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Chapter 29: Peptic Ulcer Disease

INTRODUCTION

- *Peptic ulcer disease* (PUD) refers to ulcerative disorders of the upper gastrointestinal (GI) tract that require acid and pepsin for their formation. The three common etiologies include (1) *Helicobacter pylori* infection, (2) nonsteroidal anti-inflammatory drug (NSAID) use, and (3) stress-related mucosal damage (SRMD).

PATHOPHYSIOLOGY

- Benign gastric ulcers, erosions, and gastritis can occur anywhere in the stomach, but the antrum and lesser curvature are the most common locations. Most duodenal ulcers occur in the first part of the duodenum (duodenal bulb).
- Pathophysiology is determined by the balance between aggressive factors (gastric acid and pepsin) and protective factors (mucosal defense and repair). Gastric acid, *H. pylori* infection, and NSAID use are independent factors that contribute to disruption of mucosal integrity. Increased acid secretion may be involved in duodenal ulcers, but patients with gastric ulcers usually have normal or reduced acid secretion (hypochlorhydria).
- Mucus and bicarbonate secretion, intrinsic epithelial cell defense, and mucosal blood flow normally protect the gastroduodenal mucosa from noxious endogenous and exogenous substances. Endogenous prostaglandins (PGs) facilitate mucosal integrity and repair. Disruptions in normal mucosal defense and healing mechanisms allow acid and pepsin to reach the gastric epithelium.
- *H. pylori* infection causes gastric mucosal inflammation in all infected individuals, but only a minority develops an ulcer or gastric cancer. Bacterial enzymes (urease, lipases, and proteases), bacterial adherence, and *H. pylori* virulence factors produce gastric mucosal injury. *H. pylori* induces gastric inflammation by altering the host inflammatory response and damaging epithelial cells.
- Nonselective NSAIDs (including aspirin) cause gastric mucosal damage by two mechanisms: (1) direct or topical irritation of the gastric epithelium, and (2) systemic inhibition of endogenous mucosal PG synthesis (the primary mechanism). COX-2 selective inhibitors have a lower risk of ulcers and related GI complications than nonselective NSAIDs. Addition of aspirin to a selective COX-2 inhibitor reduces its ulcer-sparing benefit and increases ulcer risk.
- Use of corticosteroids alone does not increase risk of ulcer or complications, but ulcer risk is doubled in corticosteroid users taking NSAIDs concurrently.
- Cigarette smoking has been linked to PUD, impaired ulcer healing, and ulcer recurrence. Risk is proportional to amount smoked per day.
- Psychological stress has not been shown to cause PUD, but ulcer patients may be adversely affected by stressful life events.
- Carbonated beverages, coffee, tea, beer, milk, and spices may cause dyspepsia but do not appear to increase PUD risk. Ethanol ingestion in high concentrations is associated with acute gastric mucosal damage and upper GI bleeding but is not clearly the cause of ulcers.

CLINICAL PRESENTATION

- Abdominal pain is the most frequent PUD symptom. Pain is often epigastric and described as burning but can present as vague discomfort, abdominal fullness, or cramping. Nocturnal pain may awaken patients from sleep, especially between 12 AM and 3 AM.
- Pain from duodenal ulcers often occurs 1–3 hours after meals and is usually relieved by food, whereas food may precipitate or accentuate ulcer pain in gastric ulcers. Antacids provide rapid pain relief in most ulcer patients.

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- Heartburn, belching, and bloating often accompany pain. Nausea, vomiting, and anorexia are more common in gastric than duodenal ulcers and may be signs of an ulcer-related complication.
- Severity of symptoms varies among patients and may be seasonal, occurring more frequently in spring or fall.
- Presence or absence of epigastric pain does not define an ulcer, and ulcer healing does not necessarily render the patient asymptomatic. Conversely, absence of pain does not preclude an ulcer diagnosis, especially in older persons, who may present with a "silent" ulcer complication.
- Ulcer complications include upper GI bleeding, perforation into the peritoneal cavity, penetration into an adjacent structure (eg, pancreas, biliary tract, or liver), and gastric outlet obstruction. Bleeding may be occult or present as melena or hematemesis. Perforation is associated with sudden, sharp, severe pain, beginning first in the epigastrium but quickly spreading over the entire abdomen. Symptoms of gastric outlet obstruction typically occur over several months and include early satiety, bloating, anorexia, nausea, vomiting, and weight loss.

DIAGNOSIS

- Physical examination may reveal epigastric tenderness between the umbilicus and the xiphoid process that sometimes radiates to the back.
- Routine blood tests are not helpful in establishing a diagnosis of PUD. Hematocrit, hemoglobin, and stool guaiac tests are used to detect bleeding.
- Diagnosis of PUD depends on visualizing the ulcer crater; upper GI endoscopy has replaced radiography as the procedure of choice because it provides a more accurate diagnosis and permits direct visualization of the ulcer and implementation of maneuvers to control bleeding.
- Diagnosis of *H. pylori* infection can be made using endoscopic or nonendoscopic (urea breath test [UBT], serologic antibody detection, and fecal antigen) tests. Testing for *H. pylori* is only recommended if eradication therapy is planned. If endoscopy is not planned, serologic antibody testing is reasonable to determine *H. pylori* status. Endoscopic biopsy-based tests, UBT, and fecal antigen tests are the recommended tests to verify *H. pylori* eradication but must be delayed until at least 4 weeks after completion of antibiotic treatment and after proton pump inhibitor (PPI) therapy has been discontinued for 2 weeks to avoid confusing bacterial suppression with eradication.

TREATMENT

- Goals of Treatment: Overall goals are to relieve ulcer pain, heal the ulcer, prevent ulcer recurrence, and reduce ulcer-related complications. In *H. pylori*-positive patients with an active ulcer, previously documented ulcer, or history of an ulcer-related complication, goals are to eradicate *H. pylori*, heal the ulcer, and cure the disease with a cost-effective drug regimen. The primary goal for a patient with an NSAID-induced ulcer is to heal the ulcer as rapidly as possible.

Nonpharmacologic Treatment

- Lifestyle modifications including stress reduction and smoking cessation should be implemented. NSAIDs should be avoided if possible, and alternative agents such as acetaminophen or a nonacetylated salicylate (eg, salsalate) should be used for pain relief when feasible.
- There is no specific recommended diet, but patients should avoid foods and beverages that cause dyspepsia or exacerbate ulcer symptoms (eg, spicy foods, caffeine, and alcohol).
- Elective surgery is rarely performed because of highly effective medical management. Emergency surgery may be required for bleeding, perforation, or obstruction.

Pharmacologic Treatment

- **Figure 29-1** depicts an algorithm for evaluation and management of a patient with dyspeptic or ulcer-like symptoms.
- Established indications for treatment of *H. pylori* infection include active PUD, past history of PUD (unless eradication was previously documented), mucosa-associated lymphoid tissue (MALT) lymphoma, and postendoscopic resection of gastric cancer. Treatment should be

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effective, well tolerated, convenient, and cost-effective. Drug regimens to eradicate *H. pylori* are shown in **Table 29-1**.

- *Clarithromycin triple therapy* (PPI, clarithromycin, amoxicillin) is no longer recommended in areas where *H. pylori* resistance exceeds 15%, which includes all of North America. This regimen given for 14 days remains an option in regions where clarithromycin resistance is <15% and no prior macrolide exposure is documented.

- *Bismuth quadruple therapy* (PPI or H2RA, bismuth subsalicylate, metronidazole, tetracycline) for 10–14 days is the preferred first-line therapy to eradicate *H. pylori* infection. PPIs generally produce higher *H. pylori* eradication rates and are preferred over H2RA. All medications except the PPI should be taken with meals and at bedtime. The PPI should be taken 30–60 minutes before a meal. The mean eradication rate for a 10-day course is ~90%, but limitations include the need for four-times-daily therapy (which can impair adherence), and frequent minor side effects.

- *Non-bismuth quadruple (or "concomitant") therapy* (PPI, clarithromycin, amoxicillin, metronidazole) for 10–14 days is another recommended first-line therapy. "Concomitant" therapy means that all four drugs are given at the same time twice daily for the entire duration of therapy. There is lack of evidence in North America for this regimen.

- *Sequential therapy* involves a PPI plus antibiotics given in sequence rather than together. The rationale is to treat initially with antibiotics that rarely promote resistance (eg, amoxicillin) to reduce bacterial load and preexisting resistant organisms and then to follow with different antibiotics (eg, clarithromycin and metronidazole) to kill any remaining organisms. The potential advantage of high eradication rates requires validation in the United States before this regimen can be recommended as first-line *H. pylori* eradication therapy.

- *Hybrid therapy* combines the strategies of concomitant and sequential therapy; it involves 7 days of dual therapy (PPI and amoxicillin) followed by 7 days of quadruple therapy (PPI, amoxicillin, clarithromycin, metronidazole). There is lack of evidence in North America with this regimen.

- *Levofloxacin-based regimens* include (1) triple therapy with amoxicillin and a PPI, (2) modified sequential therapy with 5–7 days of amoxicillin plus a PPI followed by 5–7 days of levofloxacin, and (3) quadruple therapy with levofloxacin, omeprazole or another PPI, nitazoxanide (Alinia), and doxycycline ("LOAD" therapy). The LOAD regimen is not currently recommended due to high cost and lack of efficacy data. In addition, concerns with fluoroquinolone use include development of resistance and adverse effects (eg, tendonitis, hepatotoxicity).

- If initial treatment fails to eradicate *H. pylori*, second-line (salvage) treatment should: (1) use antibiotics that were not included in the initial regimen, (2) be guided by region-specific or individual antibiotic resistance testing, and (3) use an extended treatment duration of 10–14 days. Patients failing clarithromycin triple therapy can be treated with either bismuth quadruple therapy or the levofloxacin triple regimen for 14 days. Other salvage regimens may also be successful. Penicillin allergy testing is recommended for patients who report penicillin allergy because many patients are not truly allergic.

- Patients with NSAID-induced ulcers should be tested to determine *H. pylori* status. If they are *H. pylori* positive, start treatment with a recommended first-line regimen (**Table 29-1**). If patients are *H. pylori* negative, discontinue the NSAID and treat with a PPI, H2RA, or sucralfate (**Table 29-2**). PPIs are generally preferred due to more rapid symptom relief and ulcer healing. If the NSAID must be continued, implement cotherapy with a PPI or misoprostol. Patients at highest risk of recurrent ulcers or ulcer-related complications should be switched to a COX-2 inhibitor.

- Limit maintenance therapy with a PPI or H2RA to high-risk patients with ulcer complications, patients who fail *H. pylori* eradication, and those with *H. pylori*-negative ulcers.

- Patients with ulcers refractory to treatment should undergo upper endoscopy to confirm a nonhealing ulcer, exclude malignancy, and assess *H. pylori* status. *H. pylori*-positive patients should receive eradication therapy. Refractory ulcers despite a complete standard PPI course should be retreated with double-dose of PPI, or consideration can be given to using a different PPI.

FIGURE 29-1

Guidelines for the evaluation and management of a patient who presents with dyspeptic or ulcer-like symptoms.

(COX-2, cyclooxygenase-2; GERD, gastroesophageal reflux disease; *H. pylori*, *Helicobacter pylori*; H2RA, histamine2-receptor antagonist; NSAID, nonsteroidal anti-inflammatory drug; NUD, nonulcer dyspepsia; PPI, proton pump inhibitor.)

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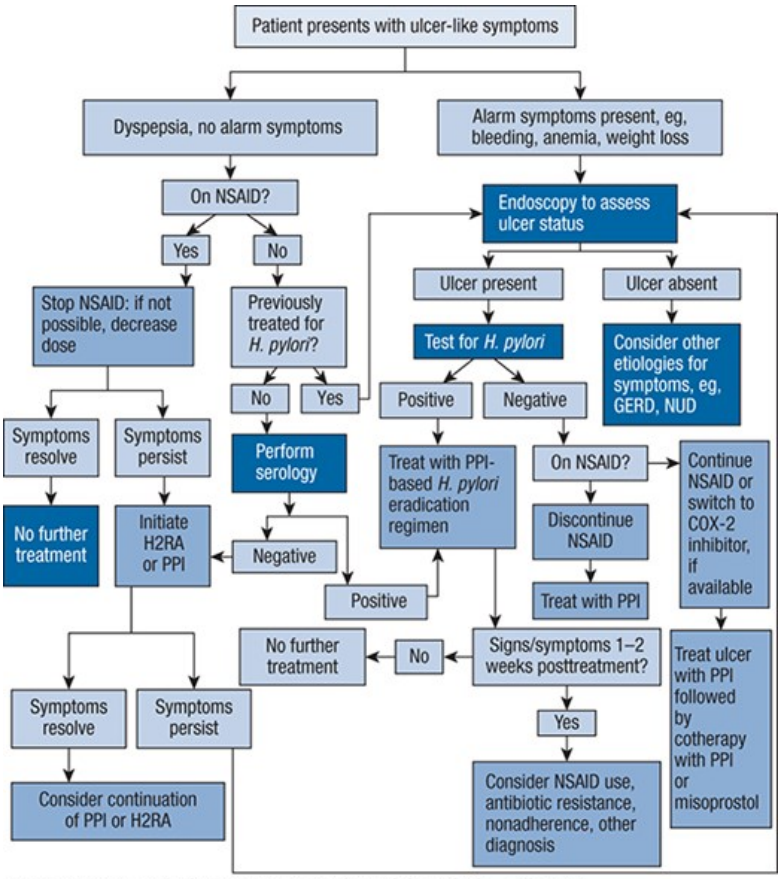

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TABLE 29-1

Drug Regimens Used to Eradicate *Helicobacter pylori*

Regimen	Duration	Drug #1	Drug #2	Drug #3	Drug #4
Proton pump inhibitor–based triple therapy[a]	14 days	PPI once or twice daily[b]	Clarithromycin 500 mg twice daily	Amoxicillin 1 g twice daily *or* metronidazole 500 mg twice daily	
Bismuth quadruple therapy[a]	10–14 days	PPI or H2RA once or twice daily[b,c]	Bismuth subsalicylate[d] 525 mg four times daily	Metronidazole 250–500 mg four times daily	Tetracycline 500 mg four times daily
Non-bismuth quadruple or "concomitant" therapy[e]	10–14 days	PPI once or twice daily on days 1–10[b]	Clarithromycin 250–500 mg twice daily on days 1–10	Amoxicillin 1 g twice daily on days 1–10	Metronidazole 250–500 mg twice daily on days 1–10
Sequential therapy[e]	10 days	PPI once or twice daily on days 1–10[b]	Amoxicillin 1 g twice daily on days 1–5	Metronidazole 250–500 mg twice daily on days 6–10	Clarithromycin 250–500 mg twice daily on days 6–10
Hybrid therapy[e]	14 days	PPI once or twice daily on days 1–14[b]	Amoxicillin 1 g twice daily on days 1–14	Metronidazole 250–500 mg twice daily on days 7–14	Clarithromycin 250–500 mg twice daily on days 7–14
Levofloxacin triple	10–14 days	PPI twice daily	Levofloxacin 500 mg daily	Amoxacillin 1 g twice daily	
Levofloxacin sequential	10 days	PPI twice daily on days 1–10	Amoxicillin 1 g twice daily on days 1–10	Levofloxacin 500 mg once daily on days 6–10	Metronidazole 500 mg twice daily on days 6–10
LOAD	7–10 days	Levofloxacin 250 mg once daily	Omeprazole (or other PPI) at high dose once daily	Nitazoxanide (Alinia) 500 mg twice daily	Doxycycline 100 mg once daily

[a]Although treatment is minimally effective if used for 7 days, 10–14 days is recommended. The antisecretory drug may be continued beyond antimicrobial treatment for patients with a history of a complicated ulcer, for example, bleeding, or in heavy smokers.

[b]Standard PPI peptic ulcer healing dosages given once or twice daily.

[c]Standard H2RA peptic ulcer healing dosages may be used in place of a PPI.

[d]Bismuth subcitrate potassium (biskalcitrate) 140 mg, as the bismuth salt, is contained in a prepackaged capsule (Pylera), along with metronidazole 125 mg and tetracycline 125 mg; three capsules are taken with each meal and at bedtime; a standard PPI dosage is added to the regimen and taken twice daily. All medications are taken for 10 days.

[e]Requires validation as first-line therapy in the United States.

H2RA, H_2>-receptor antagonist; PPI, proton pump inhibitor.

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TABLE 29-2

Drug Dosing Table

Drug	Brand Name	Initial Dose	Usual Range
Proton pump inhibitors			
Omeprazole	Prilosec, various	40 mg daily	20–40 mg/day
Omeprazole + sodium bicarbonate	Zegerid	40 mg daily	20–40 mg/day
Lansoprazole	Prevacid, various	30 mg daily	15–30 mg/day
Rabeprazole	Aciphex	20 mg daily	20–40 mg/day
Pantoprazole	Protonix, various	40 mg daily	40–80 mg/day
Esomeprazole	Nexium	40 mg daily	20–40 mg/day
Dexlansoprazole	Dexilant	30–60 mg daily	30–60 mg/day
H_2-receptor antagonists			
Cimetidine	Tagamet, various	300 mg four times daily, 400 mg twice daily, or 800 mg at bedtime	800–1600 mg/day in divided doses
Famotidine	Pepcid, various	20 mg twice daily, or 40 mg at bedtime	20–40 mg/day
Nizatidine	Axid, various	150 mg twice daily, or 300 mg at bedtime	150–300 mg/day
Ranitidine[a]	Zantac, various	150 mg twice daily, or 300 mg at bedtime	150–300 mg/day
Mucosal protectants			
Sucralfate	Carafate, various	1 g four times daily, or 2 g twice daily	2–4 g/day
Misoprostol	Cytotec	100–200 mcg four times daily	400–800 mcg/day

[a]In April 2020, the U.S. FDA asked manufacturers to withdraw all ranitidine products from the market. A contaminant known as N-Nitrosodimethylamine (NDMA) in some ranitidine products increases over time and when stored at higher than room temperatures and may result in exposure to unacceptable levels of NDMA, which is a probable human carcinogen.

EVALUATION OF THERAPEUTIC OUTCOMES

- Monitor patients for symptomatic relief of ulcer pain, potential adverse drug effects, and drug interactions.

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- Ulcer pain typically resolves in a few days when NSAIDs are discontinued and within 7 days upon initiation of antiulcer therapy. Patients with uncomplicated PUD are usually symptom free after treatment with any of the recommended antiulcer regimens.
- Persistent or recurrent symptoms within 14 days after the end of treatment suggests failure of ulcer healing or *H. pylori* eradication or presence of an alternative diagnosis such as gastroesophageal reflux disease.
- Eradication of *H. pylori* should be confirmed after treatment in all patients, particularly those who are at risk for complications.
- Monitor patients taking NSAIDs closely for signs and symptoms of bleeding, obstruction, penetration, and perforation.
- Follow-up endoscopy is justified in patients with frequent symptomatic recurrence, refractory disease, complications, or suspected hypersecretory states.

See Chapter 50, Peptic Ulcer Disease and Related Disorders, authored by Bryan L. Love and Phillip L. Mohorn, for a more detailed discussion of this topic.

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