Chapter 51: Peptic Ulcer Disease and Related Disorders

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UPDATE SUMMARY

Update Summary

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The following sections and tables were updated:

- Table 51-7: rifabutin and vonoprazan added to "Initial treatment of H. pylori infection" section
- Table 51-8: High-dose PPI dual therapy and Vonoprazan therapies added
- Table 51-9: Vonoprazan added
- Treatment of Helicobacter pylori–Positive Ulcers: new paragraph added about potassium-competitive acid blockers, and new subsection added about Dual Therapy
- Self-Assessment Questions: questions 1, 2, and 3 revised along with their answers

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 29, Peptic Ulcer Disease.

KEY CONCEPTS

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1. Psychological stress, cigarette smoking, nonsteroidal anti-inflammatory drug (NSAID) use, and certain foods/beverages can exacerbate ulcer symptoms and should be avoided.
2. Eradication of *Helicobacter pylori* (*H. pylori*) is recommended for all patients who test positive, especially in those patients with an active ulcer, a documented history of a prior ulcer, or a history of ulcer-related complications.
3. The selection of an *H. pylori* eradication regimen should be based on several factors, including efficacy, safety, antibiotic resistance, cost, and the likelihood of medication adherence. The recommended initial treatment options with the strongest level of evidence include bismuth quadruple and concomitant therapy, both administered for 10 to 14 days. Empiric clarithromycin-based triple therapy is no longer recommended due to increasing resistance and reduced eradication rates.
4. When first-line therapy fails, salvage treatment for *H. pylori* should contain different antibiotics due to potential resistance. Patients with reported penicillin allergy should be considered for penicillin skin testing after failing first-line therapy since many can safely be treated with amoxicillin containing salvage regimens.
5. PPI co-therapy reduces the risk of NSAID-related gastric and duodenal ulcers and is at least as effective as misoprostol and superior to histamine-2 receptor antagonists (H2RAs).
6. Standard PPI dosages and a nonselective NSAID are as effective as a selective cyclooxygenase-2 (COX-2) inhibitor in reducing the risk of NSAID-induced ulcers and upper gastrointestinal (GI) complications.
7. Patients with peptic ulcer disease (PUD), especially those receiving *H. pylori* eradication or misoprostol co-therapy, require patient education regarding their disease and drug treatment to successfully achieve a positive therapeutic outcome.
8. Treatment for severe peptic ulcer bleeding after appropriate endoscopic treatment includes administration of a PPI either orally or parenterally via intermittent or continuous infusion targeting cumulative daily doses of 80 to 160 mg.
9. Coagulopathy and respiratory failure requiring mechanical ventilation are the most notable risk factors for developing stress-related mucosal bleeding (SRMB). Prophylactic drug therapy should be administered to critically ill patients with either of these risk factors.
10. Selection of a PPI over an IV H2RA for SRMB prophylaxis should be based on individual patient characteristics (eg, nothing by mouth, presence of nasogastric tube, thrombocytopenia, renal failure).

BEYOND THE BOOK

BEYOND THE BOOK

Create a table with two columns, one titled PPI and one titled H2RA. Create rows for Prevention of NSAID-induced ulcer disease and Stress Ulcer Prophylaxis. In each new cell, list advantages and disadvantages of using each medication class for these conditions. The purpose of this exercise is to familiarize students with the relative safety and efficacy for medications commonly used to treat PUD.

PEPTIC ULCER DISEASE

Gastric acid is a critical component of upper gastrointestinal (GI) tract complications including gastritis, erosions, and peptic ulcer.[1–3] Peptic ulcer disease (PUD) differs from gastritis and erosions in that ulcers are larger (greater than or equal to 5 mm) and extend deeper into the muscularis

mucosa. The three common forms of peptic ulcers can be grouped according to their etiology: *Helicobacter pylori*–positive, NSAID-induced, and stress-related mucosal damage (SRMD) (Table 51-1).

TABLE 51-1

Comparison of Common Forms of Peptic Ulcer

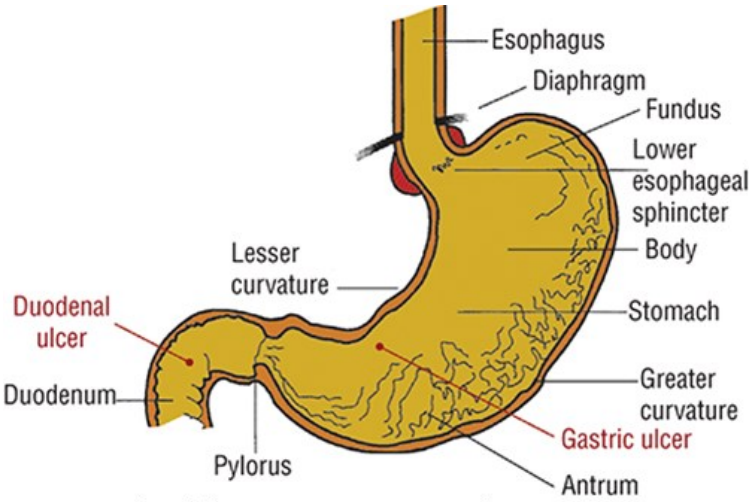
Characteristic	*H. pylori*–Induced	NSAID-Induced	SRMD
Condition	Chronic	Chronic	Acute
Site of damage	Duodenum > stomach	Stomach > duodenum	Stomach > duodenum
Intragastric pH	More dependent	Less dependent	Less dependent
Symptoms	Usually epigastric pain	Often asymptomatic	Asymptomatic
Ulcer depth	Superficial	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.

H. pylori–positive and NSAID-induced ulcers are chronic peptic ulcers that differ in etiology, clinical presentation, and tendency to recur (see Table 51-1). These ulcers develop most often in the stomach and duodenum of ambulatory patients (Fig. 51-1). Occasionally, ulcers develop in the esophagus, jejunum, ileum, or colon. The natural course of chronic PUD is characterized by frequent ulcer recurrence. The cause of ulcer recurrence is often multifactorial, although *H. pylori* infection and NSAID use are commonly associated. In addition, cigarette smoking, alcohol use, gastric acid hypersecretion, and medication nonadherence are frequently related.

FIGURE 51-1

Anatomic structure of the stomach and duodenum and most common locations of gastric and duodenal ulcers.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Conditions such as Zollinger-Ellison syndrome (ZES), radiation, chemotherapy, vascular insufficiency, and other chronic diseases (Table 51-2) are

associated with development and recurrence of peptic ulcers.[1,2] Ulcer development at the gastro-jejunal anastomosis, termed marginal ulcers, occurs in patients with history of Roux-en-Y gastric bypass surgery and shares risk factors with PUD; however, the pathogenesis is not fully understood.[4] Although a strong association exists between chronic pulmonary diseases, chronic kidney disease, and cirrhosis, the pathophysiologic mechanisms of these associations remain unclear.[2] In contrast, SRMD occurs primarily in the stomach of critically ill patients (see Table 51-1).[1]

TABLE 51-2

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)
Roux-en-Y gastric bypass surgery
Diseases and medical conditions associated with chronic peptic ulcer
Cirrhosis
Chronic kidney disease
Chronic obstructive pulmonary disease
Cardiovascular disease
Organ transplantation

NSAIDs, nonsteroidal anti-inflammatory drugs.

EPIDEMIOLOGY

4 The epidemiology of PUD is complicated, and the prevalence is difficult to estimate given the variability in *H. pylori* infection, NSAID use, and cigarette smoking. In addition, endoscopy, radiology, symptoms, or other methods have different sensitivity and specificity to detect ulcers.[1] Gastroduodenal ulcers occur in 0.1% to 0.3% of the general population annually, and the lifetime prevalence of PUD is between 5% and 10%.[2] The prevalence and incidence of PUD in the United States has decreased, reflecting improvements in drug therapy, the dramatic shift to ambulatory management, and changes in the criteria and coding system for mortality and hospitalization data. Mortality, hospitalization, and emergency department and ambulatory care visits have declined, but 30-day readmissions for upper GI hemorrhage have increased.[5] Mortality rates are higher among those 65 years and older and in males compared to females.[5] PUD remains a common GI disease, resulting in impaired quality of life, work loss, and high-cost medical care.

7 The prevalence of *H. pylori* varies by geographic location, resource limitations, ethnicity, and age. In the United States and other industrialized countries, *H. pylori* prevalence has declined with successive birth cohorts and is thought to correlate with improved hygiene and living conditions compared with developing countries.[6,7] In the United States, *H. pylori* prevalence is approximately 30% to 40%, but it is much higher in adults older

than 60 years (50%-60%) than in children younger than 12 years (10%-15%). The rate of *H. pylori* acquisition in children is declining due to improved environmental conditions in Western populations, but maternal colonization remains an important transmission factor. Disparities in *H. pylori* prevalence continue to exist among Black and Hispanic persons with infection rates approximately two to three times that of non-Hispanic White persons.[7,8] Adults with some college education have reduced prevalence of *H. pylori*, probably related to improved access to resources and living conditions.[8] Infection rates do not differ with gender or smoking status. Among Hispanic persons overall *H. pylori* seroprevalence was 38% in US born and 62% among non-US born individuals.[9]

Nonsteroidal Anti-Inflammatory Drugs

Gastroduodenal lesions including erosions, petechiae, and ulcers are visible upon endoscopy in an estimated 30% to 50% of chronic NSAID users. In most cases, the gastric mucosa adapts, and no clinical manifestations are observed. NSAIDs and low-dose aspirin increase the relative risk of PUD by an estimated 2.7 and 1.7 times, respectively. Despite the introduction of gastroprotective medications, NSAIDs represent an important cause of morbidity and mortality. NSAIDs and low-dose aspirin contribute to significant GI events, including ulceration and bleeding, in 122 per 100,000 persons/year, and 5% of deaths result from upper GI complications. Low-dose aspirin represents approximately 10% of all complications and deaths.[10]

ETIOLOGY

H. pylori infection and NSAID use are the most common risk factors for PUD. Less common factors, including ZES with hypersecretion of acid (see Table 51-2), can also be involved.[1] Disruptions in normal mucosal defense and healing mechanisms allow acid and pepsin to reach the gastric epithelium.[1] Benign gastric ulcers, erosions, and gastritis can occur anywhere in the stomach, although the antrum and lesser curvature represent the most common locations (see Fig. 51-1). Most duodenal ulcers occur in the first part of the duodenum (duodenal bulb).

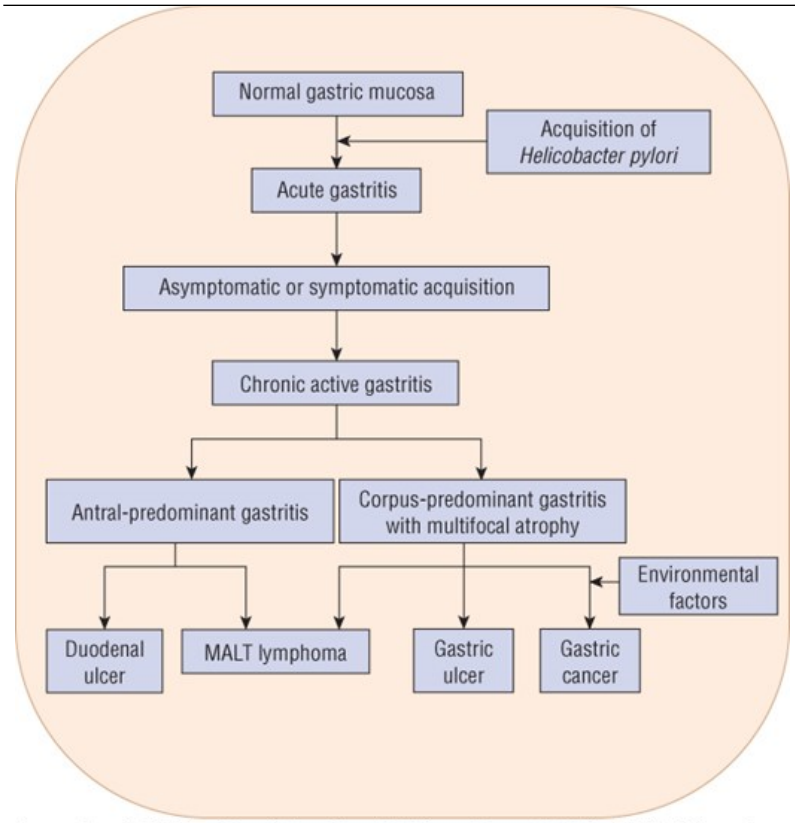
Helicobacter pylori

H. pylori are spiral, microaerophilic, gram-negative bacteria with flagella that have urease, catalase, and oxidase activity. These factors allow the bacterium to survive in the acidic environment of the stomach. Bacterial urease converts urea to ammonia that neutralizes gastric acid, thereby alkalinizing the microenvironment. Catalase activity enables the bacterium to survive reactive oxidation by phagocytes attempting to kill the organism, but the resulting inflammation damages the gastric epithelial lining allowing *H. pylori* to thrive. Bacterial flagella facilitate the initial infection and allows for colonization of the gastric mucosa.[11] *H. pylori* is primarily transmitted via person-to-person routes by either gastro–oral (vomitus) or fecal–oral (diarrhea) contact. Risk factors for acquiring *H. pylori* include close contact within households, low income status, and country of origin.[1,7]

H. pylori infection can cause both acute and chronic gastritis in infected individuals and is associated with multiple GI complications. PUD, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer (Fig. 51-2) have all been linked to *H. pylori* infection.[1,6,7] Most infected individuals remain asymptomatic, but 10% to 20% will develop PUD during their lifetime and about 1% will develop gastric cancer. Environmental factors, host genetics, and *H. pylori* strain virulence factors play an important role in the pathogenesis of PUD and gastric cancer.[2] *H. pylori* infection increases the risk of GI bleeding and peptic ulcers by threefold to sevenfold.[7] No specific link has been established between *H. pylori* and dyspepsia, non-ulcer dyspepsia (NUD), or gastroesophageal reflux disease (GERD).[7] However, some patients with dyspepsia and NUD have symptom improvement from *H. pylori* eradication. Conversely, eradication of *H. pylori* may worsen GERD symptoms in some patients, but eradication should be attempted due to the known gastric cancer risk. *H. pylori* is also associated with iron deficiency anemia, although the benefit of eradication remains unknown.[7]

FIGURE 51-2

The natural history of *Helicobacter pylori* infection in the pathogenesis of gastric ulcer and duodenal ulcer, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Nonsteroidal Anti-Inflammatory Drugs

Prescription and nonprescription NSAIDs (Table 51-3) are widely used in the United States, and have been linked to PUD. There is overwhelming evidence linking chronic NSAID (including low-dose aspirin) use to upper GI tract injury, PUD, gastritis, and superficial erosion.[1,12,13] In susceptible individuals, NSAIDs cause superficial mucosal damage consisting of petechiae (intramucosal hemorrhages) within minutes of ingestion, and progress to erosions with continued use.[14] These lesions typically heal within a few days and rarely cause ulcers or acute upper GI bleeding. NSAID-induced ulcers occur less frequently in the esophagus, small bowel, and colon.[10,14] The mechanisms by which NSAIDs damage the lower GI tract is not clear, but the enteropathy is associated with lower GI bleeding.

TABLE 51-3

Selected NSAIDs and COX-2 Inhibitors

Nonsalicylates[a] Nonselective (traditional) NSAIDs: indomethacin, piroxicam, ibuprofen, naproxen, sulindac, ketoprofen, ketorolac, flurbiprofen, diclofenac Selective COX-2 inhibitors: etodolac, nabumetone, meloxicam, celecoxib, rofecoxib,[b] valdecoxib[b]
Salicylates Acetylated: aspirin Nonacetylated: salsalate, trisalicylate

COX-2, cyclooxygenase-2; NSAIDs, nonsteroidal anti-inflammatory drugs.

[a]Based on COX-1-to-COX-2 selectivity ratio.

[b]Withdrawn from US market.

Table 51-4 lists the risk factors associated with NSAID-induced ulcers and upper GI complications. Combinations of factors confer an additive risk.[1,10,15–18] Advanced age is an independent risk factor, and the incidence of NSAID-induced ulcers increases linearly with the age of the patient.[1] The high incidence of ulcer complications in older individuals may be explained by age-related changes in gastric mucosal defense. The relative risk of NSAID complications is increased for patients with a previous peptic ulcer and may be as high as 14-fold in those with a history of an ulcer-related complication.[1,17] Although the risk of ulcer complications is greatest during the first few months after initiating continuous NSAID therapy, it does not vanish with long-term treatment.[19]

TABLE 51-4

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
  - Low-dose aspirin
  - Oral bisphosphonates (eg, alendronate)
  - Systemic 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

COX-2, cyclooxygenase-2; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs.

[a]Combinations of risk factors are additive.

Data from References 1 and 17–19.

NSAID ulcers and related complications are dependent upon the dose, duration of use, and type of NSAID. Although dose is important, low doses of nonprescription NSAIDs and low cardioprotective dosages of aspirin (81-325 mg/day) increase risk of ulcer formation.[1,2,10,16,19] Factors such as NSAID potency, longer duration of effect, and a greater propensity to inhibit cyclooxygenase-1 (COX-1) versus cyclooxygenase-2 (COX-2) isoenzymes are associated with increased risk (see Table 51-3).[1,10,19] NSAID-related dyspepsia, in itself, does not correlate directly with mucosal injury or clinical events. However, new-onset dyspepsia, changes in severity, or dyspepsia not relieved by antiulcer medications may suggest an ulcer or ulcer complication.[1] Nonacetylated salicylates (eg, salsalate) may be associated with decreased GI toxicity.[14,20,21] Buffered or enteric-coated aspirin confers no added protection from upper GI events.[10] NSAID ulcer and GI complication risk are increased with the use of multiple NSAIDs or the concomitant use of low-dose aspirin, oral bisphosphonates, systemic corticosteroids, anticoagulants, antiplatelet drugs, and selective serotonin reuptake inhibitors.[16,18,21] The risk of an ulcer-related GI complication is 10-fold greater when an NSAID or COX-2 inhibitor (see Table 51-3) is coadministered with low-dose aspirin than when either drug is taken alone.[2] The NSAID may also reduce the antiplatelet effects of aspirin, although NSAIDs vary in their effects on platelet function. Corticosteroids, when used alone, do not potentiate the risk of ulcer or complications, but the relative risk is increased twofold in corticosteroid users who are also taking concurrent NSAIDs.[1] The relative risk of GI bleeding increases up to 20-fold when NSAIDs are taken concomitantly with anticoagulants (eg, warfarin) and up to sixfold with the concurrent use of serotonin reuptake inhibitors.[21,22] Coadministration of aspirin with clopidogrel or an anticoagulant increases the risk of GI bleeding compared with either agent taken alone.[13,23]

H. pylori and NSAIDs act independently to increase ulcer risk and ulcer-related bleeding and appear to have additive effects.[7] Thus, the incidence of peptic ulcer is higher in *H. pylori*–positive individuals who use NSAIDs. Whether *H. pylori* infection is actually a risk factor for NSAID ulcers remains

controversial.[7] However, eradication is reported to reduce the incidence of peptic ulcer if undertaken prior to starting the NSAID, but does not reduce the risk for patients who were previously taking an NSAID.[7]

Cigarette Smoking

Cigarette smoking has been linked to PUD, but it is uncertain whether smoking causes peptic ulcers. The prevalence of ulcer disease is higher in current and former smokers (11.4% and 11.5%) compared to those who never smoked (6%). The risk of peptic ulcers is greatest in smokers with a large daily use, but modest when fewer than 10 cigarettes are smoked per day.[24] Cigarette smoking impairs ulcer healing, promotes ulcer recurrence, and increases ulcer risk. However, the underlying mechanisms by which cigarette smoking exerts these adverse effects remain unclear. Possible mechanisms include mucosal ischemia, inhibition of pancreatic bicarbonate secretion, and increases in gastric acid and mucous secretion, but these effects are inconsistent.[25]

Psychological Stress

Psychosocial stress may influence the pathogenesis of PUD, but it can be difficult to determine whether the stressful exposure was present before development of ulceration.[26] Clinical observation suggests that ulcer patients are adversely affected by stressful life events. However, results from controlled trials are conflicting and have failed to document a cause-and-effect relationship. Emotional stress may induce behavioral risks such as smoking and the use of NSAIDs or alter the inflammatory response or resistance to *H. pylori* infection.[26,27] The role of stress and how it affects PUD is complex and probably multifactorial.

Dietary Factors

The effects of diet and nutrition on the pathophysiology PUD is uncertain. Carbonated beverages, coffee, tea, beer, milk, and spices often cause dyspepsia, but they do not appear to increase the risk of PUD.[1] Dietary interventions such as bland or restricted diets do not alter the frequency of ulcer recurrence. Although caffeine is a gastric acid stimulant, constituents in decaffeinated coffee or tea, caffeine-free carbonated beverages, beer, and wine may also increase gastric acid secretion. In high concentrations, alcohol ingestion is associated with acute gastric mucosal damage and upper GI bleeding; however, there is insufficient evidence to confirm that alcohol causes ulcers.[1]

PATHOPHYSIOLOGY

The pathophysiology of gastric and duodenal ulcers is determined by the imbalance between aggressive (gastric acid and pepsin) and protective (mucosal defense and repair) factors.[1] Gastric acid is secreted by the parietal cells, which contain receptors for histamine, gastrin, and acetylcholine.[1] Acid (as well as *H. pylori* infection and NSAID use) is an independent factor that contributes to the disruption of mucosal integrity.[1] Acid secretion is increased in patients with duodenal ulcers and may be a consequence of *H. pylori* infection.[28] In contrast, patients with gastric ulcers usually have normal or reduced rates of acid secretion (hypochlorhydria).

The amount of acid secreted under basal or fasting conditions is referred to as basal acid output (BAO); after maximal stimulation, maximal acid output (MAO). Basal and maximal acid secretion varies with time of day and the individual's psychological state, age, gender, and health status. The BAO follows a circadian rhythm, with the highest acid secretion occurring at night and the lowest in the morning.[1] An increase in the BAO:MAO ratio suggests a basal hypersecretory state such as ZES.

Pepsin is an important enzyme cofactor in the proteolytic activity involved in ulcer formation. Pepsinogen, the inactive precursor of pepsin, is secreted by the chief cells in the gastric fundus (see Fig. 51-1). Pepsin activity is determined by pH as it is activated by acid pH (optimal pH of 1.8-3.5), reversibly inactivated at pH 4, and irreversibly destroyed at pH 7.[1]

Mucus and bicarbonate secretion, intrinsic epithelial cell defense, and mucosal blood flow protect the gastroduodenal mucosa from noxious endogenous and exogenous substances.[1] The viscous nature and near-neutral pH of the mucus–bicarbonate barrier protect the stomach from the acidic contents in the gastric lumen. Mucosal repair after injury is related to epithelial cell restitution, growth, and regeneration. Endogenous prostaglandins' (PGs) production facilitate mucosal integrity and repair. The term *cytoprotection* is often used to describe this process, but *mucosal*

defense and *mucosal protection* are more accurate terms, as PGs prevent deep mucosal injury and not superficial damage to individual cells.[14] Gastric hyperemia and increased PG synthesis characterize adaptive cytoprotection, the short-term adaptation of mucosal cells to mild topical irritants that enables the stomach to initially withstand the damaging effects of irritants. Alterations in mucosal defense that are induced by *H. pylori* or NSAIDs are the most important cofactors in the formation of peptic ulcers.[14,29]

Helicobacter pylori

In infected people, *H. pylori* resides between the gastric mucus layer and surface epithelial cells, or any location where gastric-type epithelium is found. The bacterium binds to gastric-type epithelium by adherence pedestals, which prevent the organism from being shed during cell turnover and mucus secretion. Colonization of the antrum and corpus (body) of the stomach is associated with gastric ulcer and cancer. Antral organisms colonize gastric tissue that develops in the duodenum secondary to changes in gastric acid or bicarbonate secretion leading to duodenal ulcer (see Fig. 51-2). Although *H. pylori* causes chronic gastric mucosal inflammation in all infected individuals, only a minority actually develop an ulcer or gastric cancer. The difference in the diverse clinical outcomes is related to variations in bacterial pathogenicity and host susceptibility.

Bacterial enzymes (urease, lipases, and proteases), bacterial adherence, and *H. pylori* virulence factors produce gastric mucosal injury. Lipases and proteases degrade gastric mucus, ammonia produced by urease may be toxic to gastric epithelial cells, and bacterial adherence enhances the uptake of toxins into gastric epithelial cells. *H. pylori* induces gastric inflammation by altering the host inflammatory response and damaging epithelial cells directly by cell-mediated immune mechanisms or indirectly by activated neutrophils or macrophages attempting to phagocytize bacteria or bacterial products. However, *H. pylori* strains are genetically diverse and account for differences in adaptation within the human host. Two of the most important are cytotoxin-associated gene protein (CagA) and vacuolating cytotoxin (VacA). About 60% of *H. pylori* strains in the United States possess CagA, but CagA-positive strains increase the risk for severe PUD, gastritis, and gastric cancer compared with CagA-negative strains. The VacA gene codes for the VacA cytotoxin, a vacuolating toxin. Although VacA is present in most *H. pylori* strains, strains vary in cytotoxicity and increased risk for peptic ulcer and gastric cancer. Host polymorphisms are important markers of disease susceptibility and may identify high-risk patients.[29,30]

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs, including aspirin (see Table 51-3), cause gastric mucosal damage by local and systemic mechanisms, but systemic inhibition of endogenous mucosal PG synthesis is believed to be the primary mechanism.[19] The onset of injury is initiated by the acidic properties of many of the NSAIDs, while systemic inhibition of the protective PGs limits the ability of the mucosa to defend against injury and thus plays the predominant role in the development of gastric ulcer.[19] Acidic NSAIDs (eg, aspirin) have topical irritant properties and they decrease the hydrophobicity of the mucous gel layer in the gastric mucosa. Most non-aspirin NSAIDs have topical irritant effects, but aspirin is the most damaging. Although NSAID prodrugs, enteric-coated aspirin tablets, salicylate derivatives, and parenteral or rectal preparations are associated with less acute gastric mucosal injury, they can cause ulcers and related GI complications because of systemic inhibition of endogenous PGs.

COX is the rate-limiting enzyme in the conversion of arachidonic acid to PGs and is inhibited by NSAIDs (Fig. 51-3). Two similar COX isoforms have been identified: COX-1 is found in most body tissue, including the stomach, kidney, intestine, and platelets; COX-2 is undetectable in most tissues under normal physiologic conditions, but its expression can be induced during acute inflammation and arthritis (Fig. 51-4). COX-1 produces protective PGs that regulate physiologic processes such as GI mucosal integrity, platelet homeostasis, and renal function. COX-2 is induced (unregulated) by inflammatory stimuli such as cytokines and produces PGs involved with inflammation, fever, and pain. It is also constitutionally expressed in organs such as the brain, kidney, and reproductive tract. Adverse effects (eg, GI or renal toxicity) of NSAIDs are primarily associated with the inhibition of COX-1, whereas anti-inflammatory actions result primarily from NSAID inhibition of COX-2.[14]

FIGURE 51-3

Metabolism of arachidonic acid after its release from membrane phospholipids. Broken arrow indicates inhibitory effects. (ASA, aspirin; HPETE, hydroperoxyeicosatetraenoic acid; NSAIDs, nonsteroidal anti-inflammatory drugs; PG, prostaglandin.)

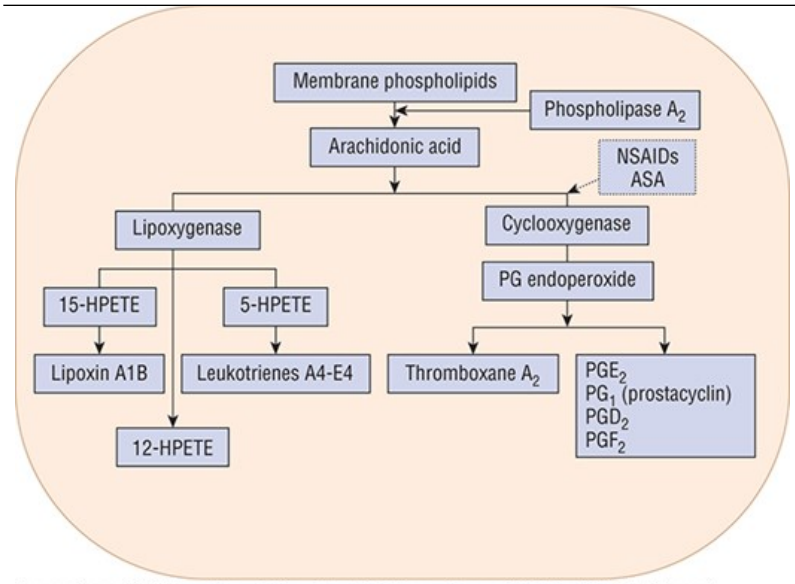
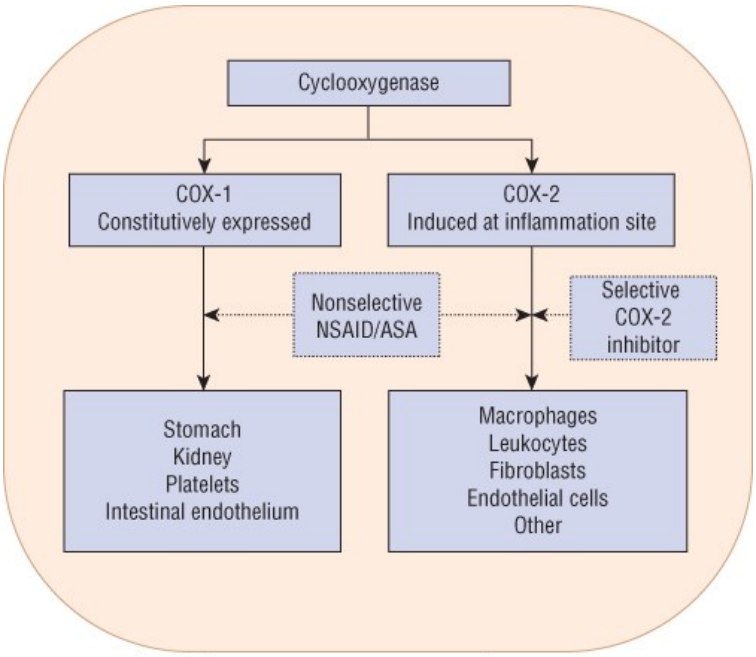


FIGURE 51-4

Tissue distribution and actions of cyclooxygenase (COX) isoenzymes. Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin (ASA) inhibit COX-1 and COX-2 to varying degrees; COX-2 inhibitors inhibit only COX-2. Broken arrow indicates inhibitory effects.



The COX-1-to-COX-2 inhibitory ratio determines the relative GI toxicity of a specific NSAID. Nonselective NSAIDs, including aspirin (see Table 51-3), inhibit both COX-1 and COX-2 to varying degrees and are associated with an increased propensity to cause gastric ulcers. In contrast, the selective COX-2 inhibitors preferentially inhibit COX-2 in vitro resulting in a reduced risk of ulcers and related GI complications (see Table 51-3). The selectivity for the COX-2 isoenzyme varies among NSAIDs. Celecoxib, meloxicam, etodolac, and nabumetone are considered only partially selective and have more risk of GI complications compared to rofecoxib and valdecoxib.[31] The addition of aspirin to a selective COX-2 inhibitor reduces its ulcer-sparing benefit and

increases ulcer risk.[10] Aspirin and non-aspirin NSAIDs irreversibly inhibit platelet COX-1, resulting in decreased platelet aggregation and prolonged bleeding times, thereby increasing the potential for upper and lower GI bleeding. Coadministration of NSAIDs may reduce the antiplatelet effects of aspirin. Clopidogrel, prasugrel, ticagrelor, and related medications that affect platelet aggregation do not cause ulcers, per se, but may impair healing of gastric erosions leading to ulceration and bleeding.[13,32,33]

Complications

The most serious, life-threatening complications of chronic PUD are upper GI bleeding, perforation, and obstruction.[1] Bleeding peptic ulcers, caused by the erosion of an ulcer into an artery, are the most common cause of non-variceal upper GI bleeding, occurring in 26% to 59% of patients.[34] It may be occult (hidden) and insidious or may present as melena (black-colored that combine clarithromycin with amoxicillin stools) or hematemesis (vomiting of blood). NSAID use (especially in older adults) is the most important risk factor for upper GI bleeding. Mortality is highest in patients with uncontrolled bleeding or who have a rebleeding event after the initial bleeding has stopped (see section "Upper Gastrointestinal Bleeding" below).[34]

Gastric perforation into the peritoneal cavity is the second most common ulcer-related complication, occurring in 4 to 14 cases per 100,000 patients.[35] Depending on location, the ulcer may penetrate into an adjacent structure (pancreas, biliary tract, or liver) rather than opening freely into a cavity. Although the incidence of perforated peptic ulcers has decreased with the availability of PPIs, the mortality and morbidity remain high. Mortality from perforated ulcers is five times higher compared with bleeding peptic ulcer and 30-day mortality is approximately 24%. Older patients and those with comorbidities have a worse prognosis.[35] The pain of perforation is usually sudden, sharp, and severe, beginning first in the epigastrium, but quickly spreading over the entire abdomen. Most patients experience ulcer symptoms prior to perforation; however, older patients who experience perforation in association with NSAID use may be asymptomatic. The duodenum can be narrowed due to chronic inflammation and scaring from ulcers, resulting in gastric outlet obstruction. Although gastric outlet obstruction is rare, patients often present with severe vomiting and hematemesis.[36] Perforation, penetration, and gastric outlet obstruction occur most often with long-standing PUD.

CLINICAL PRESENTATION

Clinical Presentation: Peptic Ulcer Disease (PUD)

There is significant variability in the clinical presentation of PUD depending on the severity of epigastric pain and the presence of complications (Table 51-5). Pain related to duodenal ulcer often occurs 1 to 3 hours after meals and is usually relieved by food, but this is variable. Food may precipitate or accentuate gastric ulcer pain. Antacids usually provide immediate pain relief in most ulcer patients. Pain usually diminishes or disappears during treatment; however, recurrence of epigastric pain after healing often suggests an unhealed or recurrent ulcer.

TABLE 51-5

Clinical Presentation of PUD

General • Mild epigastric pain or acute life-threatening upper GI complications
Symptoms • Abdominal pain that is often epigastric and described as burning but may present as vague discomfort, abdominal fullness, or cramping • A typical nocturnal pain that awakens the patient from sleep (especially between 12 and 3 AM) • The severity of ulcer pain varies between patients and may be seasonal, occurring more frequently in the spring or fall; episodes of discomfort usually occur in clusters, lasting up to a few weeks and followed by a pain-free period or remission lasting from weeks to years • Changes in the character of the pain may suggest the presence of complications • Heartburn, belching, and bloating often accompany the pain • Nausea, vomiting, and anorexia are more common for patients with gastric ulcer than with duodenal ulcer but may also be signs of an ulcer-related complication
Signs • Weight loss associated with nausea, vomiting, and anorexia • Complications including ulcer bleeding, perforation, penetration, or obstruction
Laboratory tests • Gastric acid secretory studies • The hematocrit and hemoglobin are low with bleeding, and stool hemoccult tests are positive • Tests for *Helicobacter pylori* (see Table 51-6)
Diagnostic tests • Fiber-optic upper endoscopy (esophagogastroduodenoscopy) detects more than 90% of peptic ulcers and permits direct inspection, biopsy, visualization of superficial erosions, and sites of active bleeding • Upper GI radiography with barium has been replaced with upper endoscopy as the diagnostic procedure of choice for suspected peptic ulcer

GI, gastrointestinal; PUD, peptic ulcer disease.

The presence or absence of epigastric pain does not define an ulcer and ulcer healing does not necessarily render the patient asymptomatic. Symptoms may remain because of sensitization of afferent nerves in response to mucosal injury. Conversely, the absence of pain does not preclude an ulcer diagnosis, especially in older patients who may present with a “silent” ulcer complication possibly related to differences in the way they perceive pain or the analgesic effect of NSAIDs.

Dyspepsia alone is of little clinical value when assessing subsets of patients who are most likely to have an ulcer. Patients taking NSAIDs often report dyspepsia, but these symptoms do not always correlate with an ulcer. Functional dyspepsia (FD), or nonulcer dyspepsia (NUD), refers to the lack of an ulcer upon endoscopy in a patient with ulcer-like symptoms.[37] *H. pylori* gastritis or duodenitis may cause ulcer-like symptoms in the absence of peptic ulceration. There is no one sign or symptom that differentiates between *H. pylori*–positive and NSAID-induced ulcer.

Diagnosis

Symptoms of PUD are nonspecific and are of limited predictive value for diagnosis. The diagnosis of PUD depends on visualizing the ulcer crater (see Table 51-5).[1,18] Upper endoscopy has replaced radiography as the diagnostic procedure of choice because it provides a more accurate diagnosis and

permits direct visualization of the ulcer and implementation of therapeutic maneuvers to control bleeding such as injection of epinephrine or deployment of hemostatic clips.

Tests for *Helicobacter pylori*

The diagnosis of *H. pylori* infection can be made using endoscopic or nonendoscopic tests (Table 51-6). All patients with active PUD, past history of PUD without documentation of prior cure, low-grade gastric MALT lymphoma, or history of endoscopic resection for early gastric cancer should be tested for *H. pylori*.[7] Testing that requires upper endoscopy is invasive, more expensive, and usually requires a mucosal biopsy for histology, culture, or detection of urease activity. The updated Sydney system recommends taking five tissue samples from different sites within the stomach, as patchy distribution of *H. pylori* infection can lead to false-negative results.[38] Because antibiotics, including bismuth salts, and proton pump inhibitors (PPIs) may decrease the sensitivity of rapid urease test, they should be withheld prior to endoscopic testing for 4 weeks and 2 weeks, respectively.[11,39,40] If the patient has been taking these medications, then a gastric biopsy for histology is preferred.[40]

TABLE 51-6

Tests for Detection of *Helicobacter pylori*

Test	Description	Comments
Endoscopic tests		
Histology	Microbiologic examination using various stains	Gold standard; greater than 95% sensitive and specific; permits classification of gastritis; results are not immediate; not recommended for initial diagnosis; tests for active *H. pylori* infection
Culture	Culture of biopsy	Enables sensitivity testing to determine appropriate treatment or antibiotic resistance; 100% specific; results are not immediate; not recommended for initial diagnosis; used after failure of second-line treatment; tests for active *H. pylori* infection
Biopsy (rapid) urease	*H. pylori* urease generates ammonia, which causes a color change	Test of choice at endoscopy; greater than 90% sensitive and specific; easily performed; rapid results (usually within 24 hours); tests for active *H. pylori* infection
Polymerase chain reaction	*H. pylori* DNA detected in gastric tissue	Test is highly specific and sensitive; high rate of false-positives and false-negatives; positive DNA does not directly equate to presence of the organism; considered a research technique
Nonendoscopic tests		
Antibody detection (laboratory-based)	Detects antibodies to *H. pylori* in serum using laboratory-based ELISA tests and latex agglutination techniques	Quantitative; less sensitive and specific than endoscopic tests; more accurate than in office; unable to determine if antibody is related to active or cured infection; antibody titers vary markedly among individuals and take 6 months to 1 year to return to the uninfected range; not affected by PPIs or bismuth; antibiotics given for unrelated indications may cure the infection, but antibody test will remain positive
Antibody detection (can be performed in office or near patient)	Detects IgG antibodies to *H. pylori* in whole blood or finger stick	Qualitative; quick (within 15 minutes); unable to determine if antibody is related to active or cured infection; most patients remain seropositive for at least 6 months to 1 year after *H. pylori* eradication; not affected by PPIs, bismuth, or antibiotics
Urea breath test	*H. pylori* urease breaks down ingested labeled C-urea, patient exhales labeled CO_2	Tests for active *H. pylori* infection; 95% sensitive and specific; results take about 2 days; antibiotics, bismuth, PPIs, and H2RAs may cause false-negative results; withhold PPIs or H2RAs (1-2 weeks) and bismuth or antibiotics (4 weeks) prior to testing; recommended test to confirm posttreatment eradication of *H. pylori*
Fecal antigen	Identifies *H. pylori* antigen in stool by enzyme immunoassay using polyclonal anti–*H. pylori* antibody	Tests for active *H. pylori* infection; sensitivity and specificity comparable to urea breath test when used for initial diagnosis; antibiotics, bismuth, and PPIs may cause false-negative results, but to a lesser extent than with the urea breath test; may be used posttreatment to confirm eradication, but patients may have a reluctance to obtain stool samples

ELISA, enzyme-linked immunosorbent assay; H2RA, H_2-receptor antagonist; PPIs, proton pump inhibitors.

Data from References 11,41, and 42.

Nonendoscopic tests (urea breath test [UBT], serologic antibody detection tests, and the fecal antigen test) may identify active infection or detect

antibodies (see Table 51-6) and are less invasive, more convenient, and less expensive than the endoscopic tests.[40] However, antibody tests do not differentiate between active infection and previously eradicated *H. pylori*.

The UBT is the most accurate noninvasive test and is based on *H. pylori* urease activity.[38] The ^{13}Carbon (nonradioactive isotope) and ^{14}Carbon (radioactive isotope) tests require that the patient ingest radiolabeled urea, which is then hydrolyzed by *H. pylori* (if present in the stomach) to ammonia and radiolabeled bicarbonate. The radiolabeled bicarbonate is absorbed in the blood and excreted in the breath. In addition to being noninvasive, another advantage of UBT over biopsy is that it overcomes the possible sampling error associated with endoscopic biopsy secondary to irregular distribution of *H. pylori*.[38] The fecal antigen test is less expensive and easier to perform than the UBT, and may be useful in children.

Serologic tests are a cost-effective alternative for the initial diagnosis of *H. pylori* infection in the untreated patient. Antibodies to *H. pylori* usually develop about 3 weeks after infection and remain present after successful eradication. Therefore, serology should not be used to confirm *H. pylori* eradication. Office-based tests are less expensive, widely available, and provide rapid results, but the results are less accurate and more variable than the laboratory-based tests.

Testing for *H. pylori* is only recommended if eradication therapy is planned. Serologic antibody testing is a reasonable choice if endoscopy is not planned. The diagnostic accuracy of *H. pylori* tests for patients with an active bleeding ulcer has been questioned because of the potential for false-negative results. However, endoscopic biopsy-based tests such as the rapid urease test have a high degree of specificity in these patients (see section "Peptic Ulcer–Related Bleeding").[7]

Confirmation of eradication is indicated posttreatment whenever *H. pylori* is identified and treated.[7] Endoscopic biopsy-based tests, UBT and fecal antigen are the recommended tests to confirm *H. pylori* eradication. Testing for eradication should be delayed at least 4 weeks after the completion of antibiotics and after PPI has been discontinued for 2 weeks to avoid confusing bacterial suppression with eradication.[7]

Clinical Course and Prognosis

Untreated PUD is characterized by periods of exacerbations and remissions.[1] Ulcer pain is usually recognizable and episodic, but symptoms are varied, especially in older adults and for patients taking NSAIDs. Antiulcer medications, including the histamine-2 receptor antagonists (H2RAs), PPIs, and sucralfate, relieve symptoms, accelerate ulcer healing, and reduce the risk of ulcer recurrence, but they do not cure the disease. Both duodenal and gastric ulcers recur unless the underlying cause (*H. pylori* or NSAID) is addressed. Successful *H. pylori* eradication markedly decreases ulcer recurrence and complications. Prophylactic co-therapy or a COX-2 inhibitor decreases the risk of upper GI events for patients who are taking NSAIDs. GI bleeding, perforation, and obstruction remain troublesome complications of chronic PUD. Mortality for patients with gastric ulcer is slightly higher than in duodenal ulcer and the general population. The development of gastric cancer in *H. pylori*–infected individuals is a slow process that occurs over 20 to 40 years and is associated with a lifetime risk of less than 1%.[20]

TREATMENT

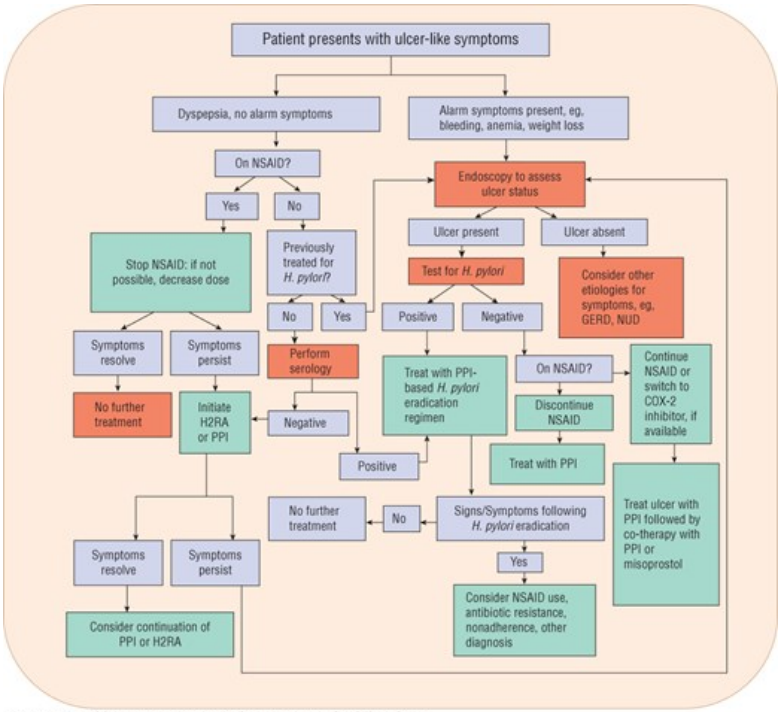
General Approach to Treatment

The treatment of PUD varies depending on the etiology of the ulcer (*H. pylori* or NSAID), whether the ulcer is initial or recurrent, and whether complications have occurred (Fig. 51-5). Treatment is aimed at relieving ulcer pain, healing the ulcer, preventing ulcer recurrence, and reducing ulcer-related complications. Antimicrobials in combination with antisecretory drugs (PPIs or H2RAs) eradicate *H. pylori* infection allowing for ulcer healing and relief of ulcer symptoms. PPIs accelerate ulcer healing and provide more effective relief of symptoms compared to H2RAs or sucralfate, and are preferred for healing *H. pylori*–negative NSAID-induced ulcers. In patients taking NSAIDs for pain, alternative agents such as acetaminophen or nonacetylated salicylate (eg, salsalate) should be used for relief of pain when possible. Patients requiring continuation of NSAID therapy at high risk of developing peptic ulcers should be switched to a selective COX-2 inhibitor NSAID or receive prophylactic co-therapy to reduce ulcer risk and related complications.

FIGURE 51-5

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; H2RA, H_2-receptor antagonist; NSAID, nonsteroidal anti-inflammatory drug; NUD, nonulcer dyspepsia; PPI, proton pump inhibitor.)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Dietary modifications can be considered for patients unable to tolerate certain foods and beverages. Lifestyle modifications such as reducing stress and smoking cessation are encouraged. Surgery is rarely necessary and is used only for patients with ulcer-related complications.[1,18]

Desired Outcome

The goal for patients with PUD, regardless of the cause, is to relieve ulcer symptoms, heal the ulcer, and prevent recurrence. In patients with NSAID-induced ulcer, withdrawal of the offending agent and careful consideration of the need for continued NSAID therapy can reduce the risk of ulcer recurrence. In *H. pylori*–positive patients with an active ulcer, a previously documented ulcer, or a history of an ulcer-related complication, the goal is to eradicate *H. pylori*, heal the ulcer, and cure the disease. Successful eradication heals ulcers and reduces the risk of recurrence for most patients.

Nonpharmacologic Therapy

1 Lifestyle modifications, including stress reduction and smoking cessation, should be implemented in patients with PUD. There is no specific recommended diet for patients with current or history of PUD; however, patients should avoid foods and beverages (eg, spicy foods, caffeine, and alcohol) that cause dyspepsia or that exacerbate ulcer symptoms. Emergent surgery for patients with ulcer-related complications, including bleeding, perforation, or obstruction, is necessary in 5% to 10% of hospitalized patients.[1]

Pharmacologic Therapy

Recommendations

2 Table 51-7 presents guidelines for the eradication of infection in *H. pylori*–positive individuals. Table 51-8 lists regimens used to eradicate *H. pylori* infection.

TABLE 51-7

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 functional 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. Several new regimens have been FDA approved since the publication of ACG guidelines including rifabutin-based and vonoprazan-based regimens. (see Table 51-8 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

MALT, mucosa-associated lymphoid tissue; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

Data from References 7,11, and 42.

TABLE 51-8

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	Amoxicillin 1 g twice daily	
Levofloxacin sequential	10 days	PPI twice daily on days 1-10	Amoxicillin 1 g twice daily on days 1-5	Levofloxacin 500 mg once daily on days 6-10	Metronidazole 500 mg twice daily on days 6-10
Levofloxacin, omeprazole, nitazoxanide, doxycycline (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
Rifabutin-based triple therapy	14 days	Omeprazole 40 mg every 8 hours	Amoxicillin 1 g every 8 hours	Ribabutin 50 mg every 8 hours	
High-dose PPI dual therapy	14 days	PPI three or four times daily	Amoxicillin 1 g every 8 hours		
Vonoprazan dual therapy	14 days	Vonoprazan 20 mg twice daily	Amoxicillin 1 g every 8 hours		
Vonoprazan triple therapy	14 days	Vonoprazan 20 mg twice daily	Amoxicillin 1 g twice daily	Clarithromycin 500 mg twice daily	

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

[a]Although treatment is minimally effective if used for 7 days, 10 to 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.

Data from References 3,7,11,42, and 43.

3 The most cost-effective drug regimen should be used whenever feasible. Several first-line therapies are recommended, but bismuth quadruple therapy for 10 to 14 days has the strongest level of recommendation and should be used preferentially. Another recommended first-line therapy is concomitant therapy (PPI, clarithromycin, amoxicillin, and metronidazole) for 10 to 14 days. Clarithromycin triple therapy is no longer recommended in areas where *H. pylori* resistance exceeds 15%, which includes all of North America.[44] If a second course of treatment is required, the salvage regimen should contain different antibiotics and patients with reported penicillin allergy should be considered for allergy testing.

H. pylori testing should be performed in patients with NSAID-induced ulcers to determine their status. If *H. pylori*–positive, treatment should be initiated with a recommended first-line regimen (see Table 51-8). If *H. pylori*–negative, the NSAID should be discontinued, and the patient treated with a PPI, H2RA, or sucralfate (see Table 51-9). If the NSAID is continued, co-therapy with a PPI or misoprostol should be implemented. Patients at highest risk of recurrent ulcers or ulcer-related complications should be switched to a selective COX-2 inhibitor.

TABLE 51-9

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	Protonix, 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

Potassium-Competitive Acid Blockers (PCABs)					
Vonoprazan	Voquezna	20 mg twice daily	20 mg twice daily	Avoid in patients with severe renal or hepatic impairment	FDA pregnancy category not assigned, no data
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
Ranitidine[a]	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

[a]Ranitidine products are no longer available in the United States.

Data from References 1 and 3.

Maintenance therapy with a PPI or H2RA should be limited to high-risk patients with ulcer complications, patients who fail eradication, and those with *H. pylori*–negative ulcers. Treatment failure is associated with poor medication adherence, antimicrobial resistance, NSAID use, cigarette smoking, acid hypersecretion, or tolerance to the antisecretory effects of an H2RA.

Treatment of *Helicobacter pylori*–Positive Ulcers

This chapter focuses on the eradication of *H. pylori* in adults. A discussion of the treatment of *H. pylori* infection in children is found elsewhere.[45]

Ideally, treatment of *H. pylori*–positive PUD should be highly effective, free of significant side effects, easy to adhere to, and cost-effective. Unfortunately, available treatments are lacking in one or more of these areas, making it difficult to identify an ideal treatment regimen.[1] The most important predictor of *H. pylori* eradication is antimicrobial resistance.[7] Additional factors that may also be important include duration of therapy, medication adherence, and genetic polymorphism.[46] The initial eradication regimen offers the highest likelihood of eradication; therefore, selection of an appropriate first-line regimen is important. No available regimen offers assurance of 100% eradication, and few recommended regimens consistently exceed 90% eradication in studies.[7,47]

Table 51-8 summarizes available first-line drug regimens with antisecretory drug, usually a PPI, in combination with multiple antibiotics and/or bismuth. The use of only one antibiotic is associated with a higher rate of antimicrobial resistance and is therefore not recommended. Clarithromycin, amoxicillin, metronidazole, and tetracycline have in vitro activity against *H. pylori* and have been extensively studied in various combinations and dosing strategies. Bismuth salts have a topical antimicrobial effect. Lesser studied antibiotics with activity include rifabutin, doxycycline, and minocycline.[48,49]

Antisecretory drugs hasten ulcer healing, relieve pain in patients with an active ulcer, and enhance antibiotic activity by increasing intragastric pH and by decreasing intragastric volume, thereby enhancing the topical antibiotic concentration. *PPIs generally produce higher H. pylori eradication rates and are preferred over H2RA.* The PPI is an integral part of the regimen and should be taken 30 to 60 minutes before a meal (see Table 51-8). Prolonged PPI treatment beyond 2 weeks after eradication is usually not necessary for ulcer healing. A single daily dose of a PPI may be less effective than a twice-daily dose. Substitution of one PPI for another is acceptable and does not enhance or diminish *H. pylori* eradication.[50] An H2RA should not be substituted for a PPI unless there are significant tolerability issues. Pretreatment with a PPI does not influence *H. pylori* eradication regardless of the pretreatment duration.[51]

A new class of antisecretory drugs, potassium-competitive acid blockers (PCABs), is now approved for use in combination with amoxicillin and clarithromycin for patients with *H. pylori* infection. Vonoprazan, the first FDA-approved PCAB, inhibits H+/K+ ATPase via a competitive interaction with the K+ site of the enzyme resulting in pronounced and durable acid suppression within 4 hours. Acid suppression tends to be more potent, and *H. pylori* eradication rates are higher when compared to PPI-based triple therapy regimens.[52]

Proton Pump Inhibitor–Based Three-Drug Regimens

PPI-based triple therapy remains an option in regions where clarithromycin resistance is <15% and no prior macrolide exposure is documented, but these regimens are no longer recommended in North America due to high clarithromycin resistance rates.[7,42,47,53] If use is indicated, regimens that combine clarithromycin with amoxicillin or metronidazole are more effective than the amoxicillin–metronidazole regimen. The clarithromycin–amoxicillin regimen is preferred initially (see Table 51-7), but metronidazole can be substituted for amoxicillin for penicillin-allergic patients unless alcohol is consumed.[7,42] In most cases, increasing the antibiotic dosage does not improve eradication rates. Since the first treatment regimen offers the highest probability of *H. pylori* eradication, the recommended duration of triple therapy is 14 days.[7] Shorter treatment durations, including 7- to 10-day courses, should no longer be used because of increased resistance and lower overall eradication rates.[7]

Bismuth-Based Quadruple Therapy

Bismuth-based quadruple therapy (bismuth salicylate, metronidazole, tetracycline, and either a PPI or H2RA) (see Table 51-8) is a recommended first-line option (see Table 51-7), particularly for those patients who are allergic to penicillin.[7] The mean eradication rate for bismuth-based quadruple therapy given for 10 days was 91%, which is considerably higher compared with PPI-based triple therapy.[7] Bismuth quadruple therapy for 10 to 14 days was superior to 7 days of clarithromycin triple therapy (85% vs 73%, RR = 1.17).[54] Eradication rates are comparable for different bismuth preparations used (see Table 51-8).[49] All medications except the PPI should be taken with meals and at bedtime. Limitations of this regimen include four times per day dosing, potential for poor medication adherence, and frequent minor side effects.[49]

Sequential Therapy

Sequential therapy is a form of eradication therapy in which the antibiotics are administered in a sequence rather than together.[7,55] The basis for sequential therapy is to initially treat with antibiotics that rarely promote resistance (eg, amoxicillin) to reduce the bacterial load and any preexisting resistant organisms that are susceptible. The second sequence follows with different antibiotics (eg, clarithromycin and metronidazole) to kill any remaining organisms.[7,55,56] See Table 51-8 for a typical treatment regimen. Although this regimen has achieved eradication rates that are superior to the PPI-based three-drug regimens containing clarithromycin,[56] the regimen requires a change in medication mid-treatment, which may contribute to nonadherence. Though promising, the advantages of sequential therapy have yet to be fully validated in the United States, and is only conditionally recommended within guidelines as a first-line *H. pylori* eradication therapy (see Table 51-7).[7]

Dual Therapy

Dual therapy is a concept for *H. pylori* eradication therapy gaining consideration due to increasing resistance to common regimen components including clarithromycin, metronidazole, and levofloxacin. Dual therapy regimens utilize high doses of PPIs or PCABs and amoxicillin, which has an extremely low rate of primary resistance approaching 1%. Amoxicillin is inactivated by low pH values present in the stomach; thus, high doses of anti-secretory PPIs or PCABs are needed to achieve goal pH values > 6 which favor antibacterial activity of amoxicillin for *H. pylori*. Although not yet recommended in the guidelines, high-dose dual therapy usually results in similar eradication rates compared with bismuth quadruple or PPI-based triple therapy regimens.[57,58]

Non-Bismuth Quadruple "Concomitant" Therapy and Hybrid Therapy

Non-bismuth quadruple therapy, also called "concomitant" therapy, is a regimen with a PPI, amoxicillin, clarithromycin, and metronidazole taken together at standard doses for 10 to 14 days. Hybrid therapy combines the strategies of concomitant and sequential therapy. Patients take dual therapy (PPI and amoxicillin) followed by 7 days of quadruple therapy (PPI, amoxicillin, clarithromycin, and metronidazole). Although clarithromycin resistance may impact efficacy rates, both concomitant and hybrid therapy may be impacted less than clarithromycin triple therapy. Both regimens are first-line alternatives to clarithromycin triple therapy, but there is a lack of evidence in North America with these regimens.[7]

Levofloxacin-Based Therapy

Levofloxacin has been studied as first-line and salvage therapy for *H. pylori* eradication, but data are scarce for levofloxacin-based first-line treatment regimens. Three regimens using levofloxacin have been studied (see Table 51-8). Eradication is similar with 7 days of clarithromycin-based or levofloxacin triple therapy; however, levofloxacin-based triple therapy for 10 to 14 days is superior to clarithromycin triple therapy for 7 days.[54] Levofloxacin sequential therapy has eradication rates higher than pooled clarithromycin-based triple and sequential regimens (87.8% vs 71.1%).[7] A first-line quadruple regimen, termed "LOAD," is not recommended within the guidelines due to cost and lack of data.[7] Concerns about using fluoroquinolones to treat *H. pylori* include development of resistance and adverse effects (eg, tendonitis and hepatotoxicity).

Probiotics

Probiotics (eg, strains of *Lactobacillus* and *Bifidobacterium*) limit *H. pylori* colonization and when taken as a supplement to antibiotic therapy, increase eradication rates compared to placebo and may reduce the adverse effects of antibiotic eradication therapy.[59,60] However, the administration of probiotics alone does not eradicate *H. pylori* infection. The optimal probiotic strains, dose, timing, and duration has yet to be determined.

Eradication of *Helicobacter pylori* After Initial Treatment Failure

H. pylori eradication is often more difficult after initial treatment fails and successful eradication after retreatment is extremely variable.[7] Treatment failures should be referred to a gastroenterologist for further diagnostic evaluation. Second-line (salvage) treatment should (a) use antibiotics that were not used during initial therapy or recently for another infection; (b) be guided by region-specific or individual antibiotic resistance testing, if available; and (c) use an extended duration of treatment up to 10 to 14 days.[7] Ideally, culture and sensitivity or molecular resistance data would be available to guide salvage regimen selection; however, these modalities may be unavailable (eg, the United States) and empiric treatment decisions are necessary. European guidelines recommend obtaining antimicrobial sensitivity information following the second failed attempt to eradicate *H. pylori*. Preferred regimens are provided in Table 51-7. A 10-day therapy containing PPI, bismuth, tetracycline, and levofloxacin achieved a high eradication rate after failure of first-line treatment with standard clarithromycin triple or non-bismuth quadruple therapy.[61] High-dose dual therapy using amoxicillin plus a PPI with both administered three-to-four times daily for 14 days is an acceptable therapy.[7] Other salvage regimens that include rifabutin are also effective, but these are discussed in more detail elsewhere.[62,63] Penicillin skin testing is now recommended for patients after failing one or two eradication attempts since amoxicillin is an important component of therapy with low prevalence of resistance and many patients reporting penicillin allergy are not truly allergic.[7]

Factors That Predict *Helicobacter pylori* Eradication Outcomes

Factors that predict successful *H. pylori* eradication can be divided into host-related and *H. pylori*–related factors. Medication adherence and

pharmacogenomic factors are important host-related considerations, and antibiotic resistance is the most important and consistent predictor of *H. pylori* eradication.[42]

Medication adherence decreases with multiple medications, increased frequency of administration, intolerable adverse effects, and costly drug regimens—all of which can be issues with recommended treatment options. Tolerability varies with different regimens, but common adverse effects include nausea, vomiting, abdominal pain, diarrhea, and taste disturbances (metronidazole and clarithromycin). Adverse effects with metronidazole are dose-related (especially when more than 1 g/day) and include a disulfiram-like reaction with alcohol. Tetracycline may cause photosensitivity and should not be used in children because of possible tooth discoloration. Bismuth salts may cause darkening of the stool and tongue. Antibiotic-associated diarrhea and *Clostridioides difficile*–associated disease can occur. Oral thrush and vaginal candidiasis may also occur.

An increasingly important predictor of eradication is the presence or absence of resistant *H. pylori* strains.[7] The following are worldwide antibiotic resistance rates among *H. pylori* strains (n = 818 isolates): clarithromycin (30.8%), metronidazole (30.5%), amoxicillin (2%), tetracycline (0%), and levofloxacin (14.2%).[44] Although amoxicillin and tetracycline resistance remains low in available surveillance, prevalence of clarithromycin resistance exceeding 20% negatively impacts successful empiric *H. pylori* eradication therapy.[53] Increasing clarithromycin resistance may explain the decrease in efficacy of triple therapy clarithromycin-containing regimens. Prior exposure to macrolide antibiotics adversely affected the success of eradication using clarithromycin-based triple therapy.[64] Bismuth-containing, concomitant, or sequential therapies may be preferred in patients with prior macrolide exposure.[7,64] Therefore, prior antibiotic use should prompt consideration for possible *H. pylori* resistance. The clinical importance of metronidazole resistance remains uncertain, as resistance can be overcome by using higher dosages and by combining metronidazole with other antibiotics. Resistance to tetracycline and amoxicillin is uncommon. Resistance to bismuth has not been reported.[7] Although the role of antibiotic sensitivity testing prior to initiating *H. pylori* treatment has not been formally established, molecular-based tests may offer quick and easy determination of *H. pylori* resistance to macrolides and fluoroquinolones allowing optimal regimen selection.[65]

Treatment of Nonsteroidal Anti-Inflammatory Drug–Induced Ulcers

NSAID therapy should be interrupted upon confirmation of an active ulcer. Once stopped, most uncomplicated NSAID ulcers heal with standard 8-week regimens of an H2RA, PPI, or sucralfate (see Table 51-9).[19] Generally, PPIs are preferred due to more rapid symptom relief and ulcer healing. In patients where the NSAID is continued despite ulceration, treatment with a PPI or misoprostol should be initiated.[66] PPIs are the drugs of choice when the NSAID is continued, as potent acid suppression is required to accelerate ulcer healing. PPI treatment duration should be extended 12 weeks if the NSAID must be continued. In addition, consideration should be given to reducing the NSAID dose, switching to acetaminophen or a nonacetylated salicylate, or using a selective COX-2 inhibitor (see Table 51-3). If the ulcer is *H. pylori*–positive, eradication should be initiated with a regimen that contains a PPI.[19]

Prevention of NSAID-Related Peptic Ulcers

Among patients who use NSAIDs, several therapeutic strategies are available to prevent gastroduodenal ulcers and related upper GI complications. These strategies include co-therapy of an NSAID with a PPI, H2RA, or misoprostol; preferential use of a COX-2 selective NSAID; or combination of a gastroprotective agent with a COX-2 selective NSAID (see Table 51-10). Although vonoprazan and other PCABs demonstrate efficacy in treatment and prevention of NSAID-related PUD, no agent is yet approved for this indication in the US. COX-2 selective NSAID in combination with a PPI offers the greatest protection against upper GI complications. This regimen is followed in effectiveness by COX-2 selective NSAIDs alone, nonselective NSAIDs with a PPI, and medical co-therapy with misoprostol.[10,67] Unfortunately, these strategies may not eliminate ulcers and complications for patients at the "highest risk." Nonselective NSAID and co-therapy with an H2RA is effective at preventing duodenal but not gastric ulcers.[10] Selection of a gastroprotective strategy should consider both the GI benefits and the cardiovascular risks associated with NSAIDs.[19] Strategies aimed at reducing the topical irritant effects of nonselective NSAIDs, for example, prodrugs, slow-release formulations, and enteric-coated products, are not effective at preventing ulcers or GI complications.

TABLE 51-10

Potential Risks and Safety Issues Associated with the PPIs

- Gastric cancers or malignancy
  - Carcinoid tumors
  - Atrophic gastritis
  - Adenocarcinoma
- Bacterial overgrowth
  - Increase in *N*-nitroso compounds from ingested nitrates (carcinogenic)
  - Enteric infections (*Clostridioides difficile, Salmonella typhimurium*, and *Campylobacter jejuni*)
  - Community-acquired pneumonia
- Decreased nutrient absorption:
  - Iron
  - Calcium
  - Cyanocobalamin (vitamin B_{12})
  - Magnesium
- Osteoporosis and related fractures
- Chronic kidney disease and acute kidney injury

PPI, proton pump inhibitor.

Data from References 50,68, and 69.

Misoprostol Co-therapy

Misoprostol, a synthetic analog of prostaglandin E1, has dual gastroprotective effects by improving mucosal blood flow and by stimulating gastric mucous and bicarbonate secretion. It has a short half-life requiring doses to be administered three-to-four times daily. Misoprostol's efficacy increases with higher doses, with prevention trials demonstrating significantly fewer endoscopically confirmed gastric and duodenal ulcers compared with placebo. Misoprostol also decreases the risk of PUD complications including perforation, gastric outlet obstruction, and bleeding.[70] Misoprostol is associated with high-rates of nausea, diarrhea, and abdominal cramping that increase with the dose, limiting its clinical utility.[2,10]

H2-Receptor Antagonist Co-therapy

Standard doses of H2RA are effective at reducing endoscopically confirmed duodenal ulcers compared to placebo, but higher doses (eg, famotidine 80 mg/day) are needed to prevent gastric ulcers.[18] In both cases, H2RAs are less effective when compared with PPI or misoprostol.[70] For this reason, H2RAs are relegated to second-line therapy for prevention of NSAID-induced gastric ulcer and related complications. Patients at higher risk (eg, prior ulcer or older patients) should receive PPIs preferentially over H2RA.[66] Candidates for H2RA as co-therapy include patients who have significant non-modifiable drug interactions or are intolerant of PPIs or misoprostol.

Proton Pump Inhibitor Co-therapy

4 PPI co-therapy reduces NSAID-related gastric and duodenal ulcer risk and is better tolerated than misoprostol.[10,17,19] PPI co-therapy is more effective than misoprostol and H2RA at preventing NSAID-induced gastric ulcer and related complications.[70] All PPIs are considered equally effective when used in standard dosages (see Table 51-9) for ulcer prevention. There is not an incremental benefit with higher doses for ulcer prevention, even among higher risk patients (ie, age >60 years, prior gastric/duodenal ulcer).[71] PPIs reduce the risk of NSAID-related upper GI bleeding, but do not protect against lower GI bleeding.[17]

Cyclooxygenase-2 Inhibitors

COX-2 inhibitors preferentially act on the cyclooxygenase-2 enzyme, exhibiting equivalent anti-inflammatory activity of traditional NSAIDs with a lower risk of gastric or duodenal ulcers. Avoidance of COX-1 isoenzyme inhibition preserves prostaglandin production and its beneficial gastroprotective effects. Celecoxib preferentially inhibits COX-2, but carries the same GI and cardiovascular thrombotic black-box warnings as nonselective NSAIDs. The pooled relative risk for GI bleeding is lower with celecoxib (RR 1.45) compared to nonselective NSAIDs, but it is not without some risk. Gastroprotective benefits of celecoxib are lessened in aspirin users, thus if low-dose aspirin is needed, co-therapy with PPI is necessary and a longer duration of treatment. Thus, the lowest effective celecoxib dose should be used for the shortest duration of time. Dyspepsia and abdominal pain, fluid retention, hypertension, and renal toxicity are associated with the COX-2 inhibitors and nonselective NSAIDs. Patients taking NSAIDs or COX-2 inhibitors should be counseled about signs and symptoms of adverse events, including upper GI bleeding and cardiovascular risks, and what to do should they occur.

COX-2 Inhibitor Versus NSAID Plus PPI

5 For high GI risk, low CV risk, *H. pylori*–negative patients, a COX-2 selective NSAID alone is at least as beneficial as a nonselective NSAID plus PPI co-therapy in reducing NSAID-related ulcer complications.[19] However, neither the COX-2 selective NSAID nor the NSAID plus a PPI guarantees elimination of upper GI events for high GI risk patients. Combining a COX-2 selective NSAID with a PPI can be considered for very high GI risk patients as it offers the best protection against PUD complications. Patients with complicated peptic ulcer history or presence of multiple risk factors are candidates for COX-2 selective NSAID combined with a PPI.[19]

Treatment of Non–*Helicobacter pylori*, Non-Nonsteroidal Anti-Inflammatory Drug Ulcers

Peptic ulcers unrelated to *H. pylori* or use of NSAIDs, including low-dose aspirin, are considered a distinct diagnosis and referred to as idiopathic ulcers. In North America, between 11% and 44% of peptic ulcers were determined to be idiopathic.[72] With more effective acid suppressive therapy, the incidence of idiopathic ulcers is believed to be increasing worldwide. Patients with idiopathic ulcer have a worse prognosis due to high relapse rate, recurrent ulcer bleeding, and increased risk of death. Possible explanations for *non–H. pylori*, non-NSAID ulcers include gastric hypersecretion, gastric outlet obstruction, genetic predisposition, concomitant diseases (see Table 51-2), and heavy tobacco use. Treatment includes conventional ulcer healing therapies (see Table 51-9). Maintenance therapy may be required to prevent PUD complications since there is a high rate of recurrent bleeding within 1 year. No significant difference was seen in recurrent bleeding between famotide 40 mg daily and lansoprazole 30 mg daily for up to 24 monhts.[72]

Long-Term Maintenance of Ulcer Healing

Long-term maintenance of ulcer healing and the prevention of ulcer-related complications may be necessary in some patients. Because *H. pylori* eradication dramatically decreases ulcer recurrence, continuous maintenance therapy is primarily used to treat high-risk patients who failed *H. pylori* eradication, have a history of ulcer-related complications, have frequent recurrences of *H. pylori*–negative ulcers, and are heavy smokers or NSAID users. For most patients, standard maintenance dosages (see Table 51-9) are effective.

Treatment of Refractory Ulcers

Refractory peptic ulcers are ulcers that persist after 8 to 12 weeks of standard antisecretory drug treatment. Persistent *H. pylori* infection and use of NSAIDs are the most common causes of refractory ulcers. Additional contributing factors may include poor patient compliance, cigarette smoking, gastric acid hypersecretion, or tolerance to the antisecretory effects of an H2RA (see section "Antiulcer Agents" below). Patients with refractory ulcers should undergo upper endoscopy to confirm a nonhealing ulcer, exclude malignancy, and reassess *H. pylori* status with two or more diagnostic methods to increase sensitivity.[73] *H. pylori*–positive patients should receive eradication therapy (see "Treatment of Helicobacter pylori–Positive Ulcers" above). Fasting plasma gastrin levels can be checked if Zollinger-Ellison syndrome is suspected. Refractory ulcers, despite a complete standard PPI course, should be retreated with double-dose of PPI. Consideration can be given to using a different PPI.[73]

Antiulcer Agents

Proton Pump Inhibitors

PPIs (see Tables 51-9 and 51-11) dose-dependently inhibit basal and stimulated gastric acid secretion. The duration of acid suppression is a function of binding to the H^+/K^+-adenosine triphosphatase (ATPase) enzyme.[2] When PPI therapy is initiated, the degree of acid suppression increases over the first 3 to 4 days of therapy, as more proton pumps are inhibited. PPIs inhibit only those proton pumps that are actively secreting acid, thus they are most effective when taken 30 to 60 minutes before meals.[3] Symptomatic acid rebound on withdrawal of a PPI has been reported in healthy volunteers after 8 weeks of treatment.[74]

TABLE 51-11

PPI Formulations and Options for Administration

	Omeprazole	Esomeprazole	Lansoprazole	Pantoprazole	Rabeprazole	Dexlansoprazole
Commercially available oral formulations						
Capsule	X[a]	X	X			X[b]
Tablet	X[c]			X	X	
Oral disintegrating tablet			X			
Packet for oral suspension	X[d]	X[e]				
Extemporaneous oral preparations						
Pellets from capsule in water		X				
Pellets from capsule in applesauce	X		X			X
Pellets from capsule in juice	X	X[e]	X			
Extemporaneous preparation of delayed-release PPI in bicarbonate (omeprazole-sodium bicarbonate)	X		X	X		
Parenteral formulations						
IV	X (not available in the United States)	X		X		

PPI, proton pump inhibitor; X, product is available.

[a]Omeprazole is available as delayed-release enteric-coated pellets in a capsule or as immediate-release capsule that contains 20 or 40 mg of omeprazole with 1,100 mg sodium bicarbonate (equivalent to 304 mg of sodium). Because 20 and 40 mg dosages contain the same amount of bicarbonate, two 20 mg capsules should not be substituted for the 40 mg immediate-release omeprazole-sodium bicarbonate capsule.

[b]Dexlansoprazole is available as a dual delayed-release formulation in capsules for oral administration. The capsule contains dexlansoprazole in a mixture of two types of enteric-coated granules with different pH-dependent dissolution profiles.

[c]Omeprazole oral tablets are available as 20 mg delayed-release nonprescription tablets.

[d]Omeprazole oral suspension is available as 20 or 40 mg omeprazole with 1,680 mg sodium bicarbonate (equivalent to 460 mg of sodium). Because 20 and 40 mg dosages contain the same amount of bicarbonate, two 20 mg packets should not be substituted for the 40 mg immediate-release omeprazole-bicarbonate packet.

[e]No published information; based on omeprazole data.

PPIs are formulated as delayed-release enteric-coated dosage forms that have pH-sensitive granules contained in gelatin capsules (omeprazole, esomeprazole, prescription and nonprescription lansoprazole, and dexlansoprazole), rapidly disintegrating tablets (lansoprazole), and delayed-release enteric-coated tablets (rabeprazole, pantoprazole, and nonprescription omeprazole) (see Table 51-11). The pH-sensitive enteric coating prevents degradation and premature protonation of the drug in stomach allowing the drug to be dissolved then absorbed in the duodenum at a higher pH. Dexlansoprazole is formulated with a dual-release mechanism that provides inhibition of proton pumps that become activated after initial release of the medication while omeprazole is also available as an immediate-release formulation (oral suspension, oral capsule) containing sodium bicarbonate, which can control intragastric pH in the absence of food.[75] Parenteral formulations include omeprazole (not available in the United States), esomeprazole, and pantoprazole.

PPIs provide similar rates of ulcer healing, symptom relief, and maintenance of ulcer healing when used in recommended dosages (see Table 51-9).[2] Higher than indicated daily doses should be divided to obtain better 24-hour control of intragastric pH. Older adults and patients with renal impairment do not require dosage reductions, but dosage reductions should be considered in patients with severe hepatic disease.[76] Short-term adverse effects of PPIs are like those observed with the H2RAs (headache, nausea, and abdominal pain). Immediate-release formulations contain sodium bicarbonate, and thus are contraindicated for patients with metabolic alkalosis and hypokalemia.

Drug Interactions

Since PPIs increase intragastric pH, they may alter the bioavailability of orally administered drugs that are weak bases (eg, ketoconazole), digoxin, or pH-dependent dosage forms. This interaction is especially important with antiretroviral therapies for treatment of HIV and direct acting antivirals for hepatitis C, as reduced absorption can lead to therapeutic failure due to development of viral resistance.[77,78] Omeprazole and esomeprazole selectively inhibit the hepatic CYP2C19 pathway and may decrease the elimination of several drugs (eg, phenytoin, warfarin, diazepam, and carbamazepine).[50] PPIs may increase the metabolic clearance and decrease the GI absorption of levothyroxine resulting in increased thyroid-stimulating hormone levels and a corresponding increase in the levothyroxine dose.[79] Few drug-drug interactions (eg, phenytoin, warfarin, methotrexate) involving PPIs are clinically significant and constitute a major clinical risk.[50]

A controversial PPI drug interaction involves the antiplatelet drug clopidogrel. Clopidogrel is converted to its active form through CYP2C19. PPIs may attenuate the antiplatelet effect of clopidogrel by inhibiting or competing for this metabolic pathway. FDA safety guidelines recommend that the coadministration of omeprazole, omeprazole/sodium bicarbonate, or esomeprazole with clopidogrel be avoided because they reduce the effectiveness of clopidogrel. Warnings regarding omeprazole, esomeprazole, and other interacting drugs (eg, cimetidine) are contained in the clopidogrel package insert as well. This interaction is further complicated since genetic polymorphisms of the CYP2C19 gene leading to decreased biotransformation of clopidogrel to its active form may also explain reduced effectiveness of clopidogrel. Whether the use of other PPIs such as pantoprazole, lansoprazole, dexlansoprazole, and rabeprazole interacts with clopidogrel remains uncertain as the capacity to inhibit CYP2C19 varies among these PPIs.[80] Although pharmacodynamic studies suggest attenuated anti-platelet effects of clopidogrel with omeprazole, it does not appear to translate to increased cardiovascular risk in most studies. In randomized, double-blind, placebo-controlled studies of clopidogrel and omeprazole,

there was no increased cardiovascular risk noted; however, the combination reduced the risk of upper GI bleeding.[81] Given the limitations of existing studies, administration of clopidogrel with PPIs should be balanced based upon cardiovascular and gastrointestinal risk.[80,82]

Potential Long-Term Safety Issues

Prolonged hypergastrinemia and chronic hypochlorhydria from long-term PPI use has been associated with numerous potential risks and safety issues (see Table 51-10).[68] Issues with study design, confounding, and subject selection make it difficult to attribute direct causality of PPIs for these potential safety issues. Patients receiving long-term PPIs can develop increases in serum gastrin levels, which exerts tropic effects on enterochromaffin-like cells. These cells have potential for inducing carcinoid tumors within the stomach during or after chronic acid suppression; however, there is very limited evidence (ie, case reports) of this effect, and a causal relationship between PPI use and gastric cancers has not yet been established.[1] There is also no evidence to support an association between PPIs and colonic polyps or colorectal cancer. Chronic PPI use is also associated with alterations of the intestinal microbiome, including small intestinal overgrowth and *C. difficile* infection because of inhibition of gastric acid and bacterial proton pumps. The full impact of changes in gastric and intestinal bacterial diversity and composition is unclear.[68,83]

Gastric acid is an important factor in nutrient absorption and protects against bacterial colonization of the stomach. Chronic acid suppression has been associated with increased risk of nutrient malabsorption and enteric infections. Acid suppression has been implicated as a risk factor for community-acquired pneumonia (CAP) and enteric infections (*C. difficile*, *Salmonella*, *Campylobacter*). There is a higher adjusted relative risk of CAP for patients using PPIs compared with controls, particularly in patients receiving higher doses or within the first 30 days of therapy.[68] The results of these retrospectively designed studies need to be interpreted cautiously because of the variability in the length of therapy for current PPI users and the inclusion of older (older than 60 years) patients with concomitant comorbidities. PPIs are linked with various enteric infections, but the most convincing data were with *C. difficile*. Sustained elevations in intragastric pH may facilitate the survival of *C. difficile* spores. However, the magnitude of risk varies and causality is difficult to establish. The risk of various infections associated with PPI therapy cannot be firmly established until the results of large prospective studies are made available.

The absorption of vitamin B_{12}, dietary iron, and calcium requires an acidic environment and may be adversely affected by long-term use of PPIs (see Table 51-12). The clinical importance of PPIs on absorption has not been established, and routine monitoring of B_{12} and iron levels cannot be routinely recommended. Adequate supplementation and monitoring should be considered in high-risk populations (eg, older patients, vegetarians, alcohol misuse) who may be already depleted. Hypomagnesemia, both symptomatic and asymptomatic, has been reported with PPI use with serious adverse events including tetany, arrhythmias, and seizures (see Table 51-12). In most cases it occurs in patients taking PPIs more than 1 year but can occur with as little as 3 months of therapy. High PPI dosage and long-term therapy have been associated with an increased risk of hip, wrist, and spine fractures related to reduction in calcium absorption. The FDA has revised the warnings and precautions of prescription and nonprescription PPIs to reflect these potential risks. Routine bone density tests for osteoporosis screening, calcium supplementation, or other precautions cannot be recommended solely based on chronic PPI therapy.[50]

TABLE 51-12

Drug Monitoring Table

Drug	Adverse Drug Reaction	Monitoring Parameter	Comments
PPIs	Headache, N/V/D, flatulence Less common: thrombocytopenia, neutropenia, hypomagnesemia, hypocalcemia, liver function abnormalities, renal impairment	Baseline and periodic CBC, serum electrolytes, renal/liver function	Well tolerated; may be associated with increased risk of fractures, pneumonia, *Clostridioides difficile* infection
H2RA	Headache, dizziness, diarrhea, somnolence, gynecomastia (cimetidine) Less common: thrombocytopenia, neutropenia, liver function abnormalities, renal impairment, pancreatitis	Baseline and periodic CBC, serum electrolytes, renal/liver function	
Sucralfate	Constipation, aluminum toxicity, gastric bezor		
Misoprostol	Diarrhea, abdominal pain, headache, nausea/vomiting, flatulence, dysmenorrhea, hypophosphatemia	Pregnancy test Serum phosphate	Avoid in pregnancy

CBC, complete blood count; H2RA, H_2-receptor antagonists; PPIs, proton pump inhibitors.

Data from References 3 and 14.

H2-Receptor Antagonists

Ulcer healing is comparable among H2RAs with equipotent multiple daily doses or a single full dose given after dinner or at bedtime (see Table 51-9), but tolerance to their antisecretory effect may occur. Twice-daily administration may be beneficial in patients with daytime ulcer pain while patients who smoke cigarettes may require higher doses or a longer duration of treatment. H2RAs are renally eliminated, thus a dosage reduction is recommended for patients with moderate-to-severe renal impairment. The short- and long-term safety of all H2RAs is similar. Thrombocytopenia is a common yet likely overestimated hematologic adverse effect that occurs with all H2RAs and is reversible (see Table 51-12). The H2RAs decrease acid secretion and may alter the bioavailability of orally administered drugs. Cimetidine inhibits several CYP450 isoenzymes, resulting in numerous drug interactions (eg, theophylline, lidocaine, phenytoin, warfarin, and clopidogrel). Famotidine and nizatidine do not interact with drugs metabolized by the hepatic CYP450 pathway. In April 2020, the Food and Drug Administration (FDA) recommended withdrawal of all ranitidine products from the US market following a report that, when stored at higher than recommended temperatures, products could contain unsafe quantities of N-nitrosodimethylamine (NDMA), a probable human carcinogen.[84]

Sucralfate

Sucralfate heals peptic ulcers but is not widely used today for this indication. Deterrents to its use include the requirement for multiple doses per day, large tablet size, and the need to separate the drug from meals and potentially interacting medications (eg, fluoroquinolones). Drug interactions can be minimized by giving the interacting drug at least 2 hours before sucralfate, or avoidance as with fluoroquinolones. Constipation may be troublesome especially in older individuals, and seizures have been observed in dialysis patients taking aluminum-containing antacids. Hypophosphatemia may develop with long-term treatment. Rarely, gastric bezoar formation has been reported (see Table 51-12).

Prostaglandins

The synthetic PGE_1 analogue, misoprostol, moderately inhibits acid secretion and enhances mucosal defense. Antisecretory effects are dose dependent over the range of 50 to 200 mcg, and cytoprotective effects occur in humans at doses of greater than 200 mcg. The most troublesome

adverse effect is diarrhea which is dose dependent; develops in 10% to 30% of patients; and is accompanied by abdominal cramping, nausea, flatulence, and headache.[2] Taking the drug with or after meals and at bedtime may minimize the diarrhea (see Table 51-12). Misoprostol is contraindicated in pregnant women because it produces uterine contractions that may endanger pregnancy. If misoprostol is prescribed to women in their childbearing years, contraceptive measures must be confirmed, and a negative serum pregnancy test should be documented within 2 weeks of initiating treatment (see Table 51-12).

Bismuth Preparations

Bismuth subsalicylate and bismuth subcitrate potassium are the only available bismuth salts in the United States. Possible ulcer healing mechanisms include an antibacterial effect, a local gastroprotective effect, and stimulation of endogenous PGs. Bismuth salts do not inhibit or neutralize acid. Bismuth subsalicylate is regarded as safe and has few adverse effects when taken in recommended dosages. Bismuth salts should be used with caution in older patients and in patients with renal failure as renal insufficiency may decrease bismuth elimination. Bismuth subsalicylate may cause salicylate sensitivity or bleeding disorders and should be used with caution for patients receiving concurrent salicylate therapy. Bismuth salts impart a black color to stool and possibly the tongue with liquid preparations. Long-term use of bismuth salts is not recommended due to the potential for bismuth toxicity.

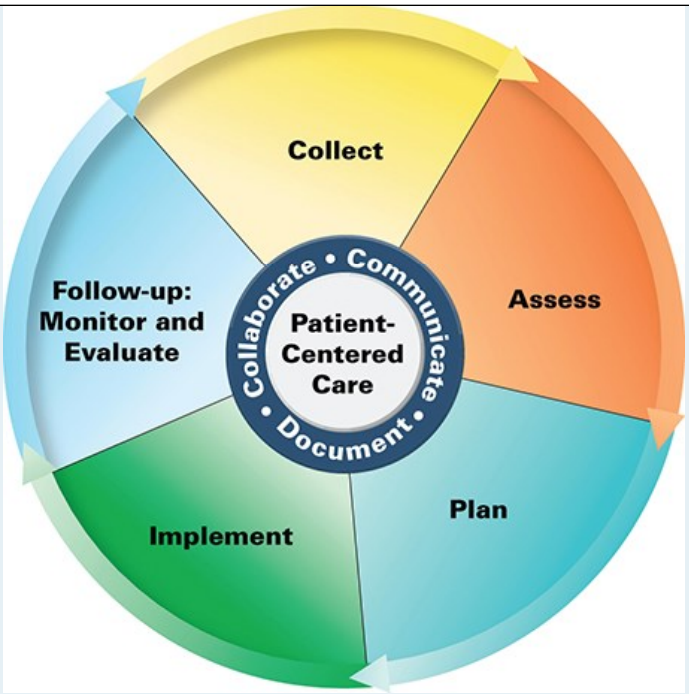
Antacids

Antacids neutralize gastric acid, inactivate pepsin, and bind bile salts. Aluminum-containing antacids also suppress *H. pylori* and enhance mucosal defense. The GI adverse effects are most common and are dose dependent: Aluminum-containing antacids cause constipation, and magnesium salts can cause an osmotic diarrhea. Aluminum-containing antacids (except aluminum phosphate) form insoluble salts with dietary phosphorus and interfere with phosphorus absorption. Hypophosphatemia occurs most often for patients with low dietary phosphate intake (eg, malnutrition or alcoholism). Combined treatment with sucralfate may amplify the hypophosphatemia and aluminum toxicity.

Magnesium excretion is impaired in patients with a creatinine clearance of less than 30 mL/min (0.5 mL/s) that may lead to toxicity; thus, magnesium-containing antacids should be avoided in these patients. Hypercalcemia may occur for patients with normal renal function taking more than 20 g/day of calcium carbonate and for patients with renal failure who are taking more than 4 g/day. The milk-alkali syndrome (ie, hypercalcemia, alkalosis, renal stones, increased blood urea nitrogen, and increased serum creatinine concentration) occurs with high calcium intake for patients with systemic alkalosis produced by either ingestion of absorbable antacids (sodium bicarbonate) or prolonged vomiting. Antacids may alter the absorption and excretion of drugs when administered concomitantly (eg, iron, warfarin, tetracycline, digoxin, quinidine, isoniazid, ketoconazole, or the fluoroquinolones). Most interactions can be avoided by separating the antacid from the oral drug by at least 2 hours.

PATIENT CARE PROCESS

Patient Care Process for Peptic Ulcer Disease (PUD)



Collect

- Patient characteristics (eg, age, sex, pregnant)
- Patient medical history (personal and family) especially prior history of *H. pylori* infection, previous peptic ulcers, or previous upper GI disorders (see Table 51-4)
- Social history (eg, tobacco and ethanol use) as well as recent medical procedures and stress levels (see Table 51-2)
- Current medications, especially NSAIDs (nonprescription and prescription) use of nonprescription proton pump inhibitors (PPIs), other acid reflux treatments, anticoagulants, and antiplatelet medications. If prior NSAID use, note medication, dosage, and duration of use
- Pain: presence or absence, rating (1-10), quality, and location (see Table 51-5)
- Objective Data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2-saturation
  - Labs including hemoglobin (Hgb), hematocrit, assessment of kidney and liver function, gastric acid secretory studies, and stool hemoccult
  - Urea breath test (UBT) for detection of *H. pylori.* Follow-up culture with endoscopy recommended (see Table 51-6)
  - Imaging studies: Upper endoscopy

Assess

- Hemodynamic stability (eg, systolic BP >90 mm Hg, Hr >110 bpm, O_2 sat <90% [0.90])
- Presence of active gastric bleeding based on imaging studies
- Presence of GI-bleed provoking factors (low platelets, anticoagulant/antiplatelet use, NSAID use, age >65, recent surgery, severe co-morbidities, eg, cardiovascular disease) (see Table 51-4)
- Presence/absence of *H. pylori*

- Emotional status (eg, anxiety, depression, stress levels)
- Ability/willingness to pay for ulcer treatment options
- Ability/willingness to discontinue NSAIDs and switch to another pain reliever, if applicable
- Ability/willingness to obtain laboratory monitoring tests (eg, *H. pylori* status to confirm eradication) (see Table 51-7)
- Ability/willingness to follow a multiple drug regimen for 10 to 14 days, with some doses to be taken at specific times

Plan

- Drug therapy regimen based on ulcer classification and patient's antibiotic tolerance (eg, penicillin allergy) (see Tables 51-7 and 51-8)
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug-specific information, medication administration)
- Self-monitoring for resolution of symptoms such as epigastric pain, dyspepsia, when to seek emergency medical attention

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (endoscopic *H. pylori* culture, lab tests: CBC, serum electrolytes, renal/liver function; see Table 51-12)

Follow-up: Monitor and Evaluate

- Resolution of PUD symptoms such as epigastric pain and dyspepsia
- Presence of adverse effects (eg, N/V/D [PPIs, H2RAs, metronidazole, other antibiotics]), headaches (PPIs and H2RAs)
- Patient adherence to treatment plan using multiple sources of information
- Monitor patient for symptoms of PUD recurrence, especially if their risk factors change

****Collaborate with patient, caregivers, and other healthcare professionals.***

EVALUATION OF THERAPEUTIC OUTCOMES

Table 51-13 lists the recommendations for treating and monitoring patients with PUD. Relief of epigastric pain should be monitored throughout the course of treatment for patients with either *H. pylori*– or NSAID-related ulcers. 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, particularly among individuals who are at risk for complications (eg, prior bleeding ulcer). 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. Many at-risk patients treated with NSAIDs do not receive adequate prophylaxis for GI complications; however, therapeutic outcomes can be improved by advocating preventive strategies. Any signs or symptoms of bleeding, obstruction, penetration, or perforation require prompt investigation to avoid complications. A follow-up endoscopy is justified for patients with frequent symptomatic recurrence, refractory disease, complications, or suspected hypersecretory states.

TABLE 51-13

Recommendations for Treating and Monitoring Patients with *Helicobacter Pylori*–Associated and NSAID-Induced Ulcers

***H. pylori*–associated ulcer**

1. Recommend drug treatment as presented in the chapter text. See Tables 51–7 and 51–8
2. Assess patient allergies to determine if allergic to penicillin (or other antibiotics) so that drug regimens that contain penicillin (or other antibiotics) can be avoided. Avoid regimens that contain tetracycline in children
3. Assess patient use of alcohol or alcohol-containing products with metronidazole and oral birth control medications with antibiotics and counsel appropriately
4. Assess likelihood of nonadherence to the drug regimen as a cause of treatment failure
5. Recommend a different antibiotic combination if *H. pylori* eradication fails and a second treatment is planned
6. Inform the patient of change in stool color when bismuth salicylate is included in an *H. pylori* eradication regimen
7. Assess and monitor patients for potential adverse effects, especially those associated with metronidazole, clarithromycin, and amoxicillin
8. Assess and monitor patients for potential drug interactions, especially those receiving metronidazole, clarithromycin, or cimetidine
9. Monitor patients for salicylate toxicity, especially patients receiving co-therapy with other salicylates and anticoagulants and patients with renal insufficiency
10. Monitor patients for persistent or recurrent symptoms within 14 days after completion of a course of *H. pylori* eradication therapy
11. Provide education to patients who are receiving *H. pylori* eradication therapy and include why antibiotic and antiulcer combinations are used; when and how to take medications; adverse effects; alarm symptoms; the importance of adherence to the entire course of drug treatment; and contact their healthcare provider if alarm symptoms develop (eg, blood in the stools, black tarry stools, vomiting, severe abdominal pain), or if symptoms persist or return after *H. pylori* eradication

NSAID-induced ulcer

1. Recommend drug treatment as presented in the chapter text
2. Assess risk factors for NSAID-induced ulcers and ulcer-related complications and recommend appropriate strategies for reducing ulcer risk (see Table 51-14)
3. Weigh patient risk factors for NSAID-related GI bleeding and cardiovascular events when selecting a strategy to reduce ulcer risk
4. Recommend eradication treatment for *H. pylori*–positive patients taking NSAIDs
5. Monitor patients for signs and symptoms of NSAID-related upper GI complications
6. Assess and monitor patients for potential drug interactions and adverse effects (especially misoprostol)
7. Provide patient education to patients who are at risk of NSAID-induced ulcers or GI-related complications and include why co-therapy is used with nonselective NSAIDs, when and how to take medications, adverse effects, alarm symptoms, when to contact their healthcare provider, and the importance of adherence to drug treatment

TABLE 51-14

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 factors.

[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 atherosclerotic cardiovascular disease [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 Cyclooxygenase-2 (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).

NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

Data from Reference 3.

RELATED DISORDERS

Upper Gastrointestinal Bleeding

Upper GI bleeding is one of the most common GI emergencies with more than 200,000 hospital admissions annually.[5] There are about 48 to 160 cases of upper GI bleeding per 100,000 adults annually in the United States, and the in-hospital mortality rate associated with acute hemorrhage remains relatively high at 2% despite a decreased incidence of PUD and improvements in the management of upper GI bleeding.[5] Upper GI bleeding is categorized as variceal or nonvariceal bleeding. A complete discussion of variceal bleeding is found elsewhere (Chapter 55). Two common types of nonvariceal bleeding are bleeding from chronic peptic ulcers, often related to antithrombotic therapy, and bleeding from SRMD.[85] Upper GI bleeding associated with chronic PUD usually precedes hospital admission. Bleeding associated with SRMD develops in critically ill patients during hospitalization.[86,87] The underlying pathophysiology of bleeding from a peptic ulcer or from SRMD is similar in that impaired mucosal defense in the presence of gastric acid and pepsin leads to mucosal damage. In chronic PUD, *H. pylori* infection and NSAID use are the most important etiologic factors. The primary pathogenic factor of SRMD in critically ill patients is thought to be mucosal ischemia, which is a result of reduced gastric blood flow resulting from splanchnic hypoperfusion.[86,87] Stress-related mucosal lesions are characteristically asymptomatic, numerous, located in the proximal stomach, and unlikely to perforate. Bleeding from SRMD occurs from superficial mucosal capillaries, whereas bleeding associated with chronic PUD usually results from a single vessel.[86,87] The mortality rate associated with clinically important stress-related mucosal bleeding (SRMB) is

approximately 50% and is related to disease severity and comorbidities in this patient population. The mortality associated with chronic PUD-related bleeding is approximately 5% but can increase dramatically in select patient populations.[86,87] Initial management of acute upper GI bleeding focuses on aggressive resuscitation and hemodynamic stability.

Peptic Ulcer–Related Bleeding

Clinical Presentation and Diagnosis

Hematemesis (vomiting up blood), melena (dark, tarry stools), or both are the most common presenting signs and symptoms of PUD-related bleeding. Risk for adverse outcomes must be rapidly assessed to determine if the patient's condition constitutes a medical emergency.[87] Two risk stratification tools exist for early assessment and triage. The Blatchford score is used to evaluate the need for urgent endoscopic intervention for patients presenting with PUD-related bleeding. The scale values range from 0 to 23, with higher scores indicating higher risk. The Rockall score is composed of two assessments: the clinical score, which is performed prior to endoscopy, and the endoscopic score. The use of these risk stratification tools can reduce the requirement of endoscopic procedures and lead to early discharge for low-risk patients while ensuring rapid intervention for patients at higher risk.[87] When considering the risk of death due to PUD bleeding, the following patients generally have poorer prognoses and usually require more aggressive intervention including admission to an intensive care unit (ICU): older age (>60 years), hypotension (SBP <100 mm Hg), tachycardia (HR <100 BPM), shock, poor overall health, comorbid conditions, low initial hemoglobin/hematocrit, active bleeding (red blood per rectum or hematemesis), sepsis, and elevated serum creatinine or serum transaminases.[88] Diagnostic endoscopy is usually performed within 24 hours of presentation to identify the source of the bleeding, assess the potential risk for rebleeding using the Forrest classification of lesions, and, if appropriate, employ therapeutic interventions to promote hemostasis.[88,89]

The appearance of the ulcer at the time of endoscopy is a prognostic indicator for the risk of rebleeding. Clean-based (Forrest type III) and flat spot (pigmented; Forrest type IIc) ulcers are most commonly seen and are associated with a low risk of rebleeding (5% and 10%, respectively). In most cases, patients with clean-based ulcers can be treated as an outpatient on antiulcer therapy, while patients with flat spot ulcers may be admitted to the general hospital ward for brief observation.[87] Patients with an adherent clot overlying the ulcer base (Forrest type IIb) are at intermediate risk of rebleeding (22%-33%), and controversy exists as to the appropriate management of these patients. Patients with a visible vessel (Forrest type IIa) or active bleeding (Forrest type Ia or Ib) are at the highest risk of rebleeding (43%-50% and 55%-90%, respectively) and should receive ICU care for at least 24 hours followed by monitoring on a general medical/surgical service for an additional 48 hours as rebleeding significantly increases mortality.[87]

Treatment

Initial therapy for patients with defined hemostatic instability should focus on correcting fluid volume loss through appropriate volume resuscitative measures. This is usually accomplished with a continuous 0.9% sodium chloride infusion or blood products if clinically indicated.[85] The use of nasogastric (NG) tubes as an aid in early assessment remains controversial, but nasogastric lavage has no impact on transfusion requirements, surgery, or mortality.[85,87] Several endoscopic treatment approaches (eg, thermocoagulation, argon plasma coagulation therapy, injection sclerotherapy, hemostatic clips, and ligation) can be used.[34]

Antisecretory agents are often used as adjuvant therapy to endoscopic procedures to prevent PUD rebleeding in high-risk patients because acid impairs clot stability. PPIs reduce the incidence of rebleeding and need for surgery but have no significant impact on overall mortality.[87] There is no difference in recurrent bleeding, need for surgery, or mortality when comparing equivalent dosing of oral and intravenous PPI therapy.[90] Oral or intermittent IV dosing of PPIs (at cumulative daily omeprazole doses of 80-160 mg) may be preferred over continuous fusion (eg, omeprazole 8 mg/hr) in order to provide a greater ease of administration. PPI therapy is not a replacement for interventional endoscopy in patients with a high risk of rebleeding, as data demonstrate that the combination of a PPI with therapeutic endoscopy is superior to either strategy alone. The risk of rebleeding is greatest within the first 72 hours, and thus antisecretory therapy to prevent rebleeding in high-risk patients should be employed in this time frame. Patients with high-risk endoscopic lesions should be transitioned to twice-daily PPI for 14 days. Patients with low-risk endoscopic lesions can be treated with once-daily PPI. Once-daily PPI treatment should be continued for 4 to 8 weeks in all patients with peptic ulcer bleeding.[87]

Patients with upper GI bleeding should be tested for *H. pylori* at the time of endoscopy (see section "Tests for Helicobacter pylori" above). However, the tests are associated with an increased rate of false-negatives when obtained during acute bleeding episodes. If the initial results of the rapid urease

test and/or histology are negative, a confirmatory test should be performed following the acute bleeding episode. Ulcer treatment, including *H. pylori* eradication, should be initiated after the acute bleeding episode has resolved (see "Treatment of H. Pylori–Positive Ulcers" and "Treatment of NSAID-Induced Ulcers" above).

Stress-Related Mucosal Bleeding

Epidemiology and Risk Factors

Clinically important bleeding increases ICU length of stay, results in excessive healthcare costs, and is associated with increased mortality. Thus, attempts to prevent SRMB are warranted in high-risk patients. Prophylactic therapy to prevent bleeding is most effective if initiated early in the patient's course.[86] The majority (75%-100%) of critically ill patients develop SRMD within the first 1 to 3 days of admission to an ICU, but the incidence of clinically important SRMB (defined as overt bleeding with concomitant hemodynamic instability and likely requirement for blood products) has decreased to 2% to 5%.[86]

Patients who are at risk for SRMB include those with respiratory failure (ie, need for mechanical ventilation for longer than 48 hours), coagulopathy (ie, INR greater than 1.5, platelet count less than 50,000/mm^3 [50×10^9/L]), hypotension, sepsis, hepatic failure, acute renal failure, high-dose corticosteroid therapy (ie, more than 250 mg/day hydrocortisone or equivalent), multiple trauma, severe burns (ie, more than 35% of body surface area), head injury, traumatic spinal cord injury, major surgery, prolonged ICU admission (ie, more than 7 days), or history of GI bleeding. The relative importance of the various risk factors remains controversial, but most clinicians concur that patients with respiratory failure or coagulopathy should receive prophylaxis, as these two factors are independent risk factors for SRMB.[91]

Prevention and Treatment

Prevention of SRMB includes resuscitative measures that restore mucosal blood flow, and pharmacotherapy that either maintains an intragastric pH of greater than 4 or provides gastric mucosal protection.[86,92] Although the benefits of enteral nutrition to patient outcome (eg, improved nutritional status enhances mucosal integrity) are of overall critical importance, its precise role as a sole modality to prevent SRMB remains controversial. Patients receiving enteral nutrition may not require medications for SRMB prophylaxis, and such therapies may increase the risk of adverse complications, particularly nosocomial pneumonia, over enteral nutrition alone.[93,94] Therapeutic options for the prevention of SRMB include antisecretory drugs (H2RAs and PPIs), and sucralfate.[86,91]

Sucralfate is an option for SRMB but requires multiple daily dosage administration (up to four times daily). Also, it may occlude nasogastric (NG) tubes, and possibly cause adverse effects previously discussed. Although sucralfate may have a lower risk of pneumonia compared to antisecretory therapy, these factors limit its use for SRMB prophylaxis. PPIs have become the most widely used therapy since they are more potent in inhibiting acid secretion and, unlike H2RAs, tolerance does not develop. Improved efficacy for SRMB when the PPIs are used as prophylaxis must be balanced against adverse events including increased risk of enteric infections, namely *C. difficile*–associated diarrhea and evidence-based nosocomial pneumonia, which are associated with increased healthcare costs.[91,95] A decision analytic model determined H2RA stress ulcer prophylaxis reduced costs, increased survival, and avoided complications compared with PPI therapy.[96] There are several evidence-based dosing regimens for SRMB prophylaxis (see Table 51-15).[86]

TABLE 51-15

Pharmacotherapy Options for Prophylaxis of Stress-Related Mucosal Bleeding

Drug and Route	Dosage
Parenteral H2RAs	
Cimetidine	300 mg IV loading dose followed by 50 mg/hr as a continuous infusion[a] or 300 mg IV every 6-8 hours
Ranitidine[b]	6.25 mg/hr as a continuous infusion or 50 mg IV every 6-8 hours
Famotidine	1.7 mg/hr as a continuous infusion or 20 mg IV every 12 hours
Oral/NG Tube PPIs	
Omeprazole	20-40 mg orally/NG tube[c] every 12-24 hours
Omeprazole/bicarbonate powder for oral suspension	40 mg orally/NG tube to start, then followed by an additional 40 mg in 6-8 hours as a loading dose, and then 40 mg every 24 hours
Lansoprazole	30 mg orally/NG tube[c,d] every 12-24 hours
Pantoprazole	40 mg orally/NG tube[c] every 12-24 hours
Parenteral PPIs	
Pantoprazole	40-80 mg IV every 12-24 hours
Esomeprazole	40 mg IV every 12-24 hours

[a]Product is FDA-approved for the prevention of stress-related mucosal bleeding.

[b]All ranitidine products were removed from the US market effective April 2020.

[c]Administered as an extemporaneously compounded suspension made with sodium bicarbonate.

[d]Administered as a rapidly disintegrating tablet given orally or by NG tube dissolved in 10 mL of water.

H2RA, histamine-2 receptor antagonist; NG, nasogastric; PPI, proton pump inhibitor.

Even though PPIs have become the most widely used prevention therapy, numerous studies and years of experience support the use of H2RAs, and they remain a recommended option for the prevention of SRMB.[86] Parenteral H2RAs may be administered as either continuous infusions or intermittent bolus doses (see Table 51-15). Cimetidine, given as a continuous IV infusion, is the only FDA-labeled H2RA for the prevention of SRMB. Drug interactions are more common with cimetidine, thus the other H2RAs (famotidine, ranitidine) have been used more frequently.[86] Adverse events associated with the use of H2RAs for the critically ill patient include thrombocytopenia, mental status changes (more common in older patients or individuals with renal or hepatic compromise), and tachyphylaxis (especially with parenteral or high-dose therapy). Given that the H2RAs are renally eliminated, dosage reductions are recommended for patients with renal dysfunction.

When deciding on the most appropriate pharmacotherapy plan for the prevention of SRMB for a specific patient, the clinical presentation, risk factors, and medication costs should be used as a guide. Oral H2RA or PPI suspension is safe and cost-effective for patients who can take oral medication or

have a working NG tube in place. For patients who are not able to utilize one of these routes, parenteral antisecretory therapies are appropriate. However, if the patient has any relative or absolute contraindications to an H2RA, then an IV PPI may be the most appropriate prophylaxis option.

Improvement in the patient's overall medical condition (resolution of risk factors, discharge from the ICU, extubation, and oral intake) suggests that prophylactic therapy can be discontinued. Often patients are continued on SRMB prophylaxis on transition to the general medical/surgical unit and frequently discharged on oral PPI therapy without an appropriate indication. This results in unnecessary costs for the patient and the healthcare system.[91] Patients in whom SRMB prophylaxis is no longer indicated should be identified. If a patient develops clinically important bleeding, endoscopic evaluation of the GI tract is indicated along with aggressive antisecretory therapy (see section "Peptic Ulcer–Related Bleeding" above).

Zollinger-Ellison Syndrome

ZES, characterized by hypersecretion of gastric acid and severe gastroesophageal PUD, is caused by a neuroendocrine tumor (gastrinoma) that is present in the duodenum or pancreas. Gastrinoma has a yearly incidence of approximately 0.1 to three cases per million in the United States with ZES being the underlying cause of PUD in 0.1% to 1% of patients. ZES occurs spontaneously in 75% to 80% of patients, but 25% to 30% of patients have the familial form associated with multiple endocrine neoplasia type 1 (MEN1), an autosomal-dominant syndrome due to a variant in the *MEN1* gene. Patients with MEN1 commonly develop hyperparathyroidism, pituitary adenomas, and neuroendocrine tumors. Half (50%) of patients with MEN1 have ZES making gastrinoma and ZES the most common functional neuroendocrine tumor and syndrome in MEN1. Gastrinomas are usually slow growing, but approximately 60% to 90% are malignant with metastases to regional lymph nodes, liver, and other distant sites at time of diagnosis.[97]

Pathophysiology

Gastrinomas are derived from the enteroendocrine cells, form tumors mainly in the pancreas and proximal small intestine, and are generally classified under the larger term of neuroendocrine tumors. Most gastrinomas arise in the duodenum. Gastrinomas located in the pancreas carry a greater malignant potential. ZES pathophysiology is related to the trophic action of gastrin on parietal cells of the gastric antrum and the resulting hypersecretion of gastric acid. Most patients consequently develop large peptic ulcers frequently in the distal duodenum and even proximal jejunum, which is an uncommon location for ulcers resulting from *H. pylori* or the use of NSAIDs.[97]

Clinical Presentation and Diagnosis

Historically, patients with ZES presented with refractory PUD or complications of acid hypersecretion (perforation, penetration, bleeding, and esophageal stricture). Due to the widespread use of PPIs and H2RAs, this form of presentation has decreased drastically.[97] Patients commonly present with severe refractory heartburn, epigastric pain, and profound diarrhea. Diarrhea may be the only symptom in 10% to 20% of patients and is due to the osmotic load of high gastric acid, inhibition of sodium and water reabsorption by the intestinal brush border of high gastric acid secretion, and a malabsorptive component from inactivation of pancreatic digestive enzymes by gastric acid.[97]

ZES diagnosis is established when the serum gastrin is greater than 1,000 pg/mL (ng/L; 481 pmol/L) and the basal acid output (BAO) is more than or equal to 15 mEq/hr (mmol/hr) for patients with an intact stomach (BAO more than or equal to 5 mEq/hr [mmol/hr] for patients with previous gastric surgery) or when hypergastrinemia is associated with a gastric pH value of more than or equal to 2.[97] In situations in which the serum gastrin is between 100 and 1,000 pg/mL (ng/L; 48 and 481 pmol/L) and gastric pH is less than or equal to 2, a secretin or calcium proactive test is used to aid the diagnosis.[97] Identification of the location of the tumor with imaging techniques is essential, as early surgical resection prior to liver metastases is often curative.[98] The widespread use of PPIs, although effective in reducing symptoms, may mask the clinical presentation and PPI-related hypergastrinemia may further complicate the diagnosis.

TREATMENT

With the development of H2RAs and PPIs, medical management of ZES is feasible in almost all patients. Because of their long duration of action and potency, PPIs are now the drugs of choice for treating gastric acid hypersecretion in patients with ZES.[97] Many of the PPIs (omeprazole, esomeprazole, lansoprazole, esomeprazole, rabeprazole, and pantoprazole) are effective in ZES. Initial doses of 80 mg/day of pantoprazole (or an equivalent dose of other available PPIs) given every 8 to 12 hours is most effective at controlling gastric acid hypersecretion and reliving symptoms. IV PPIs can be used for

those patients who do not tolerate oral therapy. PPIs must be dose adjusted in patients with ZES to normalize BAO levels to less than 15 mEq/hr (mmol/hr) or less than 5 mEq/hr (mmol/hr) in patients with reflux esophagitis or prior operations to reduce acid secretion, such as subtotal gastrectomy. PPI therapy can be gradually decreased after adequate control of hypersecretion is achieved.[97] Since 60% to 90% of gastrinomas are malignant, management of advanced disease may include surgical resection of primary and metastatic gastrinomas. Nonsurgical therapy may include treatment with chemotherapy, somatostatin analogues such as octreotide, interferon, and targeted-molecular therapies such as an mTor inhibitor (everolimus) or a tyrosine-kinase inhibitor (sunitinib).[97]

ABBREVIATIONS

ATPase	adenosine triphosphatase
BAO	basal acid output
CAP	community-acquired pneumonia
CLASS	Celecoxib Long-Term Arthritis Safety Study
COX	cyclooxygenase
COX-1	cyclooxygenase-1
COX-2	cyclooxygenase-2
CYP450	cytochrome P450
ECL	enterochromaffin-like
GERD	gastroesophageal reflux disease
H2RA	histamine-2 receptor antagonist
ICU	intensive care unit
IL	interleukin
INR	international normalized ratio
MALT	mucosa-associated lymphoid tissue
MAO	maximal acid output
MEN 1	multiple endocrine neoplasia type 1
NG	nasogastric
NSAID	nonsteroidal anti-inflammatory drug
NUD	nonulcer dyspepsia
PG	prostaglandin

PPI	proton pump inhibitor
PUD	peptic ulcer disease
SRMB	stress-related mucosal bleeding
SRMD	stress-related mucosal damage
TNF-α	tumor necrosis factor-α
UBT	urea breath test
ZES	Zollinger-Ellison syndrome

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SELF-ASSESSMENT QUESTIONS

1. *Helicobacter pylori*–associated ulcers differ from nonsteroidal anti-inflammatory drug (NSAID)–induced ulcers in that *Helicobacter pylori*–associated ulcers are most likely:

   A. Located in the duodenum

   B. Associated with more severe upper gastrointestinal (GI) bleeding

   C. Associated with a greater degree of ulcer-related epigastric pain

   D. Associated with gastric acid hypersecretion

2. In addition to the choice, dose, and duration of NSAID, which of the following patient risk factors is most likely to result in NSAID-induced ulcers and upper GI complication with NSAID use?

   A. Increased psychological stress

   B. Increased intake of caffeinated beverages

   C. Cigarette smoking

   D. Cigarette smoking Prior history of peptic ulcer complication

3. A 35-year-old woman with a medical history of chronic lower back pain is *H. pylori*–negative but undergoes endoscopy revealing an NSAID-induced ulcer. Assuming she must continue the NSAID following a brief interruption, which is the preferred medication for ulcer healing and prevention of future ulcers?

   A. Misoprostol

   B. Omperazole

   C. Famotidine

   D. Sucralfate

4. A 53-year-old white man with no known drug allergies presents to his primary care physician with a 2-week history of epigastric pain. He has no recent history of NSAID use but completed a course of azithromycin for community acquired pneumonia 3 weeks ago. A serum antibody for *H. pylori* is obtained and is positive. Which of the following 14-day regimens would be considered the preferred initial therapy for *H. pylori*?

   A. Proton pump inhibitor (PPI) + metronidazole + amoxicillin

   B. PPI + metronidazole + clarithromycin

   C. PPI + amoxicillin + clarithromycin

   D. PPI + metronidazole + bismuth + tetracycline

5. Which of the following is an endoscopic test used to diagnose *H. pylori*?

   A. Urea breath test

   B. Mucosal biopsy

   C. Fecal antigen

D. Antibody detection

6. You receive a phone call from a distressed patient who is concerned that her tongue has turned black after starting new medications for peptic ulcer disease (PUD). Which medication is causing the side effect?

   A. Amoxicillin

   B. Bismuth subsalicylate

   C. Clarithromycin

   D. Metronidazole

7. What is the recommended number of days for treatment of *H. pylori* when clarithromycin-based triple therapy is used?

   A. 5

   B. 7

   C. 14

   D. 21

8. A medical resident seeks your advice on an NSAID regimen for a 45-year-old woman with rheumatoid arthritis and major depressive disorder. She has no prior ulcer disease, no other medical conditions, and takes only sertraline 50 mg daily. Which of the following regimens should be used for prevention of NSAID-induced ulcers in this patient?

   A. Ibuprofen

   B. Naproxen

   C. Celecoxib

   D. Naproxen plus PPI

9. Chronic PUD-related bleeding differs from stress-related mucosal bleeding (SRMB) in that chronic PUD-related bleeding:

   A. Occurs due to mucosal ischemia from decreased gastric blood flow

   B. Usually occurs from a single vessel

   C. Requires aggressive resuscitation as initial management

   D. Results in a mortality rate of 50%

10. A 48-year-old patient was admitted to the medical ICU 48 hours ago with acute respiratory failure requiring subsequent intubation. They are currently receiving mechanical ventilation, has no renal insufficiency, and do not have a working NG tube. What is the best option for stress related mucosal bleeding (SRMB) prophylaxis for this patient?

    A. Pantoprazole 40 mg by mouth daily

    B. Famotidine 20 mg IV twice daily

    C. Sucralfate 1 g by mouth four times daily

    D. Pantoprazole 40 mg IV every 8 hours

11. Which of the following is true about Zollinger-Ellison syndrome (ZES)?

A. ZES is the underlying cause of PUD in 1% to 10% of patients.

B. A minority of patients develop large peptic ulcers in the distal duodenum.

C. Gastrectomy is the only effective treatment of controlling gastric acid hypersecretion.

D. Antisecretory therapy with PPIs is an effective means of medically managing ZES.

12. A medical student recently heard about a new "hybrid" treatment regimen for *H. pylori* eradication and requests a literature search on this topic. Which of the following best represents a "hybrid" regimen?

A. Omeprazole, clarithromycin, and amoxicillin taken together for 14 days.

B. Famotidine, bismuth, tetracycline, and metronidazole taken together for 10 days.

C. Pantoprazole and amoxicillin taken together on days 1 to 5, followed by pantoprazole, clarithromycin, and metronidazole on days 6 to 10.

D. Rabeprazole and amoxicillin together for days 1 to 14, along with clarithromycin and metronidazole on days 7 to 14.

13. A 52-year-old female returns to clinic 4 weeks after completing a course of esomeprazole, clarithromycin, and amoxicillin for 10 days for an endoscopically confirmed duodenal ulcer. A fecal antigen test is positive. Which of the following represents the best course of action?

A. Do nothing.

B. Repeat a course of esomeprazole, clarithromycin, and amoxicillin but increase duration to 14 days.

C. Initiate omeprazole, bismuth subcitrate, metronidazole, and tetracycline for 10 days.

D. Initiate rabeprazole, clarithromycin, amoxicillin, and metronidazole for 10 days.

14. A 59-year-old man with hypertension, hyperlipidemia, myocardial infarction (4 years ago), arthritis and history of PUD presents to clinic complaining of worsening bilateral knee pain. His medications include lisinopril 20 mg daily, atorvastatin 80 mg at bedtime, enteric coated aspirin 81 mg daily, ibuprofen 600 mg three times daily, and metoprolol 100 mg twice daily. In addition to stopping ibuprofen, which of the following would you recommend for treatment of his chronic knee pain?

A. Initiate celecoxib 100 mg daily

B. Initiate naproxen 550 mg twice daily

C. Initiate naproxen 550 mg twice daily plus famotidine 20 mg twice daily

D. Initiate celecoxib 100 mg daily plus pantoprazole 40 mg daily

15. A 61-year-old female is diagnosed with Zollinger-Ellison syndrome. Which of the following represents an evidence-based initial treatment?

A. Famotidine 40 mg twice daily

B. Rabeprazole 40 mg twice daily

C. Omeprazole 20 mg twice daily

D. Misoprostol 400 mg twice daily

SELF-ASSESSMENT QUESTION-ANSWERS

1. **A.** Characteristics of *Helicobacter pylori*–associated ulcers include preferential damage to the duodenum, superficial ulceration, involvement of a

single blood vessel, and less severe bleeding. See Table 51-1 for a comparison of common forms of peptic ulcer.

2. **D.** Prior history of peptic ulcer complications and co-administration of anticoagulant or antiplatelet medications have the highest risk of PUD and upper GI complications. Psychological stress, smoking, and dietary factors such as caffeine intake are weakly associated with peptic ulcer occurrence and GI complications.

3. **B.** PPIs (e.g. omeprazole) are more effective at ulcer healing and prevention compared with H2RA (e.g. famotidine) and sucralfate. Misoprostol is also an effective agent for prevention of ulcers but would not be effective for ulcer healing. Since this woman is of childbearing age, use of misoprostol would require confirmation of negative pregnancy test and additional counseling.

4. **D.** Bismuth quadruple therapy would be the best option for this patient. In general, clarithromycin-based triple therapy is no longer recommended as a first-line option in the United States. In this scenario, regimens containing clarithromycin should be avoided given the patient's recent macrolide exposure. Triple therapy with PPI, amoxicillin, and metronidazole is less effective than triple therapy regimens containing clarithromycin.

5. **B.** Mucosal biopsy is an invasive test requiring endoscopy. Fecal antigen, serology, and urea breath test are noninvasive tests used in the diagnosis of *H. pylori*.

6. **B.** Bismuth preparations may cause nausea and a black tongue and/or stool.

7. **C.** Clarithromycin-based triple therapy is no longer recommended as a first-line therapy due to increased resistance, but when it is used, the duration should be 14 days to maximize the efficacy.

8. **D.** This patient has no CV history but is considered high risk for PUD due to treatment with SSRI. SSRIs increase the risk of PUD and GI bleeding by sixfold. Ulcer prevention with a PPI is recommended along with either a nonselective NSAID or celecoxib. See Table 51-14 for recommendations on preventing PUD in patients receiving chronic NSAIDs.

9. **B.** Chronic PUD-related bleeding usually affects a single vessel and occurs slowly over time. However, SRMB is an acute condition with superficial ulcers, mainly affecting small capillaries, due to mucosal ischemia. Clinically significant bleeding due to SRMB is not common, but requires fluid resuscitation and has a high mortality rate.

10. **B.** The patient is receiving mechanical ventilation, so SRMB prophylaxis is indicated. Of the available choices, parenteral H2RA would be the best choice. A working nasogastric tube or feeding tube is needed for administration of oral dose forms. Intravenous PPIs at total daily doses equivalent to omeprazole 80-160 mg/day are only indicated for acute upper gastrointestinal bleeding.

11. **A.** ZES is a rare cause of PUD with an estimated incidence of 0.1% to 1% of all PUD cases. Ulcers usually form in the distal duodenum or proximal jejunum, which is a unique feature of ZES. Surgery and medical management with high-dose PPIs are both management strategies used for ZES.

12. **D.** Sequential therapy is a form of eradication therapy in which the antibiotics are administered in a sequence rather than together (Answer C). Non-bismuth quadruple therapy, also called "concomitant" therapy, is a regimen with a PPI, amoxicillin, clarithromycin, and metronidazole taken together at standard doses for 10 to 14 days. Hybrid therapy combines the strategies of concomitant and sequential therapy. Patients take 7 days of dual therapy (PPI and amoxicillin) followed by 7 days of quadruple therapy (PPI, amoxicillin, clarithromycin, and metronidazole). Table 51-8 summarizes medication regimens for *Helicobacter pylori* eradication.

13. **C** Patient has not eradicated *H. pylori* for a endoscopically confirmed duodenal ulcer, and the risk of ulcer recurrence is high. The patient has recent macrolide exposure, so regimens including clarithromycin should be avoided.

14. **D** Given the patient's prior ulcer history, ulcer prevention with a PPI is needed. Although some of the gastroprotective effect is lost in patients taking low-dose aspirin, it represents the best choice in this scenario. Since the patient is high-risk for cardiovascular disease, the lowest dose of celecoxib should be used.

15. **B.** ZES is a hypersecretory condition requiring high doses of proton pump inhibitors to reduce gastric acid. Any PPI can be used in doses equivalent to pantoprazole 80 mg given every 8 to 12 hours. The equivalent dosing of rabeprazole is 50% of the pantoprazole dose (see Table 51-9). Omeprazole would be a good choice, but the dose in this scenario is subtherapeutic for ZES. H2RA are less effective overall and the doses used

would need to be considerably higher. Misoprostol is not indicated for ZES.