Peptic Ulcer Disease

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Objectives

1. To review the epidemiology of PUD.
2. To review classic presentations and management of uncomplicated and complicated PUD.
3. To understand the pathophysiology of PUD.
4. To highlight non-*H. pylori*/non-NSAID etiologies for PUD.
5. To review treatment strategies for *H. pylori*.

Introduction

A peptic ulcer is defined histologically as a mucosal break that penetrates the muscularis mucosa of the gastrointestinal tract exposed to acid and pepsin. Mucosal breaks superficial to the muscularis mucosa are defined as erosions. Endoscopically and radiographically, both size and depth are used to separate ulcers from erosions. Ulcers are defined as mucosal breaks ≥5 mm with apparent depth; smaller and more superficial lesions are called erosions. Based on the requirement for the presence of acid, the most common ulcer locations are the distal esophagus, stomach, and duodenum. However, ectopic acid-secreting parietal cells can also occur elsewhere in the digestive tract resulting in ulcers in ectopic locations, most often in the proximal esophagus (inlet patch) and within a Meckel's diverticulum in the ileum. Typical duodenal ulcers occur in the proximal duodenum, but with excessive acid secretion (e.g., Zollinger-Ellison syndrome), ulcers occur from the duodenal bulb to the jejunum. The most common causes of ulcers are use of nonsteroidal anti-inflammatory drugs (NSAIDs) and infection with *Helicobacter pylori* (*H. pylori*). *H. pylori* infection causes traditional peptic ulcer disease (PUD) which is a chronic condition with gastric and/or duodenal ulcers recurring over many decades (i.e., the dictum "once and ulcer, always an ulcer").

Epidemiology

The lifetime risk for developing PUD in patients with *H. pylori* infection is about 17%. A recent systematic review of 31 studies reported the pooled incidence rates per 1000 person-years as 0.90 (95% C.I. = 0.78–1.04) for uncomplicated PUD, 0.57 (0.49–0.65) for peptic ulcer bleeding, 0.10 (0.08–0.13) for perforated ulcers, and 3.18 (2.05–4.92) for nonspecific PUD. However, *H. pylori* has been losing its place as the most common cause of ulcer to NSAIDs as the prevalence of *H. pylori* infections has declined. NSAID use results in a fourfold increase in ulcer risk and a doubling of risk in individuals with *H. pylori*. The discovery of that the most common cause of a PUD was *H. pylori* (i.e., a treatable infection) resulted in *H. pylori*-associated PUD becoming both preventable and, with treatment, a one-off condition. The continued decline in prevalence of *H. pylori* infections and increase in life expectancy in many parts of the world has led to an increased relative proportion of ulcers being either NSAID-induced or idiopathic (non-*H. pylori*/non-NSAIDs) ulcers.

Pathophysiology

Gastro-duodenal ulceration can be caused by any mechanism that directly or indirectly damages the gastric mucosa (e.g., drugs, ischemia, trauma, etc.) (Table 51.1; Fig. 51.1). Acid and pepsin play important roles in chronic *H. pylori*-induced PUD (e.g., Schwarz's dictum "no acid—no ulcer"). In the early twentieth century, peptic ulcers had been identified as being related to poor wound healing based on the observation that similar sized wounds produced adjacent to a

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N. T. Nguyen et al. (eds.), *The AFS Textbook of Foregut Disease*, https://doi.org/10.1007/978-3-031-19671-3_51

Table 51.1 Non-*H. pylori*/non-NSAID causes of PUD

Non-NSAID medications/drugs with ulcerogenic potential
Bisphosphonates
Glucocorticoids
Iron supplements
Potassium (especially wax matrix formulations)
Sirolimus
Spironolactone
Chemotherapy (e.g., 5-fluorouracil)
Molecular targeted therapy (e.g., erlotinib)
Localized radiation therapy (e.g., Y-90)
Cocaine
Non-H. pylori infections with ulcerogenic potential
Herpes simplex virus type I (HSV-I)
Cytomegalovirus (CMV)
Rare infections (e.g., candidiasis, mucomycosis, syphilis, tuberculosis, Epstein Barr virus)
Mechanical causes of ulcers
Obstruction (e.g., annular pancreas)
Foreign body
Post-surgical (e.g., marginal ulcer after Roux-en-Y gastric bypass, antral exclusion)
Acid hypersecretory states
Gastrinoma (including in the setting of multiple endocrine neoplasia type 1, MEN 1)
Systemic mastocytosis
Myeloproliferative disorders
Antral G-cell hyperfunction
Ischemic causes of ulcers
Arterial/venous diseases
Non-occlusive ischemia
Inflammatory and infiltrating disease
Sarcoidosis
Crohn's disease
Other gastroenteritides (e.g., eosinophilic gastroenteritis)
Other
Idiopathic hypersecretory duodenal ulcer
Stress ulcers in the intensive care unit

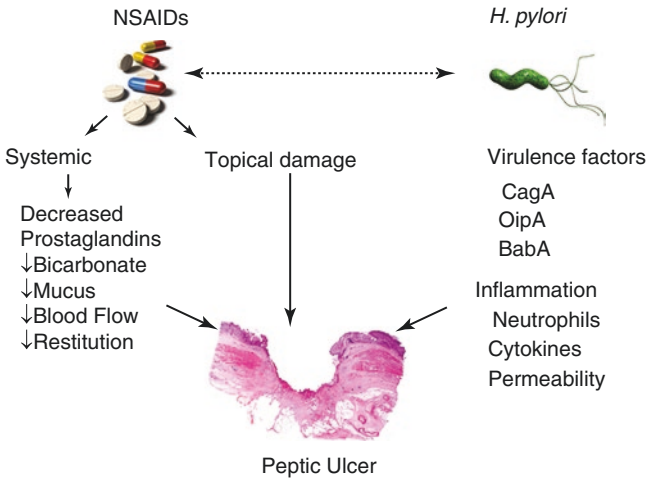

Fig. 51.1 *Helicobacter pylori* and NSAIDs are the most common causes of gastric and duodenal ulcers. (From: Yamada's Atlas of Gastroenterology. 4th ed. Hoboken: Wiley-Blackwell, 2008:237–250, with permission)

chronic ulcer healed rapidly, whereas the ulcer did not. Ulcers and gastric cancer had long been known to be tightly associated with gastritis. The breakthrough came in the 1980s when *H. pylori* infection was identified as the cause of ulcer and gastric cancer-associated gastritis.

The most common site of a gastric ulcer due to *H. pylori* is on the lesser curve near the gastric angle. The ulcer site moves proximally at, or just ahead of, the *H. pylori*-associated inflammatory front that advances proximally from the antrum (Fig. 51.2). Gastric ulcers occurring at the greater curvature of the antrum are often due to gastrotoxic medications which when swallowed fall to this most dependent portion of the stomach.

H. pylori-induced gastric inflammation results in defective downregulation of acid secretion associated with antral acidification or distention. The average *H. pylori* duodenal ulcer is associated with an increase in duodenal acid load related to the increased parietal cell mass and *H. pylori*-related dysregulation in acid secretion resulting in an average pH in the duodenal bulb of below 4. The duodenum is normally protected against *H. pylori* infection because bile, which is normally present, inhibits growth of the bacterium. However, the high duodenal acid load precipitates glycine conjugated bile acids allowing *H. pylori* to colonize ectopic gastric cells in the duodenum (Fig. 51.3). Duodenal inflammation, acid secretion by gastric metaplasia/heterotopia, and the small deformed duodenal bulb with abnormal duodenal bulb motility together with smoking which both increases acid secretion and inhibits duodenal and pancreatic bicarbonate secretion combine to produce the perfect storm resulting in chronic duodenal ulcer disease. The presence of post-bulbar ulcers should raise suspicion of a non-*H. pylori* etiology such as a hypersecretory state (e.g., Zollinger-Ellison syndrome, systemic macrocytosis), drug-induced ulcers, Crohn's disease, etc. (Table 51.1).

H. pylori

Approximately, half of the world's population is currently infected with *H. pylori*. The prevalence varies greatly from as low as <20% in affluent young North American adults to >80% in rural Africa. The populations most at risk are characterized as disadvantaged with low socioeconomic status, poor sanitation, lack of running water, overcrowding, bed sharing as children, poor household hygiene, etc. Most often the infections are acquired in childhood and are lifelong. *H. pylori* infection is the most common cause of peptic ulcers, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue (MALT) tumors.

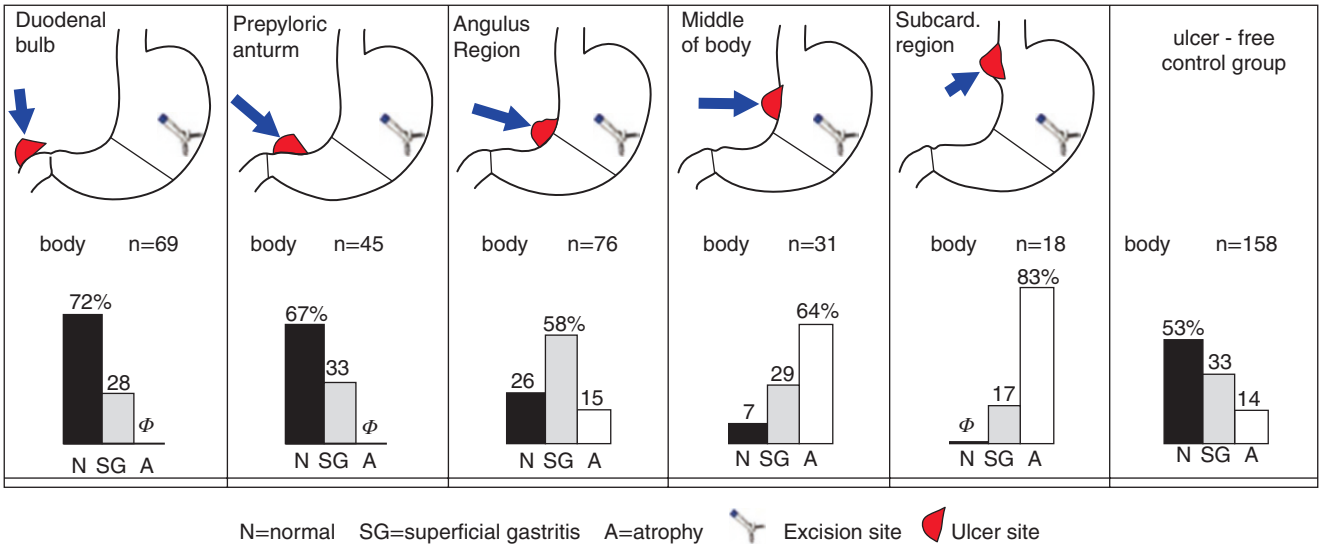

Fig. 51.2 The ulcer site moves proximally at, or just ahead of, the *H. pylori*-associated inflammatory front that advances proximally from the antrum. (From World J Gastroenterol. 2014;20(18):5191–204, with permission)

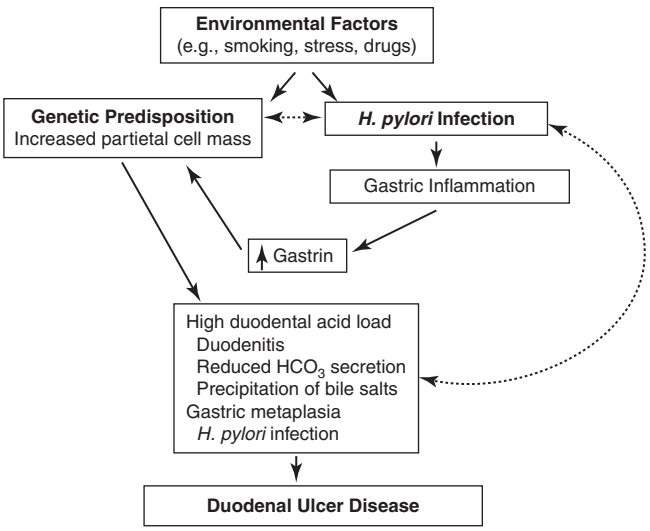

Fig. 51.3 The high duodenal acid load precipitates glycine conjugated bile acids allowing *H. pylori* to colonize ectopic gastric cells in the duodenum. (From: Yamada's Atlas of Gastroenterology. 4th ed. Hoboken: Wiley-Blackwell, 2008:237–250, with permission)

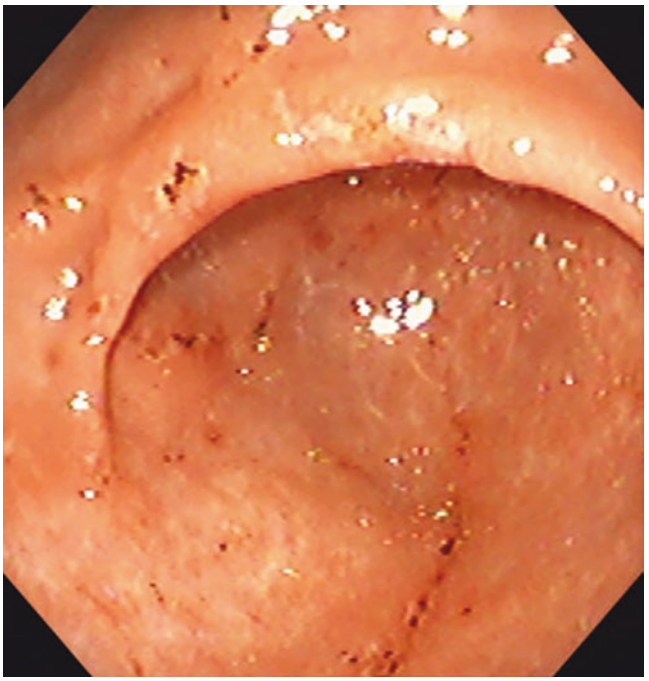

Fig. 51.4 Photograph of the distal stomach after aspirin ingestion showing multiple small erosion and red dots characteristic of acute NSAID injury

NSAIDs

NSAIDs inhibit prostaglandin synthesis which is critical in maintaining the normal protective mucosal barrier. NSAIDs decrease mucosal production of bicarbonate and glutathione as well as mucosal blood flow. The risk of developing an NSAID ulcer depends in part on the specific NSAID, the dose, and the duration of therapy (Fig. 51.4). When given at full anti-inflammatory doses, the NSAIDs with highest risk for PUD are ketorolac (adjusted RR 14.4, 95% CI 5.2–39.9) and piroxicam (RR 12.6, 95% CI 7.8–20.3). Naproxen (RR 7.3, 95% CI 4.7–11.4), ibuprofen (RR 4.1, 95% CI 3.1–5.3), and diclofenac (RR 3.1, 95% CI 2.3–4.2) have moderate risk. Long-term studies have confirmed that the selective COX-2 inhibitor, celecoxib, has a low to moderate risk when full anti-inflammatory doses are needed. When NSAIDs are primarily used for analgesia, low-dose ibuprofen (200 mg) or

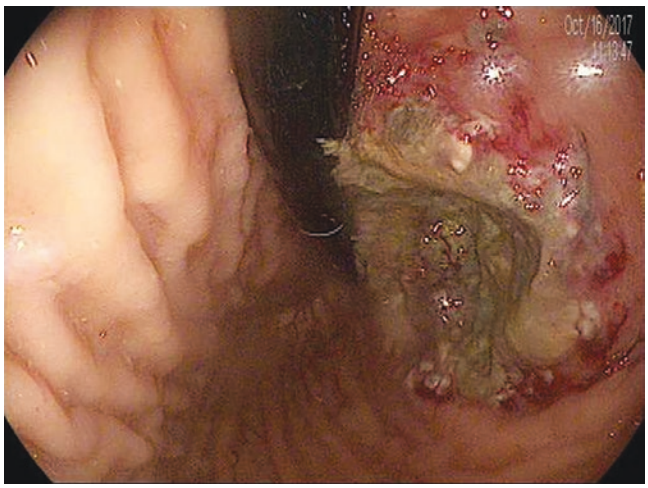

Fig. 51.5 A case of giant deep gastric ulcer due to mucormycosis in a patient status-post lung transplant for cystic fibrosis

naproxen OTC (224 mg) provides near near-maximum analgesia with low ulcer risk. Because of its widespread use for cardiovascular prophylaxis, aspirin is overall probably the most common cause of ulcers.

Non-*H. pylori*/Non-NSAID Causes of PUD

Although there are many non-*H. pylori*/non-NSAID causes of PUD (Table 51.1), false-negative testing for *H. pylori* and failure to solicit a history or denial of NSAIDs or gastrotoxic drugs remain common reasons for inappropriately reaching the conclusion of non-*H. pylori*/non-NSAIDs PUD. In addition, rare causes of ulcers (e.g., diffuse B-cell lymphoma and mucormycosis) may appear in immunocompromised patients (Fig. 51.5). Nonetheless, the relative frequency of idiopathic ulcers has increased in parallel with the decline in previously more common causes.

Clinical Manifestations

Although gastric and duodenal ulcers, especially among NSAID users, may remain asymptomatic until discovered at endoscopy or presentation as a complication, classic *H. pylori* peptic ulcer disease generally is associated with symptoms. The most common symptom, present in roughly 80% of patients with endoscopically evident PUD, is epigastric pain. Ulcer pain is typically located in the epigastrium (sometimes to the left or right), is described as "burning" pain, and is occasionally associated with radiation to the back, especially with posterior penetration of ulcers. Classically, *H. pylori* ulcer pain relates to the acid cycle: it is generally absent upon waking, appears 2–3 h after breakfast when meal-stimulated gastric acid exceeds the buffering capacity of the meal, and is relieved by food (i.e., food, milk, or antacids provide reliable, temporary relief). If a late-night snack is taken, pain may awaken the patient when the circadian pattern increases acid secretion (i.e., 11 PM to 2 AM). Symptoms are often periodic in that they resolve only to reappear again. Ulcer-like pain is a type of dyspepsia that is present in 21% (range of 1.8–57%) of adults, with greater prevalence in women, smokers, NSAIDs users, and those with *H. pylori*. Although most patients with dyspepsia do not have PUD, it is recommended that all those with dyspepsia get tested for *H. pylori*, and if present, the infection should be cured.

Complications of Peptic Ulcer Disease

The incidence of complicated PUD (i.e., bleeding, perforation, or hospitalizations) has fallen along with the decline in *H. pylori*; however, familiarity with the complications of PUD is critical to aid in prompt recognition and potentially life-saving treatments. The strongest risk factors for complicated PUD are history of PUD complications or concomitant use of aspirin or other NSAIDs in the setting of *H. pylori*.

Hemorrhage

Acute upper GI hemorrhage presenting clinically as hematemesis, coffee ground emesis, melena, and occasionally hematochezia is the most common complication of PUD, accounting for approximately 70% of PUD complications. The annual incidence of hemorrhage from PUD ranges from 19 to 57 cases per 100,000 individuals. NSAID-induced ulcers are more likely to bleed, especially in the presence of coexisting *H. pylori* infection. In addition, use of concomitant antiplatelet therapies (e.g., clopidogrel) and steroids increases risk of bleeding PUD with NSAIDs, whereas anticoagulation does not. Odd ratios for bleeding peptic ulcers associated with *H. pylori* and NSAIDs are 1.8 and 4.8, respectively, and increase to 6.1 in individuals with both risk factors.

Perforation

Perforation occurs in 2–10% of patients with PUD, with an annual incidence of perforation ranging from 4% to 14% per 100,000 individuals. Perforation typically presents as sudden, severe, diffuse abdominal pain, tachycardia, and rigid abdomen. Most perforations occur in the prepyloric stomach; the second most common site is the duodenal bulb.

Gastric Outlet Obstruction

Gastric outlet obstruction accounts for up to 3% of PUD complications. Ulcers in the pyloric channel or duodenum can cause gastric outlet obstruction with associated symptoms of early satiety, bloating, epigastric pain shortly after eating, and weight loss. With the decline in *H. pylori*-induced PUD, gastric malignancies are becoming a more common cause of gastric outlet obstruction.

Penetrating/Fistulizing PUD

Peptic ulcers may penetrate through the wall of the stomach/duodenum and into adjacent organs. Clues to presence of a penetrating ulcer include the pain becoming more severe, lasting longer, referred to new locations (typically the back), and failure to be relieved by food or antacids. Penetration of ulcers into adjacent structures may cause a wide variety of signs and symptoms depending on involved structures: gastro-duodenocolic with halitosis, feculent vomiting, and post-prandial diarrhea; vascular structures such as the aorta or cystic artery may present with exsanguination, biliary tree with choledochoduodenal fistula and extrahepatic biliary obstruction, and pancreatic duct with mild hyperamylasemia and rarely pancreatitis.

Diagnostic Testing

The choice of diagnostic test depends on the presentation, the patient's age, prior history of PUD, family history, physical exam, review of drugs used, and routine laboratory (especially anemia). For an otherwise healthy patient with dyspepsia, the first question might be "Does this patient have an *H. pylori* infection?" The Houston consensus for *H. pylori* testing recommends a proactive approach to *H. pylori* testing and treating all who are positive (Table 51.2). Testing options include non-invasive urea breath test, stool antigen test, or endoscopy with gastric biopsies. For a young healthy person (e.g., <60), non-invasive testing would be the best initial choice as cure of *H. pylori* in a patient with uncomplicated peptic ulcer will also cure the ulcer disease. However, in an older patient, one might consider early endoscopy with gastric biopsies to exclude gastric cancer and to examine the health of the gastric mucosa (e.g., atrophic vs. non-atrophic). For complicated disease, endoscopy would generally be the first choice. Indications for endoscopy first in patients <60 include significant weight loss (>5% usual weight over 6–12 months), overt GI bleeding, and >1 alarm feature (unintentional weight loss, dysphagia, odynophagia, unexplained iron deficiency anemia, persistent vomiting, palpable mass or lymphadenopathy, or family history of upper GI cancer).

Endoscopic Evaluation of Ulcers

The endoscopy report should include a description (round, smooth base vs. nodular, deep, overhanging irregular margins, protruding mass, etc.). The folds surrounding a gastric ulcer crater should be examined in terms of nodularity, fusion, clubbed, or stop short of the ulcer margin and (when overhanging, irregular, thickened ulcer margins appear, etc.) location along with high-quality photographs. The appearance of the gastric mucosa should also be described (e.g., atrophic vs. normal, smooth vs. nodular, fold size, and thickness). For gastric ulcers, all four quadrants and the base should be biopsied. For both gastric and duodenal ulcers, high-quality photography should be done (Fig. 51.6). The mucosa surrounding the ulcer should also be examined for scars or evidence of prior ulcers. In both gastric and duodenal ulcers, gastric biopsies of the antrum and corpus should be taken for *H. pylori* using the Sydney protocol (Fig. 51.7).

Table 51.2 Recommendations to test for *H. pylori* infection

Risk factor
With suspected *H. pylori* infection (e.g., active DU)
With current or past gastric or duodenal ulcers
With uninvestigated dyspepsia
With gastric mucosa-associated lymphoid tissue lymphoma
Family members residing in same household of patients with proven active *H. pylori* infections
Family history of peptic ulcer disease
With family history of gastric cancer
First-generation immigrants from high prevalence areas
High-risk groups (e.g., in the United States: Latino and African American racial or other ethnic groups)

Based on Clin Gastroenterol Hepatol. 2018;16(7):992–1002.e6

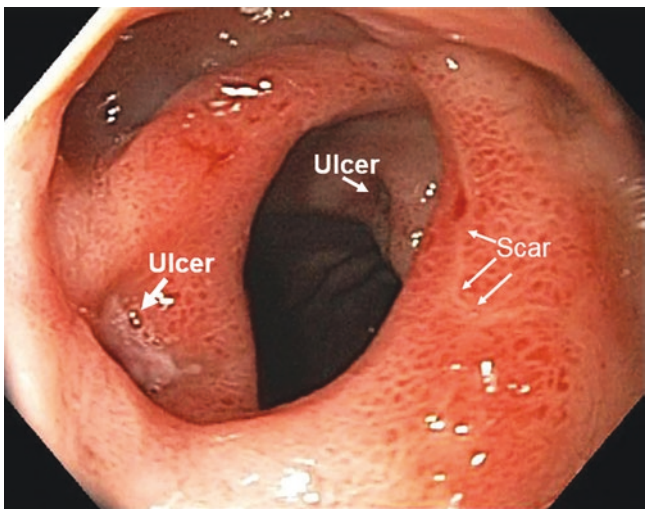

Fig. 51.6 Photograph of a very scarred duodenal bulb with active duodenal ulcers, scars from prior healed ulcers, and inflamed mucosa with lack of a villus pattern

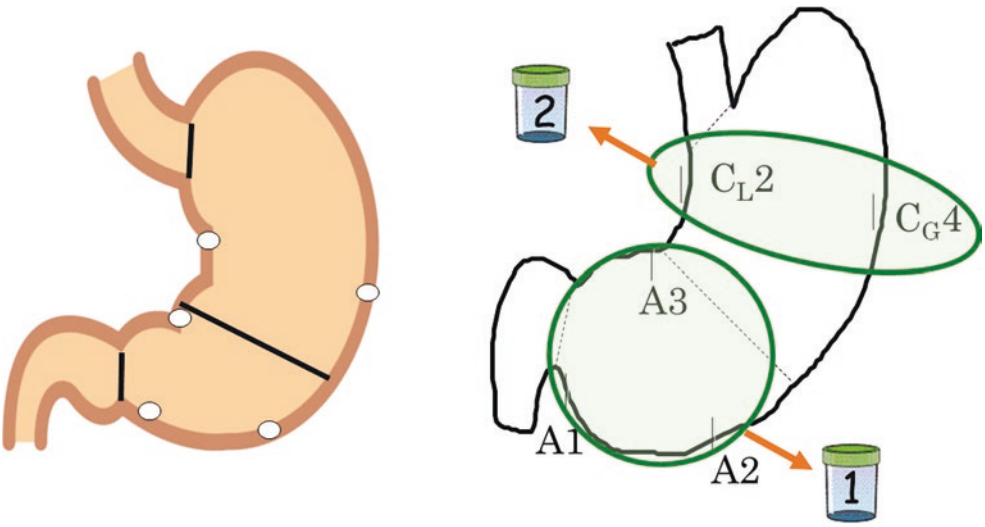

Fig. 51.7 To identify *H. pylori* and map the stomach to determine the extent and severity of damage, gastric biopsies of both the antrum and corpus should be taken for *H. pylori* using the Sydney protocol. Illustration of the biopsy sites for using the Sydney system to assess the status of the gastric mucosal and search for the presence of *H. pylori*. The figure also shows that all antral biopsies should be combined into one jar of formalin and the corpus biopsies in a separate bottle

Diagnostic Tests for *H. pylori* Infection

A wide variety of tests are available including serologic testing for *H. pylori* antibodies, stool antigen tests, the urea breath test, histology with special stains, culture, and molecular tests for the *H. pylori* genes. Serology is no longer recommended for initial testing because it has relatively poor specificity and sensitivity. A positive anti-*H. pylori* serology alone should not be the sole criteria for treatment as it may remain positive for months to years after successful *H. pylori* treatment. Treatment should be based on the results of a test for active infection such as the urea breath or stool antigen test. False-positive tests for active infection are rare when using tests that require a high density of *H. pylori* such as the rapid urease test, urea breath test, stool antigen test, or gastric mucosal biopsy. However, false-negative results with these tests may occur if there has been exposure to antibiotics with activity against *H. pylori* within 4 weeks or use of PPIs or bismuth-containing compounds within 2 weeks of testing as these may lower *H. pylori* density below levels necessary for detection. While upper gastrointestinal bleeding does not impact the yield of gastric biopsies for *H. pylori*, PPI use in the setting of bleeding may reduce *H. pylori* numbers and potential to limit diagnostic stigmata of *H. pylori* infection to the presence of mucosal inflammation.

Treatment of *H. pylori* Infection

Recently, susceptibility testing for *H. pylori* has become universally available in the USA using culture of gastric biopsies, next generation sequencing of gastric biopsies (fresh or formalin-fixed paraffin blocks) or stools (American Molecular Laboratories), or by polymerase chain reaction performed on stools for clarithromycin at Mayo Clinical Laboratories [21]. The universal availability of susceptibility testing eliminates empiric use of clarithromycin, levofloxacin, and metronidazole triple therapies. Therapies are now divided into those regimens that can be used empirically—provided they reliably achieve high cure rates—and those that should only be given as susceptibility-based regimens. Susceptibility testing should be considered for all treatment failures in order to evaluate why treatments failed. If the infection remains susceptible to the antibiotic used, consider issues with adherence or duration of therapy. When resistance has emerged during treatment—often due to heteroresistance meaning that subset of bacterial cells present was resistant to a treatment—the next therapy can be chosen rationally based on the results of susceptibility testing. The alternative for failures following susceptibility-based therapy is to choose another antibiotic from the original susceptibility test and forgo repeating the susceptibility testing to identify why treatment failed. In mid-2022, the potassium competitive acid blocker (P-CAB) vonoprazan was approved for treatment of *H. pylori* infections in the USA. However, the cure rates were unexpectedly and unacceptably low for both P-CAB-containing regimens—vonoprazan, amoxicillin, and clarithromycin triple therapy and vonoprazan with high dose amoxicillin dual therapy—as well as for the lansoprazole clarithromycin triple therapy control group, even with susceptible infections. These results are unprecedented and vonoprazan-containing regimens should not be used until they are optimized to reliably achieve acceptable cure rates. Of note, more than 90% of the clarithromycin in the vonoprazan triple therapy was unnecessary as the cure rates with resistant and susceptible strains were remarkably similar such that the clarithromycin was primarily only contributing to global antibiotic resistance, is another reason not to prescribe it. Current treatment regimens for *H. pylori* are shown in Table 51.3.

Table 51.3 Recommended *H. pylori* therapies

Empiric therapies	
Bismuth quadruple therapy Bismuth subsalicylate q.i.d. 14 days	Bismuth (e.g., PeptoBismol®) 2 tablets or 2 capsules q.i.d. 30 min before meals, tetracycline HCl 500 mg and metronidazole 500 mg 30 min after meals q.i.d. plus a PPI, 30 min b.i.d. before meals and bedtime (see PPP below)
Bismuth quadruple therapy Bismuth subsalicylate b.i.d. 14 days	Bismuth (e.g., PeptoBismol®) 2 tablets or 2 capsules q.i.d, 30 min before meals, tetracycline HCl 500 mg b.i.d. and metronidazole 500 mg, 30 min after meals q.i.d. plus a PPI, b.i.d. 30 min before morning and evening meals (see PPP below)
Bismuth quadruple therapy Pylera® formulation (bismuth citrate) 14-days	Give combination tablets with means plus a PPI, q.i.d. 30 min before meals and bedtime (see PPP below) (see text for specific details). 14-day therapy recommended with metronidazole resistance likely.
Rifabutin triple therapy. 14-days	Rifabutin 150 mg b.i.d., amoxicillin 1 g t.i.d. plus 40 mg of esomeprazole or rabeprazole 30 min before meals b.i.d. (see PPP below) (see text for specific details)
Talicia® formulation of rifabutin triple therapy. 14-days	As directed by package insert
Therapies only effective as susceptibility-based therapy *Do not use empirically unless proven to cure >90% locally*	
Clarithromycin triple therapy. 14-days	Clarithromycin 500 mg b.i.d., amoxicillin 1 g b.i.d., 30 min before meals, (see PPP below)
Metronidazole triple therapy. 14-days	Metronidazole 500 mg b.i.d., amoxicillin 1 g b.i.d., 30 min before meals, (see PPP below)
Levofloxacin triple therapy. 14-days[a]	Levofloxacin 500 mg in a.m., amoxicillin 1 g b.i.d., 30 min before meals, (see PPP below)
PPI dose should at a minimum be 40 mg of omeprazole or equivalent b.i.d. We recommend 40 mg of rabeprazole or esomeprazole b.i.d.	
Therapies that remain to be optimized for effective local use	
PPI or P-CAB-amoxicillin dual therapies	In western societies dual therapies are generally ineffective and remain to be optimized before the can be recommended
Therapies that contain unneeded antibiotics and should not be used	
All include at least one antibiotic that offers no therapeutic benefit and only serves to increase global antimicrobial resistance: concomitant, hybrid, reverse hybrid, sequential therapies, vonoprazan clarithromycin triple therapy.	

[a]The FDA recommends fluoroquinolones be used as a last choice because of the risk of serious side effects (adapted from ref. [21])

Screen for and Stop NSAIDs in Patients with PUD

Cessation of NSAIDs or other gastrotoxic drugs is critical to healing and preventing recurrence of PUD. It is possible to stop the PPI after ulcer healing of an uncomplicated ulcer in someone requiring aspirin for cardiovascular prophylaxis. For NSAID users with an uncomplicated ulcer, it is possible to restart the NSAID at the lowest effective dose or switch to celecoxib 200 mg or less per day along with a PPI, at least 30 mg of omeprazole equivalent daily (e.g., 20 mg of esomeprazole or rabeprazole). For complicated ulcers (e.g., GI bleeding), NSAIDs of all types should be avoided in the future.

Acid Suppressive Therapy

If an uncomplicated *H. pylori* PUD is detected and *H. pylori* is treated, PPI use is not indicated beyond the 14-day *H. pylori* treatment. For complicated PUD, antisecretory therapy should not be stopped until cure of the *H. pylori* infection has been proven. If non-invasive testing is planned, it is best to switch to a histamine-2-receptor antagonist for the 2 weeks prior to testing. Large duodenal and gastric ulcers, especially those due to NSAIDs, may a need longer duration of PPI therapy. Idiopathic ulcers require continued long-term PPI therapy possibly even for decades.

Other Suggestions to Promote Ulcer Healing

Smoking cessation and possibly limiting alcohol intake to one drink per day may help promote ulcer healing. However, dietary therapies and stress management have not been shown to impact ulcer healing and may require clarification for patients who may perceive that these contributed to their PUD.

Evaluation for Suspected Zollinger-Ellison Syndrome

Zollinger-Ellison syndrome (ZES) should be suspected in patients with multiple or refractory peptic ulcers, ulcers distal to the duodenal bulb, PUD with diarrhea, steatorrhea, enlarged gastric folds, MEN1, family history of PUD or MEN1, or diarrhea responsive to PPIs (Fig. 51.8). When ZES is suspected, a fasting serum gastrin concentration and gastric pH should be measured. Fasting serum gastrin levels >1000 pg/mL in the

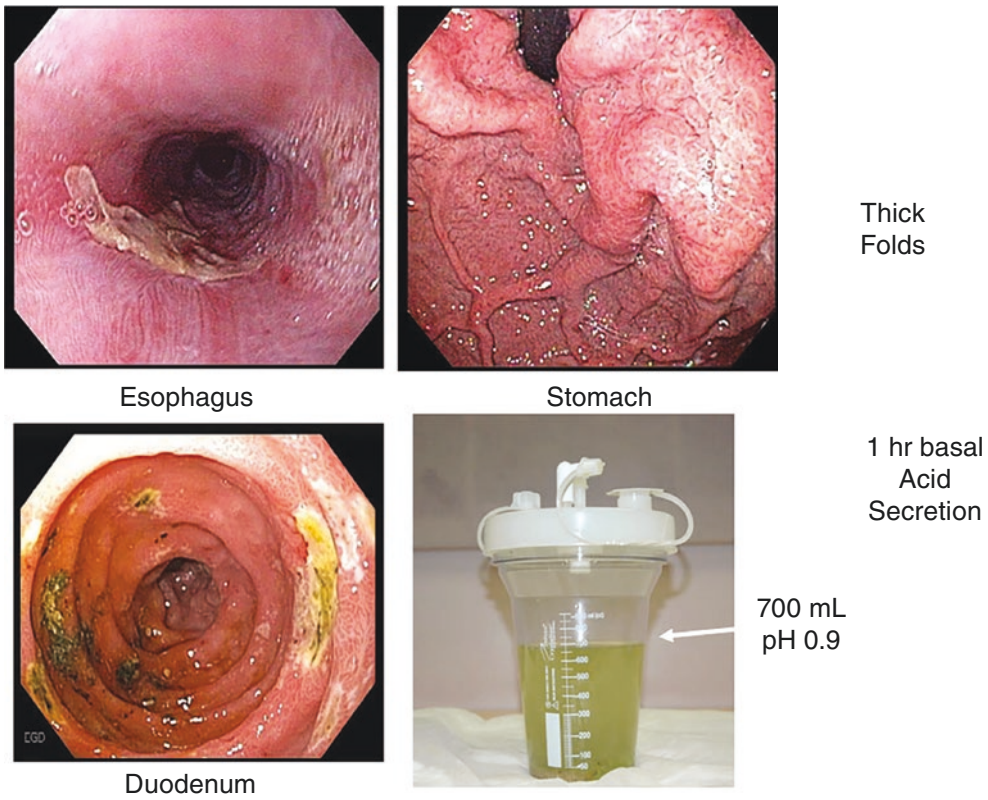

Fig. 51.8 A collage showing the spectrum of findings in Zollinger-Ellison syndrome with endoscopic findings of esophagitis, large gastric folds, extensive duodenal damage, and a very large volume of highly acidic gastric fluid obtained in 1 h of basal acid secretion. (Image courtesy of Dr. Clark Hair. Michael E. DeBakey VA Medical Center)

presence of gastric pH <2 is diagnostic of ZES. However, two-thirds of patients with ZES have fasting gastrin levels <1000 pg/mL; if the pH is <2, then a secretin stimulation test should be performed. Secretin stimulation testing requires changing from PPIs to H2RAs 1 week prior to testing, two fasting serum gastrin levels, and infusion of secretin, and repeat gastrin levels at 2, 5, and 10 min later. Positive testing is defined as an increase in gastrin levels >120 pg/mL over basal fasting levels (sensitivity 94% and specificity 100%). Secretin testing should not be done in patients with severe abdominal pain, vomiting, diarrhea, or multiple ulcers as these patients are at risk for life-threatening consequences of stopping acid suppression. Tumor localization studies (e.g., EGD/EUS, Gallium-68 DOTATATE PET imaging) are used to search for gastrinomas. Secondary hypergastrinemia is typically due to achlorhydria (e.g., atrophic gastritis, pangastritis-associated *H. pylori*, renal failure, post-vagotomy, and with use of PPIs) which can be differentiated from hypersecretory states by measuring fasting gastric pH.

Stress Ulcers

Stress ulcers are defined as acute mucosal injury and disruption of the mucosal barrier due to critical illness, classically burns (Curling's ulcer) and intracranial injuries (Cushing's ulcer). Stress ulcers are often asymptomatic and found during endoscopy for other reasons (e.g., percutaneous endoscopic gastrostomy tube placement). Bleeding is the most common presentation and occurs in <1% to 17% of stress ulcers depending in part on use of stress ulcer prophylaxis. The greatest risk factors for the development of stress ulcers are respiratory failure requiring mechanical ventilation for >48 h and coagulopathy. Other risk factors include sepsis, shock/use of vasopressors, corticosteroids, severe burns (>35% of the body surface area), recent history of gastrointestinal bleeding, head/spinal cord injuries, intensive care unit stays >1 week, and hepatic, renal, or multi-organ failure.

Measures for preventing stress ulcers include both non-pharmacologic (early enteral nutrition, oro-/nasogastric feeding tube placement without unnecessary suctioning, resuscitation with fluid and blood as needed, and correction of coagulopathy) and pharmacologic therapy such as antacids, HRAs, prostaglandins, or PPIs. Stress ulcer prophylaxis, although standard of care in some ICUs, is not necessary in lower-risk populations such as general medicine patients. Although stress ulcer prophylaxis with PPIs may be superior to HRAs for prevention of clinically significant bleeding, PPIs may not add significant benefit beyond early enteral nutrition. Lastly, in many patients the use of PPIs is inappropriately continued after discharge from hospital.

Endoscopic, Interventional Radiology, and Surgical Treatments for Complicated PUD

Most of this section will focus on management of hemorrhage due to PUD. Penetrating PUD may be identified at the time of endoscopy or on cross-sectional imaging and typically responds rapidly to antisecretory therapy and eradication of *H. pylori*.

Management of Hemorrhage Due to PUD

PUD bleeding stops spontaneously in approximately 75% of patients. The management strategy consists of stopping ongoing bleeding and preventing rebleeding. Medical management of bleeding PUD includes resuscitation with intravenous fluids and blood transfusion to a hemoglobin goal of 7–9 g/dL, endoscopy to identify the cause and apply treatment if appropriate, and PPI therapy to stop acid-induced damage and promote ulcer healing. Nasogastric tube lavage is no longer recommended, but prokinetic agents prior to endoscopy may improve gastric visualization.

Early endoscopy allows one to diagnose the cause of bleeding, to stratify the risk for rebleeding, and, when appropriate, to endoscopically intervene. The Forrest classification (Fig. 51.9) divides untreated peptic ulcers into low and high risk of rebleeding. Any lesion other than those with flat pigmented spots (class IIc) or clean base ulcers (class III) are considered higher risk for rebleeding and should receive endoscopic therapy as well as intravenous PPI therapy (80 mg push then 8 mg/h) for at least 24 h preferably for 72 h followed by oral PPI therapy with 40 mg of esomeprazole or rabeprazole. Low risk lesions (class IIc and III) that do not require endoscopic therapy and can be treated with 24 h of IV continuous PPI therapy followed by oral PPI therapy (e.g., 40 mg of esomeprazole or rabeprazole b.i.d.). PPIs require 3–4 days to reach maximum effectiveness when given orally or by intermittent injection. Whether given orally, intravenously, or intramuscularly the effects on acid secretion are the same for an individual PPI. The time the pH remains above 3 or 4 (to inhibit pepsin) differs among PPIs and dosages. It is lowest with pan-

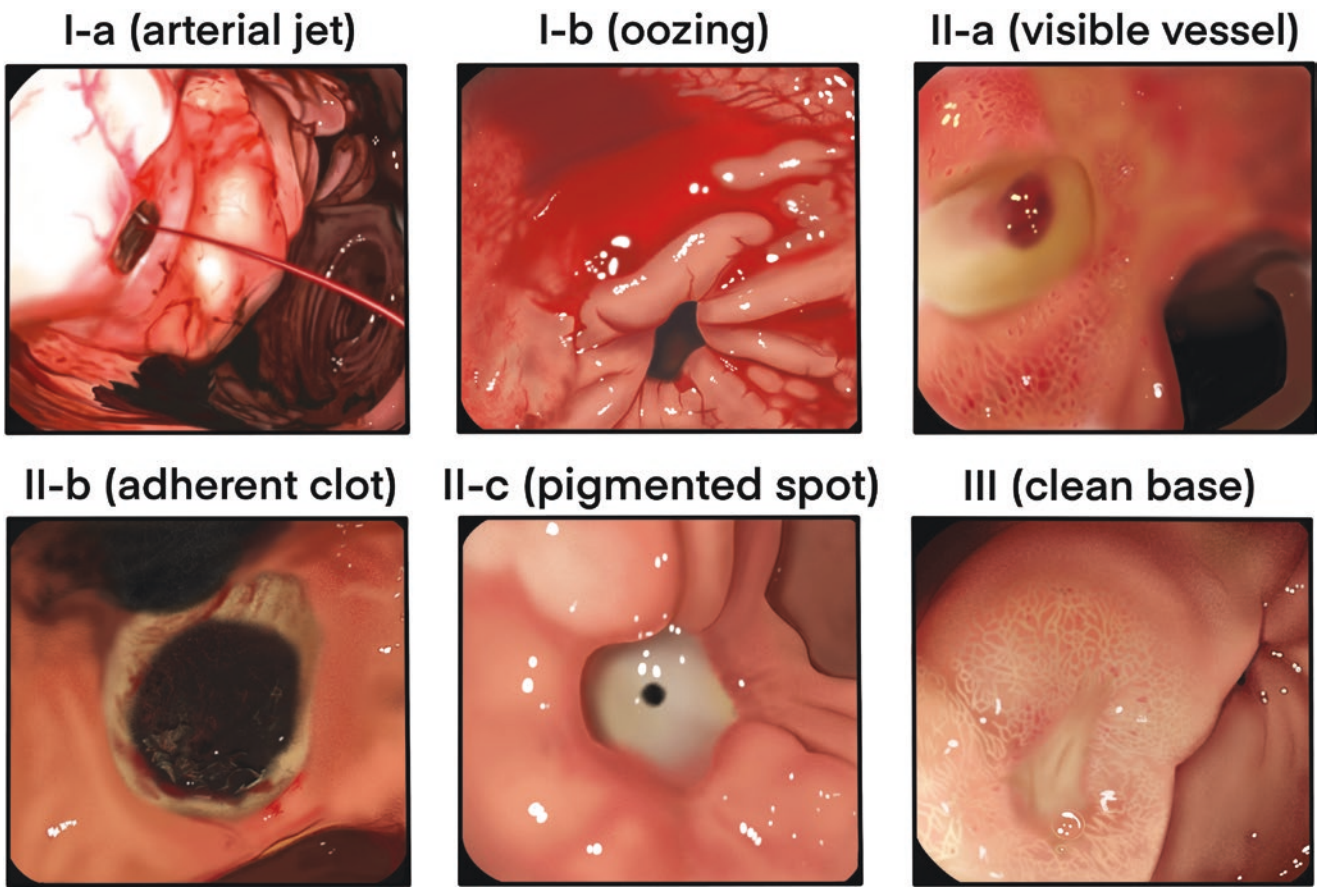

Fig. 51.9 The Forrest classification divides untreated peptic ulcers into low and high risks of rebleeding

Table 51.4 Potency of PPIs based on omeprazole equivalents (OE)

Drug at lowest available dosage	OE (mg)
Pantoprazole 20 mg	4.5
Lansoprazole 15 mg	13.5
Omeprazole 20 mg	20
Esomeprazole 20 mg	32
Rabeprazole 20 mg	36

From: Clin Gastroenterol Hepatol. 2018;16(6):800–8.e7

toprazole and higher with 40 mg of esomeprazole or rabeprazole [22] (Table 51.4).

The relative potency of pantoprazole is such that 20 mg of pantoprazole is equivalent to 4.5 mg of omeprazole; thus, the most commonly used dose of pantoprazole, 40 mg, is equal to 9 mg of omeprazole. The most effective acid control is obtained by continuous infusion of a PPI.

For high-risk ulcers, thermal coagulation or hemoclips combined with injection of epinephrine is recommended. Hemostatic nanopowder spray (Hemospray) may be used as a temporizing measure when other endoscopic techniques fail to stop the bleeding. Monotherapy with epinephrine or nanopowder is associated with rebleeding in up to 50% of patients and is not recommended.

Angiography with embolization by interventional radiology and surgical management should be considered for bleeding PUD when endoscopic management fails. Success rates for IR embolization for acutely bleeding PUD range from 52% to 98% with recurrent bleeding occurring in 10–20% of cases. The interventional radiology approach is less invasive than surgery and is preferred for hemorrhage into the biliary tree or pancreatic duct. Compared to surgical approaches, angiography is associated with lower mortality and greater risk of rebleeding and further interventions. Studies differ on whether or not there is a greater risk of complications from IR angiography.

Surgery for bleeding PUD may include oversewing of the ulcer (to ligate the bleeding artery) with truncal vagotomy (to reduce acid secretion) and pyloroplasty, antrectomy with gastrojejunostomy (Billroth II procedure), or selective vagotomy. Emergency surgery for PUD bleeding carries a mortality risk of over 30% and is becoming increasingly uncommon.

Management of Other Complications of PUD

Patients with perforations due to PUD require intravenous fluids, correction of electrolyte abnormalities, broad-spectrum antibiotics, and high-dose iv PPI, and most require surgery (open or laparoscopic). The most common surgery for perforated PUD is oversewing of the ulcer with a Graham patch. Perforations at the pylorus may be treated with a pyloroplasty which incorporates the ulcer in the closure and truncal vagotomy either done laparoscopically or with open laparotomy. Patients with contained perforations and/or development of gastrointestinal fistulae maybe managed conservatively without surgery.

Patients with partial gastric outlet obstruction should be treated with high-dose intravenous PPI, avoidance of NSAIDs, and eradication of *H. pylori*. Endoscopic dilation and surgery should be considered in those patients with complete gastric outlet obstruction and/or those failing more conservative measures.

Conclusion

PUD is a classic disease with a new, emerging look that includes an increased prevalence of non-*H. pylori* causes of PUD, overall less complicated disease, and generally treatable ulcers given the advent of evidence-based management strategies (i.e., optimization of PPI use, eradication of *H. pylori*, and endoscopic techniques for hemostasis). Today's clinician is certain to encounter new challenges such as identifying etiologies of non-*H. pylori*/non-NSAID PUD, using antibiotic stewardship principles to mitigate increasing antibiotic resistance, and providing value-based care in an increasingly complex healthcare ecosystem.

Questions

1. A 60-year-old man was brought to the hospital because of sudden onset of severe abdominal pain. For several years he has experienced recurrent non-radiating epigastric pain typically relieved by food. He also smokes one pack of cigarettes and drinks two beers daily. He was in his usual state of health until early this morning when he was awakened from sleep by severe sharp mid-epigastric pain that has spread to include his entire abdomen. He appears in acute distress lying very still and taking shallow breaths. Vital signs are as follows: T 100.2 °F; respirations 29 per min and shallow; pulse 104 per min; BP 128/70; he refused to sit up; and PO_2 saturation was 99%. Physical examination showed him to be in acute distress, lying on his back. Examination showed exquisite abdominal tenderness to light percussion and no bowel sounds. The liver and spleen were not felt. The remainder of the examination was normal. Laboratory shows a normal hemoglobin and elevated WBC count of 13,000 with 94% PMNs. Electrolytes, BUN, liver function tests, and urinalysis were normal.

   What is your most likely diagnosis?

   A. Perforated peptic ulcer
   B. Acute pancreatitis
   C. Acute cholecystitis
   D. Inflammatory bowel disease
   E. Intestinal obstruction

   Answer: A.

2. A 70-year-old man came to see you because of recurrent abdominal pain and diarrhea. He had been diagnosed with duodenal ulcer disease about 5 years ago and had been treated for *H. pylori* infection. He also has a long history of heartburn and was told he had erosive gastroesophageal reflux disease. He relates that he has loose stools approximately 5 times daily for 21 years. Since treatment for *H. pylori*, he has taken 20 mg of omeprazole daily. One year ago he experienced hematemesis and melena, was hospitalized for 3 days, and received blood transfusions. Upper gastrointestinal endoscopy showed a normal appearing mucosa with an ulcer in the duodenal bulb and another in the third portion of his duodenum. Gastric biopsy showed no *H. pylori*. He was told increase the omeprazole to twice a day. His heartburn, abdominal pain, and loose stools decreased. His vital signs, physical examination, and routine laboratory tests are normal.

   What is your most likely diagnosis?

   A. Crohn's disease
   B. Irritable bowel syndrome
   C. Functional bowel disease
   D. Zollinger-Ellison syndrome
   E. Food intolerance

Answer: D.

3. Which of the following medications does *not* need to be held prior to testing for *Helicobacter pylori* via endoscopic biopsy, stool antigen, or urea breath test?

   A. Bismuth-containing medications
   B. Histamine-2 receptor antagonists
   C. Antibiotics with activity against *H. pylori*
   D. Proton pump inhibitors

Answer: B. Histamine-2 receptor antagonists can be taken up until the day prior to *H. pylori* testing. Proton pump inhibitors should be discontinued 2 weeks or more, and antibiotics and bismuth-containing medications for 4 weeks or more before testing for *H. pylori*.

4. What is the omeprazole equivalent dose of pantoprazole 40 mg?

   A. 4.5 mg
   B. 9 mg
   C. 15 mg
   D. 30 mg

Answer: B. Pantoprazole 40 mg is equal to 9 mg of omeprazole. Dose equivalents should be considered when using proton pump inhibitor therapy to heal ulcers given that differences in potency of medications in the class may impact treatment outcomes.

Writing Help None

Support Dr. Graham is supported in part by the Office of Research and Development Medical Research Service Department of Veterans Affairs, Public Health Service grant DK56338 which funds the Texas Medical Center Digestive Diseases Center.

Potential Conflicts Dr. Graham is a consultant for RedHill Biopharma and Phathom Pharmaceuticals regarding novel *H. pylori* therapies and has received research support for culture of *Helicobacter pylori*. He is the PI of an international study of the use of antimycobacterial therapy for Crohn's disease and a consultant for Otsuka, Japan, regarding novel breath tests.

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