Pharmacotherapy 2

Peptic Ulcer Disease (PUD)

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Topic Outline

- General Principles
- Diagnosis
- Treatment
- Complications
- Monitoring/Follow-Up

Peptic Ulcer Disease (PUD)

General Principles

- ✓ PUD consists of mucosal breaks in the stomach and duodenum when corrosive effects of acid and pepsin overwhelm mucosal defense mechanisms.
- ✓ Helicobacter pylori is responsible for at least half of all PUD & the majority of ulcers that are not due to NSAIDs.
- ✓ PUD can develop in 15-25% of chronic NSAID & aspirin users.
- ✓ A gastrin-secreting tumor accounts for < 1% of all PUs.
- ✓ When none of these etiologies are evident, PUD is designated idiopathic.

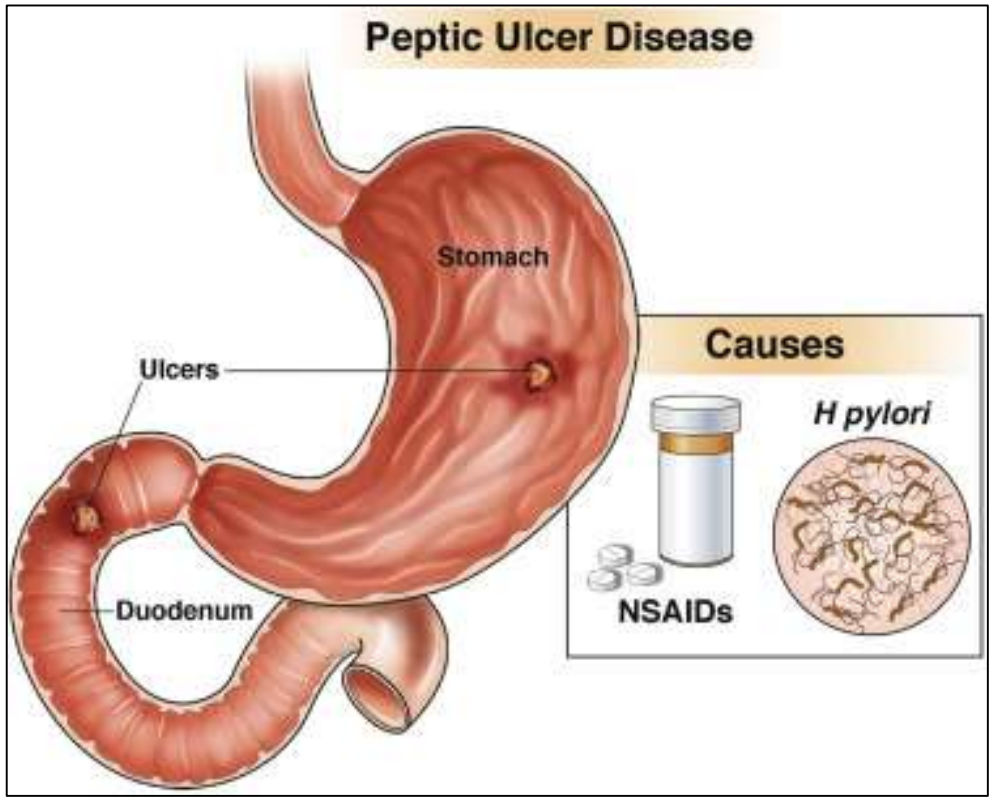


TABLE 50-1 Comparison of Common Forms of Peptic Ulcer

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

GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; SRMD, stress-related mucosal damage.

TABLE 50-2 Potential Causes of Peptic Ulcer

Common causes

Helicobacter pylori infection
NSAIDs
Critical illness (stress-related mucosal damage)

Uncommon causes of chronic peptic ulcer

Idiopathic (non–*H. pylori*, non-NSAID peptic ulcer)
Hypersecretion of gastric acid (eg, Zollinger-Ellison syndrome)
Viral infections (eg, cytomegalovirus)
Vascular insufficiency (eg, crack cocaine associated)
Radiation therapy
Chemotherapy (eg, hepatic artery infusions)
Infiltrating disease (eg, Crohn's disease)

Diseases and medical conditions associated with chronic peptic ulcer

Cirrhosis
Chronic renal failure
Chronic obstructive pulmonary disease
Cardiovascular disease
Organ transplantation

NSAIDs, nonsteroidal anti-inflammatory drugs.

TABLE 50-4 Risk Factors Associated with NSAID-Induced Ulcers and Upper GI Complications[a]

Age >65
Previous peptic ulcer
Previous ulcer-related upper GI complication
High-dose NSAIDs
Multiple NSAID use
Selection of NSAID (eg, COX-1 vs COX-2 inhibition)
NSAID-related dyspepsia
Aspirin (including cardioprotective dosages)
Concomitant use of
NSAID plus low-dose aspirin
Oral bisphosphonates (eg, alendronate)
Corticosteroids
Anticoagulant or coagulopathy
Antiplatelet drugs (eg, clopidogrel)
Selective serotonin reuptake inhibitor
Chronic debilitating disorders (eg, cardiovascular disease, rheumatoid arthritis)
Helicobacter pylori infection
Cigarette smoking
Alcohol consumption

[a]Combinations of risk factors are additive.

Diagnosis

✓ Clinical Presentation:

- Epigastric pain or dyspepsia may be presenting symptoms; however, symptoms are not always predictive of the presence of ulcers.

- In the presence of alarm symptoms (weight loss, early satiety, bleeding, anemia, persistent vomiting, epigastric mass, and lack of response to PPI), EGD should be performed to assess for complications or alternate diagnoses.

✓ Diagnostic Testing:

- Endoscopy is the gold standard for diagnosis of peptic ulcers; tissue sampling for H. pylori or cancer can also be performed.

- Carbon-labeled urea breath testing is the most accurate noninvasive test for diagnosis, with sensitivity and specificity of 95%; it is often used to document successful eradication after therapy of H. pylori infection.

Treatment

✓ Medications

- Regardless of etiology, acid suppression forms the mainstay of therapy of PUD.
- Eradication of H. pylori is recommended in all patients who test positive, esp. in patients with an active ulcer, a documented history of a prior ulcer, or a history of ulcer-related complications.
- Two antibiotics and a PPI (triple therapy) was the mainstay of treatment for H. pylori eradication but strategy has shifted toward two antibiotics, PPI, and bismuth quadruple therapy because of rising incidence of clarithromycin resistance.
- A 10-day course of quadruple therapy was shown to be more effective than 14-day triple therapy.
- Another recommended first line therapy is concomitant therapy (PPI, clarithromycin, with amoxicillin or metronidazole) for 10 to 14 days.

- Levofloxacin-based sequential or triple therapy may be superior to standard triple therapy (clarithromycin, amoxicillin, PPI).

- Other regimens may include LOAD (levofloxacin, omeprazole, nitazoxanide, and doxycycline) for 7– 10 days; ofloxacin, azithromycin, omeprazole, and bismuth for 14 days; and PPI, bismuth, tetracycline, and levofloxacin for 10 days.

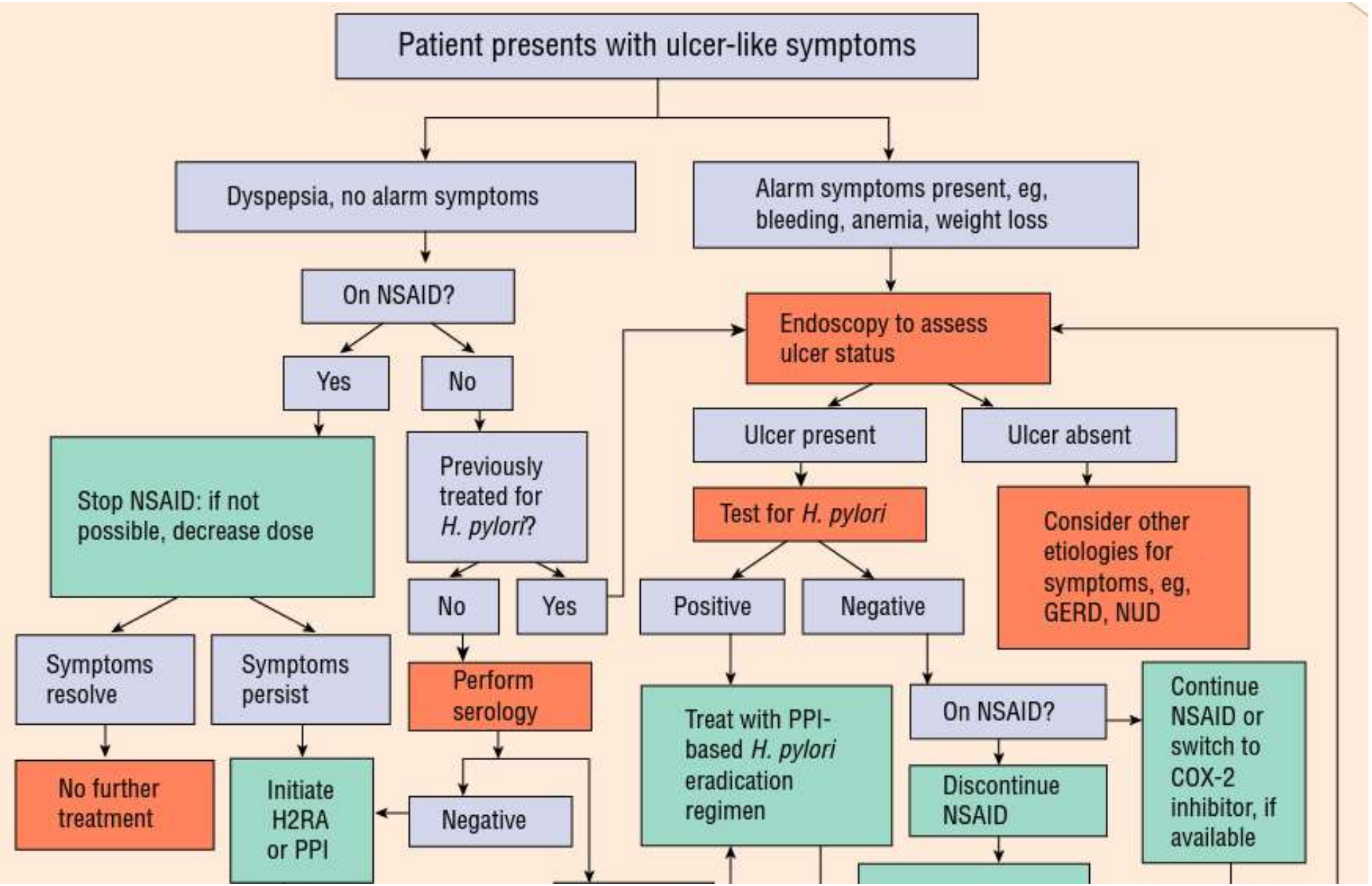
- Patients previously exposed to a macrolide antibiotic should be treated with a regimen that does not include clarithromycin.

- When using salvage regimens after initial treatment failure, choose drugs that have not been used before.

- NSAIDs and aspirin should be avoided when possible; if continued, maintenance PPI therapy is recommended.

- Antacids can be useful as supplemental therapy for pain relief in PUD.

- Nonpharmacologic measures:
  - Cessation of cigarette smoking should be encouraged.
  - Alcohol in high concentrations can damage the gastric mucosal barrier, but no evidence exists to link alcohol with ulcer recurrence.



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

NUD, nonulcer dyspepsia

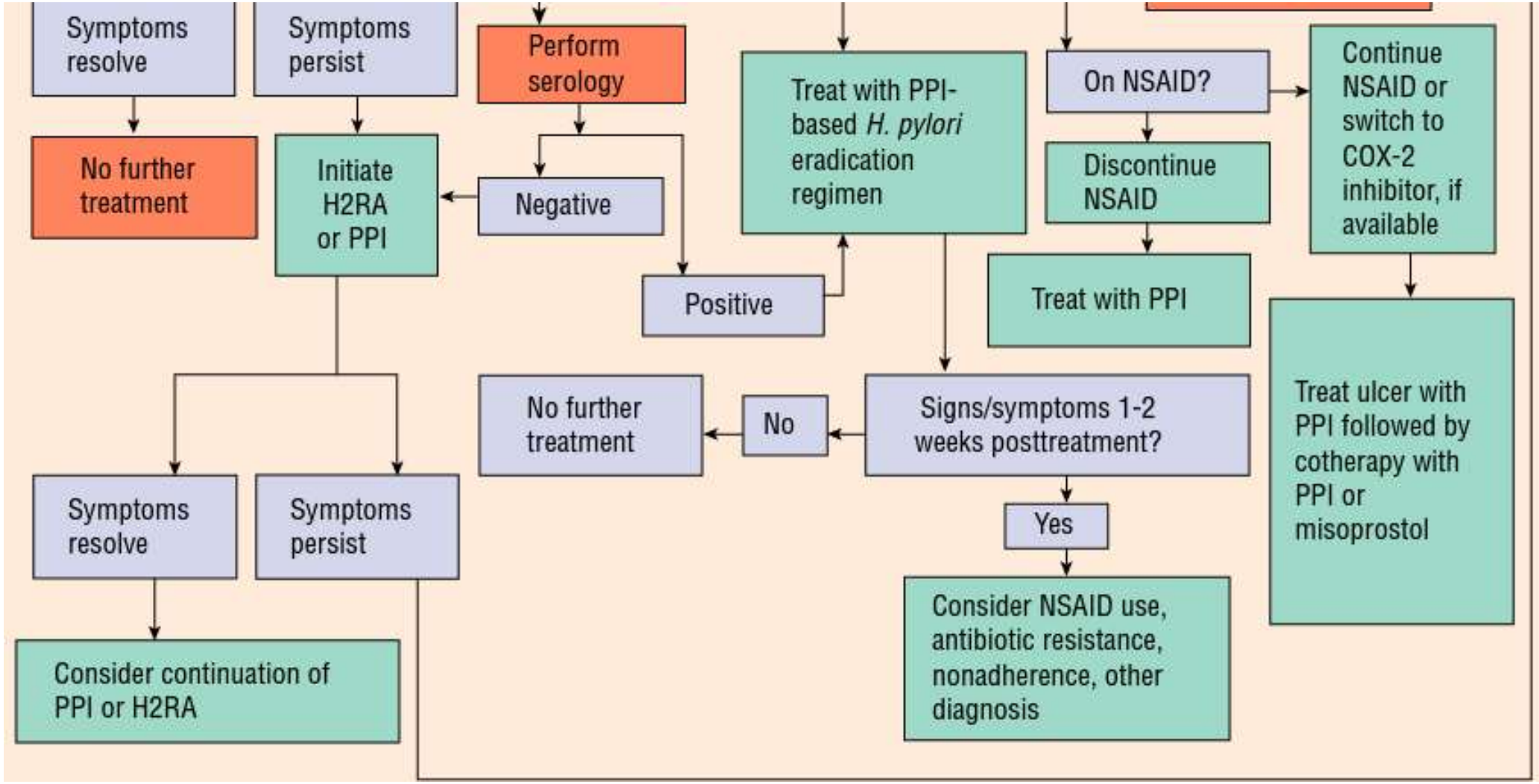

Symptoms resolve
Symptoms persist
Perform serology
Treat with PPI-based *H. pylori* eradication regimen
On NSAID?
Continue NSAID or switch to COX-2 inhibitor, if available
No further treatment
Initiate H2RA or PPI
Negative
Discontinue NSAID
Positive
Treat with PPI
Treat ulcer with PPI followed by cotherapy with PPI or misoprostol
No further treatment
No
Signs/symptoms 1-2 weeks posttreatment?
Symptoms resolve
Symptoms persist
Yes
Consider NSAID use, antibiotic resistance, nonadherence, other diagnosis
Consider continuation of PPI or H2RA

TABLE 50-7 Guidelines for the Eradication of *Helicobacter pylori* Infection

Indications for treatment of *H. pylori* infection

- Established indications for the treatment of *H. pylori* include active PUD, past history of PUD (unless eradication previously documented), MALT lymphoma, or after endoscopic resection of gastric cancer
- Controversial indications for the treatment of *H. pylori* infection include individuals with nonulcer dyspepsia, gastroesophageal reflux disease, unexplained iron deficiency anemia, or idiopathic thrombocytopenic purpura; individuals taking long-term low-dose aspirin or initiating chronic treatment with NSAIDs; and individuals at high risk for gastric cancer

Initial treatment of *H. pylori* infection

- Bismuth quadruple therapy and concomitant (non-bismuth quadruple therapy), both administered for 10-14 days, are recommended first-line treatments.
- In penicillin-allergic patients, bismuth quadruple therapy is the preferred initial treatment. Consider referral for allergy testing in patients who fail initial therapy, since many patients who report penicillin allergy are not truly allergic.
- Alternate initial therapies (conditionally recommended) include: Sequential, hybrid, levofloxacin-triple, levofloxacin sequential, and LOAD therapies (see Table 50-8 for a full description).

Eradication of *H. pylori* after initial treatment failure

- Bismuth quadruple therapy or levofloxacin regimens are preferred if the patient received initial treatment with clarithromycin.
- Clarithromycin- or levofloxacin-containing regimens are preferred if patients received initial treatment with bismuth quadruple therapy.
- Selection of the optimal salvage regimen should be based on local antibiotic resistance profile, if available, and the patient's prior antibiotic history.

TABLE 50-8 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.

TABLE 50-9 Drug Dosing Table

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Other
Proton Pump Inhibitors					
Omeprazole, sodium bicarbonate	Prilosec, Zegerid	40 mg daily	20-40 mg/day	Consider adjustment for hepatic disease	Pregnancy Category C
Lansoprazole	Prevacid, various	30 mg daily	15-30 mg/day	Consider adjustment for hepatic disease	Pregnancy Category B
Rabeprazole	Aciphex	20 mg daily	20-40 mg/day	Use with caution in severe hepatic disease	Pregnancy Category B
Pantoprazole	Pantoprazole, various	40 mg daily	40-80 mg/day	Consider adjustment for severe hepatic disease	Pregnancy Category B
Esomeprazole	Nexium	40 mg daily	20-40 mg/day	Limit dose to 20 mg/day in severe hepatic disease	Pregnancy Category B
Dexlansoprazole	Dexilant	30-60 mg daily	30-60 mg/day	Consider dose limit of 30 mg/day in moderate hepatic impairment, dose not established in severe hepatic disease	Pregnancy Category B
H2-Receptor Antagonists					
Cimetidine	Tagamet, various	300 mg four times daily, 400 mg twice daily, or 800 mg at bedtime	800-1,600 mg/day in divided doses	Adjust dose for renal and severe hepatic impairment	Pregnancy Category B
Famotidine	Pepcid, various	20 mg twice daily, or 40 mg at bedtime	20-40 mg/day	Adjust dose for renal impairment	Pregnancy Category B
Nizatidine	Axid, various	150 mg twice daily, or 300 mg at bedtime	150-300 mg/day	Adjust dose for renal impairment	Pregnancy Category B

Table 50-9 Continued: Drug Dosing Table

Ranitidine	Zantac, various	150 mg twice daily, or 300 mg at bedtime	150-300 mg/day	Adjust dose for renal impairment	Pregnancy Category B
Mucosal Protectants					
Sucralfate	Carafate, various	1 g four times daily, or 2 g twice daily	2-4 g/day		Aluminum may accumulate in renal failure, Pregnancy Category B
Misoprostol	Cytotec	100-200 mcg four times daily	400-800 mcg/day		Pregnancy Category X

TABLE 50-11 Prevention of Peptic Ulcer Disease in Patients Receiving Chronic NSAID Therapy

	Low Gastrointestinal Risk[a]	High Gastrointestinal Risk[b,c]
Low Cardiovascular Risk	Nonselective NSAIDs	Nonselective NSAIDs plus PPI; celecoxib plus PPI[d]
High Cardiovascular Risk[e]	Naproxen; add PPI if patient is taking aspirin	No NSAIDs; naproxen plus PPI; low-dose celecoxib plus aspirin plus PPI may be an alternative option[f]

a No risk factor
b Presence of risk factors (patients 60 years or older, history of peptic ulcers, receiving concomitant antiplatelet agents, anticoagulants, corticosteroids, or selective serotonin reuptake inhibitors).
c In patients with prior history of ulcers, adopt test-and-treat strategy to exclude H. pylori infection.
d Consider when patients have complicated ulcer history or presence of multiple risk factors.
e Use risk calculator (eg, Framingham or ASCVD risk calculators) to estimate cardiovascular risk on the basis of several variables. Patients with a history of cardiovascular events or diabetes are considered high cardiovascular risk.
f NSAIDs with increasing selectivity for COX-2 (ie, celecoxib) have been associated with increased cardiovascular risk, and this risk appears to be increased in patients with established cardiovascular disease. Patients with cardiovascular disease or risk factors, recommendations for pain management (in the order listed) include: acetaminophen, aspirin, tramadol, opioids (short-term), nonacetylated salicylates (eg, diflunisal), NSAIDs with low COX-2 selectivity (eg, naproxen), NSAIDs with some COX-2 selectivity (eg, nabumetone), and COX-2 selective agents (ie, celecoxib).

✓ Surgical Management

- Surgery is still occasionally required for intractable symptoms, GI bleeding, Zollinger– Ellison syndrome, and complicated PUD.

- Surgical options vary depending on the location of the ulcer and the presence of complications.

Complications

✓ GI bleeding

✓ Gastric outlet obstruction can occur with ulcers close to the pyloric channel and can manifest as nausea and vomiting, sometimes several hours after meals.

✓ Perforation occurs infrequently and usually necessitates emergent surgery.

✓ Pancreatitis can result from penetration into the pancreas from ulcers in the posterior wall of the stomach or duodenal bulb.

Monitoring/ Follow-Up

- ✓ 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 following treatment completion suggests failure of ulcer healing or H. pylori eradication or presence of an alternate diagnosis such as GERD.

- ✓ Eradication should be confirmed after treatment in all patients. Repeat EGD should be performed 8– 12 weeks after initial diagnosis of all gastric ulcers to document healing.

- ✓ Repeat endoscopic biopsy should be considered for nonhealing ulcers to exclude the possibility of a malignant ulcer.

- ✓ Duodenal ulcers are almost never malignant; therefore, documentation of healing is unnecessary in the absence of symptoms.

- ✓ The UBT and fecal antigen are the preferred methods to confirm H. pylori eradication when endoscopy is not indicated. Medication adherence should be assessed for patients who fail therapy.