelet effects of NSAIDs may worsen bleeding complications associated with PUD.

**Clinical Presentation of PUD** , **Symptoms**

* Dyspepsia and mild epigastric pain that may be described as burning, gnawing, or aching in character.
* Epigastric pain with duodenal ulcers typically occurs 1 to 3 hours after meals or at night and is often relieved by food
* Pain with gastric ulcers occurs is often aggravated by food.
* Abdominal pain may be described as burning or a feeling of discomfort.
* Pain severity pain often fluctuates and the character can vary from dull to sharp.
* Patients may also complain of heartburn, belching, bloating, nausea, or vomiting.

 **Signs**

* Weight loss may be associated with nausea and vomiting.
* Complications such as bleeding, perforation, or obstruction may occur.
* Alarm findings include family history of upper GI malignancy, unintentional weight loss, overt GI bleeding, iron deficiency anemia, progressive dysphagia or odynophagia, early satiety, persistent vomiting, palpable mass, or lymphadenopathy.

**CLINICAL PRESENTATION AND DIAGNOSIS**

**Clinical Presentation**

* Dyspepsia (upper abdominal discomfort) is found in 10% to 40% of the general population.
* PUD is found in 5% to 15% of patients with dyspepsia.
* PUD can be classified as uncomplicated or complicated.
* Uncomplicated disease is typically characterized by mild epigastric pain, whereas complicated disease involves acute upper GI complications such as GI bleeding, obstruction, or perforation.
* Bleeding may be occult or may present as melena or hematemesis.
* Up to 20% of patients who develop a PUD-related hemorrhage do not have prior symptoms.
* Gastric outlet obstruction is usually caused by ulcer-related inflammation or scar formation.
* Patients typically present with early satiety after meals, nausea, vomiting, abdominal pain, and weight loss.
* Perforation requires emergent surgical intervention, and these patients should not undergo endoscopy.

**Diagnosis**

1. Radiologic and/or endoscopic proceduresare usually required to document the presence of ulcers.
* Endoscopic testing is invasive and expensive, but it **is indicated in** patients older than 55 years with new-onset dyspepsia or any patient with alarming features.
* Patients with dyspepsia who are **younger than 55 years without alarming features may** forego endoscopy but should be tested for H. pylori and treated if positive.
* Those who **test negative for H. pylori should** be offered a trial (4–8 weeks) of acid suppression therapy or proceed to endoscopy.
* Persistent dyspepsia despite a trial of acid suppressive therapy warrants upper endoscopy evaluation.
1. Testing for H. pylori infection is indicated in patients with active PUD, history of documented PUD, or gastric mucosa associated lymphoid tissue (MALT) lymphoma.
* Diagnostic tests to detect H. pylori presence can be either **endoscopic or nonendoscopic.**
* **Endoscopic diagnosis** involves **extraction of gastric tissue samples** that are subsequently tested for H. pylori.
* Histology is the standard identification method, but culture, polymerase chain reaction (PCR), and the rapid urease test can also identify H. pylori in tissue samples.
* **Non endoscopic testing** methods for H. pylori include the urea breath test, serologic testing, and stool antigen assay. These tests are less invasive and less expensive than endoscopy.
* **The urea breath test** is usually first line because of its high sensitivity and specificity and short turnaround time.
* **Concomitant acid-suppressive or antibiotic therapy may** give false-negative results.
* The urea breath test can also be used to **confirm eradication of H. pylori infection.**
* Serologic testing provides a quick (within 15 minutes) office based assessment of exposure to H. pylori, but it cannot **differentiate active infection from previously treated infection**; patients can remain **seropositive for years after eradication.**
* **Serologic testing** is also less sensitive and specific than the urea breath test.
* Serologic testing is recommended in patients with recent or current antibiotic or acid-suppressive therapy.
* **Stool antigen assays** can be useful for initial diagnosis or to confirm H. pylori eradication.
* They have high sensitivity and specificity and **are affected less by concomitant medication use.**
* **Use of antimicrobial agents within 4 weeks**, PPIs within 2 weeks, and histamine-2 receptor antagonists (H2 RAs) within 24 hours of testing can suppress the infection and reduce the sensitivity of testing

**TREATMENT**

* The treatment selected for PUD depends on the etiology of the ulcer, whether the ulcer is new or recurrent, and whether complications have occurred.

**Desired Outcomes**

* The goals of PUD therapy are to resolve symptoms, reduce acid secretion, promote epithelial healing, prevent ulcer-related complications, and prevent ulcer recurrence.
* For H. pylori–related PUD, eradication of H. pylori is an additional outcome.

**Nonpharmacologic Therapy**

 **» Risk Factor**

* Avoidance Patients with PUD should avoid exposure to factors known to worsen the disease, exacerbate symptoms, or lead to ulcer recurrence.
* Patients should be advised to reduce psychological stress and avoid cigarette smoking, alcohol consumption, and NSAID or aspirin use if possible.
* Patients who require chronic NSAID therapy (eg, for rheumatoid arthritis) may be given prophylaxis with misoprostol or a PPI (see section on prevention of NSAID-induced ulcers).

**» Surgery**

1. The high success rates of medical therapies have reduced the need for surgical procedures. Elective surgeries performed for PUD have decreased by more than 70% since the 1980s mainly due to H. pylori eradication.
2. Surgical interventions are generally reserved for complicated or refractory PUD.
3. For patients with acute GI bleeding, endoscopic hemostasis can be achieved using contact thermal therapy, mechanical therapy using clips, or epinephrine injection followed by either thermal or mechanical therapy.
4. Angiography with embolization of bleeding lesions can be used if the bleeding cannot be stopped endoscopically and the patient is either high risk for surgery or not a surgical candidate

**Pharmacologic Therapy**

**» Treatment of H. pylori–Associated Ulcers**

1. The goal of H. pylori therapy is to eradicate the organism using an effective antibiotic-containing regimen.
2. Reliance on conventional acid-suppressive drug therapy alone as an alternative to H. pylori eradication is inappropriate because it is associated with a higher incidence of ulcer recurrence and ulcer related complications.
3. Reinfection rates are generally low after the initial course of therapy as long as the patient was adherent.
4. The selected H. pylori regimen should have a per-protocol cure rate of 90% or more or a cure rate based on intention-to-treat analysis of 80% or more.
5. In addition to proven efficacy, the optimal treatment regimen should cause minimal adverse events, have low risk for development of bacterial resistance, and be cost-effective





**Treatment of NSAID-Induced Ulcers**

1. Treatment recommendations to heal NSAID-induced ulcers or provide maintenance therapy in patients receiving NSAIDS are shown in Table 18–3.
2. Choice of regimen depends on whether NSAID use is to be continued. NSAIDs should be discontinued and replaced with alternatives (eg, acetaminophen), when possible.
3. For patients who cannot discontinue NSAID therapy, PPIs, H2 RAs, or sucralfate are effective for ulcer healing and to prevent further recurrences. PPIs are usually preferred because they provide more rapid relief of symptoms, have the strongest acid suppression, and heal ulcers more quickly than H2 RAs or sucralfate.
4. Standard doses of H2 RAs effectively heal duodenal ulcers but are minimally effective in gastric ulcers. In ulcers larger than 5 mm, the rate of ulcer healing may be as low as 25% after 8 weeks of therapy with an H2 RA. A PPI provides equivalent efficacy with treatment duration of only 4 weeks.
5. PPI therapy should only be continued for longer than 4 weeks if an ulcer is confirmed to still be present or if the patient develops severe complications from PUD.

**Prevention of NSAID-Induced Ulcers**

* Prophylactic regimens against PUD are often required in patients receiving long-term NSAID or aspirin therapy for osteoarthritis, rheumatoid arthritis, or cardioprotection.
* Misoprostol, H2 RAs, PPIs, and COX-2 selective inhibitors have been evaluated in controlled trials to reduce the risk of NSAID-induced PUD.
* In patients at risk for NSAID-induced ulcers, PPIs at standard doses reduce the risk of both gastric and duodenal ulcers as effectively as misoprostol as and more effectively than H2 RAs.
* In addition, PPIs are generally better tolerated than misoprostol.

**Misoprostol**

1. Misoprostol is a synthetic prostaglandin E1 (PGE1) analog that exogenously replaces PG stores.
2. It is indicated for reducing the risk of NSAID-induced gastric ulcers in patients at high risk of complications from ulcers (eg, the elderly and patients with concomitant debilitating disease), as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcers.
3. Misoprostol 200 mcg four times a day reduces ulcer complications by inhibiting acid secretion and promoting mucosal defense.
4. It is superior to H2 RAs for prevention of NSAID-induced ulcers.
5. Misoprostol use is limited by a high frequency of bothersome GI effects such as abdominal pain, flatulence, and diarrhea, and it is contraindicated in pregnancy due to potential abortifacient effects.
6. Arthrotec is a combination product that contains diclofenac (either 50 or 75 mg) and misoprostol 200 mcg in a single tablet

**H2 -Receptor Antagonists**

* The efficacy of H2 RAs (eg, famotidine 40 mg daily) in preventing NSAID-related ulcers varies.
* **Duodenal ulcers** appear to respond **better than gastric ulcers (**the most frequent type of ulcer associated with NSAIDs).
* **Higher doses of H2 RAs** (eg, famotidine 40 mg twice daily) may reduce the risk of NSAID-induced gastric and duodenal ulcers, but results from clinical trials are variable.
* Duexis, a prescription combination product containing ibuprofen 800 mg and famotidine 26.6 mg, is indicated for relief of signs and symptoms of rheumatoid arthritis and osteoarthritis and to decrease the risk of developing upper GI ulcers.
* The recommended dosage is one tablet orally three times daily.

**Proton Pump Inhibitors**

* PPI therapy **is more effective than H2 RAs in** reducing the risk of nonselective NSAID-related gastric and duodenal ulcers.
* PPIs are **as effective as misoprostol but better tolerated.**
* All PPIs are effective when used in standard doses.
* In patients who experience a PUD-related bleeding event while taking aspirin but who require continued aspirin therapy, the addition of a PPI reduces the incidence of recurrent GI bleeding.

**COX-2 Selective Inhibitors**

1. NSAIDs with COX-2 selectivity were developed in an attempt to reduce the incidence of PUD and its complications.
2. However, selective COX-2 inhibitors are no more effective than the combination of a PPI and a nonselective NSAID in reducing the incidence of ulcers and are associated with a higher incidence of cardiovascular events than traditional nonselective NSAIDs (eg, ischemic stroke).
3. Given the CV risk of COX-2 inhibitors, a nonselective NSAID and a PPI is recommended instead of celecoxib in patients at high risk for NSAID-related PUD.

**Sucralfate**

* This drug is a negatively charged, nonabsorbable agent that forms a complex by binding with positively charged proteins in exudates, forming a viscous, paste-like adhesive substance that protects the ulcerated area of the gastric mucosa against gastric acid, pepsin, and bile salts.
* Limitations of sucralfate include the need for multiple daily dosing, large tablet size, and interaction with a number of other medications (eg, digoxin and fluoroquinolones).
* Adverse effects of sucralfate include constipation, nausea, metallic taste, and the possibility for aluminum toxicity in patients with renal failure.
* Sucralfate is effective in the treatment of NSAID-related ulcers when the NSAID will be stopped, but it is not recommended for NSAID-related ulcer prophylaxis

» **Prevention of Stress-Related Mucosal Damage**

* Stress ulcer prophylaxis is only indicated in intensive care unit (ICU) patients with certain risk factors
* The clinician must weigh the risks and benefits of using acid suppression, especially PPIs, in low-risk patients. PPIs and H2 RAs are the drugs of choice for SUP; however, antacids and sucralfate may be acceptable options in some patients.

**Long-Term Maintenance of Ulcer Healing**

 Low-dose maintenance therapy with a PPI or H2 RA is only indicated in patients with severe complications secondary to PUD such as gastric outlet obstruction or patients who need to be on long-term NSAIDs or high-dose corticosteroids and are at high risk for bleeding.

**» Treatment of GI Bleeding**

* The immediate priorities in treating patients with a bleeding peptic ulcer are to achieve IV access, correct fluid losses, and restore hemodynamic stability.
* Insertion of a nasogastric tube is helpful in initial patient assessment, but the absence of bloody or coffee-ground material does not definitively rule out ongoing or recurrent bleeding; about 15% of patients without bloody nasogastric tube output have a high-risk lesion at endoscopy.
* Patients should be started on IV PPI therapy because optimal platelet aggregation, partially inhibited fibrinolysis, and better clot stabilization on the ulcer are achieved when the gastric pH is greater than 6.
* Intravenous PPI therapy should be continued for 72 hours (because most rebleeding occurs during this time) followed by oral PPI therapy.
* Three-day PPI infusion therapy has been shown to be as effective as twice-daily IV PPI therapy.

**» Treatment of Refractory Ulcers**

* Refractory ulcers are defined as ulcers that **fail to heal despite 8 to 12 weeks of acid suppressive therapy**.
* The presence of refractory ulcers requires a thorough assessment, including evaluation of medication adherence, extensive counseling and questioning regarding recent over-the-counter and prescription medication use, and testing for H. pylori using a different method than previously done if testing was negative.
* Changing from **H2 RA therapy to a PPI** should be considered.
* Other considerations include esophagogastroduodenoscopy (**EGD)** with biopsy of the ulcer to exclude malignancy, H. pylori testing (if not done initially), and serum gastrin measurement to exclude ZES.
* Increasing the starting dose of PPI therapy may heal up to 90% of refractory ulcers after 8 weeks of therapy.

**OUTCOME EVALUATION**

* + Obtain a baseline complete blood count (CBC). Recheck the CBC if the patient exhibits alarm signs or symptoms.
	+ Obtain a baseline serum creatinine measurement. Calculate the estimated creatinine clearance and adjust the dose of H2 RAs and sucralfate if needed.
	+ Obtain a history of symptoms from the patient. Monitor for improvements in pain symptoms (eg, epigastric or abdominal pain) daily
	+ Monitor the patient for the development of any alarm signs and symptoms.
	+ Recommend a follow-up visit if signs and symptoms worsen at any time or do not improve within the defined treatment period.
	+ Assess for potential drug interactions whenever there is a change in the patient’s medications.
	+ Educate the patient on the importance of adhering to the H. pylori eradication regimen.
	+ Monitor the patient for complications related to antibiotic therapy (eg, diarrhea or oral thrush) during and after completion of H. pylori eradication therapy.
	+ Recommend follow-up care if the patient’s signs and symptoms do not improve after completion of H. pylori eradication therapy

**Patient Care Process:**

Peptic Ulcer Disease Patient Assessment:

* Based on review of signs and symptoms and assessment of risk factors (Table 18–1), determine whether the patient is experiencing signs or symptoms of PUD.
* Obtain a history of prescription and over-the-counter medications and dietary supplements. Verify patient allergies and intolerances.
* Review available diagnostic tests (eg, serologic testing, urea breath test, stool antigen assay, endoscopy) to determine etiology of peptic ulcer

**Therapy Evaluation:**

* If patient is already receiving pharmacotherapy, assess its efficacy, safety, and patient adherence. Are there any significant drug interactions?
* If patient has been diagnosed with a peptic ulcer, determine which course-'
f therapy is indicated.
* Evaluate patient accessibility to medication (eg, formulary status, insurance coverage).

**Care Plan Development:**

* Recommend an appropriate regimen (Tables 18–2 and 18–3) that will eradicate H. pylori and/or heal the peptic ulcer.
* Avoid drug classes to which the patient is allergic. Assess the potential for drug interactions, particularly in patients taking regimens containing metronidazole, clarithromycin, and/or cimetidine.
* If the patient has been treated for H. pylori previously, recommend different antibiotics if this episode is a result of treatment failure.
* Inform patients about potential adverse drug effects and drug interactions.
* Educate the patient on the importance of adherence to eradication and ulcer healing therapy.
* Identify appropriate lifestyle modifications.

**Follow-Up Evaluation:**

* + Monitor annually for signs and symptoms of complications such as unintentional weight loss or bleeding.
	+ Evaluate the need for a prophylactic acid suppressive regimen in patients requiring chronic NSAID therapy.
	+ Assess patient adherence and progress toward efficacy and safety goals



