**College of Pharmacy**

 **Fourth year. Clinical Pharmacy**

 **Gastrointestinal disorders**

 **Peptic Ulcer Disease**

**Introduction**

1-**Peptic ulcer disease** (PUD) refers to **ulcerative disorders of the upper gastrointestinal (GI) tract** that **require acid and pepsin for their formation.**

2-The **three common etiologies** include (1) **Helicobacter pylori** infection, (2) nonsteroidal anti-inflammatory drug (**NSAID**) use, and (3) **stress-**related mucosal damage (SRMD).

**Pathophysiology**

1-Most **duodenal ulcers** occur **in the first part of the duodenum** (duodenal bulb).

2-Pathophysiology is determined by **the balance between aggressive factors** (gastric acid and pepsin) and **protective factors** (Mucus and bicarbonate secretion, mucosal blood flow normally).

3-**Increased acid** secretion may be involved in **duodenal ulcers**, but patients with **gastric ulcers** usually have **normal or reduced acid secretion** (hypochlorhydria).

4-**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**).

5**-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.

6**-Use of corticosteroids alone does not increase risk of ulcer or complications**, but ulcer risk is doubled in corticosteroid users taking NSAIDs concurrently.

7**-Cigarette smoking** has been linked to PUD, impaired ulcer healing, and ulcer recurrence. Risk is proportional to amount smoked per day.

8**-Psychological stress** **has not been shown to cause PUD**, but ulcer patients may be adversely affected by stressful life events.

9**-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**

1**-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.

2**-Nocturnal pain** may awaken patients from sleep, especially between **12 AM and 3 AM**.

3-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.

**4-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.

5-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.**

6-**Bleeding may be** **occult or present as melena or hematemesis**. **Perforation** is associated with sudden, sharp, severe **pain**.

7-**Symptoms of gastric outlet obstruction typically occur over several months** and include **early satiety, bloating, anorexia, nausea, vomiting, and weight loss**.

**Diagnosis**

**1-Routine blood tests are not helpful in establishing a diagnosis of PUD**. Hematocrit, hemoglobin, and stool guaiac tests are used **to detect bleeding**.

2**-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.

3-**Diagnosis of H. pylori infection** can be made using **endoscopic** or **nonendoscopic** (urea breath test [UBT], serologic antibody detection, and fecal antigen) tests.

4-**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**

**1-Goals of Treatment**: Overall goals are to relieve ulcer pain, heal the ulcer, prevent ulcer recurrence, and reduce ulcer-related complications.

2-In H. pylori-positive patients with an ulcer**, goals are to eradicate H. pylori**, **heal the ulcer**, and **cure the disease with a cost-effective drug regimen.**

3-The primary goal for a patient with an NSAID-induced ulcer is **to heal the ulcer as rapidly as possible.**

**Nonpharmacologic Therapy**

1-Lifestyle modifications including **stress reduction** and **smoking cessation** should be implemented. **NSAIDs should be avoided if possible**, and alternative agents such as acetaminophen should be used for pain relief when feasible.

2-**There is no specific recommended diet**, but patients should avoid foods and beverages that cause dyspepsia or exacerbate ulcer symptoms (e.g., spicy foods, caffeine, and alcohol).

3-Emergent surgery may be required for patients with ulcer related complications (e.g., bleeding, perforation, or obstruction).

**Pharmacologic Therapy**

1-**Treatment of H. pylori infection** should be effective, well tolerated, convenient, and cost-effective. Drug regimens to eradicate H. pylori are shown **in Table 1**.

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

3-**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.

4-**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.

5-**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.

6-**Hybrid therapy** combines the strategies of concomitant and sequential therapy; it **involves 7 days of dual therapy** (PPI and amoxicillin) follow**ed by 7 days of quadruple therapy** (PPI, amoxicillin, clarithromycin, metronidazole).

7-**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**).

8-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).

**Table 1:Drug Regimens Used to Eradicate Helicobacter pylori**





**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**, H2>-receptor antagonist; PPI, proton pump inhibitor.

9-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.**

10-Patients **failing clarithromycin triple therapy** can be treated with either bismuth quadruple therapy or the levofloxacin triple regimen for 14 days.

11-**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.**

12-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**. If patients are H. pylori **negative**, **discontinue the NSAID and treat with a PPI, H2RA, or sucralfate.**  PPIs are generally preferred due to more rapid symptom relief and ulcer healing.

13-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**.

14-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.

15-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**.

**Evaluation of therapeutic outcomes**

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

2-**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.

3-**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.

4-Eradication of H. pylori should be confirmed **after treatment** in all patients, particularly those who are at risk for complications.

**Reference**: **Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. 2023.**