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335 Peptic Ulcer Disease and Related Disorders

the need for diagnostic testing in most patients. When endoscopy is performed, localized ulceration or inflammation is evident. Histologically, acute inflammation is typical. Chest CT imaging will sometimes reveal esophageal thickening consistent with transmural inflammation. Although the condition usually resolves within days to weeks, symptoms may persist for months and stricture can develop in severe cases. No specific therapy is known to hasten the healing process, but antisecretory medications are frequently prescribed to remove concomitant reflux as an aggravating factor. When healing results in stricture formation, dilation is indicated.

■ ■ **FOREIGN BODIES AND FOOD IMPACTION** Food or foreign bodies may lodge in the esophagus, causing complete obstruction, which in turn can cause an inability to handle secretions (foaming at the mouth) and severe chest pain. Food impaction may occur due to peptic stricture, carcinoma, Schatzki ring, EoE, achalasia, or simply inattentive eating. If it does not resolve spontaneously, impacted food should be removed endoscopically. Use of meat tenderizer enzymes to facilitate passage of a meat bolus is discouraged because of potential esophageal injury. Glucagon (1 mg IV) is sometimes tried before endoscopic dislodgement. After emergent treatment, patients should be evaluated for potential causes of the impaction with treatment rendered as indicated. **ESOPHAGEAL MANIFESTATIONS OF SYSTEMIC DISEASE** ■ ■ **SCLERODERMA AND CONNECTIVE**

TISSUE DISORDERS Scleroderma esophagus (hypotensive LES and absent esophageal contractility) was initially described as a manifestation of scleroderma or other collagen vascular diseases and thought to be specific for these disorders. However, this nomenclature subsequently has been discarded because an estimated half of qualifying patients do not have an identifiable rheumatologic disease, and reflux disease is often the only identifiable association. When scleroderma esophagus occurs as a manifestation of a connective tissue disorder, the histopathologic findings are of infiltration and destruction of the esophageal muscularis propria with collagen deposition and fibrosis and reduction in the number of interstitial cells of Cajal. The pathogenesis of absent peristalsis and LES hypotension in the absence of a connective tissue disorder is unknown.

Regardless of the underlying cause, the manometric abnormalities predispose patients to severe GERD due to inadequate LES barrier function combined with poor esophageal clearance of refluxed acid. Dysphagia may also be manifest but is generally mild and alleviated by eating in an upright position and using liquids to facilitate solid transit.

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■ **DERMATOLOGIC DISEASES** A host of dermatologic disorders (lichen planus, pemphigus vulgaris, bullous pemphigoid, cicatricial pemphigoid, Behçet's syndrome, and epidermolysis bullosa) can affect the oropharynx and esophagus, particularly the proximal esophagus, with blisters, bullae, ulceration, webs, and strictures. Topical or systemic anti-inflammatory therapy is effective for mucosal healing. Stevens-Johnson syndrome and graft-versus-host disease can also involve the esophagus. Esophageal dilation may be necessary to treat strictures.

■ **FURTHER READING** Hirano I et al: American Gastroenterological Institute and the joint task force on allergy-immunology practice parameters clinical guide lines for the management of eosinophilic esophagitis. *Gastroenterology* 158:1776, 2020. Kahrilas PJ et al: Advances in the management of esophageal motility disorders in the era of high-resolution manometry: A focus on achalasia syndromes. *Nat Rev Gastroenterol Hepatol* 15:323, 2018. Katzka DA, Kahrilas PJ: Advances in the diagnosis and management of gastroesophageal reflux disease. *BMJ* 23:371, 2020. Katzka DA et al: Phenotypes of gastroesophageal reflux disease: Where Rome, Lyon, and Montreal meet. *Clin Gastroenterol Hepatol* 18:767, 2020.

Shaheen NJ et al: Diagnosis and management of Barrett's esophagus: An updated ACG guideline. *Am J Gastroenterol* 117:559, 2022. Straumann A, Katzka DA: Diagnosis and treatment of eosinophilic esophagitis. *Gastroenterology* 154:346, 2018. Von Arnim U et al: Monitoring patients with eosinophilic esophagitis in routine clinical practice – international expert recommendations. *Clin Gastroenterol Hepatol* 21:2526, 2023. John Del Valle

Peptic Ulcer Disease

and Related Disorders **PEPTIC ULCER DISEASE** A peptic ulcer is defined as disruption of the mucosal integrity of the stomach and/or duodenum leading to a local defect or excavation due to active inflammation. Although burning epigastric pain exacerbated by fasting and improved with meals is a symptom complex associated with peptic ulcer disease (PUD), it is now clear that >90% patients with this symptom complex (dyspepsia) do not have ulcers and that the majority of patients with peptic ulcers may be asymptomatic. Ulcers occur within the stomach and/or duodenum and are often chronic in nature. Acid peptic disorders are very common in the United States, with 4 million individuals (new cases and recurrences) affected per year. Lifetime overall prevalence of PUD in the United States is ~8.4% with a slightly higher prevalence in men. PUD significantly affects quality of life by impairing overall patient well-being and contributing substantially to work absenteeism. Moreover, an estimated 15,000 deaths per year occur as a consequence of complicated PUD. The financial impact of these common disorders has been substantial, with an estimated burden on direct and indirect health care costs of ~\$6 billion per year in the United States, with \$3 billion spent on hospitalizations, \$2 billion on physician office visits, and \$1 billion in decreased productivity and days lost from work.

■ **GASTRIC PHYSIOLOGY** Gastric Anatomy The gastric epithelial lining consists of rugae that contain microscopic gastric pits, each branching into four or five gastric glands made up of highly specialized epithelial cells. The makeup of gastric glands varies with their anatomic location. Glands within the gastric cardia comprise <5% of the gastric gland area and contain mucous and endocrine cells. The 75% of gastric glands are found

within the oxyntic mucosa and contain mucous neck, parietal, chief, endocrine, enterochromaffin, and enterochromaffin-like (ECL) cells (Fig. 335-1). Highly specialized tuft cells are located in the neck region of the gastric gland. These specialized cells are thought to sample luminal contents, which in turn may be important in regulating gastric acid secretion. Pyloric glands contain mucous and endocrine cells (including gastrin cells) and are found in the antrum. The parietal cell, also known as the oxyntic cell, is usually found in the neck or isthmus or in the oxyntic gland. The resting, or unstimulated, parietal cell has prominent cytoplasmic tubulovesicles and intracellular canaliculi containing short microvilli along its apical surface (Fig. 335-2). H^+,K^+ -adenosine triphosphatase (ATPase) is expressed in the tubulovesicle membrane; upon cell stimulation, this membrane, along with apical membranes, transforms into a dense network of apical intracellular canaliculi containing long microvilli. Acid secretion, a process requiring high energy, occurs at the apical canalicular surface. Numerous mitochondria (30–40% of total cell volume) generate the energy required for secretion.

Corpus gland Human Corpus Antrum Mouse Antral gland Corpus Antrum FIGURE 335-1

Diagrammatic representation of the oxyntic gastric gland. Cellular constituents of the stomach. The human stomach is divided into three components the cardia, the corpus and the antrum. The oxyntic gland which contains the majority of the acid producing cells are located in the corpus. Glands located in the antrum secrete predominantly mucus and also contain the important gastrin producing cells. It is also important to note that key progenitor cells are located within both the gastric corpus and antral glands. (Reproduced with permission from AC Engevik et al: The physiology of the gastric parietal cell. *Physiol Rev* 100:573, 2020, Figure 1.) Resting Stimulated Canaliculus HCl H^+,K^+ -ATPase KCl Tubulovesicles KCl Active pump H_3O^+ Active pump Ca^{2+} - cAMP Gastrin ACh Histamine FIGURE 335-2 Gastric parietal cell undergoing transformation after secretagogue-mediated stimulation. cAMP, cyclic adenosine monophosphate. (Reproduced with permission from SJ Hersey, G Sachs: Gastric acid secretion. *Am Physiol Soc* 75:155, 1995.)

Surface cells (MUC5AC) Progenitor cells Pit (foveolus) Mucous neck cells (MUC6, TFF2) Parietal cells (H/K -ATPase) Isthmus D cells (Somatostatin) ECL cells (Histidine decarboxylase) Neck EC cells (Serotonin) X Cell (Ghrelin) Base Chief cells (MIST1, PGC) Surface cells (MUC5AC) CHAPTER 335 G cells (Gastrin) D cells (Somatostatin) Pit ECL cells (Histidine decarboxylase) Peptic Ulcer Disease and Related Disorders EC cells (Serotonin) Progenitor zone Progenitor cells (LRIG1, LGR5) Base Deep mucous gland cells (MUC6, TFF2, CD44v9) Gastroduodenal Mucosal Defense The gastric epithelium is under constant assault by a series of endogenous noxious factors, including hydrochloric acid (HCl), pepsinogen/pepsin, and bile salts. In addition, a steady flow of exogenous substances such as medications, alcohol, and bacteria encounter the gastric mucosa. A highly intricate biologic system is in place to provide defense from mucosal injury and to repair any injury that may occur. The mucosal defense system can be envisioned as a three-level barrier, composed of preepithelial, epithelial, and subepithelial elements (Fig. 335-3). The first line of defense is a mucus-bicarbonate-phospholipid layer, which serves as a physicochemical barrier to multiple molecules, including hydrogen ions. Mucus is secreted in a regulated fashion by gastroduodenal surface epithelial cells. It consists primarily of water (95%) and a mixture of phospholipids and glycoproteins (mucin). The mucous gel functions as a nonstirred water layer impeding diffusion of ions and molecules such as pepsin. Bicarbonate, secreted in a regulated manner by surface epithelial cells of the gastroduodenal mucosa into the mucous gel, forms a pH gradient ranging

PART 10 Disorders of the Gastrointestinal System FIGURE 335-3 Components involved in providing gastroduodenal mucosal defense and repair. CCK, cholecystokinin; CRF, corticotropin-releasing factor; EGF, epidermal growth factor; HCl, hydrochloride; IGF, insulin-like growth factor; TGF α , transforming growth factor α ; TRF, thyrotropin releasing factor. (Republished with permission of John Wiley and Son's Inc, from Bioregulation and Its Disorders in the Gastrointestinal Tract, T Yoshikawa, T Arakawa [eds]: 1998; permission conveyed through Copyright Clearance Center, Inc.)

from 1 to 2 at the gastric luminal surface and reaching 6–7 along the epithelial cell surface. Surface epithelial cells provide the next line of defense through several factors, including mucus production, epithelial cell ionic transporters that maintain intracellular pH and bicarbonate production, and intracellular tight junctions. Surface epithelial cells generate heat shock proteins that prevent protein denaturation and protect cells from certain factors such as increased temperature, cytotoxic agents, or oxidative stress. Epithelial cells also generate trefoil factor family peptides and cathelicidins, which also play a role in surface cell protection and regeneration. If the preepithelial barrier is breached, gastric epithelial cells bordering a site of injury can migrate to restore a damaged region (restitution). This process occurs independent of cell division and requires uninterrupted blood flow and an alkaline pH in the surrounding environment. Several growth factors, including epidermal growth factor (EGF), transforming growth factor (TGF) α , and basic fibroblast growth factor (FGF), modulate the process of restitution. Larger defects that are not effectively repaired by restitution require cell proliferation. Epithelial cell regeneration is regulated by prostaglandins and growth factors such as EGF and TGF- α . In tandem with epithelial cell renewal, formation of new vessels (angiogenesis) within the injured microvascular bed occurs. Both FGF and vascular endothelial growth factor (VEGF) are important in regulating angiogenesis in the gastric mucosa. In addition, the gastric peptide gastrin (see below) has been found to stimulate cell proliferation, migration, invasion, angiogenesis, and autophagy. Finally, gastric parietal cells (see below) express sonic hedgehog, a family of proteins important in regulating cell lineage in multiple organs. This latter finding suggests that parietal cells may also have the ability to regulate gastric stem cells.

Membrane phospholipids Phospholipase A2 Arachidonic acid Stomach Kidney Platelets Endothelium Macrophages Leukocytes Fibroblasts Endothelium COX-1 housekeeping COX-2 inflammation PGI₂, PGE₂ Inflammation Mitogenesis Bone formation Other functions? TXA₂, PGI₂, PGE₂ Gastrointestinal mucosal integrity Platelet aggregation Renal function FIGURE 335-4 Schematic representation of the steps involved in synthesis of prostaglandin E₂ (PGE₂) and prostacyclin (PGI₂). Characteristics and distribution of the cyclooxygenase (COX) enzymes 1 and 2 are also shown. TXA₂, thromboxane A₂. An elaborate microvascular system within the gastric submucosal layer is the key component of the subepithelial defense/repair system, providing HCO₃⁻, which neutralizes the acid generated by the parietal cell. Moreover, this microcirculatory bed provides an adequate supply of micronutrients and oxygen while removing toxic metabolic byproducts. Several locally produced factors including nitric oxide (NO) (see below), hydrogen sulfide, and prostacyclin contribute to the vascular protective pathway through vasodilation of the microcirculation. Prostaglandins play a central role in gastric epithelial defense/repair (Fig. 335-4). The gastric mucosa contains abundant levels of prostaglandins that regulate the release of mucosal bicarbonate and mucus, inhibit parietal cell secretion, and are important in maintaining mucosal blood flow and epithelial cell restitution. Prostaglandins are derived from esterified arachidonic acid, which is formed from phospholipids (cell membrane) by the action of phospholipase A₂. A key enzyme that controls the rate-limiting step in prostaglandin synthesis is cyclooxygenase (COX), which is present in two isoforms

(COX-1, COX-2), each having distinct characteristics regarding structure, tissue distribution, and expression. COX-1 is expressed in a host of tissues, including the stomach, platelets, kidneys, and endothelial cells. This isoform is expressed in a constitutive manner and plays an important role in maintaining the integrity of renal function, platelet aggregation, and gastrointestinal (GI) mucosal integrity. In contrast, the expression of COX-2 is inducible by inflammatory stimuli, and it is expressed in macrophages, leukocytes, fibroblasts, and synovial cells. The beneficial effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on tissue inflammation are due to inhibition of COX-2; the toxicity of these drugs (e.g., GI mucosal ulceration and renal dysfunction) is related to inhibition of the COX-1 isoform. The highly COX-2-selective NSAIDs have the potential to provide the beneficial effect of decreasing tissue inflammation while minimizing toxicity in the GI tract. Selective COX-2 inhibitors have had adverse effects on the cardiovascular (CV) system, leading to increased risk of myocardial infarction. Therefore, the U.S. Food and Drug Administration (FDA) has removed two of these agents (valdecoxib and rofecoxib) from the market (see below). NO is important in the maintenance of gastric mucosal integrity. The key enzyme NO synthase is constitutively expressed in the mucosa and contributes to cytoprotection by stimulating gastric mucus, increasing mucosal blood flow, and maintaining epithelial cell barrier function. The central nervous system (CNS) and hormonal factors also play a role in regulating mucosal defense through multiple pathways (Fig. 335-3). Since the discovery of *Helicobacter pylori* and its impact on gastric pathology, it has become clear that the stomach has an elaborate and complex inherent immunologic system in place. Although a detailed description of the gastric immune system is beyond the scope of this chapter, several features are worth highlighting. The gastric immune

response to certain pathogens such as *H. pylori* (see below) involves extensive interplay between innate (dendritic cells, epithelial cells, neutrophils, and macrophages) and adaptive (B and T cells) components. Helper T cells (TH and TH regulatory cells) have been extensively studied and appear to play an important role in a broad array of gastric physiology extending from gastric secretion to epithelial cell turnover via production of a number of cytokines.

The discovery of *H. pylori* has also led to the understanding that the stomach, once thought to be devoid of microorganisms due to its highly adverse environment (acid and pepsin), can serve as host for bacterial communities consisting of hundreds of phylotypes, otherwise known as its microbiota. The conceptual framework of the microbiome has been receiving extensive attention in light of its importance in human health and disease. The overall relevance of the gastric microbiome and its impact on gastric pathology remain to be established, but it is likely that alteration of microorganism homeostasis will play a role in aspects of certain disorders such as PUD, gastritis, and gastric cancer. Physiology of Gastric Secretion Understanding of the physiology of gastric secretion is important when considering the pathophysiology of PUD and the therapeutic options available. A detailed review of the many components of gastric acid secretion is beyond the scope of this chapter, and the reader is referred to Engevik et al (see Further Reading) for a comprehensive discussion on this very important topic. For the purposes of this chapter, a brief review of acid secretion will follow. HCl and pepsinogen are the two principal gastric secretory products capable of inducing mucosal injury. Gastric acid and pepsinogen play a physiologic role in protein digestion; absorption of iron, calcium, magnesium, and vitamin B12; and killing ingested bacteria. Acid secretion should be viewed as occurring under basal and stimulated conditions. Basal acid production occurs in a circadian pattern, with the highest levels occurring during the night and lowest levels during the morning hours. Cholinergic input via the vagus nerve and hista

minergic input from local gastric sources are the principal contributors to basal acid secretion. Stimulated gastric acid secretion occurs primarily in three phases based on the site where the signal originates (cephalic, gastric, and intestinal). Sight, smell, and taste of food are the components of the cephalic phase, which stimulates gastric secretion via the vagus nerve. The gastric phase is activated once food enters the stomach. This component of secretion is driven by nutrients (amino acids and amines) that directly (via peptone and amino acid receptors) and indirectly (via stimulation of intramural gastrin-releasing peptide neurons) stimulate the G cell to release gastrin, which in turn activates the parietal cell via direct and indirect mechanisms. Distention of the stomach wall also leads to gastrin release and acid production. The last phase of gastric acid secretion is initiated as food enters the intestine and is mediated by luminal distention and nutrient assimilation. A series of pathways that inhibit gastric acid production are also set into motion during these phases. The GI hormone somatostatin is released from endocrine cells found in the gastric mucosa (D cells) in response to HCl. Somatostatin can inhibit acid production by both direct (parietal cell) and indirect mechanisms (decreased histamine release from ECL cells, ghrelin release from Gr cells, and gastrin release from G cells). Additional neural (central and peripheral) and humoral (amylin, atrial natriuretic peptide [ANP], cholecystokinin, ghrelin, interleukin 11 [IL-11], obestatin, secretin, and serotonin) factors play a role in counterbalancing acid secretion. Under physiologic circumstances, these phases occur simultaneously. Ghrelin, the appetite-regulating hormone expressed in Gr cells in the stomach, and its related peptide motilin (released from the duodenum) may increase gastric acid secretion through stimulation of histamine release from ECL cells, but this remains to be confirmed.

CHAPTER 335 Peptic Ulcer Disease and Related Disorders The acid-secreting parietal cell is located in the oxyntic gland, adjacent to other cellular elements (ECL cell, D cell) important in the gastric secretory process (Fig. 335-5). This unique cell also secretes intrinsic factor (IF) and IL-11. The parietal cell expresses receptors for several stimulants of acid secretion, including histamine (H₂), gastrin (cholecystokinin 2/gastrin receptor), and acetylcholine (muscarinic, M₃). Binding of histamine to the H₂ receptor and activation of the

CGRP PACAP ACh ACh ACh ACh ACh GRP VIP + + + - - - + EC Cell (ANP) D Cell (SST) G Cell (Gastrin) D Cell (SST) - + + - HP (Chronic Antrum) Acid HP (Acute)

FIGURE 335-5 Regulation of gastric acid secretion at the cellular level. ACh, acetylcholine; ANP, atrial natriuretic peptide; CGRP, calcitonin gene-related peptide; EC, enterochromaffin; ECL, enterochromaffin-like; GRP, gastrin-releasing peptide; PACAP, pituitary adenylate-cyclase activating peptide; SST, somatostatin; VIP, vasoactive intestinal peptide. gastrin and muscarinic receptors result in stimulation of downstream signaling pathways, which in turn regulates the acid-secreting pump, H⁺,K⁺-ATPase. Parietal cells also express receptors for ligands that inhibit acid production (glucagon-like peptide 1, prostaglandins, somatostatin, EGF, neurotensin, and urocortin). Histamine also stimulates gastric acid secretion indirectly by activating the histamine H₃ receptor on D cells, which inhibits somatostatin release.

PART 10 Disorders of the Gastrointestinal System The enzyme H⁺,K⁺-ATPase is responsible for generating the large concentration of H⁺ ions. This enzyme uses the chemical energy of adenosine triphosphate (ATP) to transfer H⁺ ions from parietal cell cytoplasm to the secretory canaliculi in exchange for K⁺. The H⁺,K⁺-ATPase is located within the secretory canaliculus and in nonsecretory cytoplasmic tubulovesicles. The tubulovesicles are impermeable to K⁺, which leads to an inactive pump in this location. The distribution of pumps between the nonsecretory vesicles and the secretory canaliculus varies according to parietal cell activity (Fig. 335-2). Proton pumps are recycled back to the inactive state in cytoplasmic vesicles once parietal cell activation ceases. In addition, acid secretion requires a number of apical and basolateral

parietal cell membrane chloride and potassium channels. Parietal cells also express members of the sonic hedgehog (Shh) family proteins, which play an important role in regulating cell types in multiple organs. This family of proteins may also regulate cell differentiation as well as restitution of mucosal defense in the gastric epithelium. The chief cell, found primarily in the gastric fundus, synthesizes and secretes pepsinogen, the inactive precursor of the proteolytic enzyme pepsin. The acid environment within the stomach leads to cleavage of the inactive precursor to pepsin and provides the low pH (<2) required for pepsin activity. Pepsin activity is significantly diminished at a pH of 4 and irreversibly inactivated and denatured at a pH of ≥ 7 . Many of the secretagogues that stimulate acid secretion also stimulate pepsinogen release. The precise role of pepsin in the pathogenesis of PUD remains to be established. ■ ■

PATHOPHYSIOLOGIC BASIS OF PUD PUD encompasses both gastric ulcers (GUs) and duodenal ulcers (DUs). Ulcers are defined as breaks in the mucosal surface >5 mm in size, with depth to the submucosa. DUs and GUs share many common features in terms of pathogenesis, diagnosis, and treatment, but several factors distinguish them from one another. *H. pylori* and NSAIDs are the most common risk factors for PUD, with estimated odds ratios in the United States of 3.7 and 3.3, respectively. Additional risk factors (odds ratio) include chronic obstructive lung disease (2.34), chronic renal insufficiency (2.29), current tobacco use (1.99), former tobacco use (1.55), older age (1.67), three or more doctor visits in a year (1.49),

Vagus + + - Parietal Cell + + H3 H2 + - - + ECL Cell (Histamine) Fundus Antrum coronary heart disease (1.46), former alcohol use (1.29), AfricanAmerican race (1.20), obesity (1.18), and diabetes (1.13). Selective serotonin reuptake inhibitors (SSRIs) and gastric bypass surgery are also associated with an increased incidence of PUD. A rise in idiopathic PUD has also been noted. The mechanisms by which some of these risk factors lead to ulcer disease are highlighted below.

Epidemiology • DUODENAL ULCERS DUs are estimated to occur in 6–15% of the Western population. The incidence of DUs declined steadily from 1960 to 1980 and has remained stable since then. The death rates, need for surgery, and physician visits have decreased by >50% over the past 30 years. The reason for the reduction in the frequency of DUs is likely related to the decreasing frequency of *H. pylori* in turn associated with overall improved sanitary conditions across the world. Before the discovery of *H. pylori*, the natural history of DUs was typified by frequent recurrences after initial therapy. Eradication of *H. pylori* has reduced these recurrence rates by >80%.

GASTRIC ULCERS GUs tend to occur later in life than duodenal lesions, with a peak incidence reported in the sixth decade. More than one-half of GUs occur in males and are less common than DUs, perhaps due to the higher likelihood of GUs being silent and presenting only after a complication develops. Autopsy studies suggest a similar incidence of DUs and GUs.

Pathology • DUODENAL ULCERS DUs occur most often in the first portion of the duodenum (>95%), with ~90% located within 3 cm of the pylorus. They are usually ≤ 1 cm in diameter but can occasionally reach 3–6 cm (giant ulcer). Ulcers are sharply demarcated, with depth at times reaching the muscularis propria. The base of the ulcer often consists of a zone of eosinophilic necrosis with surrounding fibrosis. Malignant DUs are extremely rare.

GASTRIC ULCERS In contrast to DUs, GUs can represent a malignancy and should be biopsied upon discovery. Benign GUs are most often found distal to the junction between the antrum and the acid secretory mucosa. Benign GUs are quite rare in the gastric fundus and are histologically similar to DUs. Benign GUs associated with *H. pylori* are also associated with antral gastritis. In contrast, NSAID-related GUs are not accompanied by chronic active gastritis but may instead have evidence of a chemical gastropathy, typified by foveolar hyperplasia, edema of the lamina propria, and epithelial

regeneration in the absence of *H. pylori*. Extension of smooth-muscle fibers into the upper portions of the mucosa, where they are not typically found, may also occur. Pathophysiology • DUODENAL ULCERS *H. pylori* and NSAID-induced injuries account for the majority of DUs. Many acid secretory abnormalities have been described in DU patients. Of these, average basal and nocturnal gastric acid secretion appears to be increased in DU patients as compared to controls; however, the level of overlap between DU patients and control subjects is substantial. The reason for this altered secretory process is unclear, but *H. pylori* infection may contribute. Bicarbonate secretion is significantly decreased in the duodenal bulb of patients with an active DU as compared to control subjects. *H. pylori* infection may also play a role in this process (see below). GASTRIC ULCERS As in DUs, the majority of GUs can be attributed to either *H. pylori* or NSAID-induced mucosal damage. Prepyloric GUs or those in the body associated with a DU or a duodenal scar are similar in pathogenesis to DUs. Gastric acid output (basal and stimulated) tends to be normal or decreased in GU patients. When GUs develop in the presence of minimal acid levels, impairment of mucosal defense factors may be present. H. PYLORI AND ACID PEPTIC DISORDERS Although gastric infection with the bacterium *H. pylori* was once thought to account for the majority of PUD (Chap. 168), more recent studies suggest that only one-fourth of DUs and one-sixth of GUs were associated with *H. pylori* infection. These changes are likely due to successful rates of eradication of the organism coupled with improved sanitary conditions. It appears that NSAIDs have become the most common cause of PUD (see below). This organism also plays a role in the development of gastric mucosa-associated lymphoid tissue (MALT) lymphoma and gastric adenocarcinoma. Although the entire genome of *H. pylori* has been sequenced, it is still not clear how this organism, which resides in the stomach, causes ulceration in the duodenum. *H. pylori* eradication efforts may lead to a decrease in gastric cancer in high-risk populations, particularly in individuals who have not developed chronic atrophic gastritis and gastric metaplasia. The Bacterium The bacterium, initially named *Campylobacter pylori* dis, is a gram-negative microaerophilic rod found most commonly in the deeper portions of the mucous gel coating the gastric mucosa or between the mucous layer and the gastric epithelium. It may attach to gastric epithelium but under normal circumstances does not appear to invade cells. It is strategically designed to live within the aggressive environment of the stomach. It is S-shaped (~0.5–3 μm in size) and contains multiple sheathed flagella. Initially, *H. pylori* resides in the antrum but, over time, migrates toward the more proximal segments of the stomach. The organism is capable of transforming into a coccoid form, which represents a dormant state that may facilitate survival in adverse conditions. The genome of *H. pylori* (1.65 million base pairs) encodes ~1500 proteins. Among this multitude of proteins, some factors are essential determinants of *H. pylori*-mediated pathogenesis and colonization such as the outer membrane protein (Hop proteins), urease, and the vacuolating cytotoxin (Vac A). Moreover, the majority of *H. pylori* strains contain a genomic fragment that encodes the *cag* pathogenicity island (*cag*-PAI). Several of the genes that make up *cag*PAI encode components of a type IV secretion island that translocates Cag A into host cells. Once in the cell, Cag A activates a series of cellular events important in cell growth and cytokine production. *H. pylori* also has extensive genetic diversity that in turn enhances its ability to promote disease. The first step in infection by *H. pylori* is dependent on the bacteria's motility and its ability to produce urease. Urease produces ammonia from urea, an essential step in alkalinizing the surrounding pH. Additional bacterial factors include but are not limited to, catalase, lipase, adhesins, platelet-activating factor, and pic B (induces cytokines). Multiple strains of *H. pylori* exist and are characterized by their ability to express several of these factors (Cag A, Vac A, etc.). It is possible that the different diseases related to *H. pylori* infection

can be attributed to different strains of the organism with distinct pathogenic features.

Epidemiology The prevalence of *H. pylori* varies throughout the world and depends largely on the overall standard of living in the region, with overall global prevalence decreasing. The global prevalence of *H. pylori* infection in adults has declined from 50–55% to 43% during 2014 to 2020. Contributing factors to these changes likely include

improvement of socioeconomic status and living standards as well as enhanced hygiene conditions. It is also possible that the increased use of antibiotics specifically with eradication therapies in individuals with infection could be a contributing factor to the overall decrease in global prevalence with a high variability in *H. pylori* infection throughout the world. In developing parts of the world, 80% of the population may be infected by the age of 20, whereas the prevalence is 20–50% in industrialized countries. In contrast, in the United States, this organism is rare in childhood. The overall prevalence of *H. pylori* in the United States is ~30%, with individuals born before 1950 having a higher rate of infection than those born later. About 10% of Americans <30 years of age are colonized with the bacteria. The rate of infection with *H. pylori* in industrialized countries has decreased substantially in recent decades. The steady increase in the prevalence of *H. pylori* noted with increasing age is due primarily to a cohort effect, reflecting higher transmission during a period in which the earlier cohorts were children. It has been calculated through mathematical models that improved sanitation during the latter half of the nineteenth century dramatically decreased transmission of *H. pylori*. Moreover, with the present rate of intervention, the organism ultimately will be eliminated from the United States. Two factors that predispose to higher colonization rates include poor socioeconomic status and less education about the organism. These factors, not race, are responsible for the rate of *H. pylori* infection in blacks and Hispanic Americans being double the rate seen in whites of comparable age. Other risk factors for *H. pylori* infection are (1) birth or residence in a developing country, (2) domestic crowding, (3) unsanitary living conditions, (4) unclean food or water, and (5) exposure to gastric contents of an infected individual.

CHAPTER 335 Transmission of *H. pylori* occurs from person to person, following an oral-oral or fecal-oral route. The risk of *H. pylori* infection is declining in developing countries. The rate of infection in the United States has fallen by >50% when compared to 30 years ago. **Pathophysiology** *H. pylori* infection is virtually always associated with a chronic active gastritis, but only 10–15% of infected individuals develop frank peptic ulceration. The basis for this difference is unknown but is likely due to a combination of host and bacterial factors, some of which are outlined below. Initial studies suggested that

“ 90% of all DUs were associated with *H. pylori*, but *H. pylori* is present in only one-sixth of individuals with GUs and one-fourth of patients with DUs. The pathophysiology of ulcers not associated with *H. pylori* or NSAID ingestion (or the rare Zollinger-Ellison syndrome [ZES]) is becoming more relevant as the incidence of *H. pylori* is dropping, particularly in the Western world (see below). **Peptic Ulcer Disease and Related Disorders** The particular end result of *H. pylori* infection (gastritis, PUD, gastric MALT lymphoma, gastric cancer) is determined by a complex interplay between bacterial and host factors (Fig. 335-6). Bacterial

factors Structure Adhesins Porins Enzymes (urease, vac A, cag A, etc.) Host factors Duration Location Inflammatory response Genetics?? Chronic gastritis Peptic ulcer disease Gastric MALT lymphoma Gastric cancer FIGURE 335-6 Outline of the bacterial and host factors important in determining H. pylori-induced gastrointestinal disease. MALT, mucosal-associated lymphoid tissue.

Bacterial factors: H. pylori is able to facilitate gastric residence, induce mucosal injury, and avoid host defense. Different strains of H. pylori produce different virulence factors including γ -glutamyl transpeptidase (GGT), cytotoxin-associated gene A (Cag A) product, and virulence components vacuolating toxin (Vac A), in addition to pathogen-associated molecular patterns (PAMPs) such as flagella and lipopolysaccharide (LPS). A specific region of the bacterial genome, the pathogenicity island (cag-PAI), encodes the virulence factors Cag A and pic B. Vac A also contributes to pathogenicity, although it is not encoded within the pathogenicity island. These virulence factors, in conjunction with additional bacterial constituents, can cause mucosal damage, in part through their ability to target the host immune cells. For example, Vac A targets human CD4 T cells, inhibiting their proliferation, and in addition can disrupt normal function of B cells, CD8 T cells, macrophages, and mast cells. Multiple studies have demonstrated that H. pylori strains that are cag-PAI positive are associated with a higher risk of PUD, premalignant gastric lesions, and gastric cancer than are strains that lack the cag-PAI. In addition, H. pylori may directly inhibit parietal cell H^+ , K^+ -ATPase activity through a Cag A-dependent mechanism, leading in part to the low acid production observed after acute infection with the organism. Urease, which allows the bacteria to reside in the acidic stomach, generates NH_3 , which can damage epithelial cells. The bacteria produce surface factors that are chemotactic for neutrophils and monocytes, which in turn contribute to epithelial cell injury (see below). H. pylori makes proteases and phospholipases that break down the glycoprotein lipid complex of the mucous gel, thus reducing the efficacy of this first line of mucosal defense. H. pylori expresses adhesins (outer membrane proteins like BabA), which facilitate attachment of the bacteria to gastric epithelial cells. Although LPS of gram-negative bacteria often plays an important role in the infection, H. pylori LPS has low immunologic activity compared to that of other organisms. It may promote a smoldering chronic inflammation.

PART 10 Disorders of the Gastrointestinal System **Host factors:** Studies in twins suggest that there may be genetic predisposition to acquire H. pylori. The inflammatory response to H. pylori includes recruitment of neutrophils, lymphocytes (T and B), macrophages, and plasma cells. The pathogen leads to local injury by binding to class II major histocompatibility complex (MHC) molecules expressed on gastric epithelial cells, leading to cell death (apoptosis). Moreover, bacterial strains that encode cag-PAI can introduce Cag A into the host cells, leading to further cell injury and activation of cellular pathways involved in cytokine production and repression of tumor-suppressor genes. Elevated concentrations of multiple cytokines are found in the gastric epithelium of H. pylori-infected individuals, including interleukin (IL) $1\alpha/\beta$, IL-2, IL-6, IL-8, tumor necrosis factor (TNF) α , and interferon (IFN) γ . H. pylori infection also leads to both a mucosal and a systemic humoral response, which does not lead to eradication of the bacteria but further compounds epithelial cell injury. Additional mechanisms by which H. pylori may cause epithelial cell injury include (1) activated neutrophil-mediated production of reactive oxygen or nitrogen species and

enhanced epithelial cell turnover and (2) apoptosis related to interaction with T cells (T helper 1 [TH1] cells) and IFN- γ . Finally, the human stomach is colonized by a host of commensal organisms that may affect the likelihood of

H. pylori infection and subsequent mucosal injury. Moreover, colonization of the stomach with *H. pylori* likely alters the composition of the gastric microbiota. The impact of the latter on gastric pathophysiology remains unknown but some studies suggest a potential increase in the development of gastric cancer. *H. pylori* also appears to regulate NO formation via different mechanisms that in turn may contribute to the organism's cytotoxic effects. Specifically, *H. pylori*-derived factors, such as urease, or the bacterium itself, stimulate NO synthase (NOS2) expression in macrophages and in gastric epithelial cells leading to NO release and subsequent cytotoxic effect on surrounding cells. *H. pylori* also leads to the formation of 8-nitroguanine (8-NO₂-Gua), which in conjunction with oncoprotein Cag A, may contribute to the development of gastric cancer. The basis for *H. pylori*-mediated duodenal ulceration remains unclear. Studies suggest that *H. pylori* associated with duodenal ulceration may be more virulent. In addition, certain specific bacterial

Parietal cell FUNDUS Vagus Canaliculus Acetylcholine Histamine + + H, K ATPase Tubulovesicles
ECL cell + Histamine + - - Somatostatin Somatostatin ECL cell D cell + Gastrin ANTRUM Blood
vessel Gastrin D cell G cell - Somatostatin

FIGURE 335-7 Summary of potential mechanisms by which *H. pylori* may lead to gastric secretory abnormalities. D, somatostatin cell; ECL, enterochromaffinlike cell; G, G cell. (Reproduced with permission from J Calam et al: How does *Helicobacter pylori* cause mucosal damage? Its effect on acid and gastrin physiology. *Gastroenterology* 113:543, 1997.) factors such as the DU-promoting gene A (dupA) may be associated with the development of DUs. Another potential contributing factor is that gastric metaplasia in the duodenum of DU patients, which may be due to high acid exposure (see below), permits *H. pylori* to bind to it and produce local injury secondary to the host response. Another hypothesis is that *H. pylori* antral infection could lead to increased acid production, increased duodenal acid, and mucosal injury. Basal and stimulated (meal, gastrin-releasing peptide [GRP]) gastrin release is increased in *H. pylori*-infected individuals, and somatostatin-secreting D cells may be decreased. *H. pylori* infection might induce increased acid secretion through both direct and indirect actions of *H. pylori* and proinflammatory cytokines (IL-8, TNF, and IL-1) on G, D, and parietal cells (Fig. 335-7). GUs, in contrast, are associated with *H. pylori*-induced pangastritis and normal or low gastric acid secretion. The *H. pylori*-mediated decrease in gastric acid secretion after long-term infection may be due to the bacterium's ability to inhibit H⁺,K⁺-ATPase expression. *H. pylori* infection has also been associated with decreased duodenal mucosal bicarbonate production. Data supporting and contradicting each of these interesting theories have been demonstrated. Thus, the mechanism by which *H. pylori* infection of the stomach leads to duodenal ulceration remains to be established. The development of in vitro organoids, a unique tool that replicates in part the multicellular structure of the intact organ, provides a more physiologic model for experimentation in an in vitro system. Moreover, the development of advanced microscopic optical imaging techniques will lead to increased understanding of parietal cell adaptation to *H. pylori* infection. In summary, the final effect of *H. pylori* on the GI tract is variable and determined by microbial and host factors. The type and distribution of gastritis correlate with the ultimate gastric and duodenal pathology observed. Specifically, the presence of antral-predominant gastritis is associated with DU formation; gastritis involving primarily the corpus predisposes to the

development of GUs, gastric atrophy, and ultimately gastric carcinoma (Fig. 335-8). NSAID-INDUCED DISEASE Epidemiology NSAIDs represent a group of the most commonly used medications in the world and the United States. It is estimated that

7 billion dollars per year are spent on NSAIDs worldwide, with >30 billion over-the-counter tablets sold. More than 30 million individuals take NSAIDs, with >100 million prescriptions sold yearly in the United States

High level of acid production Duodenal ulcer MALT lymphoma Antralpredominant gastritis Chronic H. pylori infection Asymptomatic H. pylori infection Nonatrophic pangastritis Normal gastric mucosa Corpuspredominant atrophic gastritis Gastric ulcer Acute H. pylori infection Intestinal metaplasia Dysplasia Gastric cancer Low level of acid production Childhood Advanced age

FIGURE 335-8 Natural history of H. pylori infection. MALT, mucosal-associated lymphoid tissue. (From The New England Journal of Medicine, Medical progress: Helicobacter pylori infection, S Suerbaum, P Michetti: 347:1175-1186. Copyright ©2002 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

alone. In fact, after the introduction of COX-2 inhibitors in the year 2000, the number of prescriptions written for NSAIDs was >111 million at a cost of \$4.8 billion. Side effects and complications due to NSAIDs are considered the most common drug-related toxicities in the United States. The spectrum of NSAID-induced morbidity ranges from nausea and dyspepsia (prevalence reported as high as 50–60%) to a serious GI complication such as endoscopy-documented peptic ulceration (15–30% of individuals taking NSAIDs regularly), which is complicated by bleeding or perforation in as many as 1.5% of users per year. It is estimated that NSAID-induced GI bleeding accounts for 60,000–120,000 hospital admissions per year, and deaths related to NSAID-induced toxicity may be as high as 16,000 per year in the United States. Approximately 4–5% of patients develop symptomatic ulcers within 1 year. Unfortunately, dyspeptic symptoms do not correlate with NSAID-induced pathology. Over 80% of patients with serious NSAID-related complications did not have preceding dyspepsia. In view of the lack of warning signs, it is important to identify patients who are at increased risk for morbidity and mortality related to NSAID usage. Even 75 mg/d of aspirin may lead to serious GI ulceration; thus, no dose of NSAID is completely safe. In fact, the incidence of mucosal injury (ulcers and erosions) in patients taking low-dose aspirin (75–325 mg) has been estimated to range from as low as 8 to as high as 60%. It appears that H. pylori infection increases the risk of PUD-associated GI bleeding in chronic users of low-dose aspirin. Established risk factors include advanced age, history of ulcer, concomitant use of glucocorticoids, high-dose NSAIDs, multiple NSAIDs, concomitant use of anticoagulants or clopidogrel, and serious or multisystem disease. Possible risk factors include concomitant infection with H. pylori, cigarette smoking, and alcohol consumption. SSRIs have a synergistic effect on the induction of GI bleeding believed to be due in part to this agent's ability to decrease platelet aggregation by decreasing serotonin content in platelets. Pathophysiology Prostaglandins play a critical role in maintaining gastroduodenal mucosal integrity and repair. It therefore follows that interruption of prostaglandin synthesis can impair mucosal defense and repair, thus facilitating mucosal injury via a systemic mechanism. Animal studies have demonstrated that neutrophil adherence to the gastric microcirculation plays an essential role in the initiation of NSAID-induced mucosal injury. A summary of the pathogenetic pathways by which systemically administered NSAIDs may lead to mucosal injury is shown in Fig. 335-9. Single nucleotide polymorphisms (SNPs) have been found in several genes, including those encoding certain subtypes of cytochrome P450 (see below), IL-1 β (IL-1 β), angiotensinogen

Gastrointestinal mucosal injury Mitochondrial uncoupling Reactive prooxidants MOS ATP Mitochondrial fission Mucosal PGHS-1 PGE 2 Mucosal defense Intestinal mucosal barrier function Mucosal inflammation Apoptosis

FIGURE 335-9 Effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on different target organs. The action of NSAIDs on major organs including stomach, small intestine, heart, liver, kidney, respiratory tract, and brain is mainly mediated through prostaglandin endoperoxide synthase (PGHS)-dependent prostanoid modulation and alteration of mitochondrial functional integrity leading to mitochondrial oxidative stress (MOS) generation, depolarization of mitochondrial transmembrane potential ($\Delta\Psi_m$), and consequent cell death. However, in heart, low-dose aspirin actually offers cardioprotection through antithrombotic effect. Upward arrows indicate upregulation/elevation; downward arrows indicate downregulation/ depletion. (From S Bindu et al: Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. *Biochem Pharmacol* 180:114147, 2020.)

(AGT), and an organic ion transporting polypeptide (SLCO1B1), but these findings need confirmation in larger-scale studies.

CHAPTER 335 Injury to the mucosa also occurs as a result of the topical use of NSAIDs, leading to increased epithelial surface permeability. Aspirin and many NSAIDs are weak acids that remain in a nonionized lipophilic form when found within the acid environment of the stomach. Under these conditions, NSAIDs migrate across lipid membranes of epithelial cells, leading to cell injury once trapped intracellularly in an ionized form. Topical NSAIDs can also alter the surface mucous layer, permitting back diffusion of H^+ and pepsin, leading to further epithelial cell damage. Moreover, enteric-coated or buffered preparations are also associated with risk of peptic ulceration. NSAIDs can also lead to mucosal injury via production of additional proinflammatory mediators such as TNF and leukotrienes through simultaneous activation of the lipoxygenase pathway.

Peptic Ulcer Disease and Related Disorders The interplay between *H. pylori* and NSAIDs in the pathogenesis of PUD is complex. Meta-analysis supports the conclusion that each of these aggressive factors is an independent and synergistic risk factor for PUD and its complications such as GI bleeding. For example, eradication of *H. pylori* reduces the likelihood of GI complications in high-risk individuals to levels observed in individuals with average risk of NSAID-induced complications. In summary, NSAID-induced mucosal injury is a multifaceted process involving the interaction of multiple, often synergistic pathophysiologic processes at the epithelium and surrounding interfaces.

PATHOGENETIC FACTORS UNRELATED TO *H. PYLORI* AND NSAIDS IN ACID PEPTIC DISEASE Cigarette smoking has been implicated in the pathogenesis of PUD. Not only have smokers been found to have ulcers more frequently than do nonsmokers, but smoking appears to decrease healing rates, impair response to therapy, and increase ulcer-related complications such as perforation. The mechanism responsible for increased ulcer diathesis in smokers is unknown. Theories have included altered gastric emptying, decreased proximal duodenal bicarbonate production, increased risk for *H. pylori* infection, and cigarette-induced generation of noxious mucosal free radicals. Genetic predisposition may play a role in ulcer development. First-degree relatives of DU patients are three times as likely to develop an ulcer; however, the potential role of *H. pylori* infection in contacts is a major consideration. Increased frequencies of blood group O and of the nonsecretor status have also been implicated as genetic risk factors for peptic diathesis. However, *H. pylori* preferentially binds to group O antigens. Additional genetic factors have been postulated to predispose certain

individuals to developing PUD and/or upper GI bleeding. Specifically, genes encoding the NSAID-metabolizing enzymes cytochrome P450 2C9 and 2C8 (CYP2C9 and CYP2C8) are potential susceptibility genes for NSAID-induced PUD, but unfortunately, the studies have not been consistent in demonstrating this association. In a United Kingdom study, the CYP2C19*17 gain-of-

function polymorphism was associated with PUD in a Caucasian cohort, irrespective of ulcer etiology. These findings need to be confirmed in broader studies. Psychological stress has been thought to contribute to PUD, but studies examining the role of psychological factors in its pathogenesis have generated conflicting results. Although PUD is associated with certain personality traits (neuroticism), these same traits are also present in individuals with nonulcer dyspepsia (NUD) and other functional and organic disorders.

Diet has also been thought to play a role in peptic diseases. Certain foods and beverages can cause dyspepsia, but no convincing studies indicate an association between ulcer formation and a specific diet. Specific chronic disorders have been shown to have a strong association with PUD: (1) advanced age, (2) chronic pulmonary disease, (3) chronic renal failure, (4) cirrhosis, (5) nephrolithiasis, (6) α 1antitrypsin deficiency, and (7) systemic mastocytosis. Disorders with a possible association are (1) hyperparathyroidism, (2) coronary artery disease, (3) polycythemia vera, (4) chronic pancreatitis, (5) former alcohol use, (6) obesity, (7) African-American race, and (8) three or more doctor visits in a year. Multiple factors play a role in the pathogenesis of PUD. The two predominant causes are *H. pylori* infection and NSAID ingestion. PUD not related to *H. pylori* or NSAIDs is increasing. Other less common causes of PUD are shown in Table 335-1. These etiologic agents should be considered as the incidence of *H. pylori* is decreasing. Independent of the inciting or injurious agent, peptic ulcers develop as a result of an imbalance between mucosal protection/repair and aggressive factors. Gastric acid plays an important role in mucosal injury.

PART 10 Disorders of the Gastrointestinal System ■ ■CLINICAL FEATURES History Abdominal pain is common to many GI disorders, including DU and GU, but it has a poor predictive value for the presence

TABLE 335-1 Causes of Ulcers Not Caused by Helicobacter pylori

and NSAIDs Pathogenesis of Non-Hp and Non-NSAID Ulcer Disease Infection Cytomegalovirus Herpes simplex virus Helicobacter heilmannii Drug/Toxin Bisphosphonates Checkpoint inhibitor Chemotherapy Clopidogrel Crack cocaine Glucocorticoids (when combined with NSAIDs) Mycophenolate mofetil Potassium chloride Miscellaneous Basophilia in myeloproliferative disease Duodenal obstruction (e.g., annular pancreas) Infiltrating disease Ischemia Radiation therapy Eosinophilic infiltration Sarcoidosis Crohn's disease Idiopathic hypersecretory state Abbreviations: Hp, *H. pylori*; NSAIDs, nonsteroidal anti-inflammatory drugs.

of either DU or GU. Approximately two-thirds of patients with PUD do not have abdominal pain, and up to 87% of patients with NSAID-induced mucosal disease can present with a complication (bleeding, perforation, and obstruction) without antecedent symptoms. Despite this poor correlation, a careful history and physical examination are essential components of the approach to a patient suspected of having peptic ulcers. Epigastric pain described as a burning or gnawing discomfort can be present in both DU and GU. The discomfort is also described as an ill-defined, aching sensation or as hunger pain. The typical pain pattern in DU occurs 90 min to 3 h after a meal and is frequently relieved by antacids or food. Pain that awakes the patient from sleep (between midnight and 3 A.M.) is the most discriminating symptom, with two-thirds of DU patients describing this complaint. Unfortunately, this symptom is also present in one-third of patients with NUD (see below). Elderly patients are less likely to have abdominal pain as a manifestation of PUD and may instead present with a complication such as ulcer bleeding or perforation. The pain pattern in GU patients may be different from that in DU patients, where discomfort may actually be precipitated by food. Nausea and weight loss occur more commonly in GU patients. Endoscopy

detects ulcers in <30% of patients who have dyspepsia. The mechanism for development of abdominal pain in ulcer patients is unknown. Several possible explanations include acid-induced activation of chemical receptors in the duodenum, enhanced duodenal sensitivity to bile acids and pepsin, and altered gastroduodenal motility. Variation in the intensity or distribution of the abdominal pain, as well as the onset of associated symptoms such as nausea and/or vomiting, may be indicative of an ulcer complication. Dyspepsia that becomes constant, is no longer relieved by food or antacids, or radiates to the back may indicate a penetrating ulcer (pancreas). Sudden onset of severe, generalized abdominal pain may indicate perforation. Pain worsening with meals, nausea, and vomiting of undigested food suggest gastric outlet obstruction. Tarry stools or coffee-ground emesis indicate bleeding. Physical Examination Epigastric tenderness is the most frequent finding in patients with GU or DU. Pain may be found to the right of the midline in 20% of patients. Unfortunately, the predictive value of this finding is low. Physical examination is critically important for discovering evidence of ulcer complication. Tachycardia and orthostasis suggest dehydration secondary to vomiting or active GI blood loss. A severely tender, board-like abdomen suggests a perforation. Presence of a succussion splash indicates retained fluid in the stomach, suggesting gastric outlet obstruction. PUD-Related Complications • GASTROINTESTINAL BLEEDING

GI bleeding is the most common complication observed in PUD. Bleeding is estimated to occur in 19.4–57 per 100,000 individuals in a general population or in ~15% of patients. Bleeding and complications of ulcer disease occur more often in individuals >60 years of age. The 30-day mortality rate is as high as 2.5–10%. The higher incidence in the elderly is likely due to the increased use of NSAIDs in this group. In addition, up to 80% of the mortality in PUD-related bleeding is due to nonbleeding causes such as multiorgan failure (24%), pulmonary complications (24%), and malignancy (34%). Greater than 50% of patients with ulcer-related hemorrhage bleed without any preceding warning signs or symptoms. PERFORATION The second most common ulcer-related complication is perforation, being reported in as many as 6–7% of PUD patients with an estimated 30-day mortality of >20%. Acute abdominal pain, tachycardia, and abdominal rigidity compose the classic triad associated with this complication. It is essential to remember that elderly patients or individuals who are immunosuppressed may not have this classic presentation. As in the case of bleeding, the incidence of perforation in the elderly appears to be increasing secondary to increased use of NSAIDs. Perforation of DUs has become less common in light of the increased rates of *H. pylori* eradication, with NSAID-induced GUs leading to perforation occurring more commonly. Penetration is

a form of perforation in which the ulcer bed tunnels into an adjacent organ. DUs tend to penetrate posteriorly into the pancreas, leading to pancreatitis, whereas GUs tend to penetrate into the left hepatic lobe. Gastrocolic fistulas associated with GUs have also been described. Mortality for this complication can be >20% within 30 days. GASTRIC OUTLET OBSTRUCTION Gastric outlet obstruction is the least common ulcer-related complication, occurring in 1–2% of patients. A patient may have relative obstruction secondary to ulcer-related inflammation and edema in the peripyloric and duodenal region. This process often resolves with ulcer healing. A fixed, mechanical obstruction secondary to scar formation in the peripyloric areas is also possible. The latter requires endoscopic (balloon dilation with or without placement of a biodegradable stent) or surgical intervention with a strictureplasty or gastrojejunostomy. Signs and symptoms relative to mechanical obstruction may develop insidiously. New onset of early satiety, nausea, vomiting, increase of postprandial abdominal pain, and weight loss should make gastric outlet obstruction a

possible diagnosis. **Differential Diagnosis** The list of GI and non-GI disorders that can mimic ulceration of the stomach or duodenum is quite extensive. The most commonly encountered diagnosis among patients seen for upper abdominal discomfort is functional dyspepsia (FD) or essential dyspepsia, which refers to a group of heterogeneous disorders typified by upper abdominal pain without the presence of an ulcer. The symptoms can range from postprandial fullness and early satiety to epigastric burning pain. The dichotomy of this symptom complex has led to the identification of two subcategories of FD including postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). Dyspepsia has been reported to occur in up to 30% of the U.S. population. Up to 80% of patients seeking medical care for dyspepsia have a negative diagnostic evaluation. The etiology of FD is not established, but postinfectious states, certain foods, and *H. pylori* infection may contribute to the pathogenesis of this common disorder. Several additional disease processes that may present with “ulcerlike” symptoms include proximal GI tumors, gastroesophageal reflux, vascular disease, pancreaticobiliary disease (biliary colic, chronic pancreatitis), and gastroduodenal Crohn’s disease. **Diagnostic Evaluation** In view of the poor predictive value of abdominal pain for the presence of a gastroduodenal ulcer and the multiple disease processes that can mimic this disease, the clinician is often confronted with having to establish the presence of an ulcer. Documentation of an ulcer requires either a radiographic (barium study, rarely done in today’s environment) or an endoscopic procedure. However, a large percentage of patients with symptoms suggestive of an ulcer have NUD; testing for *H. pylori* and antibiotic therapy (see below) are appropriate for individuals who are otherwise healthy, without red flag signs such as nausea, vomiting, weight loss, or evidence of GI bleeding and <60 years of age, before embarking on a diagnostic evaluation (Chap. 48).

FIGURE 335-10 Barium study demonstrating (A) a benign duodenal ulcer and (B) a benign gastric ulcer.

ulcer have NUD; testing for *H. pylori* and antibiotic therapy (see below) are appropriate for individuals who are otherwise healthy, without red flag signs such as nausea, vomiting, weight loss, or evidence of GI bleeding and <60 years of age, before embarking on a diagnostic evaluation (Chap. 48).

Barium studies of the proximal GI tract are rarely used as a first test for documenting an ulcer (Fig. 335-10). Endoscopy provides the most sensitive and specific approach for examining the upper GI tract (Fig. 335-11). In addition to permitting direct visualization of the mucosa, endoscopy facilitates photographic documentation of a mucosal defect and tissue biopsy to rule out malignancy (GU) or

H. pylori. Endoscopic examination is particularly helpful in identifying lesions too small to detect by radiographic examination, for evaluation of atypical radiographic abnormalities, or to determine if an ulcer is a source of blood loss. Although the methods for diagnosing *H. pylori* are outlined in Chap. 168, a brief summary will be included here (Table 335-2). Several biopsy urease tests have been developed (PyloriTek, CLOtest, Hpfast, Pronto Dry) that have a sensitivity and specificity of >90–95%. Several noninvasive methods for detecting this organism have been developed. Three types of studies routinely used include serologic testing, the ¹³C-urea breath test, and the fecal *H. pylori* (Hp) antigen test (monoclonal antibody test). A urinary Hp antigen test and a home breath test appear promising. Occasionally, specialized testing such as serum gastrin and gastric acid analysis may be needed in individuals with complicated or refractory PUD (see “Zollinger-Ellison Syndrome,” below). Screening for aspirin or NSAIDs (blood or urine) may also be necessary in refractory *H. pylori*-negative PUD patients. **CHAPTER 335 TREATMENT Peptic Ulcer Disease** Peptic Ulcer Disease and Related Disorders Before the discovery of *H. pylori*, the therapy of PUD was centered on the old dictum by Schwartz of “no acid, no ulcer.” Although acid secretion is still

important in the pathogenesis of PUD, eradication of *H. pylori* and therapy/prevention of NSAID-induced disease is the mainstay of treatment. A summary of commonly used drugs for treatment of acid peptic disorders is shown in Table 335-3. ACID-NEUTRALIZING/INHIBITORY DRUGS Antacids Before we understood the important role of histamine in stimulating parietal cell activity, neutralization of secreted acid with antacids constituted the main form of therapy for peptic ulcers. They are now rarely, if ever, used as the primary therapeutic agent

A B FIGURE 335-11 Endoscopy demonstrating (A) a benign duodenal ulcer and (B) a benign gastric ulcer. but instead are often used by patients for symptomatic relief of dyspepsia. The most commonly used agents are mixtures of aluminum hydroxide and magnesium hydroxide. Aluminum hydroxide can produce constipation and phosphate depletion; magnesium hydroxide may cause loose stools. Many of the commonly used antacids (e.g., Maalox, Mylanta) have a combination of both aluminum and magnesium hydroxide in order to avoid these side effects. The magnesium-containing preparation should not be used in chronic renal failure patients because of possible hypermagnesemia, and aluminum may cause chronic neurotoxicity in these patients. PART 10 Disorders of the Gastrointestinal System Calcium carbonate and sodium bicarbonate are potent antacids with varying levels of potential problems. The long-term use of calcium carbonate (converts to calcium chloride in the stomach) can lead to milk-alkali syndrome (hypercalcemia and hyperphosphatemia with possible renal calcinosis and progression to renal insufficiency). Sodium bicarbonate may induce systemic alkalosis. H₂ Receptor Antagonists Four of these agents are presently available (cimetidine, ranitidine, famotidine, and nizatidine), and their structures share homology with histamine. Although each has different potency, all will significantly inhibit basal and stimulated acid secretion to comparable levels when used at therapeutic doses. Moreover, similar ulcer-healing rates are achieved with each drug when used at the correct dosage. Presently, this class of drug is often used for treatment of active ulcers (4–6 weeks) in combination with antibiotics directed at eradicating *H. pylori* (see below). TABLE 335-2 Tests for Detection of *Helicobacter pylori* SENSITIVITY/ SPECIFICITY, % COMMENTS TEST Invasive (Endoscopy/Biopsy Required) Rapid urease 80–95/95–100 Simple, false negative with recent use of PPIs, antibiotics, or bismuth compounds Histology 60–90/>95 Requires pathology processing and staining; provides histologic information Culture 76–90/100 Time-consuming, expensive, dependent on experience; allows determination of antibiotic susceptibility Noninvasive Serology 74.4/59 Inexpensive, convenient; not useful for early follow-up; cannot distinguish active and prior infection Urea breath test

“ 95/>95 Simple, rapid; useful for early follow-up; false negatives with recent therapy (see rapid urease test) Stool antigen 95/>95 Inexpensive, convenient Abbreviation: PPIs, proton pump inhibitors.

Cimetidine was the first H₂ receptor antagonist used for the treatment of acid peptic disorders. Cimetidine may have weak antiandrogenic side effects resulting in reversible gynecomastia and impotence, primarily in patients receiving high doses for prolonged periods of time (months to years). In view of cimetidine's ability to inhibit cytochrome P450, careful monitoring of drugs such as warfarin, phenytoin, and theophylline is indicated with long-term usage. Other rare reversible adverse effects reported with cimetidine include confusion and elevated levels of serum

aminotransferases, creatinine, and serum prolactin. Famotidine is a more potent H₂ receptor antagonist than cimetidine. It can be used once a day at bedtime for ulcer prevention, which was commonly done before the discovery of *H. pylori* and the development of proton pump inhibitors (PPIs). Patients may develop tolerance to H₂ blockers, a rare event with PPIs (see below). Comparable nighttime dosing regimens are cimetidine 800 mg and famotidine 40 mg. Additional rare, reversible systemic toxicities reported with H₂ receptor antagonists include pancytopenia, neutropenia, anemia, and thrombocytopenia, with a prevalence rate varying from 0.01 to 0.2%. Cimetidine can bind to hepatic cytochrome P450; famotidine does not. Proton Pump (H⁺,K⁺-ATPase) Inhibitors Omeprazole, esomeprazole, lansoprazole, rabeprazole, and pantoprazole are substituted

TABLE 335-3 Drugs Used in the Treatment of Peptic Ulcer Disease

DRUG TYPE/MECHANISM	EXAMPLES	DOSE
Acid-Suppressing Drugs	Antacids	Mylanta, Maalox, Tums, Gaviscon
		100–140 meq/L 1 and 3 h after meals and hs
H ₂ receptor antagonists	Cimetidine	400 mg bid
	Famotidine	40 mg hs
Proton pump inhibitors	Omeprazole	20 mg/d
	Lansoprazole	30 mg/d
	Rabeprazole	20 mg/d
	Pantoprazole	40 mg/d
	Esomeprazole	20 mg/d
	Dexlansoprazole	30 mg/d
Mucosal Protective Agents	Sucralfate	Sucralfate 1 g qid
	Prostaglandin analogue	Misoprostol 200 µg qid
Bismuth-containing compounds	Bismuth subsalicylate (BSS)	See anti- <i>H. pylori</i> regimens (Table 335-4)

Abbreviation: hs, at bedtime (hora somni).

Peptic Ulcer Disease and Related Disorders

CHAPTER 335 benzimidazole derivatives that covalently bind and irreversibly inhibit H⁺,K⁺-ATPase. Esomeprazole is the S-enantiomer of omeprazole, which is a racemic mixture of both S- and R-optical isomers. The R-isomer of lansoprazole, dexlansoprazole, is the most recent PPI approved for clinical use. Its reported advantage is a dual delayed-release system aimed at improving treatment of gastro esophageal reflux disease (GERD). These are the most potent acid inhibitory agents available. Omeprazole and lansoprazole are the PPIs that have been used for the longest time. Both are acid-labile and are administered as enteric-coated granules in a sustained-release capsule that dissolves within the small intestine at a pH of 6. Lansoprazole is available in an orally disintegrating tablet that can be taken with or without water, an advantage for individuals who have significant dysphagia. Absorption kinetics are similar to the capsule. In addition, a lansoprazole-naproxen combination preparation that has been made available is targeted at decreasing NSAID-related GI injury (see below). Omeprazole is available as non-enteric-coated granules mixed with sodium bicarbonate in a powder form that can be administered orally or via gastric tube. The sodium bicarbonate has two purposes: to protect the omeprazole from acid degradation and to promote rapid gastric alkalization and subsequent proton pump activation, which facilitates rapid action of the PPI. Pantoprazole and rabeprazole are available as enteric-coated tablets. Pantoprazole is also available as a parenteral formulation for intravenous use. These agents are lipophilic compounds; upon entering the parietal cell, they are protonated and trapped within the acid environment of the tubulovesicular and canalicular system. These agents potentially inhibit all phases of gastric acid secretion. Onset of action is rapid, with a maximum acid inhibitory effect between 2 and 6 h after administration and duration of inhibition lasting up to 72–96 h. With repeated daily dosing, progressive acid inhibitory effects are observed, with basal and secretagogue-stimulated acid production being inhibited by >95% after 1 week of therapy. The half-life of PPIs is ~18 h; thus, it can take between 2 and 5 days for gastric acid secretion to return to normal levels once these drugs have been discontinued. Because the pumps need to be activated for these agents to be effective, their efficacy is maximized if they are administered

before a meal (except for the immediate-release formulation of omeprazole) (e.g., in the morning before breakfast). Mild to moderate hypergastrinemia has been observed in patients taking these drugs. Carcinoid tumors developed in some animals given the drugs chronically; however, extensive experience has failed to demonstrate gastric carcinoid tumor development in humans. Serum gastrin levels return to normal levels within 1–2 weeks after drug cessation. Rebound gastric acid hypersecretion has been described in *H. pylori*-negative individuals after discontinuation of PPIs. It occurs even after relatively short-term usage (2 months) and may last for up to 2 months after the PPI has been discontinued. The mechanism involves gastrin-induced hyperplasia and hypertrophy of histamine-secreting ECL cells. The clinical relevance of this observation is that individuals may have worsening symptoms of GERD or dyspepsia upon stopping the PPI. Gradual tapering of the PPI and switching to an H₂ receptor antagonist may prevent this from occurring. *H. pylori*-induced inflammation and concomitant decrease in acid production may explain why this does not occur in *H. pylori*-positive patients. IF production is also inhibited, but vitamin B₁₂ deficiency anemia is uncommon, probably because of the large stores of the vitamin. As with any agent that leads to significant hypochlorhydria, PPIs may interfere with absorption of drugs such as ketoconazole, ampicillin, iron, and digoxin. Hepatic cytochrome P450 can be inhibited by the earlier PPIs (omeprazole, lansoprazole). Rabeprazole, pantoprazole, and esomeprazole do not appear to interact significantly with drugs metabolized by the cytochrome P450 system. The overall clinical significance of this observation is not definitely established. Caution should be taken when using theophylline, warfarin, diazepam, atazanavir, and phenytoin concomitantly with PPIs. The list of potential side effects with long-term PPI use has steadily grown over the years. These agents are commonly used since several formulations have become available as over-the-counter medications. Moreover, up to 70% of current prescriptions for long-term PPIs may be unwarranted and between 35 and 60% of in-hospital use of PPIs may be inappropriate. Interpretation of the multiple studies should take into consideration that the vast majority were retrospective observational studies in which confounding factors could not be accounted for entirely. Long-term acid suppression, especially with PPIs, has been associated with a higher incidence of community-acquired pneumonia as well as community- and hospital-acquired *Clostridioides difficile*-associated disease. A meta-analysis showed a 74% increased risk of *C. difficile* infection and a 2.5-fold higher risk of reinfection as compared to nonusers. In light of these concerns, the FDA published a safety alert regarding the association between *C. difficile* infection and PPI use. Although the risk of spontaneous bacterial peritonitis in cirrhotics was thought to be increased, the data here are less supportive. The impact of PPI-induced changes in the host microbiome is postulated to play a role in the increased risk of infection, but this theory needs to be confirmed. These observations require confirmation but should alert the practitioner to take caution when recommending these agents for long-term use, especially in elderly patients at risk for developing pneumonia or *C. difficile* infection. Diarrhea is also associated with PPI use, which in some cases has been associated with the development of collagenous colitis (hazard ratio of 4.5), particularly with lansoprazole. The mechanism for PPI-induced collagenous colitis is unclear, but in vitro studies demonstrate that PPIs may induce collagen gene expression. The colitis usually resolves with cessation of the PPI. A population-based study revealed that long-term use of PPIs was associated with the development of hip fractures in older women. The absolute risk of fracture remained low and may be zero despite an observed increase associated with the dose and duration of acid suppression. The mechanism for this observation is not clear, and this finding must be confirmed before making broad recommendations regarding the discontinuation of these agents in patients who benefit from them. Long-term use of PPIs has also been implicated in the development of iron,

vitamin B12, and magnesium deficiency. A meta-analysis of nine observational studies found a 40% increase in hypomagnesemia in PPI users as compared to nonusers. One approach to consider in patients needing to take PPIs long term is to check a complete blood count looking for evidence of anemia due to iron or vitamin B12 deficiency, vitamin B12 level, and a magnesium level after 1–2 years of PPI use, but these recommendations are not evidence based or recommended by expert opinion. PPIs may exert a negative effect on the antiplatelet effect of clopidogrel. Although the evidence is mixed and inconclusive, a small increase in mortality and readmission rate for coronary events was seen in patients receiving a PPI while on clopidogrel in earlier studies. Subsequently, three meta-analyses reported an inverse correlation between clopidogrel and PPI use; therefore, the influence of this drug interaction on mortality is not clearly established. The mechanism involves the competition of the PPI and clopidogrel with the same cytochrome P450 (CYP2C19). Whether this is a class effect of PPIs is unclear; there appears to be at least a theoretical advantage of pantoprazole over the other PPIs, but this has not been confirmed. This drug interaction is particularly relevant in light of the common use of aspirin and clopidogrel for prevention of coronary events and the efficacy of PPIs in preventing GI bleeding in these patients. The FDA has made several recommendations while awaiting further evidence to clarify the impact of PPI therapy on clopidogrel use. Health care providers should continue to prescribe clopidogrel to patients who require it and should reevaluate the need for starting or continuing treatment with a PPI. From a practical standpoint, additional recommendations to consider include the following: Patients taking clopidogrel with aspirin, especially with other GI risk factors for bleeding, should receive GI protective therapy. Although high-dose H2 blockers have been considered an option, these do not appear to be as effective as PPIs. If PPIs are to be given, some have recommended that there be a 12-h separation between

Bone fracture C. difficile infection Community-acquired pneumonia (2 studies) Side effect
Hypomagnesemia Acute interstitial nephritis Acute kidney disease Chronic kidney disease 2.00
2.50 3.00 1.50 1.00 0.50 5.00 5.50 6.00 4.50 4.00 3.50 0.00 Adjusted odds ratio (95% confidence
interval) FIGURE 335-12. Evidence supporting the potential adverse effects of proton pump
inhibitor drugs. (Adapted from AJ Schoenfeld, D Grady: Adverse effects associated with proton
pump inhibitors. JAMA Intern Med 176:172, 2016.) administration of the PPI and clopidogrel to
minimize competition of the two agents with the involved cytochrome P450. One option is to give
the PPI 30 min before breakfast and the clopidogrel at bed time. Insufficient data are available to
firmly recommend one PPI over another. Additional concerning side effects with long-term PPI use
include increased cardiac risks independent of clopidogrel use, dementia, and acute and chronic
kidney injury. Again, the data are often retrospective and confounding variables were not
consistently eliminated, thus making it difficult to establish a definitive association between PPIs
and the toxicities outlined. A summary of the side effects with the corresponding relative risks is
shown in Fig. 335-12. Ultimately, heightened awareness of inappropriate long-term use of PPIs is
paramount. Patients aged ≥ 65 years of age have a higher risk for some of the long-term side
effects of PPIs highlighted above, in part due to the higher prevalence of concomitant chronic
diseases. It is therefore essential to carefully select individuals, especially among the elderly, who
need long-term PPI therapy and discontinue it in those individuals who do not need it. Abrupt
withdrawal of a PPI in a long-term user may result in a component of rebound hyperacidity; thus,
this agent should be tapered gradually over the course of 1–2 weeks with possible transition to an
H2 blocker for a short period of time. PART 10 Disorders of the Gastrointestinal System
Development of novel acid inhibitory agents continues in an attempt to primarily address the need

for better agents to treat GERD. For example, modified H₂ blockers with greater potency and duration as well as novel PPIs with longer half-life and potency are under study. For example, tenatoprazole is a PPI containing an imidazopyridine ring instead of a benzimidazole ring, which promotes irreversible proton pump inhibition. This agent has a longer half-life than the other PPIs and may be beneficial for inhibiting nocturnal acid secretion, which has significant relevance in GERD. Additional PPIs with longer half-life and combined with other agents are being studied, but the details are beyond the scope of this chapter. A second new class of agents is the potassium-competitive acid pump antagonists (P-CAPs). These compounds inhibit gastric acid secretion via potassium-competitive binding of the H⁺,K⁺-ATPase. Revaprazan, vonoprazan and tegoprazan are agents approved for use in Korea and Japan, and vonoprazan has been approved by the FDA for use in the United States. Vonoprazan may be superior to PPIs when combined with antibiotics for the treatment of *H. pylori*, and this novel agent was awarded Fast Track status by the FDA for the treatment of *H. pylori* in combination with both amoxicillin and clarithromycin and with amoxicillin alone.

CYTOPROTECTIVE AGENTS

Sucralfate Sucralfate is a complex sucrose salt in which the hydroxyl groups have been substituted by aluminum hydroxide and sulfate. This compound is insoluble in water and becomes a viscous paste within the stomach and duodenum, binding primarily to sites of active ulceration. Sucralfate may act by several mechanisms:

serving as a physicochemical barrier, promoting a trophic action by binding growth factors such as EGF, enhancing prostaglandin synthesis, stimulating mucus and bicarbonate secretion, and enhancing mucosal defense and repair. Toxicity from this drug is rare, with constipation being most common (2–3%). It should be avoided in patients with chronic renal insufficiency to prevent aluminum-induced neurotoxicity. Hypophosphatemia and gastric bezoar formation have also been reported rarely. Standard dosing of sucralfate is 1 g qid.

Bismuth-Containing Preparations

Sir William Osler considered bismuth-containing compounds the drug of choice for treating PUD. The resurgence in the use of these agents is due to their effect against *H. pylori*. Colloidal bismuth subcitrate (CBS) and bismuth subsalicylate (BSS; Pepto-Bismol) are the most widely used preparations. The mechanism by which these agents induce ulcer healing is unclear. Adverse effects with short-term use include black stools, constipation, and darkening of the tongue. Long-term use with high doses, especially with the avidly absorbed CBS, may lead to neurotoxicity. These compounds are commonly used as one of the agents in an anti-*H. pylori* regimen (see below).

6.50 Prostaglandin Analogues

In view of their central role in maintaining mucosal integrity and repair, stable prostaglandin analogues were developed for the treatment of PUD. The mechanism by which this rapidly absorbed drug provides its therapeutic effect is through enhancement of mucosal defense and repair. The most common toxicity noted with this drug is diarrhea (10–30% incidence). Other major toxicities include uterine bleeding and contractions; misoprostol is contraindicated in women who may be pregnant, and women of childbearing age must be made clearly aware of this potential drug toxicity. The standard therapeutic dose is 200 µg qid.

Miscellaneous Drugs

A number of drugs including anticholinergic agents and tricyclic antidepressants were used for treating acid peptic disorders, but in light of their toxicity and the development of potent antisecretory agents, these are rarely, if ever, used today. Newer agents such as teprenone, an acyclic polyisoprenoid compound used as a gastric mucosal protector that is employed to treat gastritis and GUs outside of the United States; plant-based therapies; and CCK₂ receptor antagonists are intriguing therapies but require further evaluation.

THERAPY OF *H. PYLORI*

The physician's goal in treating PUD is to provide relief of symptoms (pain or dyspepsia), promote ulcer healing, and ultimately prevent ulcer recurrence and complications. The greatest influence of understanding the role of *H.*

pylori in peptic disease has been the ability to prevent recurrence. Documented eradication of H. pylori in patients with PUD is associated with a dramatic decrease in ulcer recurrence to <10–20% as compared to 59% in GU patients and 67% in DU patients when the organism is not eliminated. Eradication of the organism may lead to diminished recurrent ulcer bleeding. The effect of its eradication on ulcer perforation is unclear. Extensive effort has been made in determining who of the many individuals with H. pylori infection should be treated. The common conclusion arrived at by multiple consensus conferences around the world is that H. pylori should be eradicated in patients with documented PUD. This holds true independent of time of presentation (first episode or not), severity of symptoms, presence of confounding factors such as ingestion of NSAIDs, or whether the ulcer is in remission. Some have advocated treating patients with a history of documented PUD who are found to be H. pylori positive by stool antigen or breath testing. Between 60 and 90% of patients with gastric MALT lymphoma experience complete remission of the tumor in response to H. pylori eradication. The Maastricht VI/Florence Consensus Report recommends a test-and-treat approach for patients with uninvestigated dyspepsia if the local incidence of H. pylori is >20%. The American College of Gastroenterology (ACG) clinical guidelines (developed for North America) recommend that individuals aged <60 years with uninvestigated dyspepsia should

be tested and treated for H. pylori. In addition, recommendations from this consensus report and the ACG clinical guidelines include testing and offering eradication of H. pylori in patients who will be using NSAIDs (including low-dose aspirin) on a long-term basis, especially if there is a prior history of PUD. These individuals will require continued PPI treatment as well as eradication treatment, because eradication of the organism alone does not eliminate the risk of gastroduodenal ulcers in patients already receiving longterm NSAIDs. Moreover, it appears that eradication of H. pylori decreases NSAID-induced GI bleeding. Treating patients with NUD to prevent gastric cancer or patients with GERD requiring long-term acid suppression remains controversial. Guidelines from the ACG suggest eradication of H. pylori in patients who have undergone resection of early gastric cancer. The Maastricht VI/ Florence Consensus Report also evaluated H. pylori treatment in gastric cancer prevention and recommends that eradication should be considered in the following situations: first-degree relatives of family members with gastric cancer; patients with previous gastric neoplasm treated by endoscopic or subtotal resection; individuals with a risk of gastritis (severe pangastritis or body-predominant gastritis) or severe atrophy; patients with gastric acid inhibition for >1 year; individuals with strong environmental risk factors for gastric cancer (heavy smoking; high exposure to dust, coal, quartz, or cement; and/or work in quarries); and H. pylori-positive patients with a fear of gastric cancer. Finally, the ACG clinical guidelines recommend testing and offering H. pylori eradication to patients with unexplained iron-deficiency anemia and idiopathic thrombocytopenic purpura. The Maastricht VI/Florence Consensus Report concurs with the ACG with the aforementioned recommendations and in addition recommends eradicating H. pylori in patients

TABLE 335-4 Recommended First-Line Therapies for H. pylori Infection

REGIMEN	DRUGS (DOSES)	DOSING FREQUENCY	DURATION (DAYS)	FDA APPROVAL
Clarithromycin triple	(Only in patients without prior exposure to macrolides, incidence of clarithromycin <15%, or either of the above unknown)	PPI (standard or double dose) bid		

Yes	Clarithromycin (500 mg)	Amoxicillin (1 g) or metronidazole (500 mg tid)	Bismuth quadruple (Now often recommended as first-line therapy)	PPI (standard dose) bid	10–14	No
	Bismuth subcitrate (120–300 mg) or subsalicylate (300 mg) qid	Tetracycline (500 mg) qid	Metronidazole (250–500 mg) qid	(250 mg) tid to qid	(500 mg)	Concomitant PPI (standard dose) bid

10-14 No Clarithromycin (500 mg) Amoxicillin (1 g) Nitroimidazole (500 mg)c
 Sequential PPI (standard dose) bid 5-7 No PPI, clarithromycin (500 mg) + nitroimidazole (500 mg)c bid 5-7 Hybrid PPI (standard dose) + amoxicillin (1 g) bid

No PPI, amoxicillin, clarithromycin (500 mg), nitroimidazole (500 mg)c bid

Levofloxacin triple PPI (standard or double dose) + amoxicillin (1 g) bid 5-7 No Levofloxacin (500 mg) qd Amoxicillin (1 g) bid Levofloxacin sequential PPI (standard or double dose) + amoxicillin (1 g) bid 5-7 No PPI, amoxicillin, levofloxacin (500 mg qd), nitroimidazole (500 mg)c bid 5-7 LOAD Levofloxacin (250 mg) qd 7-10 No PPI (double dose) qd Nitazoxanide (500 mg) bid Doxycycline (100 mg) qd aSeveral PPI, clarithromycin, and amoxicillin combinations have achieved FDA approval. The regimen of a PPI, clarithromycin, and metronidazole is not an FDA-approved treatment regimen. bThe regimen of a PPI, bismuth, tetracycline, and metronidazole combined with a PPI for 10 days is an FDA-approved treatment regimen. cMetronidazole or tinidazole. Abbreviations: bid, twice daily; FDA, Food and Drug Administration; PPI, proton pump inhibitor; tid, three times daily; qd, once daily; qid, four times daily. Source: Reproduced with permission from WD Chey et al: ACG clinical guideline: Treatment of Helicobacter pylori infection. Am J Gastroenterol 112:212, 2017.

with unexplained vitamin B12 deficiency. Despite this, concerns have been raised about the widespread use of antibiotics for the therapy of all cases of H. pylori positivity, including the potential for increased bacterial resistance rates, reported weight gain, and alteration of the microbiome. In fact, the increasing incidence of bacterial resistance to antibiotics coupled with variability in general prevalence of the organism worldwide and limitations in developing personalized H. pylori-driven sensitivity therapies have led to increasing challenges in effectively treating this organism.

Multiple drugs have been evaluated in the therapy of H. pylori. No single agent is effective in eradicating the organism. Combination therapy for 14 days provides the greatest efficacy, although regimens based on sequential administration of antibiotics also appear promising (see below). A shorter administration course (7-10 days), although attractive, has not proved as successful as the 14-day regimens. The agents used with the greatest frequency include amoxicillin, metronidazole, tetracycline, clarithromycin, and bismuth compounds. Moreover, the steady increase in H pylori resistance to antibiotics, in particular clarithromycin and metronidazole, has significantly impacted the approach to eradication of this organism (see below). In addition, increasing resistance to antibiotics has led to a higher incidence of H. pylori infections that are refractory to first-line therapies. Suggested treatment regimens for H. pylori are outlined in Table 335-4. Choice of a particular regimen will be influenced by several factors, including efficacy, patient tolerance, existing antibiotic resistance, prior antibiotic use, and cost of the drugs. The aim for initial eradication rates should be 85-90%. The combination of bismuth, metronidazole, and tetracycline was the first triple regimen found effective against H. pylori. The combination of two

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antibiotics plus either a PPI, H2 blocker, or bismuth compound has comparable success rates. Addition of acid suppression assists in providing early symptom relief and enhances bacterial eradication.

Triple therapy, although effective, has several drawbacks, including the potential for poor patient compliance and drug-induced side effects. Compliance is being addressed by simplifying the regimens so that patients can take the medications twice a day. Simpler (dual therapy) and shorter regimens (7 and 10 days) are not as effective as triple therapy for 14 days. One anti-*H. pylori* regimen is available in prepackaged formulation: Prevpac (lansoprazole, clarithromycin, and amoxicillin). The contents of the Prevpac are to be taken twice per day for 14 days, understanding that clarithromycin-based triple therapy should be avoided in settings where *H. pylori* resistance to this agent exceeds 15% or the patient has been recently exposed to macrolide antibiotics or if neither of these factors is known (see below). Side effects have been reported in up to 20–30% of patients on triple therapy. Bismuth may cause black stools, constipation, or darkening of the tongue. The most feared complication with amoxicillin is pseudomembranous colitis, but this occurs in <1–2% of patients. Amoxicillin can also lead to antibiotic-associated diarrhea, nausea, vomiting, skin rash, and allergic reaction. Concomitant use of probiotics may ameliorate some of the antibiotic side effects (see below). Tetracycline has been reported to cause rashes and, very rarely, hepatotoxicity and anaphylaxis. One important concern with treating patients who may not need therapy is the potential for development of antibiotic-resistant strains. The incidence and type of antibiotic-resistant *H. pylori* strains vary worldwide. Strains resistant to metronidazole, clarithromycin, amoxicillin, and tetracycline have been described, with the latter two being uncommon. Antibiotic-resistant strains are the most common cause for treatment failure in compliant patients. Unfortunately, *in vitro* resistance does not predict outcome in patients. Culture and sensitivity testing of *H. pylori* is not performed routinely. In light of this, culture-independent methods are needed to determine antibiotic resistance. Detection of resistance toward several antibiotics can be achieved by detecting different *H. pylori* mutations or other genetic changes, but the accuracy of the molecular tools available vary widely between different antibiotics. Therefore, a standardized approach to determine antibiotic resistance that is easy to use is still not readily available. In addition, the standard method of obtaining tissue through endoscopy is cost prohibitive when considering the widespread presence of this organism in certain parts of the world; thus, new efforts are aimed at developing techniques that capitalize on DNA extraction and performing polymerase chain reaction (PCR) on stool samples from patients infected with *H. pylori*. These diagnostic modalities are still in early phases of development. In light of this, most recommendations for treatment of *H. pylori* outline that if individual susceptibility testing is not available, first-line therapy in areas of a high incidence of clarithromycin resistance (>15%) or in situations where resistance to clarithromycin is not known that bismuth quadruple therapy should be the first line of treatment. If not available, non bismuth concomitant quadruple therapy may be a consideration. An algorithmic approach to the therapy of *H. pylori* as outlined in the Maastricht VI/Florence Consensus Report is provided in Fig. 335-13. Although resistance to metronidazole has been found in as many as 30% of isolates in North America and 80% in developing countries, triple therapy is effective in eradicating the organism in

“ 50% of patients infected with a resistant strain. Clarithromycin resistance is seen in 13–16% of individuals in the United States, with resistance to amoxicillin being <1% and resistance to both metronidazole and clarithromycin in the 5% range. Resistance to tetracycline and rifabutin (see below) is reported to be <2% in the United States. In light of the paucity of *H. pylori* antibiotic real-time

resistance data, asking the patient about prior antibiotic exposure should be included in the decision-making and used as a surrogate for potential antibiotic resistance, especially when it comes to prior macrolide use. Clarithromycin use should be excluded in patients with prior macrolide usage. PART 10 Disorders of the Gastrointestinal System

Failure of *H. pylori* eradication with triple therapy in a compliant patient is usually due to infection with a resistant organism. Additional important factors in treatment failure include inadequate acid suppression and inadequate adherence to the recommended regimen. Addressing both of these latter issues is critical before embarking on selecting alternative antibiotics for eradication of *H. pylori*. An in-depth review of the approach to patients with refractory *H. pylori* is beyond the scope of this chapter, and readers are referred to the American Gastroenterological Association 2021 guidelines (see Further Reading) for in-depth discussion of this important topic. A series of salvage therapies for *H. pylori* are shown in Table 335-5. The combination of PPI, amoxicillin, and rifabutin for 10 days has also been used successfully (86% cure rate) in patients infected with resistant strains. Additional regimens considered for second-line therapy include levofloxacin-based triple therapy (levofloxacin, amoxicillin, PPI) for 10 days and furazolidone-based triple therapy (furazolidone, amoxicillin, PPI) for 14 days. Unfortunately, no treatment regimen is universally accepted for patients in whom two courses of antibiotics have failed. If eradication is still not achieved in a compliant patient, then culture and sensitivity of the organism should be considered. One challenge with this approach is that culture and sensitivity testing is cumbersome and not widely available; thus, *H. pylori* resistance data within specific communities are often not available. Non-culture-based approaches using molecular markers to determine potential resistance through stool testing are being developed but are not widely available. Additional factors that may lower eradication rates include the patient's country of origin (higher in Northeast Asia than other parts of Asia or Europe) and cigarette smoking. In addition, meta-analysis suggests that even the most effective regimens (quadruple therapy including PPI, bismuth, tetracycline, and metronidazole and triple therapy including PPI, clarithromycin, and amoxicillin) may have suboptimal eradication rates (<80%), thus demonstrating the need for the development of more efficacious treatments. In view of the observation that 15–25% of patients treated with first-line therapy may still remain infected with the organism, new approaches to treatment have been explored. One promising approach is sequential therapy. Regimens examined consist of 5 days of amoxicillin and a PPI, followed by an additional 5 days of PPI plus tinidazole and clarithromycin or levofloxacin. One promising regimen that has the benefit of being shorter in duration, easier to take, and less expensive is 5 days of concomitant therapy (PPI twice daily, amoxicillin 1 g twice daily, levofloxacin 500 mg twice daily, and tinidazole 500 mg twice daily). Initial studies have demonstrated eradication rates of >90% with good patient tolerance. Confirmation of these findings and applicability of this approach in the United States are needed, although some experts are recommending abandoning clarithromycin-based triple therapy in the United States for the concomitant therapy or the alternative sequential therapies highlighted above. Innovative non-antibiotic-mediated approaches have been explored in an effort to improve eradication rates of *H. pylori*. Pretreatment of patients with N-acetylcysteine as a mucolytic agent to destroy the *H. pylori* biofilm and therefore impair antibiotic resistance has been examined, but more studies are needed to confirm the applicability of this approach. In vitro studies suggest that certain probiotics like

Lactobacillus or its metabolites can inhibit H. pylori. Administration of probiotics has been attempted in several clinical studies in an effort to maximize antibiotic-mediated eradication with varying results. Overall, it appears that the use of certain probiotics, such as Lactobacillus spp., Saccharomyces spp., Bifidobacterium spp., and Bacillus clausii, did not alter eradication rates but importantly decreased antibiotic-associated side effects including nausea, dysgeusia, diarrhea, and abdominal discomfort/ pain, resulting in enhanced tolerability of H. pylori therapies. Additional studies are needed to confirm the potential benefits of probiotics in this setting. Statins, specifically atorvastatin, have been used with some success as an adjunct to quadruple therapy in patients with NUD. Additional nonpharmacologic therapies are

Low (<15%) clarithromycin resistance Bismuth 4-drug 1st line If fails Levofloxacin 4- or 3-drug OR 2nd line If fails If fails If fails Clarithromycin 3- or 4-drug Levofloxacin 4- or 3-drug Bismuth 4-drug 3rd line If fails If fails Rifabutin 3-drug Rifabutin 3-drug Rifabutin 3-drug 4th line A High (>15%) or unknown clarithromycin resistance 1st option Bismuth 4-drug 1st line If fails Levofloxacin 4- or 3-drug 2nd line If fails Rifabutin 3-drug 3rd line 4th line B FIGURE 335-13 Empirical approach to Helicobacter pylori eradication if individual antibiotic susceptibility testing is not available. A. Low <15% clarithromycin resistance; B. High >15% or unknown clarithromycin resistance. Treatment regimens: Bismuth 4-drug—proton pump inhibitor (PPI), bismuth, tetracycline, metronidazole; Clarithromycin 3-drug—PPI, clarithromycin, amoxicillin (use only if clarithromycin sensitivity is known); Nonbismuth 4-drug—PPI, clarithromycin, amoxicillin, metronidazole; Levofloxacin 4-drug—PPI, levofloxacin, amoxicillin, bismuth; Levofloxacin 3-drug—same as levofloxacin 4-drug omitting bismuth; Rifabutin 3-drug in the setting of high fluoroquinolone resistance—rifabutin, high dose PPI, amoxicillin. (modified from Malfetheiner P, et al: Gut 71:9, 2022). (Adapted from permission from P Malfertheiner et al: Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report. Gut 71:9, 2022.) also being explored including oxygen-enriched environment or hyperbaric oxygen therapy, antimicrobial photodynamic therapy, nanomaterials, antimicrobial peptides, phase therapy, and modified lysins. Readers are referred to a recent comprehensive review on this topic (Luo et al in Further Reading). Reinfection after successful eradication of H. pylori is rare in the United States (<1% per year). If recurrent infection occurs within

OR Clarithromycin 3-drug If fails Levofloxacin 4- or 3-drug Bismuth 4-drug If fails CHAPTER 335 2nd option (bismuth 4-drug locally unavailable) Non-bismuth 4-drug (concomitant) Peptic Ulcer Disease and Related Disorders OR Levofloxacin 4- or 3-drug Bismuth 4-drug If fails If fails Levofloxacin 4- or 3-drug Bismuth 4-drug If fails If fails Rifabutin 3-drug Rifabutin 3-drug the first 6 months after completing therapy, the most likely explanation is recrudescence as opposed to reinfection. THERAPY OF NSAID-RELATED GASTRIC OR

DUODENAL INJURY Medical intervention for NSAID-related mucosal injury includes treatment of an active ulcer and primary prevention of future

TABLE 335-5 Salvage Therapies for H. pylori Infection

REGIMEN	DRUGS (DOSES)	DOSING
FREQUENCY	DURATION (DAYS)	FDA APPROVAL
Bismuth quadruple	PPI (standard dose)	bid
Noa	Bismuth subcitrate (120–300 mg) or subsalicylate (300 mg) qid	Tetracycline (500 mg) qid
	Metronidazole (500 mg) tid or qid	Levofloxacin triple PPI (standard dose) bid

No Levofloxacin (500 mg) qd Amoxicillin (1 g) bid Concomitant PPI (standard dose) bid
 10-14 No Clarithromycin (500 mg) bid Amoxicillin (1 g) bid Nitroimidazole (500 mg) bid or
 tid Rifabutin triple PPI (standard dose) bid

No Rifabutin (300 mg) qd Amoxicillin (1 g) bid High-dose dual PPI (standard to double dose)
 tid or qid

No Amoxicillin (1 g tid or 750 mg qid) tid or qid aPPI, bismuth, tetracycline, and metronidazole prescribed separately is not an FDA-approved treatment regimen. However, Pylera, a combination product containing bismuth subcitrate, tetracycline, and metronidazole, combined with a PPI for 10 days is an FDA-approved treatment regimen. Abbreviations: bid, twice daily; FDA, Food and Drug Administration; PPI, proton pump inhibitor; tid, three times daily; qd, once daily; qid, four times daily. Source: Reproduced with permission from WD Chey et al: ACG clinical guideline: Treatment of Helicobacter pylori infection. Am J Gastroenterol 112:212, 2017. injury. Recommendations for the treatment and primary prevention of NSAID-related mucosal injury are listed in Table 335-6. Ideally, the injurious agent should be stopped as the first step in the therapy of an active NSAID-induced ulcer. If that is possible, then treatment with one of the acid inhibitory agents (H2 blockers, PPIs) is indicated. Cessation of NSAIDs is not always possible because of the patient's severe underlying disease. Only PPIs can heal GUs or DUs, independent of whether NSAIDs are discontinued. PART 10 Disorders of the Gastrointestinal System The widespread use of NSAIDs has created some concern due to the increasing likelihood of GI and CV side effects associated with these agents. The approach to primary prevention has included avoiding the agent, using the lowest possible dose of the agent for the shortest period of time possible, using NSAIDs that are theoretically less injurious, using newer topical NSAID preparations, and/ or using concomitant medical therapy to prevent NSAID-induced injury. Several nonselective NSAIDs that are associated with a lower likelihood of GI and CV toxicity include naproxen and ibuprofen, although the beneficial effect may be eliminated if higher dosages of the agents are used. Primary prevention of NSAID-induced ulceration can be accomplished by a PPI and, if not tolerated, misoprostol (200 µg qid). High-dose H2 blockers (famotidine 40 mg bid) have also shown some promise in preventing endoscopically documented ulcers, although PPIs are superior. The highly selective COX-2 inhibitors, celecoxib and rofecoxib, are 100 times more selective inhibitors of COX-2 than standard NSAIDs, leading to gastric or duodenal mucosal injury that is comparable to placebo. TABLE 335-6 Recommendations for Treatment of NSAID-Related Mucosal Injury CLINICAL SETTING RECOMMENDATION Active ulcer NSAID discontinued H2 receptor antagonist or PPI NSAID continued PPI Prophylactic therapy Misoprostol PPI Selective COX-2 inhibitor H. pylori infection Eradication if tests positive for H. pylori Abbreviations: COX-2, isoenzyme of cyclooxygenase; NSAID, nonsteroidal antiinflammatory drug; PPI, proton pump inhibitor.

Their utilization led to an increase in CV events initially leading to both celecoxib and rofecoxib being withdrawn from the market. After continued analysis of available data, the FDA concluded that celecoxib is no less safe than several nonopioid pain killers and has been allowed to remain on the market with a warning label that it was associated with increased risk of heart attacks and strokes. Additional caution was engendered when the CLASS study demonstrated that the advantage of celecoxib in preventing GI complications was offset when low-dose aspirin was used simultaneously. Therefore, gastric protection therapy is required in individuals taking COX-2 inhibitors and aspirin prophylaxis. Finally, much of the work demonstrating the benefit of COX-2

inhibitors and PPIs on GI injury has been performed in individuals of average risk; it is unclear if the same level of benefit will be achieved in high-risk patients. For example, concomitant use of warfarin and a COX-2 inhibitor was associated with rates of GI bleeding similar to those observed in patients taking nonselective NSAIDs. A combination of factors, including withdrawal of the majority of COX-2 inhibitors from the market, the observation that low-dose aspirin appears to diminish the beneficial effect of COX-2-selective inhibitors, and the growing use of aspirin for prophylaxis of CV events, has significantly altered the approach to gastric protective therapy during the use of NSAIDs. A set of guidelines for the approach to the use of NSAIDs was published by the ACG and is shown in Table 335-7. TABLE 335-7 Guide to NSAID Therapy

	NO/LOW NSAID GI RISK	NSAID GI RISK
No CV risk (no aspirin)	Traditional NSAID	Coxib or Traditional NSAID + PPI or misoprostol
Consider non-NSAID therapy	CV risk (consider aspirin)	Traditional NSAID + PPI or misoprostol if GI risk warrants gastroprotection
Consider non-NSAID therapy	A gastroprotective agent must be added if a traditional NSAID is prescribed	Consider non-NSAID therapy

Abbreviations: CV, cardiovascular; GI, gastrointestinal; NSAID, nonsteroidal antiinflammatory drug; PPI, proton pump inhibitor. Source: Reproduced with permission from AM Fendrick: Am J Manag Care 10:740, 2004.

Individuals who are not at risk for CV events, do not use aspirin, and are without risk for GI complications can receive nonselective NSAIDs without gastric protection. In those without CV risk factors but with a high potential risk (prior GI bleeding or multiple GI risk factors) for NSAID-induced GI toxicity, cautious use of a selective COX-2 inhibitor and co-therapy with high-dose PPI or misoprostol are recommended. Individuals at moderate GI risk without cardiac risk factors can be treated with a COX-2 inhibitor alone or with a nonselective NSAID with PPI or misoprostol. Individuals with CV risk factors, who require low-dose aspirin and have low potential for NSAID-induced toxicity, should be considered for a non-NSAID agent or use of a traditional NSAID such as naproxen (lower CV side effects) in combination with gastric protection, if warranted. Finally, individuals with CV and GI risks who require aspirin must be considered for non-NSAID therapy, but if that is not an option, then gastric protection with any type of NSAID must be considered. Any patient, regardless of risk status, who is being considered for long-term traditional NSAID therapy should also be considered for H. pylori testing and treatment if positive. Assuring the use of GI protective agents with NSAIDs is difficult, even in high-risk patients. This is in part due to underprescribing of the appropriate protective agent; other times, the difficulty is related to patient compliance. The latter may be due to patients forgetting to take multiple pills or preferring not to take the extra pill, especially if they have no GI symptoms. Several NSAID gastroprotective-containing combination pills are now commercially available, including double-dose famotidine with ibuprofen, diclofenac with misoprostol, and naproxen with esomeprazole. Although initial studies suggested improved compliance and a cost advantage when taking these combination drugs, their clinical benefit over the use of separate pills has not been established. One additional concern with NSAID-induced GI complications is the relatively low rate of primary care provider compliance with established guidelines outlining preventative measures. An intervention including professional education, informatics to facilitate review, and financial incentives for practices to review patients' charts to assess appropriateness showed a reduced rate of high-risk prescribing of antiplatelet medications and NSAIDs with a tendency toward improved clinical outcomes. Efforts continue toward developing safer NSAIDs, including topical NSAIDs, NSAID formulations that are rapidly absorbed (diclofenac potassium powder mixed with a buffering agent, Prosorb and SoluMatrix technology), NO-releasing NSAIDs, hydrogen sulfide-releasing NSAIDs, dual COX/5-LOX inhibitors, NSAID prodrugs, and agents that can effectively sequester unbound NSAIDs without

interfering with their efficacy. **APPROACH AND THERAPY: SUMMARY** Controversy continues regarding the best approach to the patient who presents with dyspepsia (Chap. 48). The discovery of *H. pylori* and its role in pathogenesis of ulcers has added a new variable to the equation. Previously, if a patient <60 years of age presented with dyspepsia and without alarming signs or symptoms suggestive of an ulcer complication or malignancy, an empirical therapeutic trial with acid suppression was commonly recommended; today, however, a test-and-treat approach with a noninvasive diagnostic tool for *H. pylori* and eradication of the organism, if positive, is recommended (Fig. 335-14). Once an ulcer (GU or DU) is documented, the main issue to consider is whether *H. pylori* or an NSAID is involved. With *H. pylori* present, independent of the NSAID status, triple or quadruple therapy is recommended for 14 days, followed by continued acid-suppressing drugs (H₂ receptor antagonist or PPIs) for a total of 4–6 weeks. *H. pylori* eradication should be documented 4 weeks after completing antibiotics. The test of choice for documenting eradication is the laboratory-based validated monoclonal stool antigen test or a urea breath test (UBT). The patient must be off antisecretory agents for at least 7 days when being tested for eradication of *H. pylori* with UBT or stool antigen. Serologic testing is not useful for the purpose of documenting eradication because

New-Onset Dyspepsia

“ 40 years old Alarm symptoms Exclude by history GERD, biliary pain, IBS, aerophagia, medication-related – Noninvasive Hp testing

- – + or Anti-Hp therapy Refer to gastroenterologist Empiric trial H₂ blocker 4 weeks after therapy Confirm eradication UBT Symptoms remain or recur **FIGURE 335-14 Overview of new-onset dyspepsia.** GERD, gastroesophageal reflux disease; Hp, *Helicobacter pylori*; IBS, irritable bowel syndrome; UBT, urea breath test. (Reproduced with permission from BS Anand, DY Graham: State-of-the-Art: Ulcer and Gastritis, *Endoscopy* 31:215, 1999. © Georg Thieme Verlag KG.)

CHAPTER 335 antibody titers fall slowly and often do not become undetectable. Some recommend that patients with complicated ulcer disease or who are frail should be treated with long-term acid suppression, thus making documentation of *H. pylori* eradication a moot point. In view of this discrepancy in practice, it would be best to discuss with the patient the different options available. **Peptic Ulcer Disease and Related Disorders** Several issues differentiate the approach to a GU versus a DU. GUs, especially of the body and fundus, have the potential of being malignant. Multiple biopsies of a GU should be taken initially; even if these are negative for neoplasm, repeat endoscopy to document healing at 8–12 weeks should be performed, with biopsy if the ulcer is still present. About 70% of GUs eventually found to be malignant undergo significant (usually incomplete) healing. Repeat endoscopy is warranted in patients with DU if symptoms persist despite medical therapy or a complication is suspected. The majority (>90%) of GUs and DUs heal with the conventional therapy outlined above. A GU that fails to heal after 12 weeks and a DU that does not heal after 8 weeks of therapy should be considered refractory. Once poor compliance and persistent *H. pylori* infection have been excluded, NSAID use, either inadvertent or surreptitious, must be excluded. In addition, cigarette smoking must be eliminated. For a GU, malignancy must be meticulously excluded. Next, consideration should be given to a gastric acid hypersecretory state such as ZES (see “Zollinger-

Ellison Syndrome," below) or the idiopathic form, which can be excluded with gastric acid analysis. Although a subset of patients has gastric acid hypersecretion of unclear etiology as a contributing factor to refractory ulcers, ZES should be excluded with a fasting gastrin or secretin stimulation test (see below). More than 90% of refractory ulcers (either DUs or GUs) heal after 8 weeks of treatment with higher doses of PPI (omeprazole 40 mg/d; lansoprazole 30–60 mg/d). This higher dose is also effective in maintaining remission. Surgical intervention may be a consideration at this point; however, other rare causes of refractory ulcers must be excluded before recommending surgery. Rare etiologies of refractory ulcers that may be diagnosed by gastric or duodenal biopsies include ischemia, Crohn's disease, amyloidosis, sarcoidosis, lymphoma, eosinophilic gastroenteritis, smoking crack cocaine, or infection (cytomegalovirus [CMV], tuberculosis, or syphilis).

SURGICAL THERAPY Surgical intervention in PUD can be viewed as being either elective, for treatment of medically refractory disease, or as urgent/emergent, for the treatment of an ulcer-related complication. The development of pharmacologic and endoscopic approaches for the treatment of peptic disease and its complications has led to a substantial decrease in the number of operations needed for this disorder with a drop of >90% for elective ulcer surgery over the past four decades. Refractory ulcers are an exceedingly rare occurrence. Surgery is more often required for treatment of an ulcer-related complication.

Hemorrhage is the most common ulcer-related complication, occurring in ~15–25% of patients. Bleeding may occur in any age group but is most often seen in older patients (sixth decade or beyond). The majority of patients stop bleeding spontaneously, but endoscopic therapy (Chap. 333) is necessary in some. Parenterally and orally administered PPIs also decrease ulcer rebleeding in patients who have undergone endoscopic therapy. Patients unresponsive or refractory to endoscopic intervention will require angiographic intervention or surgery (~5% of transfusion-requiring patients). Free peritoneal perforation occurs in ~2–3% of DU patients, with NSAID-induced GU perforations occurring more commonly. Sudden onset of severe abdominal pain with peritoneal signs and evidence of pneumoperitoneum on abdominal imaging is the classic presentation of a perforated viscus, but this presentation occurs in only two-thirds of patients. The latter is especially true in elderly patients (>70 years old), obese individuals, and immunocompromised patients. It is important to keep in mind that, as in the case of bleeding, up to 10% of these patients will not have antecedent ulcer symptoms. Delay in diagnosis clearly leads to higher mortality; thus, early suspicion and intervention with nasogastric suction, intravenous PPI, antibiotics, and surgical consultation are essential. Concomitant bleeding may occur in up to 10% of patients with perforation, with mortality being increased substantially. Peptic ulcer can also penetrate into adjacent organs, especially with a posterior DU, which can penetrate into the pancreas, colon, liver, or biliary tree.

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Pyloric channel ulcers or DUs can lead to gastric outlet obstruction in ~2–3% of patients. This can result from chronic scarring or from impaired motility due to inflammation and/or edema with pylorospasm. Patients may present with early satiety, nausea, vomiting of undigested food, and weight loss. Conservative management with nasogastric suction, intravenous hydration/nutrition, and antisecretory agents is indicated for 7–10 days with the hope that a functional obstruction will reverse. If a mechanical obstruction persists, endoscopic intervention with balloon dilation may be effective. Surgery should be considered if all else fails.

Specific Operations for Duodenal Ulcers

Surgical treatment was originally designed to decrease gastric acid secretion. Operations most

commonly performed include (1) vagotomy and drainage (by pyloroplasty, gastroduodenostomy, or gastrojejunostomy), (2) highly selective vagotomy (which does not require a drainage procedure), and (3) vagotomy with antrectomy. The specific procedure performed is dictated by the underlying circumstances: elective versus emergency, the degree and extent of duodenal ulceration, the etiology of the ulcer (*H. pylori*, NSAIDs, malignancy), and the expertise of the surgeon. Moreover, the trend has been toward a dramatic decrease in the need for surgery for treatment of refractory PUD, and when needed, minimally invasive and anatomy-preserving operations are preferred. Vagotomy is a component of each of these procedures and is aimed at decreasing acid secretion through ablating cholinergic input to the stomach. Unfortunately, both truncal and selective vagotomy (preserves the celiac and hepatic branches) result in gastric atony despite successful reduction of both basal acid output (BAO; decreased by 85%) and maximal acid output (MAO; decreased by 50%). Drainage through pyloroplasty or gastroduodenostomy

is required in an effort to compensate for the vagotomy-induced gastric motility disorder. This procedure has an intermediate complication rate and a 10% ulcer recurrence rate. To minimize gastric dysmotility, highly selective vagotomy (also known as parietal cell, super-selective, or proximal vagotomy) was developed. Only the vagal fibers innervating the portion of the stomach that contains parietal cells are transected, thus leaving fibers important for regulating gastric motility intact. Although this procedure leads to an immediate decrease in both BAO and stimulated acid output, acid secretion recovers over time. By the end of the first postoperative year, basal and stimulated acid output are ~30 and 50%, respectively, of preoperative levels. Ulcer recurrence rates are higher with highly selective vagotomy ($\geq 10\%$), although the overall complication rates are the lowest of the three procedures. The procedure that provides the lowest rates of ulcer recurrence (1%) but has the highest complication rate is vagotomy (truncal or selective) in combination with antrectomy. Antrectomy is aimed at eliminating an additional stimulant of gastric acid secretion, gastrin. Two principal types of reanastomoses are used after antrectomy: gastroduodenostomy (Billroth I) or gastrojejunostomy (Billroth II) (Fig. 335-15). Although Billroth I is often preferred over II, severe duodenal inflammation or scarring may preclude its performance. Prospective, randomized studies confirm that partial gastrectomy followed by Roux-en-Y reconstruction leads to a significantly better clinical, endoscopic, and histologic outcome than Billroth II reconstruction. Of these procedures, highly selective vagotomy may be the procedure of choice in the elective setting, except in situations where ulcer recurrence rates are high (prepyloric ulcers and those refractory to medical therapy). Selection of vagotomy and antrectomy may be more appropriate in these circumstances. These procedures have been traditionally performed by standard laparotomy. The advent of laparoscopic surgery has led several surgical teams to successfully perform highly selective vagotomy, truncal vagotomy/pyloroplasty, and truncal vagotomy/antrectomy.

Antrum Fundus Duodenum Billroth I Billroth II

FIGURE 335-15 Schematic representation of Billroth I and II procedures.

through this approach. An increase in the number of laparoscopic procedures for treatment of PUD has occurred. Laparoscopic repair of perforated peptic ulcers is safe, feasible for the experienced surgeon, and associated with decreased postoperative pain, although it does take longer than an open approach. Moreover, no difference between the two approaches is noted in postoperative complications or length of hospital stay.

Specific Operations for GUs

The location and presence of a concomitant DU dictate the operative procedure performed for a GU. Antrectomy (including the ulcer) with a Billroth I anastomosis is the treatment of choice for an antral ulcer. Vagotomy is

performed only if a DU is present. Although ulcer excision with vagotomy and drainage procedure has been proposed, the higher incidence of ulcer recurrence makes this a less desirable approach. Ulcers located near the esophagogastric junction may require a more radical approach, a subtotal gastrectomy with a Roux-en-Y esophagogastricjejunostomy (Csendes' procedure). A less aggressive approach, including antrectomy, intraoperative ulcer biopsy, and vagotomy (Kelling-Madlener procedure), may be indicated in fragile patients with a high GU. Ulcer recurrence approaches 30% with this procedure. Surgery-Related Complications Complications seen after surgery for PUD are related primarily to the extent of the anatomic modification performed. Minimal alteration (highly selective vagotomy) is associated with higher rates of ulcer recurrence and less GI disturbance. More aggressive surgical procedures have a lower rate of ulcer recurrence but a greater incidence of GI dysfunction. Overall, morbidity and mortality related to these procedures are quite low. Morbidity associated with vagotomy and antrectomy or pyloroplasty is $\leq 5\%$, with mortality $\sim 1\%$. Highly selective vagotomy has lower morbidity and mortality rates of 1 and 0.3%, respectively. In addition to the potential early consequences of any intraabdominal procedure (bleeding, infection, thromboembolism), gas troparesis, duodenal stump leak, and efferent loop obstruction can be observed. Recurrent Ulceration The risk of ulcer recurrence is directly related to the procedure performed. Ulcers that recur after partial gastric resection tend to develop at the anastomosis (stomal or marginal ulcer). Epigastric abdominal pain is the most frequent presenting complaint ($>90\%$). Severity and duration of pain tend to be more progressive than observed with DUs before surgery. Ulcers may recur for several reasons, including incomplete vagotomy, inadequate drainage, retained antrum, and, less likely, persistent or recurrent H. pylori infection. ZES should have been excluded preoperatively. Surreptitious use of NSAIDs is an important reason for recurrent ulcers after surgery, especially if the initial procedure was done for an NSAID-induced ulcer. Once H. pylori and NSAIDs have been excluded as etiologic factors, the question of incomplete vagotomy or retained gastric antrum should be explored. For the latter, fasting plasma gastrin levels should be determined. If elevated, retained antrum or ZES (see below) should be considered. Incomplete vagotomy can be ruled out by gastric acid analysis coupled with sham feeding. In this test, gastric acid output is measured while the patient sees, smells, and chews a meal (without swallowing). The cephalic phase of gastric secretion, which is mediated by the vagus, is being assessed with this study. An increase in gastric acid output in response to sham feeding is evidence that the vagus nerve is intact. A rise in serum pancreatic polypeptide $>50\%$ within 30 min of sham feeding is also suggestive of an intact vagus nerve. Medical therapy with H₂ blockers will heal postoperative ulceration in 70–90% of patients. The efficacy of PPIs has not been fully assessed in this group, but one may anticipate greater rates of ulcer healing compared to those obtained with H₂ blockers. Repeat operation (complete vagotomy, partial gastrectomy) may be required in a small subgroup of patients who have not responded to aggressive medical management.

Afferent Loop Syndromes Although rarely seen today as a result of the decrease in the performance of Billroth II anastomosis, two types of afferent loop syndrome can occur in patients who have undergone this type of partial gastric resection. The more common of the two is bacterial overgrowth in the afferent limb secondary to stasis. Patients may experience postprandial abdominal pain, bloating, and diarrhea with concomitant malabsorption of fats and vitamin B₁₂. Cases refractory to antibiotics may require surgical revision of the loop. The less common afferent loop syndrome can present with severe abdominal pain and bloating that occur 20–60 min after meals. Pain is often followed by nausea and vomiting of bile-containing material. The pain and

bloating may improve after emesis. The cause of this clinical picture is theorized to be incomplete drainage of bile and pancreatic secretions from an afferent loop that is partially obstructed. Cases refractory to dietary measures may need surgical revision or conversion of the Billroth II anastomosis to a Roux-en-Y gastrojejunostomy.

Dumping Syndrome Dumping syndrome consists of a series of vasomotor and GI signs and symptoms and occurs in patients who have undergone vagotomy and drainage (especially Billroth procedures). Two phases of dumping, early and late, can occur. Early dumping takes place 15–30 min after meals and consists of crampy abdominal discomfort, nausea, diarrhea, belching, tachycardia, palpitations, diaphoresis, light-headedness, and, rarely, syncope. These signs and symptoms arise from the rapid emptying of hyperosmolar gastric contents into the small intestine, resulting in a fluid shift into the gut lumen with plasma volume contraction and acute intestinal distention. Release of vasoactive GI hormones (vasoactive intestinal polypeptide, neurotensin, motilin) is also theorized to play a role in early dumping. CHAPTER 335 The late phase of dumping typically occurs 90 min to 3 h after meals. Vasomotor symptoms (light-headedness, diaphoresis, palpitations, tachycardia, and syncope) predominate during this phase. This component of dumping is thought to be secondary to hypoglycemia from excessive insulin release. **Peptic Ulcer Disease and Related Disorders** Dumping syndrome is most noticeable after meals rich in simple carbohydrates (especially sucrose) and high osmolality. Ingestion of large amounts of fluids may also contribute. After vagotomy and drainage, up to 50% of patients will experience dumping syndrome to some degree early on. Signs and symptoms often improve with time, but a severe protracted picture can occur in up to 1% of patients. Dietary modification is the cornerstone of therapy for patients with dumping syndrome. Small, multiple (six) meals devoid of simple carbohydrates coupled with elimination of liquids during meals is important. Antidiarrheals and anticholinergic agents are complementary to diet. Guar and pectin, which increase the viscosity of intraluminal contents, may be beneficial in more symptomatic individuals. Acarbose, an α -glucosidase inhibitor that delays digestion of ingested carbohydrates, has also been shown to be beneficial in the treatment of the late phases of dumping. The somatostatin analogue octreotide has been successful in diet-refractory cases. This drug is administered subcutaneously (50 μ g tid), titrated according to clinical response. A long-acting depot formulation of octreotide can be administered once every 28 days and provides symptom relief comparable to the short-acting agent. In addition, patient weight gain and quality of life appear to be superior with the long-acting form. **Postvagotomy Diarrhea** Up to 10% of patients may seek medical attention for the treatment of postvagotomy diarrhea. This complication is most commonly observed after truncal vagotomy, which is rarely performed today. Patients may complain of intermittent diarrhea that occurs typically 1–2 h after meals. Occasionally, the symptoms may be severe and relentless. This is due to a motility disorder from interruption of the vagal fibers supplying the luminal gut. Other contributing factors may include decreased absorption of nutrients (see below), increased excretion of bile acids, and release of luminal factors that promote secretion. Diphenoxylate or

loperamide is often useful in symptom control. The bile salt-binding agent cholestyramine may be helpful in severe cases. Surgical reversal of a 10-cm segment of jejunum may yield a substantial improvement in bowel frequency in a subset of patients.

Bile Reflux Gastropathy A subset of post-partial gastrectomy patients who present with abdominal pain, early satiety, nausea, and vomiting will have mucosal erythema of the gastric remnant as the

only finding. Histologic examination of the gastric mucosa reveals minimal inflammation but the presence of epithelial cell injury. This clinical picture is categorized as bile or alkaline reflux gastropathy/gastritis. Although reflux of bile is implicated as the reason for this disorder, the mechanism is unknown. Prokinetic agents, cholestyramine, and sucralfate have been somewhat effective treatments. Severe refractory symptoms may require using either nuclear scanning with ^{99m}Tc -HIDA to document reflux. Surgical diversion of pancreaticobiliary secretions away from the gastric remnant with a Roux-en-Y gastrojejunostomy consisting of a long (50–60 cm) Roux limb has been used in severe cases. Bilious vomiting improves, but early satiety and bloating may persist in up to 50% of patients. Maldigestion and Malabsorption Weight loss can be observed in up to 60% of patients after partial gastric resection. Patients can experience a 10% loss of body weight, which stabilizes 3 months post operatively. A significant component of this weight reduction is due to decreased oral intake. However, mild steatorrhea can also develop. Reasons for maldigestion/malabsorption include decreased gastric acid production, rapid gastric emptying, decreased food dispersion in the stomach, reduced luminal bile concentration, reduced pancreatic secretory response to feeding, and rapid intestinal transit.

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Decreased serum vitamin B12 levels can be observed after partial gastrectomy. This is usually not due to deficiency of IF, since a minimal amount of parietal cells (source of IF) is removed during antrectomy. Reduced vitamin B12 may be due to competition for the vitamin by bacterial overgrowth or inability to split the vitamin from its protein-bound source due to hypochlorhydria. Iron-deficiency anemia may be a consequence of impaired absorption of dietary iron in patients with a Billroth II gastrojejunostomy. Absorption of iron salts is normal in these individuals; thus, a favorable response to oral iron supplementation can be anticipated. Folate deficiency with concomitant anemia can also develop in these patients. This deficiency may be secondary to decreased absorption or diminished oral intake. Malabsorption of vitamin D and calcium resulting in osteoporosis and osteomalacia is common after partial gastrectomy and gastrojejunostomy (Billroth II). Osteomalacia can occur as a late complication in up to 25% of post-partial gastrectomy patients. Bone fractures occur twice as commonly in men after gastric surgery as in a control population. It may take years before x-ray findings demonstrate diminished bone density. Elevated alkaline phosphatase, reduced serum calcium, bone pain, and pathologic fractures may be seen in patients with osteomalacia. The high incidence of these abnormalities in this subgroup of patients justifies treating them with vitamin D and calcium supplementation indefinitely. Therapy is especially important in females. Copper deficiency has also been reported in patients undergoing surgeries that bypass the duodenum, where copper is primarily absorbed. Patients may present with a rare syndrome that includes ataxia, myelopathy, and peripheral neuropathy.

Gastric Adenocarcinoma

The incidence of adenocarcinoma in the gastric stump is increased 15 years after resection. Some have reported a four- to fivefold increase in gastric cancer 20–25 years after resection. The pathogenesis is unclear but may involve alkaline reflux, bacterial proliferation, or hypochlorhydria. The role of endoscopic screening is not clear, and most guidelines do not support its use.

Additional Complications

Reflux esophagitis and a higher incidence of gallstones and cholecystitis have been reported in patients

undergoing subtotal gastrectomy. The latter is thought to be due to decreased gallbladder contractility associated with vagotomy and bypass of the duodenum, leading to decreased postprandial release of cholecystokinin.

RELATED CONDITIONS ■ ■ ZOLLINGER-ELLISON SYNDROME

Severe peptic ulcer diathesis secondary to gastric acid hypersecretion due to unregulated gastrin release from a non- β -cell, often well-differentiated neuroendocrine tumor (NET;

gastrinoma) defines the components of ZES. Initially, ZES was typified by aggressive and refractory ulceration in which total gastrectomy provided the only chance for enhancing survival. Today, it can be cured by surgical resection in up to 40% of patients with the sporadic form of the disease (see below).

Epidemiology The true incidence of ZES is unknown, but estimates suggest that it varies from 0.1 to 1% of individuals presenting with PUD, with 0.1–3 individuals per year having this rare diagnosis. Others have estimated an incidence of 0.5–3 per million population. Females are slightly more commonly affected than males, and the majority of patients are diagnosed between ages 30 and 65. In addition, the time of diagnosis is estimated to be between 4 and 7 years after the onset of symptoms. Gastrinomas are classified into sporadic tumors (80%) and those associated with multiple endocrine neoplasia (MEN) type 1 (see below). The widespread availability and use of PPIs have led to a decreased patient referral for gastrinoma evaluation, delay in diagnosis, and an increase in false-positive diagnoses of ZES. In fact, diagnosis may be delayed for ≥ 6 years after symptoms consistent with ZES are displayed.

Pathophysiology Hypergastrinemia originating from an autonomous neoplasm is the driving force responsible for the clinical manifestations in ZES. Gastrin stimulates acid secretion through gastrin receptors on parietal cells and by inducing histamine release from ECL cells. Gastrin also has a trophic action on gastric epithelial cells. Longstanding hypergastrinemia leads to markedly increased gastric acid secretion through both parietal cell stimulation and increased parietal cell mass. The increased gastric acid output leads to peptic ulcer diathesis, erosive esophagitis, and diarrhea.

Tumor Distribution Although early studies suggested that the vast majority of gastrinomas occurred within the pancreas, a significant number of these lesions are extrapancreatic. Between 60 and 90% of these tumors are found within the hypothetical gastrinoma triangle (confluence of the cystic and common bile ducts superiorly, junction of the second and third portions of the duodenum inferiorly, and junction of the neck and body of the pancreas medially). Duodenal tumors constitute the most common nonpancreatic lesion; between 60 and 100% of gastrinomas are found here. Duodenal tumors are smaller, slower growing, and less likely to metastasize than pancreatic lesions and occur primarily in the first and second portion of the duodenum (90%). Less common extrapancreatic sites include stomach, bones, ovaries, heart, liver, and lymph nodes. More than 60% of tumors are considered malignant (determined by local invasion and/or evidence of metastasis), with up to 30–50% of patients having multiple lesions or metastatic disease at presentation. Histologically, gastrin-producing cells appear well-differentiated (grade 1 or 2 histologically), expressing markers typically found in endocrine neoplasms (chromogranin, neuron-specific enolase). Although not clearly established in gastrinomas, histologic grade in pancreatic NETs generally is an important predictor of survival in these rare neoplasms (Chap. 89).

Clinical Manifestations Gastric acid hypersecretion is responsible for the signs and symptoms observed in patients with ZES. The most common clinical presentation for gastrinoma patients is abdominal pain in the presence of acid-peptic disorders. Peptic ulcer is the most common clinical manifestation, occurring in >90% of gastrinoma patients. Initial presentation and ulcer location (duodenal

bulb) may be indistinguishable from common PUD. Clinical situations that should create suspicion of gastrinoma are ulcers in unusual locations (second part of the duodenum and beyond), ulcers refractory to standard medical therapy, ulcer recurrence after acid-reducing surgery, ulcers presenting with frank complications (bleeding, obstruction, and perforation), or ulcers in the absence of *H. pylori* or NSAID ingestion. Symptoms of esophageal origin are present in up to two-thirds of patients with ZES, with a spectrum ranging from mild esophagitis to frank ulceration with

stricture and Barrett's mucosa. Diarrhea, the next most common clinical manifestation, is found in up to 70% of patients. Although diarrhea often occurs concomitantly with acid peptic disease, it may also occur independent of an ulcer and classically will abate with PPI therapy. Etiology of the diarrhea is multifactorial, resulting from marked volume overload to the small bowel, pancreatic enzyme inactivation by acid, and damage of the intestinal epithelial surface by acid. The epithelial damage can lead to a mild degree of maldigestion and malabsorption of nutrients. The diarrhea may also have a secretory component due to the direct stimulatory effect of gastrin on enterocytes or the co-secretion of additional hormones from the tumor such as vasoactive intestinal peptide. Gastrinomas can develop in the presence of MEN 1 syndrome (Chaps. 89 and 400) in ~25% of patients. This autosomal dominant disorder involves primarily three organ sites: the parathyroid glands (80–90%), pancreas (40–80%), and pituitary gland (30–60%). The syndrome is caused by inactivating mutations of the MEN1 tumor suppressor gene found on the long arm of chromosome 11q13. The gene encodes for menin, which has an important role in DNA replication and transcriptional regulation. A genetic diagnosis is obtained by sequencing of the MEN1 gene, which can reveal mutations in 70–90% of typical MEN 1 cases. A family may have an unknown mutation, making a genetic diagnosis impossible, and therefore, certain individuals will require a clinical diagnosis, which is determined by whether a patient has tumors in two of the three endocrine organs (parathyroid, pancreas/duodenum, or pituitary) or has a family history of MEN 1 and one of the endocrine organ tumors. In view of the stimulatory effect of calcium on gastric secretion, the hyperparathyroidism and hypercalcemia seen in MEN 1 patients may have a direct effect on ulcer disease. Resolution of hypercalcemia by parathyroidectomy reduces gastrin and gastric acid output in gastrinoma patients. An additional distinguishing feature in ZES patients with MEN 1 is the higher incidence of gastric carcinoid tumor development (as compared to patients with sporadic gastrinomas). ZES presents and is diagnosed earlier in MEN 1 patients, and they have a more indolent course as compared to patients with sporadic gastrinoma. Gastrinomas tend to be smaller, multiple, and located in the duodenal wall more often than is seen in patients with sporadic ZES. Establishing the diagnosis of MEN 1 is critical in order to provide genetic counseling to the patient and their family and also to determine the recommended surgical approach. Therefore, gastrinoma patients should be screened for MEN 1 by performing a detailed family history and obtaining several serum markers including calcium, parathyroid, prolactin, and pancreatic polypeptide levels. **Diagnosis** Establishing an early diagnosis is important in order to minimize the long-term sequelae of gastric acid hypersecretion, prevent metastatic disease, and counsel family members if a diagnosis of MEN 1 is established. Biochemical measurements of gastrin and acid secretion in patients suspected of having ZES play an important role in establishing this rare diagnosis. Often, patients suspected of having ZES will be treated with a PPI in an effort to ameliorate symptoms and decrease the likelihood of possible acid-related complications. The presence of the PPI, which will lower acid secretion and potentially elevate fasting gastrin levels in normal individuals, will make the diagnostic approach in these individuals somewhat difficult. Significant morbidity related to peptic diathesis has been described when stopping PPIs in gastrinoma patients; therefore, a systematic approach in stopping these agents is warranted (see below). The first step in the evaluation of a patient suspected of having ZES is to obtain a fasting gastrin level. A list of clinical scenarios that should arouse

TABLE 335-8 When to Obtain a Fasting Serum Gastrin Level Multiple ulcers Ulcers in unusual locations; associated with severe esophagitis; resistant to therapy with frequent recurrences; in the absence of nonsteroidal antiinflammatory drug ingestion or *Helicobacter pylori* infection Ulcer

patients awaiting surgery Severe or refractory GERD GERD associated with diarrhea Extensive family history for peptic ulcer disease Postoperative ulcer recurrence Basal hyperchlorhydria Unexplained diarrhea or steatorrhea Diarrhea improved with PPI Hypercalcemia Family history of pancreatic islet, pituitary, or parathyroid tumor Prominent gastric or duodenal folds suspicion regarding this diagnosis is shown in Table 335-8. Fasting gastrin levels obtained using a dependable assay are usually <150 pg/mL. A normal fasting gastrin, on two separate occasions, especially if the patient is on a PPI, virtually excludes this diagnosis. Virtually all gastrinoma patients will have a gastrin level >150 – 200 pg/mL. Measurement of fasting gastrin should be repeated to confirm the clinical suspicion. Some of the commercial biochemical assays used for measuring serum gastrin may be inaccurate. Variable specificity of the antibodies used have led to both false-positive and false-negative fasting gastrin levels, placing in jeopardy the ability to make an accurate diagnosis of ZES. CHAPTER 335 Multiple processes can lead to an elevated fasting gastrin level, the most frequent of which are gastric hypochlorhydria and achlorhydria, with or without pernicious anemia. Gastric acid induces feedback inhibition of gastrin release. A decrease in acid production will subsequently lead to failure of the feedback inhibitory pathway, resulting in net hypergastrinemia. Gastrin levels will thus be high in patients using antisecretory agents for the treatment of acid peptic disorders and dyspepsia. *H. pylori* infection can also cause hypergastrinemia. Additional causes of elevated gastrin include retained gastric antrum; G-cell hyperplasia; gastric outlet obstruction; renal insufficiency; massive small-bowel obstruction; and conditions such as rheumatoid arthritis, vitiligo, diabetes mellitus, and pheochromocytoma. Although a fasting gastrin >10 times normal is highly suggestive of ZES, two-thirds of patients will have fasting gastrin levels that overlap with levels found in the more common disorders outlined above, especially if a PPI is being taken by the patient. The effect of the PPI on gastrin levels and acid secretion will linger several days after stopping the PPI; therefore, it should be stopped for a minimum of 7 days before testing. During this period, the patient should be placed on a histamine H₂ antagonist, such as famotidine, twice to three times per day. Although this type of agent has a short-term effect on gastrin and acid secretion, it needs to be stopped 24 h before repeating fasting gastrin levels or performing some of the tests highlighted below. The patient may take antacids for the final day, stopping them ~ 12 h before testing is performed. Heightened awareness of complications related to gastric acid hypersecretion during the period of PPI cessation is critical. Peptic Ulcer Disease and Related Disorders Historically the next study typically recommended for establishing a biochemical diagnosis of gastrinoma is to assess acid secretion. Unfortunately, few centers perform this type of testing; thus, only a brief summary will be provided here. Typically, nothing further needs to be done if decreased acid output in the absence of a PPI is observed. A pH can be measured on gastric fluid obtained either during endoscopy or through nasogastric aspiration; a pH <3 is suggestive of a gastrinoma, but a pH >3 is not helpful in excluding the diagnosis. In those situations where the pH is >3 , formal gastric acid analysis should be performed if available. Normal BAO in nongastric surgery patients is typically <5 meq/h. A BAO >15 meq/h in the presence of

hypergastrinemia is considered pathognomonic of ZES, but up to 12% of patients with common PUD may have elevated BAO to a lesser degree that can overlap with levels seen in ZES patients. In an effort to improve the sensitivity and specificity of gastric secretory studies, a BAO/MAO ratio was established using pentagastrin infusion as a way to maximally stimulate acid production, with a BAO/MAO ratio >0.6 being highly suggestive of ZES. Pentagastrin is no longer available in the United States, making measurement of MAO virtually impossible. An endoscopic method for

measuring gastric acid output has been developed but requires further validation.

Gastrin provocative tests have been developed in an effort to differentiate between the causes of hypergastrinemia and are especially helpful in patients with indeterminate acid secretory studies. The tests are the secretin stimulation test and the calcium infusion study; the latter is rarely, if ever, utilized in our current environment due to the cumbersome nature of the test and its lower sensitivity and specificity than secretin stimulation. The most sensitive and specific gastrin provocative test for the diagnosis of gastrinoma is the secretin study. An increase in gastrin of ≥ 120 pg within 15 min of secretin injection has a sensitivity and specificity of $>90\%$ for ZES. PPI-induced hypochlorhydria or achlorhydria may lead to a false-positive secretin test; thus, this agent must be stopped for 1 week before testing. In light of the limited availability of the biochemical studies outlined above, more studies make a diagnosis of gastrinoma based on the presence of elevated gastrin and low gastric pH in the right clinical setting coupled with tumor localization tests outlined below and positive histology by biopsy (difficult to obtain). Revised guidelines for the best approach to establishing a diagnosis of gastrinoma taking into consideration the above outlined limitations are being considered, but none have replaced the established guidelines outlined earlier in this section (see Jensen et al in Further Reading).

PART 10 Disorders of the Gastrointestinal System

Tumor Localization Once the biochemical diagnosis of gastrinoma has been confirmed (if possible), the tumor must be located. Multiple imaging studies have been used in an effort to enhance tumor localization (Table 335-9). The broad range of sensitivity is due to the variable success rates achieved by the different investigative groups. Endoscopic ultrasound (EUS) permits imaging of the pancreas with a high degree of resolution (<5 mm). This modality is particularly helpful in excluding small neoplasms within the pancreas and in assessing the presence of surrounding lymph nodes and vascular involvement, but it is not very sensitive (43%) for finding duodenal lesions. This latter observation has led some to not include EUS in the routine preoperative evaluation of a patient suspected of having a gastrinoma. Several types of endocrine tumors express cell-surface receptors for somatostatin, in particular the subtype 2 (SSTR2). This permits the localization, staging, and prediction of therapeutic response to somatostatin analogues (see below) by gastrinomas. The original functional scintigraphic tool developed measuring

TABLE 335-9 Sensitivity of Imaging Studies in Zollinger-Ellison Syndrome

	SENSITIVITY, %	PRIMARY
GASTRINOMA		
HEPATIC METASTATIC		
GASTRINOMA		
STUDY	Ultrasound	0–28
	CT scan	15–77
	99–100	
	Selective angiography	35–68
	96–100	
	Portal venous sampling	70–90
	N/A	SASI
	55–78	N/A
	MRI	20–25
	88–100	
	OctreoScan	55–77
	90–100	
	EUS	28–86
	N/A	

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasonography; MRI, magnetic resonance imaging; N/A, not applicable; OctreoScan, imaging with ^{111}In -pentetreotide; SASI, selective arterial secretin injection.

the uptake of the stable somatostatin analogue ^{111}In -pentetreotide (OctreoScan) has demonstrated sensitivity and specificity rates of

“ 80%. Positron emission tomography (PET)–computed tomography (CT) with ^{68}Ga -DOTATATE has been developed and is superior than OctreoScan for assessing tumor presence in patients with well-differentiated NETs such as gastrinomas, with sensitivity and specificity of $>90\%$, making it the functional imaging study of choice when available. ^{18}F -Fluorodeoxyglucose (^{18}F -FDG) PET

imaging has been found to be useful in pancreatic NETs, including gastrinomas, particularly as a prognostic marker. Up to 50% of patients have metastatic disease at diagnosis. Success in controlling gastric acid hypersecretion has shifted the emphasis of therapy toward providing a surgical cure. Detecting the primary tumor and excluding metastatic disease are critical in view of this paradigm shift. Once a biochemical diagnosis has been confirmed, the patient should first undergo an abdominal CT scan, magnetic resonance imaging (MRI), or OctreoScan/PET-CT with ^{68}Ga -DOTATATE (depending on availability) to exclude metastatic disease. Once metastatic disease has been excluded, an experienced endocrine surgeon may opt for exploratory laparotomy with intraoperative ultrasound or transillumination. In other centers, careful examination of the peripancreatic area with EUS, accompanied by endoscopic exploration of the duodenum for primary tumors, will be performed before surgery. Selective arterial secretin injection may be a useful adjuvant for localizing tumors in a subset of patients. The extent of the diagnostic and surgical approach must be carefully balanced with the patient's overall physiologic condition and the natural history of a slow-growing gastrinoma.

TREATMENT Zollinger-Ellison Syndrome Treatment of functional endocrine tumors is directed at ameliorating the signs and symptoms related to hormone overproduction, curative resection of the neoplasm, and attempts to control tumor growth in metastatic disease. PPIs are the treatment of choice and have decreased the need for total gastrectomy. Initial PPI doses tend to be higher than those used for treatment of GERD or PUD. The initial dose of omeprazole, lansoprazole, rabeprazole, or esomeprazole should be in the range of 60 mg in divided doses in a 24-h period. When gastric acid analysis was more widely available, dosing was adjusted to achieve a BAO <10 meq/h (at the drug trough) in surgery-naïve patients and to

<5 meq/h in individuals who have previously undergone an acid-reducing operation. Close monitoring of clinical symptoms when starting PPIs and increasing the dose accordingly are paramount. Although the somatostatin analogue has inhibitory effects on gastrin release from receptor-bearing tumors and inhibits gastric acid secretion to some extent, PPIs have the advantage of reducing parietal cell activity to a greater degree. Despite this, octreotide or lanreotide may be considered as adjunctive therapy to the PPI in patients with tumors that express somatostatin receptors and have peptic symptoms that are difficult to control with high-dose PPI. The ultimate goal of surgery would be to provide a definitive cure. Improved understanding of tumor distribution has led to immediate cure rates as high as 33% with 10-year disease-free intervals as high as 95% in sporadic gastrinoma patients undergoing surgery. A positive outcome is highly dependent on the experience of the surgical team treating these rare tumors. Surgical therapy of gastrinoma patients with MEN 1 remains controversial because of the difficulty in rendering these patients disease-free with surgery. In contrast to the encouraging postoperative results observed in patients with sporadic disease, $<5\%$ of MEN 1 patients are disease-free 5 years after an operation. Moreover, in contrast to patients with sporadic ZES, the clinical course of MEN 1 patients tends to be benign and rarely leads to disease-related mortality, recommending that early

surgery be deferred. Some groups suggest surgery only if a clearly identifiable, nonmetastatic lesion is documented by structural studies. Others advocate a more aggressive approach, where

all patients free of hepatic metastasis are explored and all detected tumors in the duodenum are resected; this is followed by enucleation of lesions in the pancreatic head, with a distal pancreatectomy to follow. The outcome of the two approaches has not been clearly defined. Laparoscopic surgical interventions may provide attractive approaches in the future but currently seem to be of some limited benefit in patients with gastrinoma because a significant percentage of the tumors may be extrapancreatic and difficult to localize with a laparoscopic approach. Finally, patients selected for surgery should be individuals whose health status would lead them to tolerate a more aggressive operation and obtain the long-term benefits from such aggressive surgery, which are often witnessed after 10 years. Therapy of metastatic endocrine tumors in general remains suboptimal; gastrinomas are no exception. In light of the observation that in many instances tumor growth is indolent and that many individuals with metastatic disease remain relatively stable for significant periods of time, many advocate not instituting systemic tumor-targeted therapy until evidence of tumor progression or refractory symptoms not controlled with PPIs are noted. Medical approaches, including biologic therapy (IFN- α , long-acting somatostatin analogues, and peptide receptor radionuclides), systemic chemotherapy (streptozotocin, 5-fluorouracil, and doxorubicin), and hepatic artery embolization, may lead to significant toxicity without a substantial improvement in overall survival. Use of temozolomide with capecitabine has demonstrated radiographic regression and progression-free survival in patients with well-differentiated NETs in the range of 70% and 18 months, respectively. Systemic therapy with radiolabeled somatostatin analogues (peptide receptor radiotherapy [PRRT]) has been used in the therapy of metastatic NETs and appears to be very promising in terms of radiographic regression, symptoms, and progression-free survival, but additional studies are warranted. Several promising therapies are being explored, including radiofrequency ablation or cryoablation of liver lesions and use of agents that block the VEGF receptor pathway (sunitinib, sorafenib), the mammalian target of rapamycin, and immune checkpoint inhibitors (Chap. 89). Surgical approaches, including debulking surgery and liver transplantation for hepatic metastasis, have also produced limited benefit. The overall 5- and 10-year survival rates for gastrinoma patients are 62–75% and 47–53%, respectively. Individuals with the entire tumor resected or those with a negative laparotomy have 5- and 10-year survival rates >90%. Patients with incompletely resected tumors have 5- and 10-year survival rates of 43 and 25%, respectively. Patients with hepatic metastasis have <20% survival at 5 years. Favorable prognostic indicators include primary duodenal wall tumors, isolated lymph node tumor, the presence of MEN 1, and undetectable tumor upon surgical exploration. Poor outcome is seen in patients with shorter disease duration; female sex; older age at diagnosis; higher gastrin levels (>10,000 pg/mL); poor histologic differentiation; high proliferative index; certain tumor molecular changes including chromosome 1qLOH and chromosome XLOH; large pancreatic primary tumors (>2–3 cm); metastatic disease to lymph nodes, liver, and bone; and Cushing's syndrome. Rapid growth of hepatic metastases is also predictive of poor outcome. ■

■ **STRESS-RELATED MUCOSAL INJURY** Patients suffering from shock, sepsis, massive burns, severe trauma, or head injury can develop acute erosive gastric mucosal changes or frank ulceration with bleeding. Classified as stress-induced gastritis or ulcers, injury is most commonly observed in the acid-producing (fundus and body) portions of the stomach. The most common presentation is GI bleeding, which is usually minimal but can occasionally be lifethreatening. Respiratory failure requiring mechanical ventilation and underlying coagulopathy are risk factors for bleeding, which

tends to occur 48–72 h after the acute injury or insult. Histologically, stress injury does not contain inflammation or *H. pylori*; thus, “gastritis” is a misnomer. Although elevated gastric acid

secretion may be noted in patients with stress ulceration after head trauma (Cushing’s ulcer) and severe burns (Curling’s ulcer), mucosal ischemia, breakdown of the normal protective barriers of the stomach, systemic release of cytokines, poor GI motility, and oxidative stress also play an important role in the pathogenesis. Acid must contribute to injury in view of the significant drop in bleeding noted when acid inhibitors are used as prophylaxis for stress gastritis.

Improvement in the general management of intensive care unit patients has led to a significant decrease in the incidence of GI bleeding due to stress ulceration. The estimated decrease in bleeding is from 20–30% to <5%. This improvement has led to some debate regarding the need for prophylactic therapy. The high mortality associated with stress-induced clinically important GI bleeding (>40%) and the limited benefit of medical (endoscopic, angiographic) and surgical therapy in a patient with hemodynamically compromising bleeding associated with stress ulcer/gastritis support the use of preventive measures in high-risk patients (mechanically ventilated, coagulopathy, multiorgan failure, or severe burns). Meta-analysis comparing H₂ blockers with PPIs for the prevention of stress-associated clinically important and overt GI bleeding demonstrates superiority of the latter without increasing the risk of nosocomial infections, increasing mortality, or prolonging intensive care unit length of stay. Therefore, PPIs are the treatment of choice for stress prophylaxis. Oral PPI is the best option if the patient can tolerate enteral administration. Pantoprazole is available as an intravenous formulation for individuals in whom enteral administration is not possible. If bleeding occurs despite these measures, endoscopy, intra-arterial vasopressin, and embolization are options. If all else fails, then surgery should be considered. Although vagotomy and antrectomy may be used, the better approach would be a total gastrectomy, which has an exceedingly high mortality rate in this setting. Concerns with the effect of PPIs on the immune system coupled with the high cost of this agent have led to several comparative studies of PPIs and H₂ receptor antagonists for stress prophylaxis in patients requiring mechanical ventilation. Although the PEPTIC trial demonstrated comparative efficacy between the two agents regarding mortality, technical aspects of the study led to some limitation in the final interpretation of the results. A meta-analysis performed in neurocritical patients did not reach strong clinical recommendations about the utility of ulcer prophylaxis. Reasons for this conclusion included the overall high or unclear risk of bias of individual trials, the low event rates, and the modest sample size examined. Currently, a trial to determine safety and efficacy of pantoprazole compared to placebo for preventing stress-induced erosions is ongoing in mechanically ventilated patients.

CHAPTER 335 Peptic Ulcer Disease and Related Disorders ■ ■ GASTRITIS The term gastritis should be reserved for histologically documented inflammation of the gastric mucosa. Gastritis is not the mucosal erythema seen during endoscopy and is not interchangeable with “dyspepsia.” The etiologic factors leading to gastritis are broad and heterogeneous. Gastritis has been classified based on time course (acute vs chronic), histologic features, and anatomic distribution or proposed pathogenic mechanism (Table 335-10). The correlation between the histologic findings of gastritis, the clinical picture of abdominal pain or dyspepsia, and endoscopic findings noted on gross inspection of the gastric mucosa is poor. Therefore, there is no typical clinical manifestation of gastritis.

Acute Gastritis The most common causes of acute gastritis are infectious. Acute infection with *H. pylori* induces gastritis. However, *H. pylori* acute gastritis has not been extensively studied. It is reported as presenting with sudden onset of epigastric pain, nausea,

and vomiting, and limited mucosal histologic studies demonstrate a marked infiltrate of neutrophils with edema and hyperemia. If not treated, this picture will evolve into one of chronic gastritis. Hypochlorhydria lasting for up to 1 year may follow acute H. pylori infection. Bacterial infection of the stomach or phlegmonous gastritis is a rare, potentially life-threatening disorder characterized by marked and diffuse acute inflammatory infiltrates of the entire gastric wall, at times accompanied by necrosis. Elderly individuals, alcoholics, and AIDS

TABLE 335-10 Classification of Gastritis I. Acute gastritis A. Acute Helicobacter pylori infection B. Other acute infectious gastritides

1. Bacterial (other than H. pylori)
2. Helicobacter heilmannii
3. Phlegmonous
4. Mycobacterial
5. Syphilitic
6. Viral
7. Parasitic
8. Fungal II. Chronic atrophic gastritis A. Type A: Autoimmune, body-predominant B. Type B: H. pylori-related, antral-predominant C. Indeterminate III. Uncommon forms of gastritis A. Lymphocytic B. Eosinophilic C. Crohn's disease D. Sarcoidosis E. Isolated granulomatous gastritis F. Russell body gastritis patients may be affected. Potential iatrogenic causes include polypectomy and mucosal injection with India ink. Organisms associated with this entity include streptococci, staphylococci, Escherichia coli, Proteus, and Haemophilus species. Failure of supportive measures and antibiotics may result in gastrectomy. PART 10 Disorders of the Gastrointestinal System Other types of infectious gastritis may occur in immunocompromised individuals such as AIDS patients. Examples include herpetic (herpes simplex) or CMV gastritis. The histologic finding of intranuclear inclusions would be observed in the latter. Chronic Gastritis Chronic gastritis is identified histologically by an inflammatory cell infiltrate consisting primarily of lymphocytes and plasma cells, with very scant neutrophil involvement. Distribution of the inflammation may be patchy, initially involving superficial and glandular portions of the gastric mucosa. This picture may progress to more severe glandular destruction, with atrophy and metaplasia. Chronic gastritis has been classified according to histologic characteristics. These include superficial atrophic changes and gastric atrophy. The association of atrophic gastritis with the development of gastric cancer has led to the development of endoscopic and serologic markers of severity. Some of these include gross inspection and classification of mucosal abnormalities during standard endoscopy, magnification endoscopy, endoscopy with narrow band imaging and/or autofluorescence imaging, and measurement of several serum biomarkers including pepsinogen I and II levels, gastrin-17, and anti-H. pylori serologies. The clinical utility of these tools is currently being explored. The early phase of chronic gastritis is superficial gastritis. The inflammatory changes are limited to the lamina propria of the surface mucosa, with edema and cellular infiltrates separating intact gastric glands. The next stage is atrophic gastritis. The inflammatory infiltrate extends deeper into the mucosa, with progressive distortion and destruction of the glands. The final stage of chronic gastritis is gastric atrophy. Glandular structures are lost, and there is a paucity of inflammatory infiltrates. Endoscopically, the mucosa may be substantially

thin, permitting clear visualization of the underlying blood vessels. Gastric glands may undergo morphologic transformation in chronic gastritis. Intestinal metaplasia denotes the conversion of gastric glands to a small intestinal phenotype with small-bowel mucosal glands containing goblet cells. The metaplastic changes may vary in distribution from patchy to fairly extensive gastric involvement. Intestinal metaplasia is an important predisposing factor for gastric cancer (Chap. 85).

Chronic gastritis has also been classified according to the predominant site of involvement. Type A refers to the body-predominant form (autoimmune), and type B is the antral-predominant form (*H. pylori*-related). This classification is artificial in view of the difficulty in distinguishing between these two entities. The term AB gastritis has been used to refer to a mixed antral/body picture. Histologic classification is the most accurate way to approach chronic gastritis. TYPE A GASTRITIS The less common of the two forms involves primarily the fundus and body, with antral sparing. Traditionally, this form of gastritis has been associated with pernicious anemia (Chap. 104) in the presence of circulating antibodies against parietal cells and IF; thus, it is also called autoimmune gastritis. *H. pylori* infection can lead to a similar distribution of gastritis. Antibodies to parietal cells have been detected in >90% of patients with pernicious anemia and in up to 50% of patients with type A gastritis. The parietal cell antibody is directed against H⁺,K⁺-ATPase.

T cells are also implicated in the injury pattern of this form of gastritis. A subset of patients infected with *H. pylori* develop antibodies against H⁺,K⁺-ATPase, potentially leading to the atrophic gastritis pattern seen in some patients infected with this organism. The mechanism is thought to involve molecular mimicry between *H. pylori* LPS and H⁺,K⁺-ATPase. Parietal cell antibodies and atrophic gastritis are observed in family members of patients with pernicious anemia. These antibodies are observed in up to 20% of individuals aged >60 and in ~20% of patients with vitiligo and Addison's disease. About one-half of patients with pernicious anemia have antibodies to thyroid antigens, and ~30% of patients with thyroid disease have circulating anti-parietal cell antibodies. Anti-IF antibodies are more specific than parietal cell antibodies for type A gastritis, being present in ~40% of patients with pernicious anemia. Another parameter consistent with this form of gastritis being autoimmune in origin is the higher incidence of specific familial histocompatibility haplotypes such as HLA-B8 and HLA-DR3. Low pepsinogen levels have also been observed; thus, this marker has been used as an additional diagnostic tool in autoimmune gastritis. The parietal cell-containing gastric gland is preferentially targeted in this form of gastritis, and achlorhydria results. Parietal cells are the source of IF, the lack of which will lead to vitamin B₁₂ deficiency and its sequelae (megaloblastic anemia, neurologic dysfunction). Gastric acid plays an important role in feedback inhibition of gastrin release from G cells. Achlorhydria, coupled with relative sparing of the antral mucosa (site of G cells), leads to hypergastrinemia. Gastrin levels can be markedly elevated (>500 pg/mL) in patients with pernicious anemia. ECL cell hyperplasia with frank development of gastric carcinoid tumors may result from gastrin trophic effects. Hypergastrinemia and achlorhydria may also be seen in nonpernicious anemia-associated type A gastritis. TYPE B GASTRITIS Type B, or antral-predominant, gastritis is the more common form of chronic gastritis. *H. pylori* infection is the cause of this entity. Although described as "antral-predominant," this is likely a misnomer in view of studies documenting the progression of the inflammatory process toward the body and fundus of infected individuals. The conversion to a pangastritis is time dependent and estimated to require 15–20 years. This form of gastritis increases with age, being present in up to 100% of persons aged >70. Histology improves after *H.*

pylori eradication. The number of *H. pylori* organisms decreases dramatically with progression to gastric atrophy, and the degree of inflammation correlates with the level of these organisms. Early on, with antral-predominant findings, the quantity of *H. pylori* is highest and a dense chronic inflammatory infiltrate of the lamina propria is noted, accompanied by epithelial cell infiltration with polymorpho nuclear leukocytes (Fig. 335-16). Multifocal atrophic gastritis, gastric atrophy with subsequent metaplasia, has been observed in chronic *H. pylori*-induced gastritis. This may ultimately lead to development of gastric adenocarcinoma (Fig. 335-8; Chap. 85). *H. pylori* infection is now considered an independent risk factor for gastric cancer. Worldwide epidemiologic studies have documented a higher incidence of *H. pylori* infection in

FIGURE 335-16 Chronic gastritis and *H. pylori* organisms. Steiner silver stain of superficial gastric mucosa showing abundant darkly stained microorganisms layered over the apical portion of the surface epithelium. Note that there is no tissue invasion.

patients with adenocarcinoma of the stomach as compared to control subjects. Seropositivity for *H. pylori* is associated with a three- to sixfold increased risk of gastric cancer. This risk may be as high as ninefold after adjusting for the inaccuracy of serologic testing in the elderly. The mechanism by which *H. pylori* infection leads to cancer is unknown, but it appears to be related to the chronic inflammation induced by the organism. Eradication of *H. pylori* as a general preventative measure for gastric cancer is being evaluated but is not yet recommended. Infection with *H. pylori* is also associated with development of a low-grade B-cell lymphoma, gastric MALT lymphoma (Chap. 113). The chronic T-cell stimulation caused by the infection leads to production of cytokines that promote the B-cell tumor. The tumor should be initially staged with a CT scan of the abdomen and EUS. Tumor growth remains dependent on the presence of *H. pylori*, and its eradication is often associated with complete regression of the tumor. The tumor may take more than a year to regress after treating the infection. Such patients should be followed by EUS every 2–3 months. If the tumor is stable or decreasing in size, no other therapy is necessary. If the tumor grows, it may have become a high-grade B-cell lymphoma. When the tumor becomes a high-grade aggressive lymphoma histologically, it loses responsiveness to *H. pylori* eradication.

TREATMENT Chronic Gastritis

Treatment in chronic gastritis is aimed at the sequelae and not the underlying inflammation. Patients with pernicious anemia will require parenteral vitamin B12 supplementation on a long-term basis. Eradication of *H. pylori* is often recommended even if PUD or a low-grade MALT lymphoma is not present. Expert opinion suggests that patients with atrophic gastritis complicated by intestinal metaplasia without dysplasia should undergo surveillance endoscopy every 3 years.

Miscellaneous Forms of Gastritis

Lymphocytic gastritis is characterized histologically by intense infiltration of the surface epithelium with lymphocytes. The infiltrative process is primarily in the body of the stomach and consists of mature T cells and plasmacytes. The etiology of this form of chronic gastritis is unknown. It has been described in patients with celiac sprue, but whether there is a common factor associating these two entities is unknown. No specific symptoms suggest lymphocytic gastritis. A subgroup of patients has thickened folds noted on endoscopy. These folds are often capped by small nodules that contain a central depression or erosion; this form of the disease is called varioliform gastritis. *H. pylori* probably plays no significant

role in lymphocytic gastritis. Therapy with glucocorticoids or sodium cromoglycate has obtained unclear results.

Marked eosinophilic infiltration involving any layer of the stomach (mucosa, muscularis propria, and serosa) is characteristic of eosinophilic gastritis. Affected individuals will often have circulating

eosinophilia with clinical manifestation of systemic allergy. Involvement may range from isolated gastric disease to diffuse eosinophilic gastroenteritis. Antral involvement predominates, with prominent edematous folds being observed on endoscopy. These prominent antral folds can lead to outlet obstruction. Patients can present with epigastric discomfort, nausea, and vomiting. Treatment with glucocorticoids has been successful. Several systemic disorders may be associated with granulomatous gastritis. Gastric involvement has been observed in Crohn's disease. Involvement may range from granulomatous infiltrates noted only on gastric biopsies to frank ulceration and stricture formation. Gastric Crohn's disease usually occurs in the presence of small-intestinal disease. Several rare infectious processes can lead to granulomatous gastritis, including histoplasmosis, candidiasis, syphilis, and tuberculosis. Other unusual causes of this form of gastritis include sarcoidosis, idiopathic granulomatous gastritis, and eosinophilic granulomas involving the stomach. Establishing the specific etiologic agent in this form of gastritis can be difficult, at times requiring repeat endoscopy with biopsy and cytology. Occasionally, a surgically obtained full-thickness biopsy of the stomach may be required to exclude malignancy. Russell body gastritis (RBG) is a mucosal lesion of unknown etiology that has a pseudotumoral endoscopic appearance. Histologically, it is defined by the presence of numerous plasma cells containing Russell bodies (RBs) that express kappa and lambda light chains. Only 10 cases have been reported, and 7 of these have been associated with *H. pylori* infection. The lesion can be confused with a neoplastic process, but it is benign in nature, and the natural history of the lesion is not known. There have been cases of resolution of the lesion when *H. pylori* was eradicated.

CHAPTER 335 Peptic Ulcer Disease and Related Disorders

Immune checkpoint inhibitor-induced enterocolitis and gastritis are recognized sequelae of these oncologic therapies. The gastritis typically occurs later in the course of therapy. The diagnosis is made by the histologic findings on gastric mucosal biopsies obtained endoscopically. This is an important diagnosis to make since therapy with glucocorticoids and potentially IL-6 receptor blockers will be required. Moreover, this side effect will have an effect on the oncologic therapy prescribed.

■ ■ **MÉNÉTRIER'S DISEASE** Ménétrier's disease (MD) is a very rare gastropathy characterized by large, tortuous mucosal folds. MD has an average age of onset of 40–60 years with a male predominance. The differential diagnosis of large gastric folds includes ZES, malignancy (lymphoma, infiltrating carcinoma), infectious etiologies (CMV, histoplasmosis, syphilis, tuberculosis), gastritis polyposa profunda, and infiltrative disorders such as sarcoidosis. MD is most commonly confused with large or multiple gastric polyps (prolonged PPI use) or familial polyposis syndromes. The mucosal folds in MD are often most prominent in the body and fundus, sparing the antrum. Histologically, massive foveolar hyperplasia (hyperplasia of surface and glandular mucous cells) and a marked reduction in oxyntic glands and parietal cells and chief cells are noted. This hyperplasia produces the prominent folds observed. The pits of the gastric glands elongate and may become extremely dilated and tortuous. Although the lamina propria may contain a mild chronic inflammatory infiltrate including eosinophils and plasma cells, MD is not considered a form of gastritis. The etiology of this unusual clinical picture in children is often CMV, but the etiology in adults is unknown. Overexpression of the growth factor TGF- α has been demonstrated in patients with MD. The overexpression of TGF- α in turn results in overstimulation of the epidermal growth factor receptor (EGFR) pathway and increased proliferation of mucous cells, resulting in the observed foveolar hyperplasia. The clinical presentation in adults is usually insidious and progressive. Epigastric pain, nausea, vomiting, anorexia, peripheral edema,