INTRODUCTION AND EPIDEMIOLOGY

**Peptic ulcer disease** is a chronic illness manifested by recurrent ulcerations in the stomach and proximal duodenum. Acid and pepsin are thought to be crucial to ulcer development, but the great majority of peptic ulcers are directly related to infection with *Helicobacter pylori* or nonsteroidal anti-inflammatory drug (NSAID) use.\(^1\),\(^2\) Gastritis is acute or chronic inflammation of the gastric mucosa and has various etiologies. Dyspepsia is continuous or recurrent upper abdominal pain or discomfort with or without associated symptoms (e.g., nausea, bloating).\(^3\) Dyspepsia may be caused by a number of diseases or may be functional.

Uncomplicated peptic ulcer disease has an incidence of more than 5 cases per 1000 persons per year, and about 10% of people living in the Western world will experience a peptic ulcer at some point during their lives.\(^4\),\(^5\) In the United States, peptic ulcer disease costs an estimated $5.65 billion per year in total direct and indirect costs.\(^6\) *H. pylori* infection, one of the main risk factors of peptic ulcer disease, is one of the most prevalent human infections in the world, affecting at least 50% of the world’s population.\(^7\) The age-adjusted prevalence of *H. pylori* infection is decreasing in industrialized countries, likely due to an improved standard of living\(^7\) and the increased use of proton pump inhibitors (PPIs) and antimicrobial therapy.\(^2\),\(^8\) This may explain the decreasing incidence of peptic ulcer disease in the United States, but this may be partially offset by the widespread use of low-dose aspirin and NSAIDs.\(^2\),\(^9\) Over 70 million prescriptions for NSAIDs are written, and over 30 billion tablets are sold over the counter annually in the United States.\(^10\) Risk factors for ulcers not due to *H. pylori* or NSAIDs include antiplatelet agents, stress, *Helicobacter heilmannii*, cytomegalovirus infections, Behçet’s disease, Zollinger-Ellison syndrome, Crohn’s disease, cirrhosis with portal hypertension, older age, and African American ethnicity.\(^2\)

Dyspepsia affects 20% to 40% of the world’s population.\(^3\) There is no consistent association with sex, age, socioeconomic status, smoking, or alcohol use; however, it is more common in people infected with *H. pylori* and who take NSAIDs, as well as some other medications.\(^3\)
Hydrochloric acid and pepsin destroy gastric and duodenal mucosa. Mucus and bicarbonate ion secretions protect mucosa. Prostaglandins protect mucosa by enhancing mucus and bicarbonate production and by enhancing mucosal blood flow, thereby supporting metabolism. The balance between these protective and destructive forces determines whether peptic ulcer disease occurs. *H. pylori* bacteria or NSAIDs are thought to be the causal agents of peptic ulcer disease in most cases. \(^1\), \(^2\) Although traditional treatment of peptic ulcers by various modalities heals most ulcers, eradication of *H. pylori* cures peptic ulcers in over 80% of patients whose ulcers are not associated with the use of NSAIDs.\(^7\), \(^1\)\(^1\)

*H. pylori* is a spiral, gram-negative, urease-producing, flagellated bacterium that is found living between the mucous gel and the mucosa. The bacterium's production of urease, cytotoxins, proteases, and other compounds is thought to disturb the mucous gel and cause tissue injury. In addition, increased gastrin levels and decreased mucus and bicarbonate production are associated with *H. pylori* infection. Chronic active (usually asymptomatic) gastritis is an almost universal finding with *H. pylori* infection, but only 1% to 10% of infected people develop peptic ulcer disease.\(^7\) It is unclear why most infected persons do not develop symptomatic peptic ulcer disease, but it most likely reflects an interaction of factors, including characteristics of host and pathogen (different virulence of strains of bacteria). In 2005, Marshal and Warren were awarded the Nobel Prize in Physiology or Medicine for their discovery of *H. pylori* and its role in gastritis and peptic ulcer disease.

*H. pylori* is a causative agent of mucosa-associated lymphoid tissue lymphoma, and eradication of infection causes a remission in a sizable percentage of patients with low-grade tumors.\(^7\) In addition, *H. pylori* infection is a risk factor for adenocarcinoma of the stomach, and as such, the World Health Organization has classified it as a human carcinogen.\(^7\) However, because the prevalence of gastric cancer in the United States is very low and the *H. pylori* infection rate is high, other factors undoubtedly are involved. It is not clear whether eradication of the infection reduces the risk of gastric cancer.\(^7\) *H. pylori* infection has been associated with the development of iron deficiency anemia, with possible mechanisms including decreased iron absorption and/or occult blood loss from chronic gastritis. A direct cause-and-effect relationship is yet to be determined.\(^1\)\(^2\), \(^1\)\(^3\) Improvement in the platelet count in some patients with idiopathic thrombocytopenic purpura has been demonstrated with *H. pylori* eradication, but much more work remains to be done in this regard.\(^1\)\(^2\), \(^1\)\(^4\)

NSAIDs inhibit prostaglandin synthesis, thereby decreasing mucus and bicarbonate production and mucosal blood flow, which allows ulcer formation. Gastrin-secreting tumors produce ulceration due to high levels of acid and pepsin production, but acid alone rarely causes ulceration. However, inhibition of acid secretion may allow ulcers to heal and is the basis for traditional ulcer treatments.

Hereditary factors cause a predisposition to peptic ulcer disease, as does smoking. There is an association between chronic renal failure, renal transplantation, cirrhosis, chronic obstructive pulmonary disease, and peptic ulceration, but the precise mechanism is unclear. Emotional stress may predispose to peptic ulcer disease, but diet and alcohol use do not.
Acute gastritis may be related to ischemia from severe illness (e.g., shock, trauma, severe burns, organ failure) or to the direct toxic effects of agents (e.g., NSAIDs, steroids, bile acids). *H. pylori* infection causes acute and chronic gastritis (both usually asymptomatic). Chronic gastritis may also be caused by autoimmune factors that destroy gastric parietal cells; this results in the loss of acid production and the loss of intrinsic factor production, which in turn cause malabsorption of vitamin B\(_{12}\) and, hence, pernicious anemia.

Dyspepsia has multiple causes. Endoscopy of patients with dyspepsia demonstrates that about 13% have erosive esophagitis, 8% have peptic ulcer disease, and less than 0.3% have gastric or esophageal cancer.\(^3\) Other abnormalities such as gastritis, duodenitis, and gastric erosions may be present, but these may or may not be related to symptoms. About 70% to 80% of patients have no definite abnormal findings on endoscopy and are said to have "functional dyspepsia."\(^3\) Patients with functional dyspepsia have evidence of abnormal gastric emptying, abnormal sensitivity to distention, abnormal ability of the stomach to distend with a meal, abnormalities in acid clearance, and abnormal duodenal sensitivity to acid. In addition, there appears to be an as yet poorly characterized interaction between the stomach and intestine and the central nervous system, which may contribute to symptoms.\(^3\)

**CLINICAL FEATURES**

Burning epigastric pain is the most classic symptom of peptic ulcer disease. The pain also may be described as sharp, dull, an ache, or an "empty" or "hungry" feeling. Pain may be relieved by ingestion of milk, food, or antacids, presumably due to buffering and/or dilution of acid. **Pain recurs as the gastric contents empty, and the recurrent pain may classically awaken the patient at night.** Pain tends to occur daily for weeks, resolve, and then recur in weeks to months. Postprandial pain, food intolerance, nausea, retrosternal pain, and belching are not related to peptic ulcer disease. Atypical presentations are common in those >65 years old, including no pain, epigastric pain not relieved by eating, nausea, vomiting, anorexia, weight loss, and bleeding.

A change in the character of typical pain may herald a complication. Abrupt onset of severe or generalized pain may indicate perforation with peritoneal spillage of gastric or duodenal contents. Rapid onset of mid-back pain may be due to posterior penetration into the pancreas, resulting in pancreatitis. Nausea and vomiting may indicate gastric outlet obstruction from scarring or edema. Vomiting of bright red blood or coffee-ground emesis or passage of tarry or melanotic stool or hematochezia may indicate ulcer bleeding.

On physical examination, the only positive finding in patients with uncomplicated peptic ulcer disease may be epigastric tenderness. This finding is neither sensitive nor specific for the diagnosis. Other physical findings may be indicative of complications: a rigid abdomen consistent with peritonitis in perforation; abdominal distention or a succussion splash due to obstruction; or occult or gross rectal blood or blood in the nasogastric aspirate signaling ulcer bleeding.
Epigastric pain, nausea, and vomiting may be present with acute gastritis, but the most common presentation of gastritis is GI bleeding, ranging from occult blood loss in the stool to massive upper GI hemorrhage. Physical findings may be normal, may reflect only the GI bleeding, or may reflect a severe underlying associated illness (as listed earlier).

**DIAGNOSIS**

A definitive diagnosis of peptic ulcer disease cannot be made on clinical grounds alone. Uncomplicated peptic ulcer disease can be strongly suspected in the presence of a "classic" history, including epigastric burning pain; relief of pain with ingestion of milk, food, or antacids; and night pain accompanied by "benign" physical examination findings, including normal vital signs with or without mild epigastric tenderness. The differential diagnosis of epigastric pain is extensive and, in addition to peptic ulcer disease, includes gastritis, gastroesophageal reflux disease, cholelithiasis, pancreatitis, hepatitis, abdominal aortic aneurysm, gastroparesis, and functional dyspepsia. Careful history taking may elicit features that point away from peptic ulcer disease: burning pain radiating into the chest, water brash, and belching may suggest gastroesophageal reflux disease; more severe pain radiating to the right upper quadrant and around the right or left side suggests cholelithiasis; radiation through to the back indicates pancreatitis or abdominal aortic aneurysm; chronic pain, anorexia, or weight loss may indicate gastric cancer. Myocardial ischemic pain may also present as epigastric pain and should be strongly considered in the appropriate clinical setting.

Physical examination findings may suggest other diagnoses: right upper quadrant tenderness points to cholelithiasis or hepatitis, an epigastric mass to pancreatitis (pseudocyst) or pancreatic or gastric neoplasm, a pulsatile mass to abdominal aortic aneurysm, jaundice to hepatitis, and peritoneal findings to an acute abdomen.

**ANCILLARY TESTING**

Ancillary tests may help exclude peptic ulcer disease complications and narrow the differential diagnosis. Normal results for CBC rule out anemia from chronic GI bleeding due to peptic ulcer disease, gastritis, or cancer (but do not rule out acute blood loss). Elevated liver function test results may indicate hepatitis, and an elevated lipase level may indicate pancreatitis. An acute abdominal series may show free air associated with perforation. A limited ED US examination may show gallstones or an abdominal aortic aneurysm. An ECG and cardiac enzyme determination are indicated if there is a suspicion of myocardial ischemic pain.

The gold standard for diagnosis of peptic ulcer disease is visualization of an ulcer by upper GI endoscopy. Although not all patients with undiagnosed dyspepsia require endoscopy, those with "alarm features" do (Table 78-1). Alarm features raise the index of suspicion for gastric or esophageal cancer, as well as other potentially serious conditions, but the features are not specific.
TABLE 78-1

"Alarm Features” for Endoscopy

- Age >50 y, with new-onset symptoms
- Unexplained weight loss
- Persistent vomiting
- Dysphagia or odynophagia
- Iron deficiency anemia or GI bleeding
- Abdominal mass or lymphadenopathy
- Family history of upper GI malignancy

H. pylori Tests

Because most peptic ulcers are caused by H. pylori infection and eradication of H. pylori dramatically decreases the ulcer recurrence rate, it is important to know how to diagnose infection. H. pylori infection can be diagnosed by endoscopic tests, including the rapid urease test, histologic study, and culture, all of which rely on a biopsy of the gastric mucosa.\(^1,7,11\) Noninvasive tests include serologic tests, urea breath tests, and stool antigen tests.\(^1,7,11\)

The rapid urease test detects the presence of urease in a biopsy specimen (presumptive evidence of H. pylori infection) with >90% sensitivity and >95% specificity.\(^7\) Histologic studies allow direct assessment of H. pylori infection and culture of the organism, but these tests require highly trained technicians and appropriate facilities and are not widely available.\(^7,11\) The major disadvantage of all the aforementioned tests is the cost in time, dollars, and potential complications of endoscopy.

Serologic studies detect immunoglobulin G antibodies to H. pylori and are readily available, but the sensitivity and specificity are not very good (85% and 79%, respectively).\(^7,11\) Serologic studies are not useful as a test of cure, because antibodies remain for several months to years after eradication of infection.

The urea breath test relies on the presence of urease produced by H. pylori. Urea labeled with carbon-13 or carbon-14 instead of carbon-12 is ingested and, in the presence of bacterial urease, is broken down into labeled carbon dioxide and ammonia. The labeled carbon dioxide is detected in the breath later. Sensitivity and specificity are >95%.\(^7,11\) The urea breath test can be used to determine the presence of infection after eradication therapy.\(^11\)

H. pylori antigens can be detected in the stool with >90% sensitivity and specificity.\(^1,7\) Testing performed ≥4 weeks after completion of H. pylori eradication therapy is useful as a test of cure. The sensitivity of all tests
that rely on active infection with \textit{H. pylori} is decreased significantly by recent treatment with PPIs, histamine-2 (H$_2$) antagonists, antibiotics, and bismuth compounds.\textsuperscript{7,11}

**TREATMENT**

After peptic ulcer disease is diagnosed, the goal of treatment is to heal the ulcer while relieving pain and preventing complications and recurrence. Traditional ulcer therapy heals the ulcer, relieves pain, and prevents complications, but does not prevent recurrence. Treatment of \textit{H. pylori} infection, when present, dramatically decreases the recurrence rate.\textsuperscript{7,11} If NSAID-associated ulcers are present, the offending agent should be stopped whenever possible. Traditional therapy includes PPIs, H$_2$ receptor antagonists (H$_2$RAs), sucralfate, and antacids.

Traditional ED treatment would entail initiating a trial of a PPI or an H$_2$RA, with antacids for breakthrough pain, and referring to a primary care provider to direct evaluation and subsequent treatment. This usually remains the best option. There is some evidence that a short course of a PPI provides better symptomatic relief than an H$_2$RA for undiagnosed dyspepsia, although the evidence is not from an ED setting.\textsuperscript{3} Immediate referral for definite diagnosis is mandated if alarm features are present\textsuperscript{3,4} (Table 78-1). Practice guidelines and reviews support treatment of \textit{H. pylori}–positive dyspeptic patients with antimicrobial and antisecretory therapy followed by endoscopic study only in those with persistent symptoms.\textsuperscript{3} It might be reasonable for the ED physician to begin symptomatic therapy, order a test for \textit{H. pylori}, and refer the patient for early follow-up with a primary care provider for initiation of antibacterial therapy if the test results are positive. However, this strategy has not been tested.

**PPIs**

PPIs decrease acid production by irreversibly binding with an H$^+$K$^+$ATPase molecule (proton pump) located on the gastric parietal cell, thus blocking hydrogen ion secretion.\textsuperscript{1} PPIs are most effective if taken 30 to 60 minutes prior to a meal. PPIs generally heal ulcers faster than do H$_2$RAs and also have some in vitro inhibitory effect against \textit{H. pylori}.\textsuperscript{1} PPIs are metabolized in the liver by the cytochrome P-450 system and therefore may decrease the metabolism of many other drugs. In addition, PPIs may inhibit the absorption of drugs that rely on gastric acidity. PPIs are well tolerated by most patients.\textsuperscript{1} There are six U.S. Food and Drug Administration–approved PPIs, and two (\textit{omeprazole} and \textit{lansoprazole}) have "over-the-counter" formulations.\textsuperscript{1} If a patient develops an ulcer while taking NSAIDs and must continue therapy, PPIs heal ulcers faster than any other potential treatment.\textsuperscript{1}

**H$_2$RAs**
H₂RAs competitively inhibit the actions of histamine on the H₂ receptors of the gastric parietal cells. All four H₂RAs (cimetidine, famotidine, nizatidine, and ranitidine) heal ulcers approximately equally and are available in over-the-counter preparations.⁷ Because of renal excretion, make dosage adjustments in patients with renal failure. Side effects are uncommon but can include headache, confusion, lethargy, depression, and hallucinations.⁷ Cimetidine has more significant drug interactions than do the other H₂RAs due to inhibition of cytochrome P-450 activity.⁷

**OTHER AGENTS**

Sucralfate, an aluminum hydroxide complex of sucrose, appears to protect the ulcer from acid exposure by forming a sticky gel that adheres to the ulcer crater and allows healing to occur but does not relieve pain as well as PPIs and H₂RAs.¹ Sucralfate has few side effects but can cause constipation and aluminum toxicity, as well as inhibit absorption of a number of medications.¹ Antacids heal ulcers by buffering gastric acid. Magnesium- and aluminum-containing antacids can inhibit absorption of drugs and should be avoided in patients with renal insufficiency or renal failure. In renal failure, aluminum can accumulate and cause osteoporosis and encephalopathy, and hypermagnesemia can also result. Due to the simplicity of PPI and H₂RA dosing requirements, antacids currently are used mainly on an as-needed basis for ulcer pain until healing occurs.

Although NSAIDs should be stopped in patients with peptic ulcer disease whenever possible, misoprostol may prevent ulcer formation in those concurrently receiving NSAID therapy. Misoprostol is a prostaglandin analog that may act by increasing mucus and bicarbonate production and by increasing mucosal blood flow. Because it is an abortifacient, do not use misoprostol in women who could become pregnant.¹

**H. PYLORI ERADICATION**

If H. pylori infection is diagnosed in the presence of peptic ulcer disease, eradication is clearly indicated.¹,⁷,¹¹ Multiple regimens have been proposed and studied, most commonly "triple therapy" with a PPI, clarithromycin, and either amoxicillin or metronidazole.¹,⁷,¹¹ Authorities in the United States recommend 10- to 14-day regimens for the best cure rates.¹,⁷,¹¹ In areas where clarithromycin resistance is high, quadruple therapy or sequential therapy may be the preferred option.¹,⁷,¹²

Patients generally do not present to the ED with a definitive diagnosis of peptic ulcer disease but rather with a symptom, such as epigastric pain. If appropriate history, physical examination, and laboratory evaluation result in a physician's impression of "possible peptic ulcer disease" or "dyspepsia," the physician is left with three main options: empiric treatment with conventional antiulcer medication, immediate referral for definite diagnosis (endoscopic study), or noninvasive testing for H. pylori followed by antibiotic therapy for patients with positive test results.
COMPLICATIONS

HEMORRHAGE

About 400,000 patients per year are admitted to the hospital in the United States due to nonvariceal upper GI bleeding, and peptic ulcer disease is the most common cause.15,16 As many as 15% of peptic ulcers bleed, resulting in an overall mortality rate of 10%.2 Bleeding from peptic ulcers is most common in the elderly.

ED treatment for ulcer bleeding focuses on restoring hemodynamic stability by IV administration of isotonic saline solution and packed red blood cells (see chapter 75, "Upper Gastrointestinal Bleeding" for details of treatment). Early upper endoscopy is recommended in most patients to confirm the diagnosis and target endoscopic treatment.8,15,16 Before endoscopy, a bolus dose of a PPI followed by a continuous infusion can be considered, as can use of a prokinetic agent, such as erythromycin, given IV. Neither has been consistently shown to improve clinical outcomes.8,16 Nasogastric or orogastric lavage is not required for diagnosis. Up to 18% of upper GI bleeds may have clear or bile-stained aspirate.16 Likewise neither is required for prognostic purposes, to improve visualization, or for specific therapy.16

Most patients should undergo upper GI endoscopy within 24 hours for diagnostic, prognostic, and treatment purposes.8,15,16 Lesions can be described using the Forrest classification or descriptive terms.16 Ranging from highest to lowest risk of rebleeding, these classifications include an ulcer with active spurting of blood; active oozing; nonbleeding visible vessel; adherent clot; flat pigmented spot; and an ulcer with a clean base.16 Actively bleeding ulcers (including both active spurting and oozing ulcers) have a 55% risk of rebleeding and an 11% mortality rate, whereas those with a clean base have rates of 5% and 2%, respectively.16 Treatment through endoscopy includes injection therapy (epinephrine, sclerosing agents), thermal therapy (electrocoagulation, heater probe), and mechanical clipping.16 All of these treatments stop bleeding, prevent recurrences, and decrease transfusion rates and length of hospital stay. The technique chosen depends on the equipment available and the experience of the endoscopist.

Rebleeding after endoscopic therapy can be treated by repeat endoscopy.16 If further bleeding occurs, then surgery or transcatheter arterial embolization should be considered.16

Hospitalization in an intensive care setting is indicated for patients with significant upper GI bleeding due to peptic ulcers. If clinical and endoscopic features suggest a low risk of rebleeding, a ward bed may be acceptable.

PERFORATION

Perforation is heralded by the abrupt onset of severe epigastric pain as gastric or duodenal contents spill into the peritoneal cavity, followed by the development of chemical and then bacterial peritonitis. Patients may
not have a history of peptic ulcer disease and may in fact have no history of ulcer-like symptoms. Elderly patients may not have dramatic pain or impressive peritoneal findings.

When the diagnosis is suspected, obtain appropriate laboratory tests, including a CBC, type, and cross-match, and a lipase level determination; place two large-bore IV lines; provide oxygen for hypoxemia, and place a cardiac monitor; insert a nasogastric tube with suction; and obtain an acute abdominal series. Free air is not always evident. Give broad-spectrum antibiotics and obtain a surgical consult promptly. In some cases, nonsurgical therapy has been successful, but operative intervention is the standard in the United States.

**OBSTRUCTION**

Obstruction occurs because of scarring of the gastric outlet due to chronic peptic ulcer disease, edema due to an active ulcer, or some combination of both. Resulting symptoms include abdominal fullness, nausea, and vomiting, and signs may include abdominal distention and a succussion splash. Dehydration and electrolyte imbalances may occur. Treatment includes rehydration with IV fluids, correction of electrolyte abnormalities, and relief of distention with nasogastric suction. Hospitalization is almost always indicated. The outlet may open as edema subsides, but surgical correction is often necessary.

**DISPOSITION AND FOLLOW-UP**

Patients with complications always require consultation, and most require admission to an appropriate inpatient unit based on the diagnosis and hemodynamic stability. Most patients with epigastric pain or dyspepsia do not leave the ED with a definitive diagnosis, but, if critical diagnoses (e.g., abdominal aortic aneurysm or myocardial ischemia) are still in the differential, obtain consultation for admission, and further evaluation is indicated. When uncomplicated peptic ulcer disease, gastritis, or dyspepsia is strongly suspected, the great majority of patients can be discharged with acid-suppressive therapy with a PPI or an H₂RA and instructions to follow up with their primary care providers. If alarm features (indicating possible cancer or bleeding) are present, obtain consultation for early endoscopy.

Discharge instructions should include an explanation of the diagnosis and home treatment, specific follow-up instructions, and warning symptoms that should prompt immediate reevaluation. The explanation of the diagnosis should specify that peptic ulcer disease is a presumptive diagnosis and that more definitive diagnostic testing may be necessary. Instructions for home treatment should include a reminder to take medications as directed; a warning against use of alcohol, tobacco products, and aspirin or other NSAIDs; and a recommendation to avoid foods that appear to upset the individual's "stomach." Specific follow-up instructions should include the name and phone number of the appropriate provider whenever possible and a time frame for reevaluation, generally 24 to 48 hours if not improving or 1 to 2 weeks if improving. Warning symptoms that merit immediate reevaluation include those that may be attributed to ulcer complications or confounding illness: worsening pain, increased vomiting, hematemesis or melena, weakness or syncope, fever, chest pain, radiation of pain to the neck or back, and shortness of breath.
REFERENCES

   [PubMed: 21860368]

   [PubMed: 21872087]

   [PubMed: 23990632]

   [PubMed: 20363407]

   [PubMed: 20362756]

   [PubMed: 21494041]

   [PubMed: 20427808]

   [PubMed: 22468083]

   [PubMed: 22867043]

    [PubMed: 22554233]

    [PubMed: 23483862]


**USEFUL WEB RESOURCES**
