PEPTIC ULCERS

Peptic ulcers are chronic, most often solitary, lesions that occur in any portion of the gastrointestinal tract exposed to the aggressive action of acid/peptic juices. Peptic ulcers are usually solitary lesions less than 4 cm in diameter, located in the following sites, in order of decreasing frequency:

- Duodenum, first portion
- Stomach, usually antrum
- At the gastroesophageal junction, in the setting of gastroesophageal reflux or Barrett esophagus
- Within the margins of a gastrojejunostomy
- In the duodenum, stomach, and/or jejunum of patients with Zollinger-Ellison syndrome
- Within or adjacent to an ileal Meckel diverticulum that contains ectopic gastric mucosa.

Epidemiology.

In the United States, approximately 4 million people have peptic ulcers (duodenal and gastric), and 350,000 new cases are diagnosed each year. Around 180,000 patients are hospitalized yearly, and about 5000 people die each year as a result of peptic ulcer disease. The lifetime likelihood of developing a peptic ulcer is about 10% for American males and 4% for females.

Peptic ulcers are relapsing lesions that are most often diagnosed in middle-aged to older adults, but they may first become evident in young adult life. They often appear without obvious precipitating conditions and may then, after a period of weeks to months of active disease, heal with or without therapy. Even with healing, however, the tendency to develop peptic ulcers remains, in part because of recurrent infections with H. pylori. Although it is difficult to obtain estimates of the prevalence of active disease, autopsy studies and population surveys indicate a prevalence of 6% to 14% for men and 2% to 6% for women. The male-to-female ratio for duodenal ulcers is about 3:1, and for gastric ulcers about 1.5 to 2:1. Women are most often affected at or after menopause. For unknown reasons, there has been a significant decrease in the prevalence of duodenal ulcers over the past decades but little change in the prevalence of gastric ulcers.

Pathogenesis.

Peptic ulcers are produced by an imbalance between gastroduodenal mucosal defense mechanisms and the damaging forces, particularly gastric acid and pepsin (Fig. 17-17). However, hyperacidity is not a prerequisite, as only a minority of patients with duodenal ulcers has hyperacidity, and it is even less common in those with gastric ulcers. Rather, gastric ulceration occurs when mucosal defenses fail, as when mucosal blood flow drops, gastric emptying is delayed, or epithelial restitution is impaired.
**Figure 17-17** Diagram of causes of, and defense mechanisms against, peptic ulceration.

Diagram of the base of a nonperforated peptic ulcer, demonstrating the layers of necrosis (N), inflammation (I), granulation tissue (G), and scar (S), moving from the luminal surface at the top to the muscle wall at the bottom.

*H. pylori* infection is a major factor in the pathogenesis of peptic ulcer. It is present in virtually all patients with duodenal ulcers and in about 70% of those with gastric ulcers. Furthermore, antibiotic treatment of *H. pylori* infection promotes healing of ulcers and tends to prevent their recurrence. Hence, much interest is focused on the possible mechanisms by which this tiny spiral organism tips the balance of mucosal defenses. Some likely possibilities include:

- Although *H. pylori* does not invade the tissues, it induces an intense inflammatory and immune response. There is increased production of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, tumor necrosis factor (TNF), and, most notably, IL-8. This cytokine is produced by the mucosal epithelial cells, and it recruits and activates neutrophils.

- Several bacterial gene products are involved in causing epithelial cell injury and induction of inflammation. *H. pylori* secretes a urease that breaks down urea to form toxic compounds such as ammonium chloride and monochloramine. The organisms also elaborate phospholipases that damage surface epithelial cells. Bacterial proteases and phospholipases break down the glycoprotein-lipid complexes in the gastric mucus, thus weakening the first line of mucosal defense.

- *H. pylori* enhances gastric acid secretion and impairs duodenal bicarbonate production, thus reducing luminal pH in the duodenum. This altered milieu seems to favor gastric metaplasia
(the presence of gastric epithelium) in the first part of the duodenum. Such metaplastic foci provide areas for *H. pylori* colonization.

Several *H. pylori* proteins are immunogenic, and they evoke a robust immune response in the mucosa. Both activated T cells and B cells can be seen in chronic gastritis caused by *H. pylori*. The B lymphocytes aggregate to form follicles. The role of T and B cells in causing epithelial injury is not established, but T-cell-driven activation of B cells may be involved in the pathogenesis of gastric lymphomas.

Thrombotic occlusion of surface capillaries is promoted by a bacterial platelet-activating factor.

Other antigens (including lipopolysaccharide) recruit inflammatory cells to the mucosa. The chronically inflamed mucosa is more susceptible to acid injury.

Damage to the mucosa is thought to permit leakage of tissue nutrients into the surface microenvironment, thereby sustaining the bacillus.

With the unraveling of the *H. pylori* genome, the basis of the pathogenicity of this organism is beginning to be understood. Over 80% of patients with duodenal ulcers are infected by strains that are cytotoxin-associated antigen (CagA) positive. This antigen elicits a strong serologic response, but more importantly it is a marker for the Cag pathogenicity island, a 37 kb DNA fragment that encodes 29 genes, some of which are involved in the pro-inflammatory and tissue damaging effects of *H. pylori*. In keeping with this, infection with Cag positive strains is associated with greater number of organisms in the tissue, more severe epithelial damage, greater acute and chronic inflammation, higher likelihood of peptic ulceration and an increased risk for gastric cancer (discussed later). One of the important genes regulated by CagA is the vacuolating toxin (VacA); the CagA gene is essential for the expression of VacA. This toxin causes cell injury (characterized by vacuole formation) in vitro and gastric tissue damage in vivo. VacA also behaves as a passive urea transporter thereby increasing the permeability of the epithelium to urea. As discussed above, urea is broken down into toxic intermediates by bacterial urease.

Only 10% to 20% of individuals worldwide infected with *H. pylori* actually develop peptic ulcer. Why most infected persons are spared and some are susceptible remains an enigma. Perhaps there are unknown interactions between *H. pylori* and the mucosa that occur only in some individuals. Another perplexing observation is that in patients with duodenal ulcer, the actual infection by *H. pylori* is limited to the stomach. Increased acid production by *H. pylori* infection seems to play a role. Suffice it to say that while the link between *H. pylori* infection and gastric and duodenal ulcers is well established, the interactions leading to ulceration remain to be defined.

Other events may act alone or in concert with *H. pylori* to promote peptic ulceration. Gastric hyperacidity, when present, may be strongly ulcerogenic. Hyperacidity may arise from increased parietal cell mass, increased sensitivity to secretory stimuli, increased basal acid secretory drive, or impaired inhibition of stimulatory mechanisms such as gastrin release. The classic example is *Zollinger-Ellison syndrome*, in which there are multiple peptic ulcerations in the stomach, duodenum, and even jejunum, owing to excess gastrin secretion by a tumor and, hence, excess gastric acid production.
Chronic use of NSAIDs suppresses mucosal prostaglandin synthesis; aspirin also is a direct irritant. Cigarette smoking impairs mucosal blood flow and healing. Alcohol has not been proved to directly cause peptic ulceration, but alcoholic cirrhosis is associated with an increased incidence of peptic ulcers. Corticosteroids in high dose and with repeated use promote ulcer formation. In some patients with duodenal ulcers, there is too-rapid gastric emptying, exposing the duodenal mucosa to an excessive acid load. Duodenal ulcer also is more frequent in patients with alcoholic cirrhosis, chronic obstructive pulmonary disease, chronic renal failure, and hyperparathyroidism. In the latter two conditions, hypercalcemia stimulates gastrin production and therefore acid secretion. Genetic influences appear to play no major role in peptic ulceration. Finally, there are compelling arguments that personality and psychological stress are important contributing factors, even though hard data on cause and effect are lacking. Indeed, we might develop ulcers by trying to fathom their cause(s).

Morphology.

At least 98% of peptic ulcers are located in the first portion of the duodenum or in the stomach, in a ratio of about 4:1. Most duodenal ulcers occur within a few centimeters of the pyloric ring. The anterior wall of the duodenum is affected more often than the posterior wall. Gastric ulcers are predominantly located along the lesser curvature, in or around the border zone between the oxyntic mucosa and the antral mucosa. Less commonly, gastric ulcers may occur on the anterior or posterior walls, or along the greater curvature. Although the great majority of individuals have a single ulcer, in 10% to 20% of patients with gastric ulceration there may be a coexistent duodenal ulcer.

Wherever they occur, chronic peptic ulcers have a fairly standard, virtually diagnostic gross appearance (Fig. 17-18). Small lesions (<0.3 cm) are most likely to be shallow erosions; those over 0.6 cm are likely to be ulcers. Although over 50% of peptic ulcers have a diameter less than 2 cm, about 10% of benign ulcers are greater than 4 cm. Since carcinomatous ulcers may be less than 4 cm in diameter and may be located anywhere in the stomach, size and location do not differentiate a benign from a malignant ulcer.

![Figure 17-18](image-url) Peptic ulcer of the duodenum. Note that the ulcer is small (2 cm) with a sharply punched-out appearance. Unlike cancerous ulcers, the margins are not elevated. The ulcer base is clean. (Courtesy of Robin Foss, University of Florida, Gainesville, FL.)
The classic peptic ulcer is a round to oval, sharply punched-out defect with relatively straight walls. The mucosal margin may overhang the base slightly, particularly on the upstream portion of the circumference. The margins are usually level with the surrounding mucosa or only slightly elevated. Heaping-up of these margins is rare in the benign ulcer but is characteristic of the malignant lesion. The depth of these ulcers varies, from superficial lesions involving only the mucosa and muscularis mucosa to deeply excavated ulcers having their bases on the muscularis propria. When the entire wall is penetrated, the base of the ulcer may be formed by adherent pancreas, omental fat, or liver. Free perforation into the peritoneal cavity may occur.

The base of a peptic ulcer is smooth and clean, owing to peptic digestion of any exudate that may form. At times, thrombosed or even patent blood vessels (the source of life-threatening hemorrhage) are evident in the base of the ulcer. Scarring may involve the entire thickness of the stomach; puckering of the surrounding mucosa creates mucosal folds that radiate from the crater in spokelike fashion. The gastric mucosa surrounding a gastric ulcer is somewhat edematous and reddened, owing to the almost invariable gastritis.

The histologic appearance varies from active necrosis, to chronic inflammation and scarring, to healing (see Fig. 2-26, Chapter 2). In active ulcers with ongoing necrosis, four zones are demonstrable: (1) the base and margins have a superficial thin layer of necrotic fibrinoid debris not visible to the naked eye; (2) beneath this layer is a zone of non-specific inflammatory infiltrate, with neutrophils predominating; (3) in the deeper layers, especially in the base of the ulcer, there is active granulation tissue infiltrated with mononuclear leukocytes; and (4) the granulation tissue rests on a more solid fibrous or collagenous scar. Vessel walls within the scarred area are typically thickened by the surrounding inflammation and are occasionally thrombosed.

Chronic gastritis is virtually universal among patients with peptic ulcer disease, occurring in 85% to 100% of patients with duodenal ulcers and in 65% with gastric ulcers. *H. pylori* infection is almost always demonstrable in patients with gastritis. Gastritis remains after the ulcer has healed; recurrence of the ulcer does not appear to be related to progression of the gastritis. This feature is helpful in distinguishing peptic ulcers from acute erosive gastritis or stress ulcers, since the adjacent mucosa is generally normal in the latter two conditions.

**Clinical Features.**

The great majority of peptic ulcers cause epigastric gnawing, burning, or aching pain. A significant minority first comes to light with complications such as iron-deficiency anemia, frank hemorrhage, or perforation. The pain tends to be worse at night and occurs usually 1 to 3 hours after meals during the day. Classically, the pain is relieved by alkalis or food, but there are many exceptions. Nausea, vomiting, bloating, belching, and significant weight loss (raising the possibility of some hidden malignancy) are additional manifestations. With penetrating ulcers, the pain is occasionally referred to the back, the left upper quadrant, or chest. This type of pain may be misinterpreted as being of cardiac origin.
Peptic ulcers are notoriously chronic, recurring lesions. They more often impair the quality of life than shorten it. When untreated, it takes an average of 15 years for healing a duodenal or gastric ulcer. With present-day therapies aimed at neutralization of gastric acid, promotion of mucus secretion, inhibition of acid secretion (H₂ receptor antagonists and parietal cell H⁺,K⁺-ATPase pump inhibitors), and eradication of *H. pylori* infection, most ulcers heal within a few weeks, and victims usually escape the surgeon's knife.

The complications of peptic ulcer disease are listed in Table 17-3. Malignant transformation does not occur with duodenal ulcers and is extremely rare with gastric ulcers. When it occurs, it is always possible that a seemingly benign lesion was, from the outset, a deceptive ulcerative gastric carcinoma.

<table>
<thead>
<tr>
<th>Table 17-3 -- Complications of Peptic Ulcer Disease</th>
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<tr>
<td><strong>Bleeding</strong></td>
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<tr>
<td>? Occurs in 15% to 20% of patients</td>
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<td>? Most frequent complication</td>
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<td>? May be life-threatening</td>
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<tr>
<td>? Accounts for 25% of ulcer deaths</td>
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<td>? May be the first indication of an ulcer</td>
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<tr>
<td><strong>Perforation</strong></td>
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<tr>
<td>? Occurs in about 5% of patients</td>
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<tr>
<td>? Accounts for two thirds of ulcer deaths</td>
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<tr>
<td>? Rarely, is the first indication of an ulcer</td>
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<tr>
<td><strong>Obstruction from edema or scarring</strong></td>
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<tr>
<td>? Occurs in about 2% of patients</td>
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<tr>
<td>? Most often due to pyloric channel ulcers</td>
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<tr>
<td>? May also occur with duodenal ulcers</td>
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<tr>
<td>? Causes incapacitating, crampy abdominal pain</td>
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<tr>
<td>? Rarely, may lead to total obstruction with intractable vomiting</td>
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**ACUTE GASTRIC ULCERATION**

Focal, acutely developing gastric mucosal defects are a well-known complication of therapy with NSAIDs. Alternatively, they may appear following severe physiologic stress, whatever its nature—hence the term *stress ulcers*. Generally, there are multiple lesions located mainly in the stomach and occasionally in the duodenum. They range in depth from mere shedding of the superficial epithelium (*erosion*) to deeper lesions that involve the entire mucosal thickness.
The shallow erosions are, in essence, an extension of acute erosive gastritis. The deeper lesions comprise well-defined ulcerations, but they are not precursors of chronic peptic ulcers.

Stress erosions and ulcers are most commonly encountered in patients with shock, extensive burns, sepsis, or severe trauma; in any intracranial injury that raises intracranial pressure; and following intracranial surgery. Those occurring in the proximal duodenum and associated with severe burns or trauma are called Curling ulcers. Gastric, duodenal, and esophageal ulcers arising in patients with intracranial injury, operations, or tumors are designated Cushing ulcers and carry a high incidence of perforation.

The genesis of the acute mucosal defects in these varied clinical settings is poorly understood. No doubt, many factors are shared with acute gastritis, such as impaired oxygenation. NSAID-induced ulcers are related to decreased prostaglandin production from the inhibition of cyclooxygenase. In the case of lesions associated with intracranial injury, the proposed mechanism involves the direct stimulation of vagal nuclei by increased intracranial pressure, leading to hypersecretion of gastric acid, which is common in these patients. Systemic acidosis, a frequent finding in these clinical settings, may contribute to mucosal injury by lowering the intracellular pH of mucosal cells. These cells are also hypoxic as a consequence of stress-induced splanchnic vasoconstriction.

Morphology.

Acute stress ulcers are usually less than 1 cm in diameter and are circular and small. The ulcer base is frequently stained a dark brown by the acid digestion of extruded blood (Fig. 17-19). Unlike chronic peptic ulcers, acute stress ulcers are found anywhere in the stomach, the gastric rugal pattern is essentially normal and the margins and base of the ulcers are not indurated. While they may occur singly, more often there are multiple stress ulcers throughout the stomach and duodenum. Microscopically, acute stress ulcers are abrupt lesions, with essentially unremarkable adjacent mucosa. Depending on the duration of the ulceration, there may be a suffusion of blood into the mucosa and submucosa and some inflammatory reaction. Conspicuously absent are scarring and thickening of blood vessels, as seen in chronic peptic ulcers. Healing with complete reepithelialization occurs after the causative factors are removed. The time required for complete healing varies from days to several weeks.

Figure 17-19 Multiple stress ulcers of the stomach, highlighted by dark digested blood on
Clinical Features.

Most critically ill patients admitted to hospital intensive care units develop histologic evidence of gastric mucosal damage. Bleeding from superficial gastric erosions or ulcers sufficient to require transfusion develops in 1% to 4% of these patients. Although prophylactic H₂-receptor antagonists and proton pump inhibitors may blunt the impact of stress ulceration, *the single most important determinant of clinical outcome is the ability to correct the underlying condition(s)*. The gastric mucosa can recover completely if the patients do not succumb to their primary disease.